nodular densities. The cavities are often thin-walled and have less surrounding parenchymal infiltrate than is commonly seen with MTB infections. Evidence of contiguous spread and pleural involvement is often present. HRCT of the chest may show multiple small nodules with or without multifocal bronchiectasis. Progression of pulmonary infiltrates during therapy or lack of radiographic improvement over time are poor prognostic signs and also raise concerns about secondary or alternative pulmonary processes. Clearing of pulmonary infiltrates due to NTM is slow.

Treatment

NTM infection does not mandate treatment in all cases, for two reasons. First, clinical disease may never develop in some patients, particularly asymptomatic patients with few organisms isolated from single specimens. Second, the spectrum of clinical disease severity is very wide; in patients with mild or slowly progressive symptoms, traditional antimicrobial regimens using a combination of agents may lead to drug-induced side effects worse than the disease itself. These features at least partly explain variability of adherence to treatment guidelines in practice.

Specific treatment regimens and responses to therapy vary with the species of NTM. HIV-seronegative patients with MAC pulmonary disease usually receive a combination of daily clarithromycin or azithromycin, rifampin or rifabutin, and ethambutol. For patients with severe fibrocavitary disease, streptomycin or amikacin is added for the first 2 months. The optimal duration of treatment is unknown, but therapy should be continued for 12 months after sputum conversion. Medical treatment is initially successful in about two-thirds of cases, but relapses after treatment are common; long-term benefit is demonstrated in about half of all patients. Those who do not respond favorably generally have active but stable disease. Surgical resection is an alternative for the patient with progressive disease that responds poorly to antimicrobials. Disease caused by *M kansasii* responds well to drug therapy. A daily regimen of rifampin, isoniazid, and ethambutol for at least 18 months with a minimum of 12 months of negative cultures is usually successful. Rapidly growing mycobacteria (*M abscessus*, *M fortuitum*, *M chelonae*) are generally resistant to standard antituberculous therapy.

Treatment recommendations for less common NTM (including *M chelonae*, *M fortuitum*, *M genavense*, *M gordonae*, *M malmoense*, *M simiae*, and *M szulgai*), based primarily on case reports and case series, were published in 2022; expert consultation should be sought to determine need for treatment.

When to Refer

Patients with rapidly growing mycobacteria or uncommon NTM should be referred for expert management.

Abate G et al. Variability in the management of adults with pulmonary nontuberculous mycobacterial disease. Clin Infect Dis. 2021;72:1127. [PMID: 32198521]

Daley CL et al. Treatment of nontuberculous mycobacterial pulmonary disease: official ATS/ERS/ESCMID/IDSA clinical practice guideline. Eur Respir J. 2020;56:2000535. [PMID: 32636299]

Lange C et al. Consensus management recommendations for less common non-tuberculous mycobacterial pulmonary diseases. Lancet Infect Dis. 2022;22:e178. [PMID: 35090639]

PULMONARY NEOPLASMS

See Chapter 41 for discussions of Lung Cancer, Secondary Lung Cancer, and Mesothelioma.

SCREENING FOR LUNG CANCER

Lung cancer remains the leading cause of cancer-related mortality, in large part secondary to advanced stage at diagnosis (Chapter 41). Annual low-dose CT (LDCT) screening is recommended for those at high risk by multiple organizations, including the USPSTF, the American Cancer Society, the American College of Chest Physicians, and the National Comprehensive Cancer Network. High-risk criteria include age 50–80 years, at least a 20-pack-year smoking history, and either current smoking or quit date within past 15 years. Screening should be stopped once 15 years have elapsed since quitting smoking or if a comorbid condition renders the benefits of screening null. Simulation models have found yearly screening using these parameters to be the most efficient in reducing lung cancer–related deaths, though more false-positive test results are expected.

Annual CXRs are not recommended for lung cancer screening in current or former smokers as no mortality benefit has been demonstrated with serial exams in two large RCTs: the Prostate, Lung, Colorectal and Ovarian Randomized Trial (PLCO) and the National Lung Cancer Screening Trial (NLST). The NLST enrolled 53,454 current or former smokers who were randomly assigned to three annual posterior-anterior CXRs or three LDCT scans and monitored for an additional 6.5 years. Compared with CXR, LDCT detected more early-stage lung cancers and fewer advanced-stage lung cancers, indicating that LDCT screening systematically shifted the time of diagnosis to earlier stages, thereby providing more persons the opportunity for effective treatment. Furthermore, the cohort that received three annual LDCT scans had a significant mortality benefit, with reductions in both lung cancer deaths (20.0%) and all-cause mortality (6.7%).

Potential harms of LDCT screening include false positive findings, overdiagnosis, radiation, and anxiety and patient distress which ought to be discussed prior to patient's referral for screening. Other issues that remain of concern include **(1) Generalizability to practice:** NLST-participating institutions demonstrated a high level of expertise in imaging interpretation and diagnostic evaluation. Ninety-six percent of findings on CT were false positives but the vast majority of patients were monitored with serial imaging. Invasive diagnostic evaluations were uncommon and were associated with a low complication rate (1.4%). **(2) Duration of screening:** The rate of

detection of new lung cancers did not fall with subsequent annual screening over the 3-year trial. Since new lung cancers become detectable during each year-long screening interval, the optimal number of annual CT scans is unknown as is the optimal screening interval. **(3) Overdiagnosis:** After 6.4 years of post-screening observation, there were more lung cancers in the NLST CT cohort than the CXR cohort (1089 and 969, respectively). Since the groups were randomized and well matched, lung cancer incidence should have been identical. Therefore, 18.5% of the lung cancers detected by CT remained clinically silent and invisible on CXR for 6.4 years. Many, perhaps most, of these lung cancers would never cause clinical disease and represent overdiagnosis. **(4) Cost effectiveness:** Studies in the United States, Canada, and Europe suggest screening for lung cancer is cost effective; however, whether it is cost effective in all countries has not been determined. All patients participating in a screening program who still smoke should receive smoking cessation interventions.

Adams SJ et al. Lung cancer screening. Lancet. 2023;401:390. [PMID: 36563698]
Becker N et al. Lung cancer mortality reduction by LDCT screening–results from the randomized German LUSI trial. Int J Cancer. 2020;146:1503. [PMID: 31162856]
de Koning HJ et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. N Engl J Med. 2020;382:503. [PMID: 31995683]
Krist AH et al. Screening for lung cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2021;325:962. [PMID: 33687470]
Leiter A et al. The global burden of lung cancer: current status and future trends. Nat Rev Clin Oncol. 2023;20:624. [PMID: 37479810]
Sadate A et al. Systemic review and meta-analysis on the impact of lung cancer screening by low-dose computed tomography. Eur J Cancer. 2020;134:107. [PMID: 32502939]

SOLITARY PULMONARY NODULE

A solitary pulmonary nodule, sometimes referred to as a "coin lesion," is a less-than-3-cm isolated, rounded opacity on chest imaging outlined by normal lung. Pulmonary nodules may be solid or subsolid with ground glass or mixed consistency. Most are asymptomatic and represent an incidental finding on CXR or CT scanning. Solitary nodules may be benign or malignant; the risk of malignancy varies depending on the patient population under study. Most benign nodules are infectious granulomas. Benign neoplasms, such as hamartomas, account for less than 5% of solitary nodules. The probability of cancer in pulmonary nodules detected by LDCT is estimated at 1% of nodules. Malignant nodules are rare in persons under age 30. Above age 30, the likelihood of malignancy increases with age and smoking history. Patients with a prior malignancy have a higher likelihood of having a malignant solitary nodule.

The goals of evaluation are to identify and resect malignant tumors in patients who will benefit from resection while avoiding invasive procedures in benign disease. The task is to identify nodules with a sufficiently high probability of malignancy to warrant biopsy or resection or a sufficiently low probability of malignancy to justify observation.

Clinical and imaging data can be used to assess the probability of malignancy. Comparison of prior and current imaging studies allows estimation of doubling time, which is an important marker for malignancy. Rapid progression (doubling time less than 30 days) suggests infection, while long-term stability (doubling time greater than 465 days) suggests benignity. Radiographic features including size help in estimating the probability of malignancy. Chest CT is indicated for any suspicious solitary pulmonary nodule. Solitary nodules identified by CT scan showed a 1% malignancy rate in those measuring 2–5 mm, 24% in 6–10 mm, 33% in 11–20 mm, and 80% in 21–45 mm nodules. The appearance of a smooth, well-defined edge is characteristic of a benign process. Ill-defined margins or a lobular appearance suggest malignancy. A HRCT finding of spiculated margins and a peripheral halo are both highly associated with malignancy. Calcification and its pattern are also helpful clues. Benign lesions tend to have dense calcification in a central or laminated pattern. Malignant lesions are associated with sparser calcification that is typically stippled or eccentric. Cavitary lesions with thick (greater than 16 mm) walls are more likely to be malignant. HRCT offers better resolution of these characteristics than CXR and is more likely to detect lymphadenopathy or the presence of multiple lesions.

Treatment

Based on clinical and radiologic data, the clinician should assign a specific probability of malignancy to the lesion. The decision whether to recommend a biopsy or surgical excision depends on the interpretation of this probability in light of the patient's clinical situation. Quantitative prediction models (Brock model, VA Cooperative model) are available to assess risk of malignancy. The probabilities in parentheses below represent guidelines only and should not be interpreted as definitive.

In the case of solitary pulmonary nodules, a continuous probability function may be grouped into three categories. In patients with a **low probability (less than 5%) of malignancy** (eg, age under 30, lesions stable for more than 2 years, characteristic pattern of benign calcification), watchful waiting is appropriate. Management consists of serial imaging studies at intervals that could identify growth suggestive of malignancy. Three-dimensional reconstruction of HRCT images provides a more sensitive test for growth.

Patients with a **high probability (greater than 60%) of malignancy** should proceed directly to resection following staging, provided the surgical risk is acceptable. Biopsies rarely yield a specific benign diagnosis and are not indicated.

Optimal management of patients with an **intermediate probability of malignancy (5–60%)** remains controversial. The traditional approach is to obtain a diagnostic biopsy, either through bronchoscopy or transthoracic needle aspiration (TTNA). Bronchoscopy yields a diagnosis in

10–80% of procedures depending on the size of the nodule and its location. In general, the bronchoscopic yield for nodules that are less than 2 cm and peripheral is low, although complications are generally rare. Newer bronchoscopic modalities, such as electromagnetic navigation and ultrathin bronchoscopy, are being studied, although their impact upon diagnostic yield remains uncertain. TTNA has a higher diagnostic yield, reported to be between 50% and 97%. The yield is strongly operator-dependent, however, and is affected by the location and size of the lesion. Complications are higher than bronchoscopy, with pneumothorax occurring in up to 30% of patients, with up to one-third of these patients requiring placement of a chest tube.

Disappointing diagnostic yields and a high false-negative rate (up to 20–30% in TTNA) have prompted alternative approaches. **PET** has a high sensitivity (85–97%) and specificity (70–85%) for malignant lesions and may be useful in the assessment of patients with inconclusive HRCT findings. A positive PET increases the likelihood of malignancy, and a negative PET excludes most cancers. False-negative PET scans can occur with tumors with low metabolic activity (most notably, carcinoid tumors and adenocarcinomas, particularly minimally invasive or in situ adenocarcinomas), so follow-up CT imaging is typically performed at discrete intervals to ensure absence of growth. PET has several other drawbacks: resolution below 1 cm is poor, the test is expensive, and availability remains limited.

Sputum cytology is highly specific but lacks sensitivity. It is used in central lesions and in patients who are poor candidates for invasive diagnostic procedures.

Some centers recommend **video-assisted thoracoscopic surgery (VATS)** resection of all solitary pulmonary nodules with intermediate probability of malignancy. In some cases, the surgeon will remove the nodule and evaluate it in the operating room with frozen section. If the nodule is malignant, he or she will proceed to lobectomy and lymph node sampling, either thoracoscopically or through conversion to standard thoracotomy. This approach is less common when preoperative PET scanning is available.

All patients should be provided with an estimate of the likelihood of malignancy and their preferences used to guide diagnostic and therapeutic decisions. A strategy that recommends observation may not be preferred by a patient who desires a definitive diagnosis. Similarly, a surgical approach may not be agreeable to all patients unless the presence of cancer is definitive. Patient preferences should be elicited, and patients should be well informed regarding the specific risks and benefits associated with the recommended approach as well as the alternative strategies.

RIGHT MIDDLE LOBE SYNDROME

Right middle lobe syndrome is recurrent or persistent atelectasis of the right middle lobe. This collapse is related to the relatively long length and narrow diameter of the right middle lobe bronchus and the oval ("fish mouth") opening to the lobe, in the setting of impaired collateral ventilation. Fiberoptic bronchoscopy or CT scan is often necessary to rule out obstructing tumor. Foreign body or other benign causes are common.

BRONCHIAL CARCINOID TUMORS

Bronchial carcinoid tumors are malignant low- and intermediate-grade neuroendocrine tumors of the lung, with a favorable prognosis compared to high-grade neuroendocrine tumors such as small cell lung cancer. Bronchial carcinoids typically occur as pedunculated or sessile growths in central bronchi. Common symptoms are hemoptysis, cough, focal wheezing, and recurrent postobstructive pneumonia. Peripherally located tumors are rare and present as asymptomatic solitary pulmonary nodules. **Carcinoid syndrome** (flushing, diarrhea, wheezing, hypotension) and paraneoplastic Cushing syndrome are rare. Fiberoptic bronchoscopy may reveal a pink or purple tumor in a central airway. These lesions have a well-vascularized stroma, and biopsy may be complicated by significant bleeding. CT scanning is helpful to localize the lesion and to follow its growth over time. Octreotide scintigraphy is also available for localization of these tumors.

Bronchial carcinoid tumors grow slowly; the aggressiveness is determined by the cell histology, with "typical carcinoid," a low-grade tumor, demonstrating a more indolent and favorable course than "atypical carcinoid," an intermediate-grade tumor. Bronchial carcinoid tumor staging follows the same TNM classification as other lung cancers. Surgical excision, including lymph node dissection and resection, is recommended for localized disease, and the prognosis is generally favorable. Most bronchial carcinoid tumors respond poorly to radiation and chemotherapy (see Chapter 41).

Adenomas, carcinomas, and other malignancies may rarely metastasize to the bronchi and present with endobronchial lesions. Hamartomas, myxomas, and amyloid are other rarer entities in the differential diagnosis of endobronchial mass lesions.

Chen B et al. Malignancy risk stratification for solitary pulmonary nodule: a clinical practice guideline. J Evid Based Med. 2022;15:142. [PMID: 35775869]

Nadig TR et al. Guided bronchoscopy for the evaluation of pulmonary lesions: an updated meta-analysis. Chest. 2023;163:1589. [PMID: 36640994]

Girelli L et al. Results of surgical resection of locally advanced pulmonary neuroendocrine tumors. Ann Thorac Surg. 2021;112:405. [PMID: 33130114]

Koehler K et al. Carcinoid tumors outside the abdomen. Cancer Med. 2023r;12:7893. [PMID: 36560885]

Singh S et al. Commonwealth Neuroendocrine Tumour Research Collaboration and the North American Neuroendocrine Tumor Society Guidelines for the Diagnosis and Management of Patients with Lung Neuroendocrine Tumors: an international collaborative endorsement and update of the 2015 European Neuroendocrine Tumor Society Expert Consensus Guidelines. J Thorac Oncol. 2020;15:1577. [PMID: 32663527]

MEDIASTINAL MASSES

Various developmental, neoplastic, infectious, traumatic, and cardiovascular disorders may cause mediastinal masses. A useful convention arbitrarily divides the mediastinum into three compartments—anterior, middle, and posterior—in order to classify mediastinal masses and assist in differential diagnosis based on contents of these anatomic regions. The anterior compartment is bounded by the sternum anteriorly and the surface of the great vessels and pericardium posteriorly. The middle compartment extends from the anterior pericardium to the anterior surface of the thoracic spine. The posterior compartment is paravertebral. Specific mediastinal masses have a predilection for one or more of these compartments; most are located in the anterior or middle compartment.

The differential diagnosis of an **anterior mediastinal mass** includes tumors of the thymus, including thymoma and thymic carcinoma; teratoma; thyroid lesions; lymphoma; and mesenchymal tumors (lipoma, fibroma). The differential diagnosis of a **middle mediastinal mass** includes lymphadenopathy, pulmonary artery enlargement, aneurysm of the aorta or innominate artery, developmental cyst (bronchogenic, enteric, pleuropericardial), dilated azygous or hemiazygous vein, and foramen of Morgagni hernia. The differential diagnosis of a **posterior mediastinal mass** includes hiatal hernia, neurogenic tumor, meningocele, esophageal tumor, foramen of Bochdalek hernia, thoracic spine disease, and extramedullary hematopoiesis. The neurogenic tumor group includes neurilemmoma, neurofibroma, neurosarcoma, ganglioneuroma, and pheochromocytoma.

Symptoms and signs of mediastinal masses are nonspecific and are usually caused by the effects of the mass on surrounding structures. Insidious onset of retrosternal chest pain, dysphagia, or dyspnea is often an important clue to the presence of a mediastinal mass. In about half of cases, symptoms are absent, and the mass is detected on routine CXR. Physical findings vary depending on the nature and location of the mass.

CT scanning is helpful in management; additional radiographic studies of benefit include upper endoscopy if esophageal disease is suspected, Doppler sonography or venography of brachiocephalic veins and the superior vena cava, and angiography. MRI provides better delineation of hilar structures and distinction between vessels and masses. Tissue diagnosis via either needle or excisional biopsy is generally necessary when a neoplastic process is considered. Treatment and prognosis depend on the underlying cause of the mediastinal mass.

Ahuja J et al. Approach to imaging of mediastinal masses. Diagnostics (Basel). 2023;13:3171. [PMID: 37891992]
Miyazawa R et al. Incidental mediastinal masses detected at low-dose CT screening: prevalence and radiological characteristics. Jpn J Radiol. 2020;38:1150. [PMID: 32638279]
Taka M et al. Diagnostic approach for mediastinal masses with radiopathological correlation. Eur J Radiol. 2023;162:110767. [PMID: 36921376]

INTERSTITIAL LUNG DISEASE (Diffuse Parenchymal Lung Disease)

ESSENTIALS OF DIAGNOSIS

- Insidious onset of progressive dyspnea and nonproductive chronic cough.
- Tachypnea, bibasilar dry rales; digital clubbing and right HF with advanced disease.
- Lung CT scan with patchy distribution of ground glass, reticular, nodular, reticulonodular, or cystic opacities.
- PFTs with reduced lung volumes and diffusing capacity.
- Hypoxemia with exercise.

Interstitial lung disease (ILD) comprises a heterogeneous group of disorders that share common presentations (dyspnea), physical findings (late inspiratory crackles), and CXRs (septal thickening and reticulonodular changes). Table 9–16 outlines a selected list of differential diagnoses of ILD. In most patients, no specific cause can be identified. In the remainder, the principal causes are medications, a variety of organic and inorganic dusts, and connective tissue diseases (rheumatoid arthritis, SLE, systemic sclerosis [scleroderma], polymyositis-dermatomyositis, Sjögren syndrome, and other overlap conditions). The history—particularly the occupational and medication history—may provide evidence of a specific cause.

Known causes of interstitial lung disease are dealt with in their specific sections. The important idiopathic forms are discussed below.

DIFFUSE INTERSTITIAL PNEUMONIAS

ESSENTIALS OF DIAGNOSIS

- Important to identify specific fibrosing disorders. May be associated with connective tissue diseases or be idiopathic.
- Diagnosis commonly is made by HRCT scan with characteristic features or less commonly by lung biopsy.
- Accurate diagnosis identifies patients most likely to benefit from therapy.

General Considerations

Interstitial lung disease may be categorized based on the clinical risk factors listed in Table 9–16. The most common diagnosis among patients with diffuse interstitial lung disease is one of the interstitial pneumonias, which are

Table 9–16. Differential diagnosis of interstitial lung disease (listed alphabetically within category).

Medication-related
Antiarrhythmic agents (amiodarone)
Antibacterial agents (nitrofurantoin, sulfonamides)
Antineoplastic agents (bleomycin, cyclophosphamide, methotrexate, nitrosoureas)
Antirheumatic agents (gold salts, penicillamine)
Phenytoin
Environmental and occupational (inhalation exposures)
Dust, inorganic (asbestos, beryllium, hard metals, silica)
Dust, organic (thermophilic actinomycetes, avian antigens, *Aspergillus* species)
Gases, fumes, and vapors (chlorine, isocyanates, paraquat, sulfur dioxide)
Ionizing radiation
Talc (injection drug users)
Infections
Fungus, disseminated (*Blastomyces dermatitidis, Coccidioides immitis, Histoplasma capsulatum*)
Mycobacteria, disseminated
Pneumocystis jirovecii
Viruses
Primary pulmonary disorders
Cryptogenic organizing pneumonia
Idiopathic interstitial pneumonia: acute interstitial pneumonia, desquamative interstitial pneumonia, nonspecific interstitial pneumonia, usual interstitial pneumonia, respiratory bronchiolitis–associated interstitial lung disease
Pulmonary alveolar proteinosis
Systemic disorders
Acute respiratory distress syndrome
Amyloidosis
Ankylosing spondylitis
Autoimmune disease: dermatomyositis, polymyositis, rheumatoid arthritis, SLE, systemic sclerosis (scleroderma)
Chronic eosinophilic pneumonia
Goodpasture syndrome
Granulomatosis polyangiitis
IBD
Idiopathic pulmonary hemosiderosis
Langerhans cell histiocytosis (eosinophilic granuloma)
Lymphangitic spread of cancer (lymphangitic carcinomatosis)
Lymphangioleiomyomatosis
Pulmonary edema
Pulmonary venous hypertension, chronic
Sarcoidosis

categorized in Table 9–17 by histopathology, and HRCT scan radiographic criteria. Only a small number of patients undergo surgical lung biopsy for diagnosis. Accurate diagnosis dictates treatment and prognosis.

Clinical Findings

A. Symptoms, Signs, and Imaging

The most common of the diffuse interstitial pneumonias is pulmonary fibrosis associated with the histopathologic pattern of **usual interstitial pneumonia (UIP).** When no associated cause is evident, it is classified as **idiopathic pulmonary fibrosis (IPF).** Serologic studies should be obtained to rule out rheumatologic diseases associated with UIP, including ANA, RF, CCP, and, in selected cases, Jo1, SSA, SSB, and Scl70. A diagnosis of IPF can be made in patients who have (1) idiopathic disease by history and inspiratory crackles on physical examination, (2) restrictive physiology on PFTs, and (3) characteristic UIP pattern on high-resolution chest CT (peripheral, basilar predominant opacities associated with honeycombing and traction bronchiectasis) (Figure 9–4). Such patients do not need surgical lung biopsy. Assessment of pulmonary hypertension is recommended in advanced disease.

B. Special Studies

Three diagnostic techniques are in common use: bronchoalveolar lavage (BAL), transbronchial biopsy, and surgical lung biopsy, either through an open procedure or using VATS.

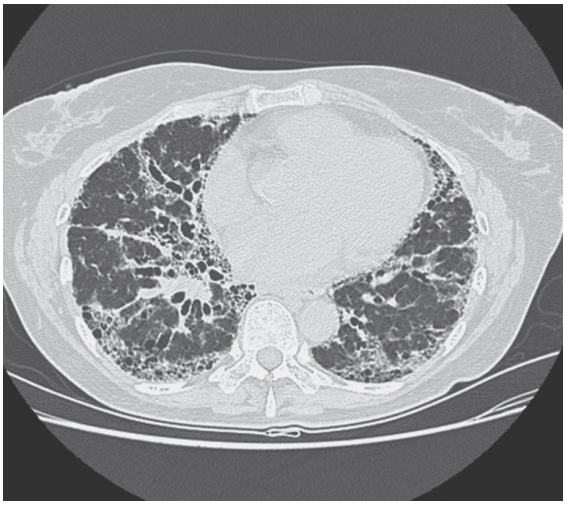
BAL may be indicated to diagnose cases of infection, particularly with *P jirovecii* or mycobacteria, or malignancy. Additionally, BAL may be diagnostic of eosinophilic pneumonia, Langerhans cell histiocytosis, or alveolar proteinosis.

Transbronchial biopsy through the flexible bronchoscope is easily performed in most patients with a low risk of complications. It can make a definitive diagnosis of sarcoidosis, lymphangitic spread of carcinoma, pulmonary alveolar proteinosis, miliary tuberculosis, and Langerhans cell histiocytosis. In IPF, transbronchial biopsy cannot

Table 9–17. Idiopathic interstitial pneumonias.

Name and Clinical Presentation	Histopathology	Radiographic Pattern	Response to Therapy and Prognosis
Usual interstitial pneumonia (UIP) Age 55–60, slight male predominance. Insidious dry cough and dyspnea lasting months to years. Clubbing present at diagnosis in 25–50%. Diffuse fine late inspiratory crackles on lung auscultation. Restrictive ventilatory defect and reduced diffusing capacity on PFTs. ANA and RF positive in ~25% in the absence of documented collagen-vascular disease.	Patchy, temporally and geographically nonuniform distribution of fibrosis, honeycomb change, and normal lung. Type I pneumocytes are lost, and there is proliferation of alveolar type II cells. "Fibroblast foci" of actively proliferating fibroblasts and myofibroblasts. Inflammation is generally mild and consists of small lymphocytes. Intra-alveolar macrophage accumulation is present but is not a prominent feature.	Diminished lung volume. HRCT scanning shows increased linear or reticular bibasilar and subpleural opacities, with associated honeycombing. Unilateral disease is rare. Minimal ground-glass. Areas of normal lung may be adjacent to areas of advanced fibrosis.	No randomized study has demonstrated improved survival compared with untreated patients. Inexorably progressive. Median survival ~3 years, depending on stage at presentation. Nintedanib and pirfenidone reduce rate of decline in lung function. Refer early for lung transplantation evaluation.
Respiratory bronchiolitis–associated interstitial lung disease (RB-ILD)[1] Age 40–45. Presentation like that of UIP though in younger patients. Similar results on PFTs, but less severe abnormalities. Patients with respiratory bronchiolitis are invariably heavy smokers.	Increased numbers of macrophages evenly dispersed within the alveolar spaces. Rare fibroblast foci, little fibrosis, minimal honeycomb change. In RB-ILD the accumulation of macrophages is localized within the peribronchiolar air spaces; in DIP[1], it is diffuse. Alveolar architecture is preserved.	HRCT shows nodular or reticulonodular pattern, more likely to reveal diffuse ground-glass opacities. Honeycombing is rare. May also show upper lobe emphysema.	Spontaneous remission occurs in up to 20% of patients, so natural history unclear. Smoking cessation is essential. Prognosis clearly better than that of UIP: median survival > 10 years. Corticosteroids thought to be effective, but there are no randomized clinical trials to support this view.
Acute interstitial pneumonia (AIP) Clinically known as Hamman-Rich syndrome. Wide age range, many young patients. Acute onset of dyspnea followed by rapid development of respiratory failure. Half of patients report a viral syndrome preceding lung disease. Clinical course indistinguishable from that of idiopathic ARDS.	Pathologic changes reflect acute response to injury within days to weeks. Resembles organizing phase of diffuse alveolar damage. Fibrosis and minimal collagen deposition. May appear like UIP but more homogeneous and there is no honeycomb change—though this may appear if the process persists for more than a month in a patient on mechanical ventilation.	Diffuse bilateral airspace consolidation with areas of ground-glass attenuation on HRCT scan.	Supportive care (mechanical ventilation) critical but effect of specific therapies unclear. High initial mortality: 50–90% die within 2 months after diagnosis. Not progressive if patient survives. Lung function may return to normal or may be permanently impaired.
Nonspecific interstitial pneumonia (NSIP) Age 45–55. Slight female predominance. Like UIP but onset of cough and dyspnea over months, not years.	Nonspecific in that histopathology does not fit into better-established categories. Varying degrees of inflammation and fibrosis, patchy in distribution but uniform in time, suggesting response to single injury. Most have lymphocytic and plasma cell inflammation without fibrosis. Honeycombing present but scant. Some have advocated division into cellular and fibrotic subtypes.	May be indistinguishable from UIP. Most typical picture is bilateral areas of ground-glass attenuation and fibrosis on HRCT. Honeycombing is rare.	Treatment with corticosteroids thought to be effective, but no prospective clinical studies have been published. Overall prognosis good but depends on the extent of fibrosis at diagnosis. Median survival > 10 years.
Cryptogenic organizing pneumonia (COP) Typically age 50–60 but wide variation. Abrupt onset, frequently weeks to a few months following a flu-like illness. Dyspnea and dry cough prominent, but constitutional symptoms are common: fatigue, fever, and weight loss. PFTs usually show restriction, but up to 25% show concomitant obstruction.	Included in the idiopathic interstitial pneumonias on clinical grounds. Buds of loose connective tissue (Masson bodies) and inflammatory cells fill alveoli and distal bronchioles.	Lung volumes normal. CXR typically shows interstitial and parenchymal disease with discrete, peripheral alveolar and ground-glass infiltrates. Nodular opacities common. HRCT shows subpleural consolidation and bronchial wall thickening and dilation.	Rapid response to corticosteroids in two-thirds of patients. Long-term prognosis generally good for those who respond. Relapses are common.

[1]Includes desquamative interstitial pneumonia (DIP).
ARDS, acute respiratory distress syndrome; RF, rheumatoid factor; UIP, usual interstitial pneumonia.



▲ **Figure 9–4.** Idiopathic pulmonary fibrosis. CT scan of the lungs showing the typical radiographic pattern of idiopathic pulmonary fibrosis, with a predominantly basilar, peripheral pattern of traction bronchiectasis, reticulation, and early honeycombing.

confirm the diagnosis since the histologic diagnosis requires a pattern of changes rather than a single pathognomonic finding; therefore, surgical lung biopsy is preferred.

Surgical lung biopsy is the standard for diagnosis of diffuse interstitial lung disease. Two or three biopsies taken from multiple sites in the same lung, including apparently normal tissue, may yield a specific diagnosis as well as prognostic information regarding the extent of fibrosis versus active inflammation. Patients under age 60 without a specific diagnosis based on clinical and radiographic features should undergo surgical lung biopsy. In older and sicker patients, the risks and benefits must be weighed carefully, as (1) the morbidity of the procedure can be significant; (2) a definitive diagnosis may not be possible even with surgical lung biopsy; and (3) when a specific diagnosis is made, there may be no effective treatment. Empiric therapy or no treatment may be preferable to surgical lung biopsy in some patients.

Treatment

Treatment by a pulmonologist is recommended for diffuse interstitial pneumonia whenever possible. Clinical experience suggests that patients with RB-ILD, nonspecific interstitial pneumonia, or cryptogenic organizing pneumonia (Table 9–17) frequently respond to corticosteroids and should be given a trial of therapy—typically prednisone, 1–2 mg/kg/day for a minimum of 2 months. Corticosteroid therapy is ineffective in patients with IPF and is not recommended. Nintedanib and pirfenidone are approved for the treatment of IPF based on reduction in rate of decline in lung function and longer time to first exacerbation, but neither agent improves survival. The only definitive treatment for IPF is lung transplantation. Supportive care includes supplemental oxygen, when needed, and pulmonary rehabilitation. Surveillance for pulmonary hypertension is advised.

When to Refer

- Patients with diffuse interstitial pneumonia should be referred early to a pulmonologist for expert diagnosis and management.
- Patients with IPF should be referred early to a lung transplant program for evaluation.

Clark KP et al. Supplemental oxygen therapy in interstitial lung disease: a narrative review. Ann Am Thorac Soc. 2023;20:1541. [PMID: 37590496]

Pitre T et al. Medical treatments for idiopathic pulmonary fibrosis: a systematic review and network meta-analysis. Thorax. 2022;77:1243. [PMID: 35145039]

Raghu G et al. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2022;205:e18. [PMID: 35486072]

SARCOIDOSIS

ESSENTIALS OF DIAGNOSIS

- Symptoms may involve the lung, skin, eyes, peripheral nerves, liver, kidney, heart.
- Diagnosis made by demonstration of noncaseating granulomas in a biopsy specimen.

General Considerations

Sarcoidosis is a systemic disease of unknown etiology characterized by granulomatous inflammation, primarily in the lungs. The incidence is highest in North American Black persons and northern European White persons. Among Black persons, women are more frequently affected than men. Onset of disease is usually in the third or fourth decade.

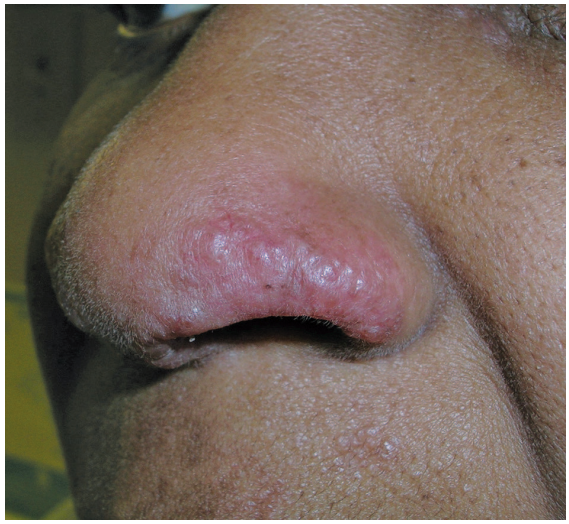
Clinical Findings

A. Symptoms and Signs

Patients may be asymptomatic or have dyspnea of insidious onset. Other systemic involvement include skin (erythema nodosum, lupus pernio [Figure 9–5]), iritis, peripheral neuropathy, arthritis (Chapter 22), or cardiomyopathy. Physical findings of interstitial lung disease with crackles are uncommon. Other findings may include parotid gland enlargement, hepatosplenomegaly, and lymphadenopathy.

B. Laboratory Findings

Laboratory tests may show leukopenia, an elevated ESR, and hypercalcemia (about 5% of patients) or hypercalciuria (20%). ACE levels are elevated in 40–80% of patients with active disease, though this finding is neither sensitive nor



▲ **Figure 9–5.** Skin involvement in sarcoidosis (lupus pernio), here involving the nasal rim. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

specific. Physiologic testing may reveal evidence of airflow obstruction or restriction with decreased lung volumes and diffusing capacity, or both. ECG may show heart block and dysrhythmias.

C. Imaging

Radiographic findings are variable and include bilateral hilar adenopathy alone (radiographic stage I), hilar adenopathy and parenchymal involvement (radiographic stage II), parenchymal involvement alone (radiographic stage III), or advanced fibrotic changes principally in the upper lobes (radiographic stage IV). Parenchymal involvement is usually manifested radiographically by diffuse reticular infiltrates, but focal infiltrates, acinar shadows, nodules, and, rarely, cavitation may be seen.

D. Special Examinations

The diagnosis of sarcoidosis generally requires histologic demonstration of noncaseating granulomas in biopsies from a patient with other typical associated manifestations. Other granulomatous diseases (eg, berylliosis, tuberculosis, fungal infections) and lymphoma must be excluded. Biopsy of easily accessible sites (eg, palpable lymph nodes, skin lesions, or salivary glands) may be an initial step. Transbronchial lung biopsy has a high yield (75–90%) as well, especially in patients with radiographic evidence of parenchymal involvement. Some clinicians believe that tissue biopsy is not necessary when stage I radiographic findings are detected in a clinical situation that strongly favors the diagnosis of sarcoidosis. Biopsy is essential whenever clinical and radiographic findings suggest the possibility of an alternative diagnosis, such as lymphoma. Patients require a yearly ophthalmologic evaluation, liver and renal function testing, PFTs, and an ECG. Cardiac MRI is favored over PET scan for patients with suspected cardiac involvement. Screening for pulmonary hypertension with EX is recommended in advanced disease.

Treatment

Oral corticosteroids (prednisone, 0.5–1.0 mg/kg/day) are indicated for patients with disabling constitutional symptoms, hypercalcemia, iritis, uveitis, arthritis, CNS involvement, cardiac involvement, granulomatous hepatitis, cutaneous lesions other than erythema nodosum, and progressive pulmonary lesions. Long-term therapy is usually required over months to years. Immunosuppressive medications, most commonly methotrexate, azathioprine, or infliximab, are used in patients who are intolerant of corticosteroids or who have corticosteroid-refractory disease. A favorable response is defined by a decrease in symptoms, reduction of radiographic abnormalities, and improvement in PFTs.

Prognosis

The outlook is best for patients with hilar adenopathy alone or with erythema nodosum; radiographic involvement of the lung parenchyma is associated with a worse prognosis. About 20% of patients with lung involvement suffer irreversible lung impairment, characterized by progressive fibrosis, bronchiectasis, and cavitation. Pneumothorax, hemoptysis, mycetoma formation in lung cavities, pulmonary hypertension, and respiratory failure may often complicate this advanced stage. Myocardial sarcoidosis occurs in 5% of patients, sometimes leading to restrictive cardiomyopathy, cardiac dysrhythmias, and conduction disturbances. Death from respiratory insufficiency occurs in 5% of patients. Patients require long-term follow-up.

Aitken M et al. Diagnostic accuracy of cardiac MRI versus FDG PET for cardiac sarcoidosis: a systematic review and meta-analysis. Radiology. 2022;304:566. [PMID: 35579526]

Baughman RP et al. ERS clinical practice guidelines on treatment of sarcoidosis. Eur Respir J. 2021;58:2004079. [PMID: 34140301]

Fernández-Ramón R et al. Systemic treatment in sarcoidosis: Experience over two decades. Eur J Intern Med. 2023;108:60. [PMID: 36446677]

PULMONARY ALVEOLAR PROTEINOSIS

Pulmonary alveolar proteinosis is a rare disease characterized by accumulation of lipoproteinaceous material within alveolar spaces. The condition may be primary (idiopathic) or secondary (occurring in immunodeficiency; hematologic malignancies; inhalation of mineral dusts; or following lung infections, including tuberculosis and viral infections). Progressive dyspnea is the usual presenting symptom. CXR shows bilateral alveolar infiltrates, and chest CT features a characteristic "crazy-paving" that refers to ground-glass opacities with superimposed interlobular and intralobular septal thickening. The diagnosis is based on demonstration of characteristic findings on BAL (milky appearance and periodic acid-Schiff [PAS]-positive lipoproteinaceous material) in association with clinical and

radiographic features. In secondary disease, an elevated anti-GM-CSF (anti-granulocyte-macrophage colony-stimulating factor) titer in serum or BAL fluid is highly sensitive and specific.

The course of the disease varies. Some patients experience spontaneous remission; others develop progressive respiratory insufficiency. For patients with minimal symptoms, supportive care with oxygen is recommended. Therapy for advanced disease consists of periodic whole-lung lavage, inhalational or subcutaneous GM-CSF, or both. Pulmonary superinfection with *Nocardia* or fungi may occur.

Iftikhar H et al. Update on diagnosis and treatment of adult pulmonary alveolar proteinosis. Ther Clin Riks Manag. 2021;17:701. [PMID: 34408422]
Kim C et al. Characteristics of hospital admissions for pulmonary alveolar proteinosis: analysis of the nationwide inpatient sample (2012-2014). BMC Pulm Med. 2022;22:365. [PMID: 36153570]

EOSINOPHILIC PULMONARY SYNDROMES

Eosinophilic pulmonary syndromes are a diverse group of disorders typically characterized by peripheral blood eosinophilia (typically more than 500 cells/mcL [0.5×10^9/L]), eosinophilic pulmonary infiltrates, dyspnea, and cough. Many patients have constitutional symptoms, including fever. Common causes include medications (nitrofurantoin, daptomycin, phenytoin, NSAIDs, acetaminophen, mesalamine, sulfasalazine) or infection with helminths (eg, *Ascaris*, hookworms, *Strongyloides*) or filariae (eg, *Wuchereria bancrofti*, *Brugia malayi*, tropical pulmonary eosinophilia). **Löffler syndrome** refers to acute eosinophilic pulmonary infiltrates in response to transpulmonary passage of helminth larvae. Pulmonary eosinophilia can also be a feature of other illnesses, including ABPA, eosinophilic granulomatosis with polyangiitis, systemic hypereosinophilic syndromes, eosinophilic granuloma of the lung (properly referred to as pulmonary Langerhans cell histiocytosis), neoplasms, and numerous interstitial lung diseases. If an extrinsic cause is identified, therapy consists of removal of the offending medication or treatment of the underlying parasitic infection.

One-third of cases are idiopathic, and there are two common syndromes. **Acute eosinophilic pneumonia** is an acute, febrile illness characterized by cough and dyspnea, sometimes rapidly progressing to respiratory failure. The CXR is abnormal but nonspecific. BAL fluid frequently shows eosinophilia, but peripheral blood eosinophilia is rare at the onset of symptoms. **Chronic eosinophilic pneumonia** has a subacute-chronic presentation, characterized by fever, night sweats, weight loss, and dyspnea. Asthma or atopy is present in half of cases. CXRs often show peripheral infiltrates, the "photographic negative" of pulmonary edema. BAL typically has a marked eosinophilia, and peripheral blood eosinophilia is present in greater than 80%. Both acute and chronic eosinophilic pneumonia are treated with steroids, which usually results in dramatic improvement. Therapies targeting IL-5 are increasingly utilized.

Cottin V. Eosinophilic lung diseases. Immunol Allergy Clin North Am. 2023;43:289. [PMID: 37055090]
Rosenberg CE et al. Approach to eosinophilia presenting with pulmonary symptoms. Chest. 2021;159:507. [PMID: 33002503]

DISORDERS OF THE PULMONARY CIRCULATION

PULMONARY VENOUS THROMBOEMBOLISM

ESSENTIALS OF DIAGNOSIS

- Third most common cardiovascular cause of death in the United States.
- May present with one or more of the following: dyspnea, pleuritic chest pain, hemoptysis, syncope.
- Tachypnea, tachycardia, hypoxia may be present.
- Risk stratification with clinical scores, cardiac biomarkers, and right ventricular imaging is key for management.

General Considerations

PE is a common, serious, and potentially fatal result of thrombus formation within the deep venous circulation that then migrates to the pulmonary circulation. It is the third leading cause of death among hospitalized patients. Management demands a vigilant systematic approach to diagnosis and an understanding of risk factors so that appropriate therapy can be initiated.

Many substances can embolize to the pulmonary circulation. Although thrombus is most common, others include air (during neurosurgery, from central venous catheters), amniotic fluid (during active labor), fat (long bone fractures), foreign bodies (talc in injection drug users), parasite eggs (schistosomiasis), septic emboli (acute infective endocarditis), and tumor cells (renal cell carcinoma). Pulmonary emboli will develop in 50–60% of patients with proximal DVT; half of these embolic events will be asymptomatic. Approximately 50–70% of patients who have symptomatic pulmonary emboli will have lower extremity DVT when evaluated.

Risk factors include venous stasis, injury to the vessel wall, and hypercoagulability (Virchow triad). Venous stasis increases with immobility (obesity, stroke, bed rest—especially postoperative), injury to vessels (caused by orthopedic surgery or trauma), hypercoagulability (caused by medications [oral contraceptives, hormonal replacement therapy]), diseases (malignancy, surgery), inherited gene defects (factor V Leiden, prothrombin mutation), or acquired thrombophilias (protein C and protein S deficiency, antithrombin deficiency, antiphospholipid antibodies).

PE has multiple physiologic effects. Thrombus occlusion of greater than 20–25% of the pulmonary vascular bed

causes right ventricular dilation or dysfunction and increased pulmonary vascular resistance. Vascular obstruction increases physiologic dead space (wasted ventilation) and leads to hypoxemia through right-to-left shunting and decreased cardiac output.

Clinical Findings

A. Symptoms and Signs

The clinical diagnosis of PE is notoriously challenging because the clinical symptoms and signs are similar to those of other cardiopulmonary conditions. Dyspnea and chest pain on inspiration are common. Diagnosis primarily relies on clinical prediction scores to calculate the pretest probability of PE. Wells score is most commonly used and quantifies clinical risk assessment, allowing separation of patients into low, intermediate, or high probability groups, or PE-likely versus PE-unlikely groups (Table 9–18). The Pulmonary Embolism Rule-out Criteria (PERC) may be used to identify patients for whom no further testing is indicated (Table 9–19).

B. Laboratory Findings

The **ECG** is abnormal in 70% of patients with PE. However, the most common abnormalities are sinus tachycardia and nonspecific ST and T wave changes, each seen in approximately 40% of patients. Five percent or less of patients in the PIOPED I study had P pulmonale, RVH, right axis deviation, and right bundle branch block.

ABGs usually reveal acute respiratory alkalosis due to hyperventilation and may show hypoxemia.

Plasma levels of **D-dimer,** a degradation product of cross-linked fibrin, are elevated in the presence of thrombus. A normal D-dimer may be used to exclude the diagnosis of PE in those patients who have low pretest probability of PE or are PE-unlikely on Wells score. Additionally, an age-adjusted D-dimer value has increased specificity than the usually specified cutoff. Due to much higher false-positive rates, D-dimer is not useful for hospital inpatients.

Serum troponin I, troponin T, and plasma BNP levels are elevated in approximately 25% of patients with PE and are useful in the risk stratification of PE because they correlate with adverse outcomes, including mechanical ventilation, prolonged hospitalization, shock, and death.

Table 9–18. Clinical prediction rule for PE.

Variable	Points
Clinical symptoms and signs of DVT (leg swelling and pain with palpation of deep veins)	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate > 100 beats/minute	1.5
Immobilization for > 3 days or surgery in previous 4 weeks	1.5
Previous PE or DVT	1.5
Hemoptysis	1.0
Cancer (with treatment within past 6 months or palliative care)	1.0
Add **Points** *to determine* **Score**, *then refer to* **probability assessments** *below*:	
Three-tiered clinical probability assessment (Wells criteria)	**Score**
High	> 6.0
Moderate	2.0 to 6.0
Low	< 2.0
Dichotomous clinical probability assessment (Modified Wells criteria)	**Score**
PE likely	> 4.0
PE unlikely	< or = 4.0

Data from Wells PS et al. Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the models' utility with the SimpliRED D-dimer. Thromb Haemost. 2000;83:416.

Table 9–19. Pulmonary Embolism Rule-out Criteria (PERC) for low-risk patients.

For patients with a Modified Wells Score ≤ 4[1] who meet ALL of the following criteria, PE is excluded, monitor off anticoagulation, and search for alternative diagnoses.

- Age < 50 years
- Heart rate < 100 bpm
- Oxyhemoglobin saturation on room air ≥ 95%
- No prior history of VTE
- No recent (within 4 weeks) trauma or surgery requiring hospitalization
- No presenting hemoptysis
- No estrogen therapy
- No unilateral leg swelling

[1]See Table 9–18.

Data from Kline JA et al. Impact of a rapid rule-out protocol for pulmonary embolism on the rate of screening, missed cases, and pulmonary vascular imaging in an urban US emergency room. Ann Emerg Med. 2004;44:490.

C. Imaging and Special Examinations

1. Chest radiography—A CXR is necessary to exclude other common lung diseases but does not establish the diagnosis of PE by itself. The CXR is usually normal. Profound hypoxia with a normal CXR is highly suspicious for PE.

2. Pulmonary CT-angiography—Helical CT-PA with intravenous radiocontrast dye timed for the pulmonary artery is the gold standard diagnostic study for suspected PE due to its high sensitivity and specificity as well as wide availability across hospitals. CT-PA usually is recommended for patients with low or intermediate pretest probability (or PE-unlikely) who have a positive D-dimer as well as those with high pretest probability (or PE-likely).

3. Ventilation-perfusion ($\dot{V}/\dot{Q}$) lung scanning—$\dot{V}/\dot{Q}$ scanning may be used as an alternative to CT-PA in patients in whom contrast is contraindicated, such as severe contrast-induced anaphylaxis or kidney dysfunction. A defect in

perfusion without a corresponding defect in ventilation may indicate a PE but is not specific for the diagnosis. A normal V̇/Q̇ scan excludes the diagnosis of clinically significant PE (negative predictive value of 91% in the PIOPED I study).

4. Venous thrombosis studies—Venous ultrasonography is the test of choice to detect DVT. Inability to compress the common femoral or popliteal veins in symptomatic patients is diagnostic (positive predictive value of 97%); full compressibility of both sites excludes proximal DVT (negative predictive value of 98%). A normal venous ultrasound does not rule out PE.

5. Pulmonary angiography—Although pulmonary angiography is the historical reference standard for the diagnosis of PE, it is now only used during catheter-directed therapy (for administration of a thrombolytic or for mechanical thrombectomy) in the treatment of acute PE or to confirm the diagnosis of chronic PE in chronic thromboembolic pulmonary hypertension.

Risk Stratification of Pulmonary Embolism

After a PE diagnosis is made, the next step is risk stratification since this will guide management. There are three categories based on mortality data: high-risk PE, intermediate-risk PE, and low-risk PE. Patients with high-risk PE, also known as massive PE, have hemodynamic compromise, defined as systolic blood pressure less than 90 mm Hg or a systolic blood pressure drop by 40 mm Hg or more for longer than 15 minutes, requiring a vasopressor, or causing a cardiac arrest. Patients with an intermediate-risk PE, also known as submassive PE, are hemodynamically stable but do have signs of right ventricular strain or dysfunction, either by imaging (CT-PA or echocardiogram) or elevated troponin. Patients with low-risk PE have normotension without signs of right ventricular dysfunction.

PE severity scores, such as PE Severity Score Index (PESI) or the simplified PESI, compile useful patient characteristics that predict patient outcome. Such scores may also be used to decide which patients may be appropriate for outpatient PE treatment. Imaging of the right ventricle, usually using CT-PA or echocardiogram, and cardiac biomarkers (troponin) are other useful tools that may help predict adverse outcomes.

Prevention

Discussion of strategies for the prevention of VTE can be found in Chapter 16.

Treatment

A. Anticoagulation

Anticoagulation is the mainstay therapy for VTE. It impedes additional thrombus formation, allowing endogenous fibrinolytic mechanisms to lyse existing clot, thereby decreasing mortality and recurrence of PE. Initiation of anticoagulation should be considered even prior to a confirmed diagnosis when there is high clinical suspicion and low risk of bleeding.

DOACs are recommended over vitamin K antagonist (VKA or warfarin) as first-line anticoagulation for most patients. DOACs offer predictable pharmacokinetics and pharmacodynamics with fixed dosing, fewer drug interactions, and relatively short half-life. Unfractionated heparin binds to and accelerates the ability of antithrombin to inactivate thrombin, factor Xa, and factor IXa. Compared to unfractionated heparin, low-molecular-weight heparins (LMWHs) are as effective but have faster therapeutic activity in the treatment of VTE.

The optimal duration of anticoagulation therapy for VTE depends on the risk factors for VTE recurrence. Extended anticoagulation should be considered for patients with no identifiable risk factor for the index PE event, those with recurrent VTE, those with major persistent risk factors (malignancy), or those with a minor risk factor (such as immobility due to prolonged car or air travel, obesity, pregnancy, or increased age). However, those with major transient/reversible risk factors (such as fracture of lower limb; hip or knee surgery; or hospitalization for HF, atrial fibrillation, or MI) may be considered for discontinuation of anticoagulation after 3 months. Additionally, duration of therapy needs to take into consideration the patient's age, likelihood and potential consequences of hemorrhage, and preferences for continued therapy. In patients who continue taking extended anticoagulation, an annual risk-benefit assessment of continuing anticoagulation therapy should be done.

The major complication of anticoagulation is hemorrhage. Risk factors for hemorrhage include the intensity of the anticoagulation; duration of therapy; concomitant administration of medications, such as aspirin or NSAIDs, that interfere with platelet function; and patient characteristics, particularly increased age, previous GI hemorrhage, and coexistent kidney or liver disease.

B. Thrombolytic Therapy

Streptokinase, urokinase, and recombinant tissue plasminogen activator (rt-PA; alteplase) increase plasmin levels and thereby directly lyse intravascular thrombi accelerating resolution of emboli. Guidelines support systemic thrombolysis for high-risk or massive PE (hemodynamically unstable) with low risk of bleeding. Intermediate-risk or submassive PE patients (hemodynamically stable with evidence of right heart strain) do not have a mortality benefit with thrombolytic therapy but do have a significant decrease in incidence of hemodynamic collapse; however, they also have an increase in major hemorrhagic complications, including intracranial hemorrhage. Absolute contraindications to thrombolytic therapy include active bleeding and stroke within the past 3 months. Relative contraindications include uncontrolled hypertension and surgery or trauma within the past 4 weeks.

Catheter-directed thrombolysis delivers a low-dose of the thrombolytic agent directly into the PE, thereby reversing right ventricular dilation faster than anticoagulation alone. This procedure may be considered for patients with high-risk PE (though with higher risks of bleeding) and for those with intermediate-risk PE at increased risk of hemodynamic collapse.

C. Additional Therapies

Mechanical/suction pulmonary embolectomy or surgical embolectomy may be considered for selected patients with contraindications to thrombolysis or failure of thrombolysis, primarily those with intermediate-risk (submassive) with signs of clinical decompensation (such as severe hypoxemia, severe right ventricular dysfunction, persistent tachycardia) or high-risk PE with contraindications to thrombolysis.

Inferior vena cava filters should be inserted in patients with contraindications to anticoagulation (active bleeding) and PE with lower extremity DVT or those with recurrent PE despite adequate anticoagulation. Consideration should be given for those with acute PE and presence of free-floating proximal end DVT, since it carries an increased risk of embolization. Once placed, it must be assessed for removal at the earliest opportunity.

When to Admit

Most patients with acute PE require hospitalization. The decision to admit patients with acute PE requires assessment of factors placing them at high risk, including their severity of illness (eg, severe hypoxemia), comorbidities (eg, DVT, cardiac dysfunction), educational needs (eg, lack of knowledge about PE and its management), and/or problematic social situations (eg, prior nonadherence with follow-up care). Carefully selected patients with low-risk PE can be safely and effectively managed as outpatients with the aid of integrated clinical decision support systems.

Freund Y et al. Acute pulmonary embolism: a review. JAMA. 2022;328:1336. [PMID: 36194215]
Roy PM et al. Contemporary management of acute pulmonary embolism. Trends Cardiovasc Med. 2022;32:259. [PMID: 34214598]
Stevens SM et al. Antithrombotic therapy for VTE disease: second update of the CHEST Guideline and Expert Panel Report. Chest. 2021;160:e545. [PMID: 34352278]
Triantafyllou GA et al. Risk stratification in acute pulmonary embolism: the latest algorithms. Semin Respir Crit Care Med. 2021;42:183. [PMID: 33548934]

PULMONARY HYPERTENSION

ESSENTIALS OF DIAGNOSIS

- Dyspnea, fatigue, chest pain, and syncope on exertion.
- Narrow splitting of second heart sound with loud pulmonary component; findings of RVH and HF in advanced disease.
- Echocardiographic evidence of right ventricular dilation, dysfunction, or hypertrophy; right atrial enlargement; or elevated right ventricular systolic pressure.
- Right heart catheterization required for confirmation of diagnosis

General Considerations

Pulmonary hypertension is a complex problem characterized by pathologic elevation in pulmonary arterial pressure. Normal pulmonary artery systolic pressure at rest is 15–30 mm Hg, with a mean pressure less than 20 mm Hg. The pulmonary circulation is a low-pressure, low-resistance system due to its large cross-sectional area, and it can accommodate significant increase in blood flow during exercise. The primary pathologic mechanism in pulmonary hypertension is an increase in pulmonary vascular resistance that leads to an increase in the pulmonary systolic pressure. Pulmonary hypertension is defined by a mean pulmonary arterial pressure of 20 mm Hg or more on a resting cardiac catheterization.

The World Symposium on Pulmonary Hypertension (WSPH) updated clinical classification includes five groups that are based on etiology and mechanism.

Group 1 (pulmonary arterial hypertension [PAH]): This group comprises diseases to the pulmonary arteries that lead to structural changes, smooth muscle hypertrophy, and endothelial dysfunction. It includes idiopathic (formerly primary) PAH; heritable PAH; drug- and toxin-induced PAH; PAH associated with HIV infection, portal hypertension, connective tissue disorders (most commonly scleroderma), congenital heart disease, and schistosomiasis; and PAH with features of veno-occlusive disease and pulmonary capillary hemangiomatosis. PAH is defined on a resting cardiac catheterization by a mean pulmonary arterial pressure of 20 mm Hg or more with a pulmonary capillary wedge pressure of 15 mm Hg or less and a pulmonary vascular resistance of 2 Wood units or more.

Group 2 (pulmonary venous hypertension due to left heart disease): This group includes LV systolic or diastolic dysfunction and valvular heart disease.

Group 3 (pulmonary hypertension due to lung disease or hypoxemia): This group is caused by advanced lung disease, including COPD, interstitial lung disease, pulmonary fibrosis, as well as other causes of chronic hypoxemia, such as sleep-disordered breathing, alveolar hypoventilation syndromes, and high-altitude exposure.

Group 4 (pulmonary hypertension due to pulmonary obstruction): This group primarily includes chronic thromboembolic pulmonary hypertension but also other causes of pulmonary obstructions, such as sarcoma, metastatic malignancies, and congenital pulmonary artery stenosis.

Group 5 (pulmonary hypertension secondary to unclear or multifactorial mechanisms): These patients have pulmonary hypertension secondary to hematologic disorders (eg, chronic hemolytic anemia, sickle cell anemia, myeloproliferative disorders, splenectomy), systemic disorders (eg, sarcoidosis, vasculitis, pulmonary Langerhans cell histiocytosis, neurofibromatosis type 1), metabolic disorders (eg, glycogen storage disease, Gaucher disease, thyroid disease), and miscellaneous causes (eg, ESKD with or without hemodialysis, fibrosing mediastinitis).

The clinical severity of pulmonary hypertension is classified according to the NYHA/WHO classification system based primarily on symptoms and functional status. **Class I:** No limitation of physical activity; no dyspnea, fatigue,

chest pain, or near syncope is present with exertion. **Class II:** Slight limitation of physical activity; no symptoms at rest, but ordinary physical activity causes dyspnea, fatigue, chest pain, or near syncope. **Class III:** Marked limitation of physical activity; no symptoms at rest, but less than ordinary activity causes dyspnea, fatigue, chest pain, or near syncope. **Class IV:** Inability to perform any physical activity without symptoms; dyspnea and fatigue are present at rest and symptoms worsen with any activity.

Clinical Findings

A. Symptoms and Signs

There are no specific symptoms or signs of pulmonary hypertension, which may delay its diagnosis and significantly affect its mortality. Typical symptoms include dyspnea with exertion. With advanced disease, there may be dyspnea at rest or syncope. Patients may have chest pain, nonproductive cough, and fatigue.

Findings on physical examination can include jugular venous distention, accentuated pulmonary valve component of the second heart sound, right-sided third heart sound, tricuspid regurgitation murmur, hepatomegaly, and lower extremity edema.

B. Laboratory Findings

BNP or pro-BNP is usually elevated. All patients should be evaluated for HIV, liver dysfunction, and connective tissue disorders.

The ECG is typically normal except in advanced disease, where RVH (right axis deviation, incomplete right bundle branch block) and right atrial enlargement (peaked P wave in the inferior and right-sided leads) can be noted.

C. Imaging and Special Examinations

Radiographs and CT scans of the chest are useful in diagnosis. Enlargement of the right and left main pulmonary arteries is common; right ventricular and right atrial enlargement are seen in advanced disease. Chest CT scanning, PFTs, sleep studies, or a combination of these are also useful in determining the cause of pulmonary hypertension for patients in Group 3 (pulmonary hypertension due to lung disease).

Echocardiography is the best screening study. Right ventricular assessment is made by measuring right ventricular size, function, and systolic pressure. Additionally, the echocardiogram is useful for assessing underlying cardiac disease (eg, pulmonary hypertension due to left heart disease).

Right-sided cardiac catheterization remains the gold standard for diagnosis and assessment of disease severity; it should be performed prior to initiation of vasodilator therapies. Although estimated pressures on echocardiogram correlate with right heart catheterization measurement, they vary by at least 10 mm Hg in more than 50% of cases so should not be used to direct therapy. Cardiac catheterization is helpful in differentiating PAH from pulmonary venous hypertension by assessment of the drop in pressure across the pulmonary circulation, also known as the transpulmonary gradient. A vasodilator challenge can be performed during right heart catheterization; a significant acute vasodilator response consists of a drop in mean pulmonary pressure of greater than 10 mm Hg (or 20%) to less than 40 mm Hg.

In all patients, especially those with a history of PE or risk factors for thromboembolic disease, chronic thromboembolic pulmonary hypertension (Group 4) should be excluded prior to diagnosing idiopathic pulmonary hypertension with $\dot{V}/\dot{Q}$ lung scanning. If abnormal, CT-PA or pulmonary angiography is the next step in confirming the diagnosis and establishing the distribution and extent of disease.

Treatment

Advanced therapies, such as pulmonary vasodilators, are available to treat pulmonary hypertension. Such therapies are chosen based on the patient's functional status according to the NYHA/WHO classification. The mechanisms of action for pulmonary vasodilators follow three main pathways: (1) the nitric oxide pathway: phosphodiesterase inhibitors (sildenafil, tadalafil) and soluble guanylate cyclase stimulators (riociguat); (2) the endothelin pathway: endothelin receptor antagonists (bosentan, ambrisentan, macitentan); and (3) the prostacyclin pathway: prostacyclin analogs (intravenous epoprostenol; intravenous, subcutaneous, inhaled, or oral treprostinil; inhaled iloprost) and prostacyclin receptor agonist (selexipag). These vasodilators are only FDA approved for patients with Group 1 PAH based on their improvement in symptoms, 6-minute walk distance, WHO functional status, and hemodynamic measurements. A major RCT showed reduction in a composite outcome (death, hospitalization, progression, or unsatisfactory response) for combination therapy (using tadalafil and ambrisentan) compared to monotherapy. As a result, most patients with WHO/NYHA functional class II and III, should receive a combination of endothelin receptor antagonists and phosphodiesterase inhibitors as first-line therapy. For patients in WHO/NYHA functional class IV, a more aggressive approach is recommended with continuous prostacyclin infusion. Oral calcium channel blockers may be used in patients with a significant vasodilator response during cardiac catheterization. Anticoagulation was commonly used in the past but has fallen out of favor due to lack of efficacy.

Treatment of patients with Group 2 pulmonary hypertension (due to left HF) is discussed in Chapter 10. The main goal is to decrease pulmonary venous pressure by treating HF and volume overload, primarily with the use of diuretics.

Patients with Group 3 pulmonary hypertension (due to lung disease) should be assessed for hypoxemia at rest or with physical activity and, if present, should receive supplemental oxygen. Patients with COPD, interstitial lung disease, or obstructive sleep apnea should receive treatment for underlying disease. Inhaled treprostinil is the only pulmonary vasodilator approved for patients with pulmonary hypertension due to interstitial lung disease since it improved exercise capacity based on 6-minute walk assessment.

For patients with Group 4 pulmonary hypertension (due to chronic thromboembolic disease), long-term

anticoagulation is recommended. Additionally, patients with surgically accessible lesions and acceptable perioperative risk should undergo pulmonary thromboendarterectomy. For patients unable to undergo surgery or those with residual pulmonary hypertension postoperatively, medical therapy with riociguat, pulmonary artery balloon angioplasty, or both should be considered.

Lung transplantation is a treatment option for selected patients with pulmonary hypertension when medical therapy is no longer effective. Double-lung transplant is the preferred method; in some cases, transplantation of the heart and both lungs is needed.

When to Refer

Patients in whom pulmonary hypertension is suspected or has been diagnosed should be referred early to a specialized pulmonary hypertension center for expert management.

When to Admit

- Patients with pulmonary hypertension, severe symptoms, and evidence of decompensated right HF with volume overload should be admitted to the hospital for aggressive diuresis.
- Patients with Group 1 pulmonary hypertension and functional class IV symptoms should be admitted to a specialized center for initiation of advanced therapies, such as intravenous prostacyclins.

Humbert M et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43:3618. [PMID: 36017548]
Mayeux JD et al. Management of pulmonary arterial hypertension. Curr Cardiovasc Risk Rep. 2021;15:2. [PMID: 33224405]
Sommer N et al. Current and future treatments of pulmonary arterial hypertension. Br J Pharmacol. 2021;178:6. [PMID: 32034759]
Waxman A et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. N Engl J Med. 2021;384:325. [PMID: 33440084]

PULMONARY VASCULITIS

The pulmonary vasculature may be involved in several vasculitis syndromes. These include **antineutrophil cytoplasmic autoantibody (ANCA)–associated vasculitides, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and anti-glomerular basement membrane (anti-GBM) antibody disease.** These are reviewed in Chapter 22.

ALVEOLAR HEMORRHAGE SYNDROMES

Diffuse alveolar hemorrhage may occur in a variety of immune and nonimmune disorders. Acute dyspnea, anemia, hemoptysis and, occasionally, fever are characteristic. CXR or CT chest with rapid clearing of diffuse lung infiltrates may be indicative of the diagnosis of diffuse alveolar hemorrhage. Sequential BAL on bronchoscopy is the preferred method for diagnosis with lavage aliquots becoming progressively more hemorrhagic.

Causes of diffuse **immune alveolar hemorrhage** include anti-basement membrane antibody disease (Goodpasture syndrome), granulomatosis with polyangiitis, systemic necrotizing vasculitis, pulmonary capillaritis associated with idiopathic rapidly progressive glomerulonephritis, SLE, and other vasculitic and collagen vascular diseases (Chapter 22). **Nonimmune causes** of diffuse hemorrhage include coagulopathy, mitral stenosis, necrotizing pulmonary infection, drugs (penicillamine), toxins (trimellitic anhydride), and idiopathic pulmonary hemosiderosis.

Idiopathic pulmonary hemosiderosis is a disease of children or young adults characterized by recurrent pulmonary hemorrhage; iron deficiency is typical. It is frequently associated with celiac disease. Treatment of acute episodes of hemorrhage with corticosteroids may be useful. Recurrent episodes of pulmonary hemorrhage may result in interstitial fibrosis and respiratory failure.

Reisman S et al. A review of clinical and imaging features of diffuse pulmonary hemorrhage. AJR Am J Roentgenol. 2021;216:1500. [PMID: 33826359]
Saha BK et al. Adult patients with idiopathic pulmonary hemosiderosis: a comprehensive review of the literature. Clin Rheumatol. 2022;41:1627. [PMID: 35179664]

ENVIRONMENTAL & OCCUPATIONAL LUNG DISORDERS

SMOKE INHALATION

The inhalation of products of combustion may cause serious respiratory complications. As many as one-third of patients admitted to burn-treatment units have pulmonary injury from smoke inhalation. Morbidity and mortality due to smoke inhalation may exceed those attributed to the burns themselves. Pulmonary complications following burns and inhalation injury account for up to 77% of deaths.

All patients in whom significant smoke inhalation is suspected must be assessed for three consequences of smoke inhalation: impaired tissue oxygenation, thermal injury to the upper airway, and injury to the lower airways and lung parenchyma. Impaired tissue oxygenation may result from inhalation of a hypoxic gas mixture, carbon monoxide or cyanide, or from alterations in $\dot{V}/\dot{Q}$ matching, and is an immediate threat to life. Immediate treatment with 100% oxygen is essential. The management of patients with carbon monoxide and cyanide poisoning is discussed in Chapter 40.

Thermal injury to the mucosal surfaces of the upper airway occurs from inhalation of super-heated gases. Complications, including mucosal edema, upper airway obstruction, and impaired ability to clear oral secretions, usually become evident by 18–24 hours and produce inspiratory stridor. Respiratory failure occurs in severe cases. Early management (Chapter 39) includes the use of a high-humidity face mask with supplemental oxygen, gentle

suctioning to evacuate oral secretions, elevation of the head 30 degrees to promote clearing of secretions, and topical epinephrine to reduce edema of the oropharyngeal mucous membrane. Helium-oxygen gas mixtures (Heliox) may reduce labored breathing due to critical upper airway narrowing. Close monitoring with ABGs and later with oximetry is important. Examination of the upper airway with a fiberoptic laryngoscope or bronchoscope is superior to routine physical examination. Endotracheal intubation is often necessary to maintain airway patency and is likely to be necessary in patients with deep facial burns or oropharyngeal or laryngeal edema. Tracheotomy should be avoided, if possible, because of an increased risk of pneumonia and death from sepsis.

Injury to the lower airways and lung parenchyma results from inhalation of toxic gases and products of combustion, including aldehydes and organic acids. The site of lung injury depends on the solubility of the gases inhaled, the duration of exposure, and the size of inhaled particles that transport noxious gases to distal lung units. Bronchorrhea and bronchospasm occur early after exposure along with dyspnea, tachypnea, and tachycardia. Labored breathing and cyanosis may follow. Physical examination at this stage reveals diffuse wheezing and rhonchi. Bronchiolar and alveolar edema (eg, ARDS) may develop within 1–2 days after exposure. Sloughing of the bronchiolar mucosa may occur within 2–3 days, leading to airway obstruction, atelectasis, and worsening hypoxemia. Bacterial colonization and pneumonia are common by 5–7 days after the exposure.

Treatment of smoke inhalation consists of supplemental oxygen, bronchodilators, suctioning of mucosal debris and mucopurulent secretions via an indwelling endotracheal tube, chest physical therapy to aid clearance of secretions, and adequate humidification of inspired gases. Positive end-expiratory pressure (PEEP) has been advocated to treat bronchiolar edema. Judicious fluid management and close monitoring for secondary bacterial infection round out the management protocol.

The routine use of corticosteroids for lung injury from smoke inhalation has been shown to be ineffective and may even be harmful. Routine or prophylactic use of antibiotics is not recommended.

Patients who survive should be watched for the late development of bronchiolitis obliterans.

Galeiras R et al. Prevalence and prognostic impact of inhalation injury among burn patients: a systematic review and meta-analysis. J Trauma Acute Care Surg. 2020;88:330. [PMID: 31688831]

Mercel A et al. Emerging therapies for smoke inhalation injury: a review. J Transl Med. 2020;18:141. [PMID: 32228626]

E-CIGARETTE OR VAPING PRODUCT–ASSOCIATED LUNG INJURY

General Considerations

E-cigarette- or vaping product–associated lung injury (EVALI) began in the United States in 2019. Approximately 66% of patients have been male and 80% are under age 35. Over 95% of reported cases required hospitalization: 47% were admitted to intensive care, 22% were intubated, and many died. Based on the characteristics of these patients, the diagnosis of EVALI requires reported use of e-cigarette or vaping products within 3 months of symptom onset, compatible chest imaging findings, and an evaluation that excludes infectious etiologies.

No single causative agent has been identified. Most cases involved vaping products containing tetrahydrocannabinol (THC) or nicotine or both. Postulated factors contributing to the development of EVALI include e-cigarette flavorings, exposure to diacetyl (a popcorn flavoring that has been associated with lung injury), THC, adulteration of THC, adulteration of delivery devices, and vitamin E acetate (used as a thickening agent).

Clinical Findings

A. Symptoms and Signs

Patients with EVALI have respiratory symptoms (95%), including cough, shortness of breath, chest pain, and hemoptysis; GI symptoms (77%), including nausea, vomiting, and diarrhea; and constitutional symptoms (85%), including fever and chills. The illness is usually acute to subacute with patients having symptoms for days to weeks before seeking health care.

Tachycardia and tachypnea are present in 55% and 45% of patients, respectively, and 57% have a room air oxygen saturation of less than 95%. Given the nonspecific nature of the presentation especially during influenza season and the COVID-19 pandemic, providers must have a high degree of clinical suspicion and ask patients specifically about vaping.

B. Laboratory Findings

There are no laboratory findings specific for the diagnosis of EVALI. There may be leukocytosis, elevated CRP, and elevated ESR. It is important to exclude other possible etiologies such as infectious or eosinophilic pneumonia.

C. Imaging

Imaging findings in EVALI show various patterns of lung injury. CXRs typically show bilateral diffuse pulmonary opacities. Chest CT scan findings are nonspecific and may show bilateral distribution with ground-glass densities with subpleural sparing.

Differential Diagnosis

The EVALI case definition requires a negative work-up for infectious causes. Other diagnoses to consider include acute eosinophilic pneumonia, ARDS, hypersensitivity pneumonitis, lipoid pneumonia, and organizing pneumonia. Influenza testing should be done in season, and SARS-CoV-2 testing, as indicated.

Treatment

In published reports of hospitalized patients with EVALI who have received corticosteroids, rapid improvement has been described. Symptoms of fatigue, dyspnea, decreased exercise capacity, and cough may persist for months.

O'Callaghan M et al. Vaping-associated lung injury: a review. Medicina (Kaunas). 2022;58:412. [PMID: 35334588]
Park JA et al. Carcinoid tumors outside the abdomen. Cancer Med. 2023;12:7893. [PMID: 36560885]
Rebuli ME et al. The e-cigarette or vaping product use-associated lung injury epidemic: pathogenesis, management, and future directions: an official American Thoracic Society workshop report. Ann Am Thorac Soc. 2023;20:1. [PMID: 36584985]

PULMONARY ASPIRATION SYNDROMES

1. Acute Aspiration of Gastric Contents (Mendelson Syndrome)

Acute aspiration of gastric contents may be catastrophic. The pulmonary response depends on the characteristics and amount of gastric contents aspirated. The more acidic the material, the greater the degree of chemical pneumonitis. Aspiration of pure gastric acid (pH < 2.5) causes extensive desquamation of the bronchial epithelium, bronchiolitis, hemorrhage, and pulmonary edema and may lead to ARDS. The clinical picture is one of abrupt onset of respiratory distress, with cough, wheezing, fever, and tachypnea. Crackles may be audible at the bases of the lungs. Hypoxemia may be noted immediately after aspiration occurs. Radiographic abnormalities, consisting of patchy alveolar opacities in dependent lung zones, appear within a few hours. If particulate food matter has been aspirated along with gastric acid, radiographic features of bronchial obstruction may be observed. Fever and leukocytosis are common even in the absence of infection.

Treatment of acute aspiration of gastric contents consists of supplemental oxygen, measures to maintain the airway, and the usual measures for treatment of acute respiratory failure. There is no evidence to support the routine use of prophylactic antibiotics or corticosteroids. Secondary pulmonary infection, which occurs in about one-fourth of patients, typically appears 2–3 days after aspiration. Hypotension or shock secondary to alveolar capillary membrane injury and intravascular volume depletion may occur and is managed with typical supportive care.

2. Chronic Aspiration of Gastric Contents

Chronic aspiration of gastric contents may result from primary disorders of the larynx or the esophagus, such as achalasia, esophageal stricture, systemic sclerosis (scleroderma), esophageal carcinoma, esophagitis, and GERD. In GERD, relaxation of the tone of the lower esophageal sphincter allows reflux of gastric contents into the esophagus and predisposes to chronic pulmonary aspiration, especially when supine. Cigarette smoking, consumption of alcohol or caffeine, and theophylline use are all known to relax the lower esophageal sphincter. Pulmonary disorders linked to GERD and chronic aspiration include asthma, chronic cough, bronchiectasis, and pulmonary fibrosis. Even in the absence of aspiration, acid in the esophagus may trigger bronchospasm or bronchial hyperreactivity through reflex mechanisms.

The diagnosis and management of GERD and chronic aspiration are challenging. A discussion of strategies for the evaluation, prevention, and management of extraesophageal reflux manifestations can be found in Chapter 17.

3. Retention of an Aspirated Foreign Body

Retention of an aspirated foreign body in the tracheobronchial tree may produce both acute and chronic conditions, including atelectasis, postobstructive hyperinflation, acute or recurrent pneumonia, bronchiectasis, and lung abscess. Occasionally, a misdiagnosis of asthma, COPD, or lung cancer is made in adult patients who have aspirated a foreign body. The plain CXR usually suggests the site of the foreign body. In some cases, an expiratory film, demonstrating regional hyperinflation due to a check-valve effect, is helpful. Bronchoscopy is usually necessary to establish the diagnosis and attempt removal of the foreign body.

Jang G et al. Foreign-body aspiration into the lower airways in adults; multicenter study. PLoS One. 2022;17:e0269493. [PMID: 35793276]
Santos JMLG et al. Interventions to prevent aspiration pneumonia in older adults: an updated systematic review. J Speech Lang Hear Res. 2021;64:464. [PMID: 33405973]
Simpson AJ et al. BTS clinical statement on aspiration pneumonia. Thorax. 2023;78:s3. [PMID: 36863772]

OCCUPATIONAL PULMONARY DISEASES

Many acute and chronic pulmonary diseases are related to inhalation of noxious substances encountered in the workplace. Disorders linked to occupational exposures may be classified as: (1) pneumoconioses, (2) hypersensitivity pneumonitis, (3) obstructive airway disorders, (4) toxic lung injury, (5) lung cancer, (6) pleural diseases, and (7) other.

1. Pneumoconioses

Pneumoconioses are chronic fibrotic lung diseases caused by the inhalation of inert inorganic dusts. Pneumoconioses range from asymptomatic disorders with diffuse nodular opacities on CXR to severe, symptomatic, life-shortening disorders. Clinically important pneumoconioses include coal worker's pneumoconiosis, silicosis, and asbestosis (Table 9–20). Treatment for each is supportive; pulmonary rehabilitation may be considered.

A. Coal Worker's Pneumoconiosis

In coal worker's pneumoconiosis, ingestion of inhaled coal dust by alveolar macrophages leads to the formation of coal macules, usually 2–5 mm in diameter, that appear on CXR as diffuse small opacities that are especially prominent in the upper lung. Simple coal worker's pneumoconiosis is usually asymptomatic with minimal impact on PFTs. In complicated coal worker's pneumoconiosis **("progressive massive fibrosis"),** conglomeration and contraction in the upper lung zones occur, with radiographic features resembling complicated silicosis.

Table 9–20. Selected pneumoconioses.

Disease	Agent	Occupations
Asbestosis	Asbestos	Mining, insulation, construction, shipbuilding
Baritosis	Barium salts	Glass and insecticide manufacturing
Coal worker's pneumoconiosis	Coal dust	Coal mining
Kaolin pneumoconiosis	Sand, mica, aluminum silicate	Mining of china clay; pottery and cement work
Shaver disease	Aluminum powder	Manufacture of corundum
Siderosis	Metallic iron or iron oxide	Mining, welding, foundry work
Silicosis	Free silica (silicon dioxide)	Rock mining, quarrying, stone cutting, tunneling, sandblasting, pottery, diatomaceous earth
Stannosis	Tin, tin oxide	Mining, tin-working, smelting
Talcosis	Magnesium silicate	Mining, insulation, construction, shipbuilding

B. Silicosis

In silicosis, extensive or prolonged inhalation of free silica (silicon dioxide) particles (sandblasters, foundry, granite and stone cutting, molding, ceramics) in the respirable range (0.3–5 mcm) causes the formation of small rounded opacities (silicotic nodules) throughout the lung. Calcification of the periphery of hilar lymph nodes ("eggshell" calcification) is an unusual radiographic finding that strongly suggests silicosis. Simple silicosis is usually asymptomatic and without change on routine PFTs; in complicated silicosis, large conglomerate densities appear in the upper lung and are accompanied by dyspnea and obstructive and restrictive pulmonary dysfunction. The incidence of pulmonary tuberculosis is increased in patients with silicosis. All patients with silicosis should have a tuberculin skin test and a CXR to rule out tuberculosis.

C. Asbestosis

Asbestosis is a nodular interstitial fibrosis occurring in workers exposed to asbestos fibers (shipyard and construction workers, pipe fitters, insulators) over many years (typically 10–20 years). Patients with asbestosis usually first seek medical attention at least 15 years after exposure with the following symptoms and signs: progressive dyspnea, inspiratory crackles, and in some cases, clubbing and cyanosis. The radiographic features of asbestosis include linear streaking at the lung bases, opacities of various shapes and sizes, and honeycomb changes in advanced cases. The presence of pleural plaques may be a clue to diagnosis. HRCT scanning is the best imaging method for asbestosis because of its ability to detect parenchymal fibrosis and define the presence of coexisting pleural plaques. Cigarette smoking in asbestos workers increases the prevalence of radiographic pleural and parenchymal changes and markedly increases the incidence of lung carcinoma. It may also interfere with the clearance of short asbestos fibers from the lung. PFTs show restrictive dysfunction and reduced diffusing capacity. There is no specific treatment.

Leonard R et al. Coal mining and lung disease in the 21st century. Curr Opin Pulm Med. 2020;26:135. [PMID: 31815751]
Reynolds C et al. Occupational contributions to interstitial lung disease. Clin Chest Med. 2020;41:697. [PMID: 33153688]

2. Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (also called extrinsic allergic alveolitis) is a nonatopic, nonasthmatic inflammatory pulmonary disease precipitated by exposure to an inhaled organic antigen such as microbial, avian, and animal antigens, and less commonly to an inorganic agent (Table 9–21). The immunologic hypersensitivity reaction leads to an acute illness. Prompt diagnosis is essential since symptoms are usually reversible if the offending antigen is removed from the patient's environment early in the course of illness. Continued exposure may lead to progressive fibrotic or nonfibrotic disease The histopathology of acute hypersensitivity pneumonitis is characterized by interstitial infiltrates of lymphocytes and plasma cells, with noncaseating granulomas in the interstitium and air spaces.

Clinical Findings

A. Acute Illness

Cough and dyspnea develop within days to weeks of exposure; constitutional symptoms such as low-grade fever, chills, and malaise are less common. Inspiratory squeaks on chest auscultation are characteristic when present. Small nodular densities sparing the apices and bases of the lungs are noted on CXR. Laboratory studies reveal an increase in the WBC count with a shift to the left, hypoxemia, and the presence in serum of precipitating antibodies to the offending agent. Hypersensitivity pneumonitis antibody panels against common offending antigens are available; positive results, while supportive, do not establish a definitive diagnosis. PFTs reveal restrictive dysfunction and reduced diffusing capacity.

B. Subacute and Chronic Illness

A subacute hypersensitivity pneumonitis syndrome (15% of cases) is characterized by the insidious onset of

Table 9–21. Selected causes of hypersensitivity pneumonitis.

Disease	Antigen	Source
Farmer's lung	*Saccharopolyspora rectivirgula* (formerly, *Micropolyspora faeni*), *Thermoactinomyces vulgaris*	Moldy hay
"Humidifier" lung	Thermophilic actinomycetes	Contaminated humidifiers, heating systems, or air conditioners
Bird fancier's lung	Avian proteins	Bird serum and excreta
Bagassosis	*Thermoactinomyces sacchari* and *T vulgaris*	Moldy sugar cane fiber (bagasse)
Sequoiosis	*Graphium, Aureobasidium,* and other fungi	Moldy redwood sawdust
Maple bark stripper's disease	*Cryptostroma (Coniosporium) corticale*	Rotting maple tree logs or bark
Mushroom picker's disease	Same as farmer's lung	Moldy compost
Suberosis	*Penicillium frequentans*	Moldy cork dust
Detergent worker's lung	*Bacillus subtilis* enzyme	Enzyme additives

chronic cough and, with continued exposure, slowly progressive dyspnea, anorexia, and weight loss. Characteristic HRCT findings of nonfibrotic disease include upper- or mid-lung ground-glass or nodular opacities and signs of air trapping. Fibrotic disease is characterized by reticulation either in a random or mid-lung zone distribution. Surgical lung biopsy may be necessary for the diagnosis of subacute and chronic hypersensitivity pneumonitis, although the histopathologic patterns are nonspecific and overlap with several idiopathic interstitial pneumonias.

Treatment

Treatment of acute hypersensitivity pneumonitis consists of identification of the offending agent and avoidance of further exposure. In severe acute or protracted cases, oral corticosteroids (prednisone, 0.5 mg/kg daily as a single morning dose for 2 weeks, tapered to nil over 4–6 weeks) may be given. Change in occupation is often required.

Barnes H et al. Management of fibrotic hypersensitivity pneumonitis. Clin Chest Med. 2021;42:311. [PMID: 34024406]
Koster MA et al. Diagnosis of hypersensitivity pneumonitis in adults, 2020 clinical practice guideline: summary for clinicians. Ann Am Thorac Soc. 2021;18:559. [PMID: 33141595]

3. Other Occupational Pulmonary Diseases

Occupational diseases of the pleura may result from exposure to asbestos or talc. Inhalation of talc causes pleural plaques that are like those caused by asbestos. In some asbestos workers, benign asbestos pleural effusions (BAPE) occur, which are typically small, unilateral, and precede the onset of interstitial lung disease. Pleural adhesions at the site of BAPE may cause a "rounded atelectasis" appearance on CXR. Occupational agents are also responsible for other pulmonary disorders, with a range of pathologies including occupational asthma, occupational COPD, interstitial lung diseases, and lung cancer. For this reason, it is important to obtain a thorough occupational history in any patient presenting with pulmonary symptoms.

Specific examples of inorganic agents associated with interstitial lung disease include anthracite coal dust (coal workers' pneumoconiosis), crystalline and nonfibrous silicates (silicosis), asbestos (asbestosis, pleural plaques, benign pleural effusion, adenoma, malignant mesothelioma), beryllium (berylliosis), and cobalt (hard metal lung disease). Organic dust from farm work, animal or bird exposure, or vegetable stores may cause extrinsic allergic alveolitis or hypersensitivity pneumonitis.

Unusual outbreaks (including "popcorn-worker's lung" and other diacetyl flavoring exposure causing bronchiolitis obliterans, "flock worker's lung" following synthetic fiber exposure) are occasionally reported.

Barnes H et al. Occupational interstitial lung diseases. Immunol Allergy Clin North Am. 2023;43:323. [PMID: 37055091]
Carroll MB et al. Imaging of occupational and environmental lung disease. Semin Respir Crit Care Med. 2022;43:824. [PMID: 36181760]
Cohen RA et al. Global trends in occupational lung disease. Semin Respir Crit Care Med. 2023;44:317. [PMID: 37072021]

MEDICATION-INDUCED LUNG DISEASE

Typical patterns of pulmonary response to medications implicated in medication-induced respiratory disease are summarized in Table 9–22. Pulmonary injury due to medications occurs because of allergic reactions, idiosyncratic reactions, overdose, or undesirable side effects. In most patients, the mechanism of pulmonary injury is unknown.

Precise diagnosis of medication-induced pulmonary disease is often difficult because results of routine laboratory studies are not helpful and radiographic findings are not specific. A high index of suspicion and a thorough history of medication usage are critical to establishing the diagnosis of medication-induced lung disease. The clinical response to cessation of the suspected offending agent is also helpful. Acute episodes of medication-induced pulmonary disease may disappear 24–48 hours after the medication has been discontinued, but chronic syndromes may take longer to resolve. Challenge tests to confirm the diagnosis are risky and rarely performed.

Treatment of medication-induced lung disease consists of discontinuing the offending agent immediately, managing the pulmonary symptoms appropriately, and treating with corticosteroids if pulmonary toxicity is

Table 9–22. Pulmonary manifestations of selected medication toxicities.

Asthma	**Pulmonary edema**
Beta-blockers	Noncardiogenic
Aspirin	Aspirin
NSAIDs	Chlordiazepoxide
Histamine	Cocaine
Methacholine	Ethchlorvynol
Acetylcysteine	Heroin/opiates
Aerosolized pentamidine	Cardiogenic
Any nebulized medication	Beta-blockers
Chronic cough	**Pleural effusion**
ACE inhibitors	Bromocriptine
Pulmonary infiltration	Nitrofurantoin
Without eosinophilia	Any drug inducing SLE
Amitriptyline	Methysergide
Azathioprine	Chemotherapeutic agents (eg, carmustine, cyclophosphamide, dasatinib, docetaxel, GM-CSF, methotrexate)
Amiodarone	Tyrosine kinase inhibitors
With eosinophilia	**Mediastinal widening**
Sulfonamides	Phenytoin
L-Tryptophan	Corticosteroids
Nitrofurantoin	Methotrexate
Penicillin	**Respiratory failure**
Methotrexate	Neuromuscular blockade
Crack cocaine	Aminoglycosides
Drug-induced SLE	Paralytic agents
Hydralazine	**CNS depression**
Procainamide	Sedatives
Isoniazid	Hypnotics
Chlorpromazine	Opioids
Phenytoin	Alcohol
Interstitial pneumonitis/fibrosis	Tricyclic antidepressants
Nitrofurantoin	
Bleomycin	
Busulfan	
Cyclophosphamide	
Immune checkpoint inhibitors	
Methysergide	
Phenytoin	

GM-CSF, granulocyte-macrophage colony-stimulating factor.

rapidly progressive. Observational data support the use of corticosteroids in severe cases ;however, controlled data are lacking. Immune checkpoint inhibitors, commonly used treatments for a variety of malignant and nonmalignant conditions, are associated with a 5% risk of pneumonitis with up to 20% mortality when severe. Observational data support concurrent corticosteroid treatment in these cases.

Inhalation of crack cocaine may cause a spectrum of acute pulmonary syndromes, including pulmonary infiltration with eosinophilia, pneumothorax and pneumomediastinum, bronchiolitis obliterans, and acute respiratory failure associated with diffuse alveolar damage and alveolar hemorrhage. Corticosteroids have been used with variable success to treat alveolar hemorrhage.

Conte P et al. Drug-induced interstitial lung disease during cancer therapies: expert opinion on diagnosis and treatment. ESMO Open. 2022;7:100404. [PMID: 35219244]

RADIATION LUNG INJURY

The lung is an exquisitely radiosensitive organ that can be damaged by external beam radiation therapy. The degree of pulmonary injury is determined by the volume of lung irradiated, the dose and rate of exposure, and potentiating factors (eg, concurrent chemotherapy, previous radiation therapy in the same area, and simultaneous withdrawal of corticosteroid therapy). Symptomatic radiation lung injury occurs in about 10% of patients treated for carcinoma of the breast, 5–15% of patients treated for carcinoma of the lung, and 5–35% of patients treated for lymphoma. Two phases of the pulmonary response are apparent: an acute phase (radiation pneumonitis) and a chronic phase (radiation fibrosis).

1. Radiation Pneumonitis

Acute radiation pneumonitis usually occurs 4–12 weeks (range 1–6 months) after completion of radiotherapy and is characterized by insidious onset of dyspnea, intractable dry cough, chest fullness or pain, weakness, and fever. Late radiation pneumonitis may develop 6–12 months after completion of radiation. Occasionally, patients who are months to years removed from radiation therapy will experience "radiation recall" with an inflammatory reaction in the radiated region after treatment with a new round of chemotherapy; this phenomenon has also been reported with immune checkpoint inhibitors. Inspiratory crackles may be heard in the involved area. In severe disease, respiratory distress and cyanosis occur that are characteristic of ARDS. An increased WBC count and elevated ESR are common. PFTs reveal reduced lung volumes, reduced lung compliance, hypoxemia, reduced diffusing capacity, and reduced maximum voluntary ventilation. CXR, which correlates poorly with the presence of symptoms, usually demonstrates alveolar or nodular opacities limited to the irradiated area. Air bronchograms are often observed. Sharp borders of an opacity may help distinguish radiation pneumonitis from other conditions, such as infectious pneumonia, lymphangitic spread of carcinoma, and recurrent tumor; however, the opacity may extend beyond the radiation field.

No specific therapy is proven effective in radiation pneumonitis. Spontaneous resolution may occur in mild disease, but prednisone (1 mg/kg/day orally) is commonly given immediately to patients with a more severe presentation or pulmonary function decline; higher doses may be given in patients who are critically ill. After 1 week, the dose is reduced and maintained at 20–40 mg/day for several weeks, then slowly tapered. Radiation pneumonitis may improve in 2–3 weeks following onset of symptoms as the exudative phase resolves. Acute respiratory failure, if present, is treated supportively. Death from ARDS is unusual in radiation pneumonitis.

Arroyo-Hernández M et al. Radiation-induced lung injury: current evidence. BMC Pulm Med. 2021;2:9. [PMID: 33407290]
Chen F et al. Re-evaluating the risk factors for radiation pneumonitis in the era of immunotherapy. J Clin Med. 2023;12:1442. [PMID: 36835977]

2. Pulmonary Radiation Fibrosis

Radiation fibrosis may occur with or without antecedent radiation pneumonitis. Radiographic findings include obliteration of normal lung markings, dense interstitial and pleural fibrosis, reduced lung volumes, tenting of the diaphragm, and sharp delineation of the irradiated area. No specific therapy is proven effective, and corticosteroids have no value. Pulmonary fibrosis may develop after an intervening period (6–12 months) of well-being in patients who experience radiation pneumonitis. Pulmonary radiation fibrosis occurs in most patients who receive a full course of radiation therapy for cancer of the lung or breast. Most patients are asymptomatic, although slowly progressive dyspnea may occur.

Giuranno L et al. Radiation-induced lung injury (RILI). Front Oncol. 2019;9:877. [PMID: 31555602]

PLEURAL DISEASES

PLEURITIS

Pleuritic pain or "pleurisy" is due to inflammation of the parietal pleura. It is typically well localized, sharp, fleeting, and made worse by coughing, sneezing, deep breathing, or movement. The pain, which is felt over the chest wall, is due to the cutaneous distribution of the intercostal nerves innervating the rib cage and lateral portion of each hemidiaphragm. Inflammation of the parietal pleura or central diaphragm, which are innervated by phrenic nerve fibers, may cause pain that is referred to the ipsilateral shoulder or neck. There are numerous causes of pleuritis. In young, otherwise healthy individuals, pleuritis is usually caused by viral respiratory infections or pneumonia (including tuberculosis in endemic regions). Other causes include PE, inflammatory disorders (serositis), malignancy, and drug reactions. The presence of pleural effusion, pleural thickening, or air in the pleural space requires further diagnostic and therapeutic measures, including pleural fluid sampling and analysis.

Treatment of pleuritis consists of treating the underlying condition. Anti-inflammatory analgesic medications are often helpful for pain relief.

Bader AS et al. Imaging in the evaluation of chest pain in the primary care setting, part 2: sources of noncardiac chest pain. Am J Med. 2020;133:1135. [PMID: 32442508]

PLEURAL EFFUSION

ESSENTIALS OF DIAGNOSIS

- May be asymptomatic; chest pain frequently seen in the setting of pleuritis, trauma, or infection; dyspnea is common with large effusions.
- Dullness to percussion and decreased breath sounds over the effusion.
- Radiographic evidence of pleural effusion.
- Diagnostic findings on thoracentesis.

General Considerations

A pleural effusion is an abnormal accumulation of fluid in the pleural space. Pleural effusions may be classified by differential diagnosis (Table 9–23) or by underlying pathophysiology. Five pathophysiologic processes account for most effusions: increased production of fluid in the setting of normal capillaries due to increased hydrostatic or decreased oncotic pressures **(transudates);** increased production of fluid due to abnormal capillary permeability **(exudates);** decreased lymphatic clearance of fluid from the pleural space **(exudates);** infection in the pleural space **(empyema);** and bleeding into the pleural space **(hemothorax).**

Diagnostic thoracentesis should be performed whenever there is a new pleural effusion and no clinically apparent cause. Observation is appropriate in some situations (eg, symmetric bilateral pleural effusions in the setting of HF), but an atypical presentation or failure of an effusion to resolve as expected warrants thoracentesis to identify the underlying process.

Clinical Findings

A. Symptoms and Signs

Patients with pleural effusions most often report dyspnea, cough, or respirophasic chest pain. Symptoms are more common in patients with existing cardiopulmonary disease. Small pleural effusions are less likely to be symptomatic than larger effusions. Physical findings are usually

Table 9–23. Causes of pleural fluid transudates and exudates.

Transudates	Exudates
HF	Pneumonia (parapneumonic effusion, including empyema)
Cirrhosis with ascites	Cancer
Nephrotic syndrome	PE
Peritoneal dialysis	Bacterial infection (including empyema)
Myxedema	Tuberculosis
Atelectasis (acute)	Connective tissue disease
Constrictive pericarditis	Viral infection
Superior vena cava obstruction	Fungal infection
PE	Rickettsial infection
Hypoalbuminemia	Parasitic infection
Pulmonary arterial hypertension	Asbestos
	Meigs syndrome
	Pancreatic disease
	Uremia
	Chronic atelectasis
	Trapped lung
	Chylothorax
	Sarcoidosis
	Drug reaction (eg, dasatinib)
	Post–myocardial injury syndrome
	Esophageal perforation
	Chest radiation therapy

absent in small effusions. Larger effusions may present with dullness to percussion and diminished or absent breath sounds over the effusion. Compressive atelectasis may cause bronchial breath sounds and egophony just above the effusion. A massive effusion with increased intrapleural pressure may cause contralateral shift of the trachea and bulging of the intercostal spaces. A pleural friction rub indicates pulmonary infarction or pleuritis.

B. Laboratory Findings

The gross appearance of pleural fluid helps identify several types of pleural effusion. Grossly purulent fluid signifies empyema. Milky white pleural fluid should be centrifuged. A clear supernatant above a pellet of white cells indicates empyema, whereas a persistently turbid supernatant suggests a **chylous effusion;** analysis of this supernatant reveals chylomicrons and a high triglyceride level (greater than 100 mg/dL [1 mmol/L]), often from disruption of the thoracic duct. **Hemorrhagic pleural effusion** is a mixture of blood and pleural fluid. Ten thousand red cells per microliter create blood-tinged pleural fluid; 100,000 red cells/mcL (100×10^9/L) create grossly bloody pleural fluid. **Hemothorax** is the presence of gross blood in the pleural space, usually following chest trauma or instrumentation. It is defined as a ratio of pleural fluid hematocrit to peripheral blood hematocrit greater than 0.5.

Pleural fluid samples should be sent for measurement of protein, glucose, and LD in addition to total and differential WBC counts. Chemistry determinations are used to classify effusions as transudates or exudates. This classification is important because the differential diagnosis and subsequent evaluation for each entity varies (Table 9–23). A **pleural exudate** is an effusion that has one or more of the following laboratory features: (1) ratio of pleural fluid protein to serum protein greater than 0.5; (2) ratio of pleural fluid LD to serum LD greater than 0.6; and/or (3) pleural fluid LD greater than two-thirds the upper limit of normal serum LD. Alternative diagnostic criteria that do not require the simultaneous sampling of serum but that perform similarly include the "two-test" (pleural fluid cholesterol greater than 40–55 mg/dL, pleural fluid LD greater than 0.67 times upper limit of normal serum LD) and the "three-test" (which adds pleural fluid protein greater than 3.0 g/dL). **Pleural transudates** occur in the setting of normal capillary integrity and have none of the laboratory features of exudates. A transudate suggests the absence of local pleural disease; characteristic laboratory findings include a glucose near to serum glucose, pH between 7.40 and 7.55, and fewer than 1000 WBCs/mcL (1.0×10^9/L) with a predominance of mononuclear cells. Discrimination of exudate from transudate is less reliable near the cutoff values for any of the criteria. In conditions such as HF, effective diuresis may increase the protein or LD concentration in the transudative pleural fluid as water is reabsorbed, thus creating a borderline "pseudoexudative" chemistry.

HF accounts for most transudates. Bacterial pneumonia, cancer, and tuberculosis (in endemic regions) are the most common causes of exudative effusion. Other causes of exudates with characteristic laboratory findings are summarized in Table 9–24.

Pleural fluid pH (normal = 7.60) is useful in the assessment of parapneumonic effusions, if it can be reliably measured, and is more useful than glucose measurement in determining need for drainage. A pH less than 7.20 suggests a complex parapneumonic pleural effusion that may require drainage; however, other causes include rheumatoid arthritis, lupus, malignancy, esophageal rupture, hemothorax, and pancreatic-pleural fistula. An elevated pleural fluid amylase suggests acute pancreatitis, pancreatic pseudocyst, adenocarcinoma of the lung or pancreas, or esophageal rupture.

Suspected tuberculous pleural effusion should be evaluated by thoracentesis with culture, although pleural fluid culture positivity for *M tuberculosis* is low. Tests for pleural fluid adenosine deaminase (approximately 90% sensitivity and specificity for pleural tuberculosis at levels greater than 60 U/L, tuberculosis rare if level is less than 40 U/L) and interferon-gamma (89% sensitivity, 97% specificity) can be helpful diagnostic aids, particularly in making decisions to pursue invasive testing in complex patients. Closed pleural biopsy is more sensitive than pleural fluid culture for diagnosis, revealing granulomatous inflammation in approximately 60% of patients; culture of three pleural biopsy specimens combined with histologic examination of a pleural biopsy for granulomas yields a diagnosis in up to 90% of patients.

Between 40% and 80% of exudative pleural effusions are malignant, while over 90% of malignant pleural effusions are exudative. Almost any form of cancer may cause effusions, but the most common are lung (one-third) and breast cancer. In 5–10% of malignant pleural effusions, no primary tumor is identified.

Pleural fluid specimens should be sent for cytologic examination in all cases of exudative effusions in patients suspected of harboring an underlying malignancy. The diagnostic yield depends on the nature and extent of the underlying malignancy. Sensitivity is 50–65% but may increase with serial sampling. In a patient with a high prior probability of malignancy, a negative cytologic examination should be followed by one repeat thoracentesis. If that examination is negative, thoracoscopy (sensitivity 92–96%) is preferred to closed pleural biopsy.

C. Imaging

The lung is less dense than water and floats on pleural fluid that accumulates in dependent regions. On a standard upright CXR (Figure 9–6), approximately 75–100 mL of pleural fluid must accumulate in the posterior costophrenic sulcus to be visible on the lateral view and 175–200 mL in the lateral costophrenic sulcus to be visible on the frontal view. On the decubitus view, at least 1 cm of fluid is necessary to permit blind thoracentesis. Ultrasonography increases the safety of thoracentesis and should be incorporated routinely by trained users. Chest CT scans may identify as little as 10 mL of fluid and allows assessment of the entire thorax.

Pleural fluid may become trapped (loculated) by pleural adhesions, thereby forming unusual collections along the lateral chest wall or within lung fissures. Round or oval fluid collections in fissures that resemble intraparenchymal masses are called pseudotumors.

Table 9–24. Characteristics of important exudative pleural effusions.

Etiology or Type of Effusion	Gross Appearance	WBC Count (cells/mcL)	RBC Count (cells/mcL)	Glucose	Comments
Malignancy	Turbid to bloody; occasionally serous	1000–100,000 ($1.0–100 \times 10^9$/L) M	100 (0.1×10^9/L) to several hundred thousand	Equal to serum levels; < 60 mg/dL in 15% of cases	Eosinophilia uncommon; positive results on cytologic examination
Uncomplicated parapneumonic	Clear to turbid	5000–25,000 ($5.0–25 \times 10^9$/L) P	< 5000 (5.0×10^9/L)	Equal to serum levels	Tube thoracostomy unnecessary
Empyema	Turbid to purulent	25,000–100,000 ($25–100 \times 10^9$/L) P	< 5000 (5.0×10^9/L)	Less than serum levels; often very low	Drainage necessary; putrid odor suggests anaerobic infection
Tuberculosis	Serous to serosanguineous	5000–10,000 ($5.0–10 \times 10^9$/L) M	< 10,000 (10×10^9/L)	Equal to serum levels; occasionally < 60 mg/dL	Protein > 4.0 g/dL (may exceed 5 g/dL); frequently lymphocyte predominant (> 50%); eosinophils (> 10%) or mesothelial cells (> 5%) make diagnosis unlikely; see text for additional diagnostic tests
Rheumatoid	Turbid; greenish yellow	1000–20,000 ($1.0–20 \times 10^9$/L) M or P	< 1000 (1.0×10^9/L)	< 40 mg/dL	Secondary empyema common; high LD, low complement, high rheumatoid factor, cholesterol crystals are characteristic
Pulmonary infarction	Serous to grossly bloody	1000–50,000 ($1.0–50 \times 10^9$/L) M or P	100 (0.1×10^9/L) to > 100,000 (100×10^9/L)	Equal to serum levels	Variable findings; no pathognomonic features
Esophageal rupture	Turbid to purulent; red-brown	< 5000 (5.0×10^9/L) to > 50,000 (50×10^9/L) P	1000–10,000 ($1.0–10 \times 10^9$/L)	Usually low	High amylase level (salivary origin); pneumothorax in 25% of cases; effusion usually on left side; pH < 6.0 strongly suggests diagnosis
Pancreatitis	Turbid to serosanguineous	1000–50,000 ($1.0–50 \times 10^9$/L) P	1000–10,000 ($1.0–10 \times 10^9$/L)	Equal to serum levels	Usually left-sided; high amylase level

M, mononuclear cell predominance; P, polymorphonuclear leukocyte predominance.

Treatment

A. Transudative Pleural Effusion

Transudative pleural effusions characteristically occur in the absence of pleural disease. Therefore, treatment is directed at the underlying condition. Therapeutic thoracentesis for severe dyspnea typically offers only transient benefit. Pleurodesis or indwelling pleural catheters are rarely indicated but are appropriate for management of symptoms in selected patients whose symptoms respond to drainage and whose effusions are refractory to maximal medical therapy.

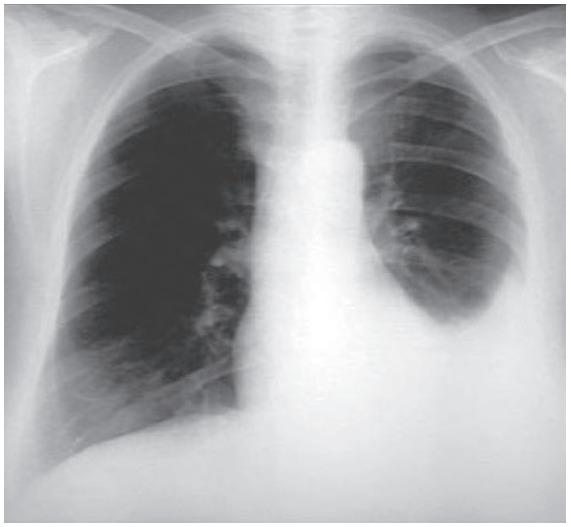
B. Malignant Pleural Effusion

Chemotherapy, radiation therapy, or both offer temporary control in some malignant effusions but are generally ineffective in lung cancer in the pleural space except for small-cell lung cancer. Asymptomatic malignant effusions usually do not require specific treatment. Symptomatic patients should be offered pleural drainage, either via initial therapeutic thoracentesis to determine symptomatic response to drainage, following which an indwelling pleural catheter can be placed, or via immediate placement of an indwelling pleural catheter.

C. Parapneumonic Pleural Effusion

Parapneumonic pleural effusions are divided into three categories, the classification of which can only be determined by sampling the fluid: uncomplicated (simple), complicated, and empyema. **Uncomplicated (simple) parapneumonic effusions** are free-flowing sterile exudates of modest size that resolve quickly with antibiotic treatment of pneumonia. They do not need drainage.

Complicated parapneumonic effusions present the most difficult management decisions. They tend to be larger than simple parapneumonic effusions and to show more evidence of inflammatory stimuli, such as low glucose level, low pH, or evidence of loculation. Inflammation



▲ **Figure 9–6.** Left pleural effusion. Frontal CXR showing a meniscus-shaped density at the left costophrenic angle sulcus indicative of a moderate-sized pleural effusion. (Reproduced, with permission, from Lechner AJ, Matuschak GM, Brink DS. *Respiratory: An Integrated Approach to Disease*. McGraw-Hill, 2012.)

probably reflects ongoing bacterial invasion of the pleural space despite negative bacterial cultures. Tube thoracostomy usually is indicated when pleural fluid glucose is less than 60 mg/dL (less than 3.3 mmol/L), or the pH is less than 7.2. The clinician may also consider drainage of a complicated effusion if the pleural fluid pH is between 7.2 and 7.3 or the LD is greater than 1000 U/L (greater than 20 mckat/L). Pleural fluid cell count and protein have little diagnostic value in this setting.

Empyema is gross infection of the pleural space indicated by positive Gram stain or culture. Empyema should be drained and the patient referred to a thoracic specialist to determine whether tube thoracostomy versus decortication is needed to facilitate clearance of infection and to reduce the probability of permanent fibrous encasement of the lung.

Tube thoracostomy drainage of empyema or complicated parapneumonic effusions is frequently complicated by loculation that prevents adequate drainage. Intrapleural instillation of fibrinolytic agents alone has not been shown in controlled trials to improve drainage. The combination of intrapleural tissue plasminogen activator and deoxyribonuclease (DNase), an enzyme that catalyzes extracellular DNA and degrades biofilm formation within the pleural cavity, has been found to improve clinical outcome (increased drainage, decreased length of stay, and decreased surgical referral) compared with placebo or either agent alone, and should be considered when fever, leukocytosis, or anorexia persist despite antibiotics and tube thoracostomy, or when the lung fails to re-expand.

D. Hemothorax

A small volume hemothorax that is stable or improving on CXRs may be managed by close observation. In all other cases, hemothorax is treated by immediate insertion of a thoracostomy tube to (1) drain existing blood and clot and prevent lung entrapment, (2) quantify the amount of bleeding, (3) reduce the risk of fibrothorax, and (4) permit apposition of the pleural surfaces to reduce hemorrhage. Thoracic surgery consultation is indicated. Thoracotomy may be required to control hemorrhage, remove clot, and treat complications.

Bedawi EO et al. ERS/ESTS statement on the management of pleural infection in adults. Eur Respir J. 2023;61:2201062. [PMID: 36229045]
Porcel JM et al. Pleural fluid analysis: are Light's criteria still relevant after half a century? Clin Chest Med. 2021;42:599. [PMID: 34774168]
Roberts ME et al. British Thoracic Society Guideline for pleural disease. Thorax. 2023;78(Suppl 3):s1. [PMID: 37433578]
Zheng WQ et al. Pleural fluid biochemical analysis: the past, present and future. Clin Chem Lab Med. 2023;60:233. [PMID: 36383033]

PNEUMOTHORAX

ESSENTIALS OF DIAGNOSIS

- Acute onset of unilateral chest pain and dyspnea.
- Minimal physical findings in mild cases; unilateral chest expansion, decreased tactile fremitus, hyperresonance, diminished breath sounds, mediastinal shift, cyanosis, and hypotension in tension pneumothorax.
- Presence of pleural air on CXR.

General Considerations

Pneumothorax, or accumulation of air in the pleural space, is classified as spontaneous (primary or secondary), traumatic, or iatrogenic. **Primary spontaneous pneumothorax** occurs in the absence of an underlying lung disease, whereas **secondary spontaneous pneumothorax** is a complication of preexisting pulmonary disease. **Traumatic pneumothorax** results from penetrating or blunt trauma and includes **iatrogenic pneumothorax** following procedures, such as thoracentesis, pleural biopsy, subclavian or internal jugular vein catheter placement, percutaneous lung biopsy, bronchoscopy with transbronchial biopsy, and positive-pressure mechanical ventilation. **Tension pneumothorax** usually occurs in the setting of penetrating trauma, lung infection, CPR, or positive-pressure mechanical ventilation. In tension pneumothorax, the pressure of air in the pleural space exceeds alveolar and venous pressures throughout the respiratory cycle, resulting in compression of lung and reduction of venous return to the hemithorax; a check-valve mechanism may allow air to enter the pleural space on inspiration and to prevent egress of air on expiration.

Primary spontaneous pneumothorax is more likely among tall, thin, young (age less than 45 years) individuals, more commonly men. It is thought to occur from rupture

of subpleural apical blebs in response to high negative intrapleural pressures. Cigarette smoking is correlated with occurrence of primary spontaneous pneumothorax, as are connective tissue disorders such as Marfan and Ehlers-Danlos syndromes.

Secondary pneumothorax occurs as a complication of COPD, interstitial lung disease, asthma, cystic fibrosis, tuberculosis, *Pneumocystis* pneumonia, necrotizing bacterial pneumonia, menstruation (catamenial pneumothorax), and a wide variety of cystic lung diseases, including lymphangioleiomyomatosis, tuberous sclerosis, Langerhans cell histiocytosis, and Birt-Hogg-Dube syndrome (a hereditary condition with multiple benign skin tumors, lung cysts, and increased risk of both benign and malignant kidney tumors). Secondary pneumothorax, particularly in patients with underlying symptomatic lung disease, is more poorly tolerated due to the decreased respiratory reserve in this group.

Clinical Findings

A. Symptoms and Signs

Chest pain ranging from minimal to severe on the affected side and dyspnea occur in nearly all patients, and cough is commonly reported. Pneumothorax may present with life-threatening respiratory failure if underlying lung disease is present or if tension pneumothorax physiology ensues.

If pneumothorax is small (less than 15% of a hemithorax), physical findings, other than mild tachycardia, are normal. If pneumothorax is large, diminished breath sounds, decreased tactile fremitus, decreased movement of the chest, and hyperresonant percussion note are often found. Tension pneumothorax should be suspected in the presence of marked tachycardia, hypotension, and mediastinal or tracheal shift.

B. Laboratory Findings

ABG analysis is often unnecessary but reveals hypoxemia and acute respiratory alkalosis in most patients. Left-sided primary pneumothorax may produce QRS axis and precordial T-wave changes on the ECG that may be misinterpreted as acute MI.

C. Imaging

Demonstration on CXR of lucency without lung markings between the chest wall and lung, and visualization of the visceral pleura (a "pleural line") is diagnostic. A few patients have secondary pleural effusion that demonstrates a characteristic air-fluid level on CXR. In supine patients, pneumothorax on a conventional CXR may appear as an abnormally radiolucent costophrenic sulcus (the "deep sulcus" sign). In patients with tension pneumothorax, CXRs show a large amount of air in the affected hemithorax and contralateral shift of the mediastinum.

Chest ultrasonography, performed at the bedside by experienced clinicians or technicians, demonstrates characteristic findings in the region of the pneumothorax. Ultrasound may be more sensitive than supine CXR (supine positioning necessitated by clinical circumstance) for detecting pneumothorax in trauma patients, and is frequently used in critical care, though comparisons of ultrasound to CXR or to CT scan report variable test characteristics.

HRCT may be considered with the first spontaneous pneumothorax to evaluate for underlying cystic lung disease.

Differential Diagnosis

If the patient is young with typical clinical characteristics, the diagnosis of primary spontaneous pneumothorax is usually obvious and can be confirmed by CXR. Occasionally, pneumothorax may mimic MI, PE, or pneumonia.

Complications

Tension pneumothorax may be life-threatening. Pneumomediastinum and subcutaneous emphysema may occur as complications of spontaneous pneumothorax. If pneumomediastinum is detected, rupture of the esophagus or a bronchus should be considered in the differential diagnosis.

Treatment

Treatment depends on the severity of the pneumothorax, based on size and symptoms, and the nature of the underlying disease. In a reliable patient with a stable, spontaneous primary pneumothorax, observation alone may be appropriate; many cases resolve spontaneously as air is absorbed from the pleural space. A 2020 US study demonstrated that even moderate to large pneumothoraces in a stable patient (no oxygen requirement, no limitation to ambulation, and no increase in size of pneumothorax over 4 hours of monitoring) can be managed without intervention provided the patient is reliable. Simple needle aspiration drainage of pleural air with a small-bore catheter (eg, 16-gauge angiocatheter or larger drainage catheter) can be performed for spontaneous primary pneumothoraxes that are large or progressive. Length of hospital stay appears to be shorter for conservative management (observation or needle aspiration) of primary spontaneous pneumothorax. Placement of a small-bore chest tube (7F to 14F) attached to a one-way Heimlich valve provides protection against development of tension pneumothorax and may permit observation from home. The patient should be treated symptomatically for cough and chest pain and monitored with serial CXRs every 24 hours. A 2021 observational report of pneumothorax following percutaneous lung biopsy found monitoring and noninvasive management to be sufficient in most patients.

Patients with secondary pneumothorax, tension pneumothorax, or severe symptoms or those who have a pneumothorax on mechanical ventilation should undergo chest tube placement (tube thoracostomy). The chest tube is placed under water-seal drainage, and suction is applied

until the lung expands. The chest tube can be removed after the air leak subsides.

All patients who smoke should be advised to discontinue smoking and warned that the risk of recurrence is higher if cigarette smoking is continued.

Indications for surgical management (video-assisted thoracoscopic surgery) include recurrences of spontaneous pneumothorax, any occurrence of bilateral pneumothorax, and failure of tube thoracostomy for the first episode (failure of lung to re-expand or persistent air leak). Surgical intervention is also generally recommended for any patient with a secondary pneumothorax (presence of underlying lung disease) because the risk of recurrence is high, and the consequences of recurrences are greater. Surgery permits resection or repair of blebs or bullae responsible for the pneumothorax as well as mechanical or chemical pleurodesis. Patients who are not acceptable surgical candidates can be treated with chemical pleurodesis via a chest tube.

Prognosis

About 30% of patients with spontaneous pneumothorax experience recurrence after either observation or tube thoracostomy for the first episode. Recurrence after surgical therapy is less frequent. Following successful therapy, there are no long-term complications. Secondary pneumothorax has up to a 50% likelihood of recurrence following the first event if surgical intervention is not undertaken.

Roberts ME et al. British Thoracic Society Guideline for pleural disease. Thorax. 2023;78(Suppl 3):s1. [PMID: 37433578]

DISORDERS OF CONTROL OF VENTILATION

The principal influences on ventilatory control are arterial P_{CO_2}, pH, P_{O_2}, and brainstem tissue pH. These variables are monitored by peripheral and central chemoreceptors. Under normal conditions, the ventilatory control system maintains arterial pH and P_{CO_2} within narrow limits; arterial P_{O_2} is more loosely controlled.

Abnormal control of ventilation can be seen with a variety of conditions ranging from rare disorders, such as primary alveolar hypoventilation, neuromuscular disorders, myxedema, starvation, and carotid body resection, to more common disorders, such as asthma, COPD, obesity, HF, and sleep-related breathing disorders. A few of these disorders will be discussed in this section.

HYPERVENTILATION SYNDROMES

Hyperventilation is an increase in alveolar minute ventilation that leads to hypocapnia. It may be caused by a variety of conditions, such as pregnancy, hypoxemia, obstructive and infiltrative lung diseases, sepsis, liver dysfunction, fever, and pain. Functional hyperventilation may be acute or chronic. **Acute hyperventilation** presents with hyperpnea, anxiety, paresthesia, carpopedal spasm, and tetany.

Chronic hyperventilation may present with various nonspecific symptoms, including fatigue, dyspnea, anxiety, palpitations, and dizziness. The diagnosis of chronic hyperventilation syndrome is established if symptoms are reproduced during voluntary hyperventilation. When the symptoms are associated with paresthesia and dizziness, the diagnosis is often overlooked. Once organic causes of hyperventilation have been excluded, treatment of acute hyperventilation consists of breathing through pursed lips or through the nose with one nostril pinched or rebreathing expired gas from a paper bag held over the face to decrease respiratory alkalemia and its associated symptoms. Anxiolytic drugs may also be useful.

Tavel ME. Hyperventilation syndrome: why is it regularly overlooked? Am J Med. 2021;134:13. [PMID: 32791056]

OBESITY-HYPOVENTILATION SYNDROME (Pickwickian Syndrome)

In obesity-hypoventilation syndrome, awake alveolar hypoventilation appears to result from a combination of blunted ventilatory drive and increased mechanical load imposed upon the chest by obesity. Voluntary hyperventilation returns the P_{CO_2} and the P_{O_2} toward normal values, a correction not seen in lung diseases causing chronic respiratory failure such as COPD. Diagnostic criteria include a BMI greater than 30, an arterial partial pressure of carbon dioxide greater than 45 mm Hg, sleep disordered breathing, and exclusion of other causes of alveolar hypoventilation. Most patients with obesity-hypoventilation syndrome also suffer from obstructive sleep apnea (90% of patients with obesity hypoventilation syndrome), which must be treated aggressively if identified as a comorbid disorder. Therapy of obesity-hypoventilation syndrome consists mainly of weight loss, which improves hypercapnia and hypoxemia as well as the ventilatory responses to hypoxia and hypercapnia. Avoidance of sedative-hypnotics, opioids, and alcohol is also recommended. NIPPV is helpful in many patients. Patients with obesity-hypoventilation syndrome have a higher risk of complications in the perioperative period, including respiratory failure, intubation, and HF. Recognition of these patients in the perioperative period is an important safety measure.

Kaw R et al. Obesity and obesity hypoventilation, sleep hypoventilation, and postoperative respiratory failure. Anesth Analg. 2021;132:1265. [PMID: 33857968]
Ramírez Molina VR et al. Effectiveness of different treatments in obesity hypoventilation syndrome. Pulmonology. 2020;26:370. [PMID: 32553827]

SLEEP-RELATED BREATHING DISORDERS

Abnormal ventilation during sleep is manifested by apnea (breath cessation for at least 10 seconds) or hypopnea (decrement in airflow with drop in oxygen saturation of at least 4%). Episodes of apnea are **central** if ventilatory effort is

absent for the duration of the apneic episode, **obstructive** if ventilatory effort persists throughout the apneic episode but no airflow occurs because of transient obstruction of the upper airway, or **mixed**. Obstructive and mixed sleep apneas are more common and may be associated with daytime somnolence that impacts quality of life and, in severe form, is associated with severe hypoxemia during sleep that may cause life-threatening cardiac arrhythmias, pulmonary hypertension, right-sided HF, systemic hypertension, and secondary erythrocytosis. Central sleep apnea is less prevalent in the general population. It may be an isolated finding or may occur in patients with HF, stroke with brainstem lesions, and opioid medication use.

Folmer RL et al. Prevalence and management of sleep disorders in the Veterans Health Administration. Sleep Med Rev. 2020; 54:101358. [PMID: 32791487]
Gandhi KD et al. Excessive daytime sleepiness: a clinical review. Mayo Clin Proc. 2021;96:1288. [PMID: 33840518]

OBSTRUCTIVE SLEEP APNEA

ESSENTIALS OF DIAGNOSIS

- Daytime somnolence or fatigue.
- A history of loud snoring with witnessed apneic events.
- Overnight polysomnography demonstrating apneic episodes with hypoxemia.

General Considerations

Upper airway obstruction during sleep occurs when loss of normal pharyngeal muscle tone allows the pharynx to collapse passively during inspiration. Patients with anatomically narrowed upper airways (eg, micrognathia, macroglossia, obesity, tonsillar hypertrophy) are predisposed to the development of obstructive sleep apnea. Ingestion of alcohol or sedatives before sleeping or nasal obstruction of any type, including the common cold, may precipitate or worsen the condition. Hypothyroidism and cigarette smoking are additional risk factors for obstructive sleep apnea. Before making the diagnosis of obstructive sleep apnea, a drug history should be obtained and a seizure disorder, narcolepsy, and depression should be excluded.

Clinical Findings

A. Symptoms and Signs

Most patients with obstructive or mixed sleep apnea are middle-aged men with obesity. Arterial hypertension is common. Patients may report excessive daytime somnolence, morning sluggishness and headaches, daytime fatigue, cognitive impairment, recent weight gain, and impotence. Bed partners usually report loud cyclical snoring, breath cessation, witnessed apneas, restlessness, and thrashing movements of the extremities during sleep. Personality changes, poor judgment, work-related problems, depression, and intellectual deterioration (memory impairment, inability to concentrate) may also be observed. The USPSTF does not recommend screening asymptomatic adults for sleep apnea.

Physical examination may be normal or may reveal systemic and pulmonary hypertension with right-sided HF. The patient may appear sleepy or even fall asleep during the evaluation. The oropharynx is frequently found to be narrowed by excessive soft tissue folds, large tonsils, elongated uvula, or prominent tongue. Nasal obstruction by a deviated nasal septum, poor nasal airflow, and a nasal twang to the speech may be observed. A "bull neck" appearance is common.

B. Laboratory Findings

Erythrocytosis is common. Thyroid function tests (serum TSH, FT_4) should be obtained to exclude hypothyroidism.

C. Other Studies

Observation of the sleeping patient may reveal loud snoring interrupted by episodes of increasingly strong respiratory effort that fail to produce airflow. A loud snort often accompanies the first breath following an apneic episode. Definitive diagnostic evaluation for suspected sleep apnea includes otorhinolaryngologic examination and overnight polysomnography (the monitoring of multiple physiologic factors during sleep). A complete **polysomnography** examination includes electroencephalography, electro-oculography, electromyography, ECG, pulse oximetry, and measurement of respiratory effort and airflow. Home sleep studies are best performed in patients without cardiorespiratory disease and a moderate to high pretest probability of obstructive sleep apnea. While home studies cannot quantify the stages of sleep, they can provide a reliable index of respiratory and desaturation events. Obstructive sleep apnea is determined by the calculated apnea hypopnea index. Treatment is considered if the calculated apnea hypopnea index is above 5 events per hour with sleep symptoms or above 15 events per hour without symptoms.

Treatment

Weight loss and strict avoidance of alcohol and hypnotic medications are the first steps in management. Weight loss may be curative, but most patients are unable to lose the 10–20% of body weight required. **Continuous positive airway pressure (CPAP)** at night is curative in many patients. Auto-titrating airway pressure machines (APAP) allow a range of pressures (5–20 cm H_2O) that auto-adjust based on airflow obstruction. Unfortunately, CPAP adherence is suboptimal, and only 75% of patients continue to use nasal CPAP after 1 year. Supplemental oxygen may lessen the severity of nocturnal desaturation but may also lengthen apneas; it should not be routinely prescribed for treatment of obstructive sleep apnea. An **oral mandibular device** (mandibular repositioning device) at bedtime to hold the jaw forward and prevent pharyngeal occlusion is

as effective as CPAP for treatment of mild to moderate obstructive sleep apnea.

Hypoglossal nerve stimulation can be an option for selected patients with moderate to severe obstructive sleep apnea (apnea hypopnea index between 15–100 events/hour) who do not tolerate or respond to CPAP. Patients are eligible who have absence of complete concentric collapse of the airway during drug-induced sleep endoscopy, BMI less than or equal to 35 (FDA recently approved for BMI less than 40), and less than 25 percent of respiratory events are due to central apneas.

Uvulopalatopharyngoplasty (UPPP), a procedure consisting of resection of pharyngeal soft tissue and amputation of approximately 15 mm of the free edge of the soft palate and uvula, is helpful in approximately 50% of selected patients. It is more effective in eliminating snoring than apneic episodes. **Nasal septoplasty** is performed if gross anatomic nasal septal deformity is present. **Tracheostomy** relieves upper airway obstruction and its physiologic consequences and represents the definitive treatment for obstructive sleep apnea. However, it has numerous adverse effects, including granuloma formation, difficulty with speech, and stoma and airway infection. Furthermore, the long-term care of the tracheostomy, especially in patients with obesity, can be difficult. Tracheostomy and other maxillofacial surgery approaches are reserved for patients with life-threatening arrhythmias or severe disability who have not responded to conservative therapy.

Implantable Upper airway stimulation for obstructive sleep apnea (OSA): summary of safety and effectiveness data (SSED). US Food and Drug Administration (FDA). Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130008S090b.pdf

Randerath W et al. European Respiratory Society guideline on non-CPAP therapies for obstructive sleep apnoea. Eur Respir Rev. 2021;30:210200. [PMID: 34853097]

Suurna MV et al. Obstructive sleep apnea: non-positive airway pressure treatments. Clin Geriatr Med. 2021;37:429. [PMID: 34210448]

ACUTE RESPIRATORY FAILURE

Respiratory failure is defined as respiratory dysfunction resulting in abnormalities of oxygenation or ventilation (CO_2 elimination) severe enough to threaten the function of vital organs. ABG criteria for respiratory failure are not absolute but may be arbitrarily established as a Po_2 under 60 mm Hg (7.8 kPa) or a Pco_2 over 50 mm Hg (6.5 kPa). Acute respiratory failure may occur in a variety of pulmonary and nonpulmonary disorders (Table 9–25). Only a few selected general principles of management will be reviewed here.

Table 9–25. Selected causes of acute respiratory failure in adults.

Airway disorders
Asthma
Acute exacerbation of chronic bronchitis or emphysema
Obstruction of pharynx, larynx, trachea, mainstem bronchus, or lobar bronchus by edema, mucus, mass, or foreign body
Pulmonary edema
Increased hydrostatic pressure
LV dysfunction (eg, myocardial ischemia, HF)
Mitral regurgitation
Left atrial outflow obstruction (eg, mitral stenosis)
Volume overload states
Increased pulmonary capillary permeability
Acute respiratory distress syndrome
Acute lung injury
Unclear etiology
Neurogenic
Negative pressure (inspiratory airway obstruction)
Re-expansion
Tocolytic-associated
Parenchymal lung disorders
Pneumonia
Interstitial lung diseases
Diffuse alveolar hemorrhage syndromes
Aspiration
Lung contusion
Pulmonary vascular disorders
Thromboembolism
Air embolism
Amniotic fluid embolism
Chest wall, diaphragm, and pleural disorders
Rib fracture
Flail chest
Pneumothorax
Pleural effusion
Massive ascites
Abdominal distention and abdominal compartment syndrome
Neuromuscular and related disorders
Primary neuromuscular diseases
Guillain-Barré syndrome
Myasthenia gravis
Poliomyelitis
Polymyositis
Drug- or toxin-induced
Botulism
Organophosphates
Neuromuscular blocking agents
Aminoglycosides
Spinal cord injury
Phrenic nerve injury or dysfunction
Electrolyte disturbances
Hypokalemia
Hypophosphatemia
Myxedema
CNS disorders
Drugs: sedatives, hypnotics, opioids, anesthetics
Brainstem respiratory center disorders: trauma, tumor, vascular disorders, hypothyroidism
Intracranial hypertension
CNS infections
Increased CO_2 production
Fever
Infection
Hyperalimentation with excess caloric and carbohydrate intake
Hyperthyroidism
Seizures
Rigors
Drugs

Clinical Findings

Symptoms and signs of acute respiratory failure are those of the underlying disease combined with those of hypoxemia or hypercapnia. The chief symptom of hypoxemia is dyspnea, though profound hypoxemia may exist in the absence of complaints. Signs of hypoxemia include cyanosis, restlessness, confusion, anxiety, delirium, tachypnea, bradycardia or tachycardia, hypotension or hypertension, cardiac dysrhythmias, and tremor. Dyspnea and headache are the cardinal symptoms of hypercapnia. Signs of hypercapnia include peripheral and conjunctival hyperemia, hypertension, tachycardia,

tachypnea, impaired consciousness, papilledema, myoclonus, and asterixis. The symptoms and signs of acute respiratory failure are both insensitive and nonspecific; therefore, the clinician must maintain a high index of suspicion and obtain ABG analysis if respiratory failure is suspected.

Treatment

Treatment of the patient with acute respiratory failure consists of (1) specific therapy directed toward the underlying disease, (2) respiratory supportive care directed toward the maintenance of adequate gas exchange, and (3) general supportive care. Only the last two aspects are discussed below.

A. Respiratory Support

Respiratory support has both nonventilatory and ventilatory aspects.

1. Nonventilatory aspects—The main therapeutic goal in acute hypoxemic respiratory failure is to ensure adequate oxygenation of vital organs. Inspired oxygen concentration should be the lowest value that results in an arterial hemoglobin saturation of 88% (Po_2 55 mm Hg or 7.3 kPa) or more. Higher arterial oxygen tensions are of no proven benefit and may be deleterious. Restoration of normoxemia may rarely cause hypoventilation in patients with chronic hypercapnia; however, oxygen therapy should not be withheld for that concern. Hypoxemia in patients with obstructive airway disease is usually easily corrected by administering low-flow oxygen by nasal cannula (1–3 L/minute) or Venturi mask (24–40%). Higher concentrations of oxygen are necessary to correct hypoxemia in patients with ARDS, pneumonia, and other parenchymal lung diseases. Humidified, high-flow nasal cannulae provide adjustable oxygen delivery and flow-dependent clearance of carbon dioxide from the upper airway, resulting in reduced work of breathing and better matching of respiratory demand during respiratory distress. In hypoxemia due to acute respiratory failure, oxygenation with use of humidified, high-flow nasal cannulae has been shown to be similar and, in some cases, superior to conventional low-flow oxygen supplementation and noninvasive positive-pressure ventilation (NIPPV); however, the use of high-flow nasal cannulae has no impact on mortality, and the impact on intubation rates, length of stay, dyspnea, and comfort are uncertain.

2. Ventilatory aspects—Ventilatory support consists of maintaining patency of the airway and ensuring adequate alveolar ventilation. Mechanical ventilation may be provided via mask (noninvasive) or through tracheal intubation.

A. Noninvasive positive-pressure ventilation—NIPPV delivered via a full-face mask or nasal mask is first-line therapy in COPD patients with hypercapnic respiratory failure who can protect and maintain the patency of their airway, handle their own secretions, and tolerate the mask apparatus. Several studies have demonstrated the effectiveness of this therapy in reducing intubation rates and ICU stays in patients with ventilatory failure. A bilevel positive-pressure ventilation mode is preferred for most patients. Patients with acute lung injury or ARDS or those who suffer from severely impaired oxygenation are less likely to benefit and should be intubated if they require mechanical ventilation.

B. Tracheal intubation—Indications for tracheal intubation include (1) hypoxemia despite supplemental oxygen; (2) upper airway obstruction; (3) impaired airway protection; (4) inability to clear secretions; (5) respiratory acidosis; (6) progressive general fatigue, tachypnea, use of accessory respiratory muscles, or mental status deterioration; and (7) apnea. Patients in respiratory failure who undergo a trial of NIPPV and do not improve within 30–90 minutes should be intubated. In general, orotracheal intubation is preferred to nasotracheal intubation in urgent or emergency situations because it is easier, faster, and less traumatic. The tip of the endotracheal tube should be positioned 2–4 cm above the carina and be verified by CXR immediately following intubation. Only tracheal tubes with high-volume, low-pressure air-filled cuffs should be used. Cuff inflation pressure should be kept below 20 mm Hg, if possible, to minimize tracheal mucosal injury.

C. Mechanical ventilation—Indications for mechanical ventilation include (1) apnea, (2) acute hypercapnia that is not quickly reversed by appropriate specific therapy, (3) severe hypoxemia, and (4) progressive patient fatigue despite appropriate treatment.

Several modes of positive-pressure ventilation are available. Controlled mechanical ventilation (CMV; also known as assist-control [A-C]) and synchronized intermittent mandatory ventilation (SIMV) are ventilatory modes in which the ventilator delivers a minimum number of breaths of a specified pattern (either a set volume or a set pressure) each minute. In both CMV and SIMV, the patient may trigger the ventilator to deliver additional breaths. Numerous alternative modes of mechanical ventilation now exist, the most popular being pressure support ventilation (PSV), proportional-assist ventilation, and CPAP.

Positive end-expiratory pressure (PEEP) is useful in improving oxygenation in patients with diffuse parenchymal lung disease, such as ARDS. It should be used cautiously in patients with localized parenchymal disease, emphysema, hyperinflation, or very high airway pressure requirements during mechanical ventilation.

D. Complications of mechanical ventilation—Potential complications of mechanical ventilation are numerous. Migration of the tip of the endotracheal tube into a main bronchus can cause atelectasis of the contralateral lung and overdistention of the intubated lung. Barotrauma refers to rupture and loss of integrity of the alveolar space secondary to high transmural pressures applied during positive-pressure ventilation. Barotrauma is manifested by subcutaneous emphysema, pneumomediastinum, subpleural air cysts, pneumothorax, or systemic gas embolism. Volutrauma is sometimes used to refer to

subtle parenchymal injury due to overdistention of alveoli from excessive tidal volumes without alveolar rupture, mediated through inflammatory rather than physical mechanisms. The principal strategy to avoid volutrauma is the use of low tidal volume ventilation (a tidal volume of 6 mL/kg of ideal body weight is supported by the ARDS literature).

Acute respiratory alkalosis caused by overventilation is common. Hypotension induced by elevated intrathoracic pressure that results in decreased return of systemic venous blood to the heart may occur in patients treated with PEEP, particularly those with intravascular volume depletion, and in patients with severe airflow obstruction at high respiratory rates that promote dynamic hyperinflation ("breath stacking"). Ventilator-associated pneumonia is another serious complication of mechanical ventilation.

B. General Supportive Care

Hypokalemia and hypophosphatemia may worsen hypoventilation due to respiratory muscle weakness. Sedative-hypnotics and opioid analgesics should be titrated carefully to avoid oversedation and delirium, leading to prolongation of intubation. Temporary paralysis with a nondepolarizing neuromuscular blocking agent is used to facilitate mechanical ventilation and to lower oxygen consumption. Prolonged muscle weakness due to an acute myopathy is a potential complication of these agents.

Psychological and emotional support of the patient and family, skin care to avoid pressure injuries, and meticulous avoidance of health care–associated infection and complications of endotracheal tubes are vital aspects of comprehensive care for patients with acute respiratory failure.

Attention must also be paid to preventing complications associated with serious illness. The risk of DVT and PE may be reduced by subcutaneous administration of heparin or low-molecular-weight heparin (LMWH) (see Table 16–14), or placement of sequential compression devices on the lower extremities.

Course & Prognosis

The course and prognosis of acute respiratory failure vary and depend on the underlying disease. The prognosis of acute respiratory failure caused by uncomplicated sedative or opioid overdose is excellent. Acute respiratory failure in patients with COPD who do not require intubation and mechanical ventilation has a good immediate prognosis. On the other hand, ARDS and respiratory failure associated with sepsis have a poor prognosis.

Grieco DL et al. Physiological comparison of high-flow nasal cannula and helmet noninvasive ventilation in acute hypoxemic respiratory failure. Am J Respir Crit Care Med. 2020;201:303. [PMID: 31687831]

Qaseem A et al. Appropriate use of high flow nasal oxygen in hospitalized patients for initial or postextubation management of acute respiratory failure: a clinical guideline from the American College of Physicians. Ann Intern Med. 2021; 174:977. [PMID: 33900796]

Richards H et al. Clinical benefits of prone positioning in the treatment of non-intubated patients with acute hypoxic respiratory failure: a rapid systematic review. Emerg Med J. 2021;38:594. [PMID: 34162630]

Schjørring OL et al; HOT-ICU Investigators. Lower or higher oxygenation targets for acute hypoxemic respiratory failure. N Engl J Med. 2021;384:1301. [PMID: 33471452]

ACUTE RESPIRATORY DISTRESS SYNDROME

ESSENTIALS OF DIAGNOSIS

- Onset of respiratory distress, often progressing to respiratory failure, within 7 days of a clinical insult.
- New, bilateral radiographic pulmonary opacities not explained by pleural effusion, atelectasis, or nodules.
- Respiratory failure not fully explained by HF or volume overload.
- Impaired oxygenation, with ratio of partial pressure of oxygen in arterial blood (Pao_2) to fractional concentration of inspired oxygen (FIO_2) < 300 mm Hg, with PEEP ≥ 5 cm H_2O.

General Considerations

Acute respiratory distress syndrome (ARDS) as a clinical syndrome is based on three inclusion criteria plus one exclusion criterion, as detailed above. The severity of ARDS is based on the level of oxygenation impairment: **mild,** Pao_2/FIO_2 ratio between 200 mm Hg and 300 mm Hg; **moderate,** Pao_2/FIO_2 ratio between 100 mm Hg and 200 mm Hg; and **severe,** Pao_2/FIO_2 ratio less than 100 mm Hg.

ARDS may follow a wide variety of clinical events (Table 9–26). Common risk factors for ARDS include sepsis, aspiration of gastric contents, shock, infection, lung contusion, nonthoracic trauma, toxic inhalation, near-drowning, and multiple blood transfusions. About one-third of ARDS patients initially have sepsis syndrome. Damage to capillary endothelial cells and alveolar epithelial cells is common to ARDS regardless of cause or mechanism of lung injury and results in increased vascular permeability and decreased production and activity of surfactant. These abnormalities in turn lead to interstitial and alveolar pulmonary edema, alveolar collapse, and hypoxemia.

Clinical Findings

ARDS is marked by the rapid onset of profound dyspnea that usually occurs 12–48 hours after the initiating event. Labored breathing, tachypnea, intercostal retractions, and

Table 9–26. Selected disorders associated with ARDS.

Systemic Insults	Pulmonary Insults
Trauma	Aspiration of gastric contents
Sepsis	Embolism of thrombus, fat, air, or amniotic fluid
Pancreatitis	Miliary tuberculosis
Shock	Diffuse pneumonia (eg, SARS, COVID-19)
Multiple transfusions	Acute eosinophilic pneumonia
Disseminated intravascular coagulation	Cryptogenic organizing pneumonitis
Burns	Upper airway obstruction
Drugs and drug overdose	Free-base cocaine smoking
Opioids	Near-drowning
Aspirin	Toxic gas inhalation
Phenothiazines	Nitrogen dioxide
Tricyclic antidepressants	Chlorine
Amiodarone	Sulfur dioxide
Chemotherapeutic agents	Ammonia
Nitrofurantoin	Smoke
Protamine	Oxygen toxicity
Thrombotic thrombocytopenic purpura	Lung contusion
Cardiopulmonary bypass	Radiation exposure
Head injury	High-altitude exposure
Paraquat	Lung reexpansion or reperfusion

ARDS, acute respiratory distress syndrome; SARS, severe acute respiratory syndrome.

crackles are noted on physical examination. CXR shows diffuse or patchy bilateral infiltrates that rapidly become confluent; these characteristically spare the costophrenic angles. Air bronchograms occur in about 80% of cases. Heart size is usually normal, and pleural effusions are small or nonexistent. Marked hypoxemia occurs that is refractory to treatment with supplemental oxygen. Many patients with ARDS demonstrate multiple organ failure, particularly involving the kidneys, liver, gut, CNS, and cardiovascular system.

Differential Diagnosis

Since ARDS is a physiologic and radiographic syndrome rather than a specific disease, the concept of differential diagnosis does not strictly apply. Normal-permeability ("cardiogenic" or hydrostatic) pulmonary edema must be excluded because specific therapy is available for that disorder. Diffuse alveolar hemorrhage, inflammatory or autoimmune causes, and bilateral pneumonia should be excluded. Emergent echocardiogram or measurement of pulmonary capillary wedge pressure by means of a flow-directed pulmonary artery catheter may be required in selected patients with suspected cardiac dysfunction; however, routine use in ARDS is discouraged.

Prevention

No measures that effectively prevent ARDS have been identified. Specifically, neither PEEP, prophylactic aspirin, nor intravenous methylprednisolone prevents ARDS when given early to patients with sepsis syndrome or septic shock.

Treatment

The first principle in management is to identify and treat the primary condition that has led to ARDS. Meticulous supportive care must then be provided to compensate for the severe dysfunction of the respiratory system associated with ARDS and to prevent complications.

Treatment of the hypoxemia seen in ARDS usually requires tracheal intubation and positive-pressure mechanical ventilation. The lowest levels of PEEP (used to recruit atelectatic alveoli) and supplemental oxygen required to maintain the Pao_2 above 55 mm Hg (7.13 kPa) or the Sao_2 above 88% should be used. Efforts should be made to decrease Fio_2 as soon as possible to avoid oxygen toxicity. PEEP can be increased as needed if cardiac output and oxygen delivery do not decrease and airway pressures do not increase excessively (ie, plateau pressures remain below 30 cm H_2O). Prone positioning frequently improves oxygenation by helping recruit atelectatic alveoli and has been shown in some trials to provide a mortality benefit in severe ARDS. Routine use of neuromuscular blockade is controversial; one major trial showed improved mortality but a subsequent trial (intended to be confirmatory) did not.

A variety of mechanical ventilation strategies are available. Over the past 20 years, the recognition of the potential for excessive alveolar stretch to cause lung injury has led to widespread adoption of low tidal volume ventilation. A multicenter study of 800 patients demonstrated that a protocol using volume-control ventilation with low tidal volumes (6 mL/kg of ideal body weight) resulted in an 8.8% absolute mortality reduction over therapy with standard tidal volumes (defined as 12 mL/kg of ideal body weight). Varying ventilator modes have been used; conventional modes of ventilation are essentially equivalent, while high-frequency oscillatory ventilation should not be used an as initial mode.

Approaches to hemodynamic monitoring and fluid management in patients with acute lung injury have been carefully studied. Based on a prospective RCT comparing hemodynamic management guided either by a pulmonary artery catheter or a central venous catheter, a pulmonary artery catheter should not be routinely used for the management of acute lung injury. A subsequent randomized, prospective clinical study of restrictive fluid intake and diuresis as needed to maintain CVP less than 4 mm Hg or pulmonary artery occlusion pressure less than 8 mm Hg (conservative strategy group) versus a fluid management protocol to target a CVP of 10–14 mm Hg or a pulmonary artery occlusion pressure 14–18 mm Hg (liberal strategy group) showed that patients in the conservative strategy group experienced faster improvement in lung function and spent significantly fewer days on mechanical ventilation and in the ICU without an improvement in death by 60 days or worsening nonpulmonary organ failure at 28 days. Oxygen delivery can be increased in anemic patients by

ensuring that the hemoglobin concentration is at least 7 g/dL (70 g/L); patients are not likely to benefit from higher levels.

Numerous innovative therapeutic interventions to improve outcomes in ARDS patients have been or are being investigated. Unfortunately, to date, none has consistently shown benefit in clinical trials. Systemic corticosteroids have been studied extensively with variable and inconsistent results and are not recommended.

Another therapeutic intervention is extracorporeal membrane oxygenation (ECMO). A 2018 trial comparing the early use of ECMO in very severe ARDS with conventional strategies built on low-tidal-volume ventilation failed to show a difference in 60-day mortality; however, 28% of the control group crossed over to receive ECMO. ECMO seems unlikely to become a standard first-line therapy but is likely to remain a salvage option for patients with very severe ARDS.

Course & Prognosis

ARDS mortality with low tidal volume ventilation is around 30%. The major causes of death are the primary illness and secondary complications, such as multiple organ system failure or sepsis. Many patients who die of ARDS and its complications die after withdrawal of mechanical ventilation (see Chapter 5). Mortality of ARDS in community hospitals continues to be higher than at academic hospitals, possibly because community hospitals still have not adopted low tidal volume ventilation.

Different clinical syndromes that lead to ARDS carry different prognoses. For example, patients with trauma-associated ARDS have better prognosis, with a mortality rate close to 20%, whereas those with end-stage liver disease have an 80% mortality rate. A hyperinflammatory phenotype associated with high levels of IL-6 and soluble TNF receptor in ARDS patients precipitated by sepsis is associated with more multiorgan dysfunction and higher mortality.

Failure to improve in the first week of treatment is a poor prognostic sign, although this may not be true of ARDS from certain etiologies, including COVID-19. Persons who have been impacted by ARDS tend to be young and pulmonary function generally recovers over 6–12 months, although residual abnormalities often remain, including restrictive or obstructive defects, low diffusion capacity, and impaired gas exchange with exercise. These persons also have diminished health-related and pulmonary disease–specific quality of life as well as systemic effects, such as muscle wasting, weakness, and fatigue.

Grasselli G et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive Care Med. 2023;49:727. [PMID: 37326646]

Pfortmueller CA et al. COVID-19-associated acute respiratory distress syndrome (CARDS): current knowledge on pathophysiology and ICU treatment—a narrative review. Best Pract Res Clin Anaesthesiol. 2021;35:351. [PMID: 34511224]

LUNG TRANSPLANTATION

Introduction

Lung transplantation is a therapeutic option for patients with end-stage lung disease who have not responded to other therapies. The full topic is beyond the scope of this text; therefore, only issues related to candidate selection and post-transplant care will be discussed.

Candidate Selection

Patients should be considered for lung transplantation if they have advanced, progressive lung disease despite appropriate medical therapy. The most common indications are interstitial lung disease, COPD, cystic fibrosis, and pulmonary arterial hypertension. The International Society of Heart and Lung Transplantation has produced guidelines for candidate selection; broadly speaking, the ideal candidate has a high (greater than 50%) risk of dying within 2 years without lung transplantation, has minimal other comorbidities, is very likely to survive transplantation, and has good social support. Contraindications are numerous and include obesity, active smoking or substance abuse, uncontrolled infection, active malignancy, significant organ dysfunction (eg, cirrhosis, CKD, HF, non-revascularizable coronary disease), and medical noncompliance. Each transplant center has a slightly different selection process; however, common practice includes a detailed multidisciplinary evaluation. Patients should ideally be referred to transplant centers before the need for transplantation is emergent.

Care After Transplantation

As with other solid organ transplantation, care of the post–lung transplant patient is particularly concerned with immunosuppression and prophylaxis against infection, as well as with management of the side effects of immunosuppression. Most patients are immunosuppressed with a combination of a calcineurin inhibitor (eg, tacrolimus), a cell-cycle inhibitor (eg, mycophenolate mofetil), and glucocorticoids. Most centers screen for rejection with regular PFTs as well as bronchoscopies and biopsies, particularly in the first 1–2 years after transplantation.

Common complications include acute cellular rejection (treated with intensified immunosuppression), infection, chronic rejection (for which few effective treatments exist), and sequelae of immunosuppression. These include hypertension, dyslipidemia, diabetes mellitus, CKD, osteopenia/osteoporosis, and increased risk of malignancy, especially skin cancers. Post-transplant care thus necessitates close cooperation between the patient's transplant team and his or her other physicians.

Outcomes After Transplantation

While lung transplantation can be transformative for those living with advanced lung disease, long-term

survival remains limited to those receiving kidney or liver transplants. As of the 2021 International Society of Heart and Lung Transplantation Report, median survival after lung transplantation was approximately 7 years. Survival is affected by many variables; two consistent findings have been that survival is improved in double (versus single) lung transplant patients, and in those transplanted for cystic fibrosis (versus other indications).

Bos S et al. Survival in adult lung transplantation: where are we in 2020? Curr Opin Organ Transplant. 2020;25:268. [PMID: 32332197]

Chambers DC et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-Eighth Adult Lung Transplantation Report—2021; Focus on recipient characteristics. J Heart Lung Transplant. 2021;40:1060. [PMID: 34446355]

Gutierrez-Arias R et al. Exercise training for adult lung transplant recipients. Cochrane Database Syst Rev. 2021;7:CD012307. [PMID: 34282853]

van der Mark SC et al. Developments in lung transplantation over the past decade. Eur Respir Rev. 2020;29:190132. [PMID: 32699023]

10 Coronary Artery Disease, Valvular Disease, & Other Key Topics in Cardiology

Todd Kiefer, MD

ADULT CONGENITAL HEART DISEASE

In the United States, there are many more adults with congenital heart disease than children, with an estimated 2 million adults in the United States surviving with congenital heart disease. In 2018, the American College of Cardiology (ACC) and American Heart Association (AHA) released updated guidelines for the assessment and treatment of patients with adult congenital heart disease. The European Society of Cardiology (ESC) completed their update on the same topic in 2020. As the number of patients with adult congenital heart disease has grown, there has been an increased appreciation of the need for more training and guidelines. A specific subspecialty board and training program has been established. The AHA also issued a scientific statement in 2015 reviewing common issues for adults with underlying congenital heart disease, another statement in 2017 for pregnant patients with congenital heart disease, and a statement in 2017 regarding noncardiac issues in these patients.

Baumgartner H et al. 2020 ESC Guidelines for the management of adult congenital heart disease. Eur Heart J. 2021;42:563. [PMID: 32860028]

Stout KK et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73:e81. [PMID: 30121239]

PULMONARY VALVE STENOSIS

ESSENTIALS OF DIAGNOSIS

- Severe cases may present with right-sided HF.
- P_2 delayed and soft or absent.
- Pulmonary ejection click often present and decreases with inspiration—the only right heart sound that *decreases* with inspiration; all other right heart sounds increase.
- Echocardiography/Doppler is diagnostic.
- Patients with peak pulmonic valve gradient greater than 64 mm Hg or a mean of 35 mm Hg by echocardiography/Doppler should undergo intervention regardless of symptoms. Otherwise, operate for symptoms or evidence for RV dysfunction.

General Considerations

Stenosis of the pulmonary valve or RV infundibulum increases the resistance to RV outflow, raises the RV pressure, and limits pulmonary blood flow. Pulmonic stenosis is often congenital and associated with other cardiac lesions. Pulmonary blood flow preferentially goes to the left lung in valvular pulmonic stenosis. In the absence of associated shunts, arterial saturation is normal. Peripheral pulmonic stenosis can accompany valvular pulmonic stenosis and may be part of a variety of clinical syndromes, including the congenital rubella syndrome. Patients who have had the **Ross procedure** for aortic valve disease (transfer of the pulmonary valve to the aortic position with a homograft pulmonary valve placed in the pulmonary position) may experience noncongenital postoperative pulmonic valvular or main pulmonary artery (PA) stenosis due to an immune response in the homograft. RV outflow obstructions can also occur when there is a conduit from the RV to the PA that becomes stenotic from degenerative changes over time or when there is degeneration of a bioprosthetic replacement pulmonary valve.

Clinical Findings

A. Symptoms and Signs

Mild cases of pulmonic stenosis are asymptomatic; moderate to severe pulmonic stenosis may cause symptoms of dyspnea on exertion, syncope, chest pain, and eventually RV failure.

On examination, there is often a palpable parasternal lift due to RVH and the pulmonary outflow tract may be palpable if the PA is enlarged. A loud, harsh systolic murmur and occasionally a prominent thrill are present in the left second and third interspaces parasternally. The murmur radiates toward the left shoulder due to the flow pattern within the main PA and increases with inspiration.

In mild to moderate pulmonic stenosis, a loud ejection click can be heard to precede the murmur; this sound decreases with inspiration as the increased RV filling from inspiration prematurely opens the valve during atrial systole when inspiratory increased blood flow to the right heart occurs. The valve excursion during systole is thus less with inspiration than with expiration, and the click is therefore less audible with inspiration. *This is the only right-sided auscultatory event that decreases with inspiration.* All of the other auscultatory events increase with the increased right heart output that occurs with inspiration. In severe pulmonic stenosis, the second sound is obscured by the murmur and the pulmonary component of S_2 may be diminished, delayed, or absent. A right-sided S_4 and a prominent *a* wave in the venous pulse are present when there is RV diastolic dysfunction or a *c-v* wave may be observed in the jugular venous pressure if tricuspid regurgitation is present. Pulmonary valve regurgitation is relatively uncommon in primary pulmonic stenosis and may be very difficult to hear, as the gradient between the reduced PA diastolic pressure and the elevated RV diastolic pressure may be quite small (low-pressure pulmonary valve regurgitation).

B. ECG and Chest Radiography

Right axis deviation or RVH is noted; peaked P waves provide evidence of right atrial (RA) overload. Heart size may be normal on radiographs, or there may be a prominent RV and RA or gross cardiac enlargement, depending on the severity. There is often poststenotic dilation of the main and left pulmonary arteries. Pulmonary vascularity is usually normal, although there tends to be preferential flow to the left lung.

C. Diagnostic Studies

Echocardiography/Doppler is the diagnostic tool of choice, can provide evidence for a doming valve versus a dysplastic valve, can determine the gradient across the valve, and can provide information regarding subvalvular obstruction and the presence or absence of tricuspid or pulmonic valvular regurgitation. Grading the severity of pulmonic stenosis is based on the peak or mean gradient by echocardiography/Doppler (see Table 10–1). A lower gradient may be significant if there is RV dysfunction. Catheterization is usually unnecessary for the diagnosis; it should be used only if the data are unclear or in preparation for either percutaneous intervention or surgery.

Table 10–1. Severity of pulmonary valve stenosis.

Mild	Moderate	Severe
Peak velocity < 3 m/sec Peak gradient < 36 mm Hg	Peak velocity 3–4 m/sec Peak gradient 36–64 mm Hg	Peak velocity > 4 m/sec Peak gradient > 64 mm Hg

Adapted from J Am Coll Cardiol. 2019;73:e81.

Prognosis & Treatment

Patients with mild pulmonic stenosis have a normal life span with no intervention. Moderate stenosis may be asymptomatic in childhood and adolescence, but symptoms often appear as patients grow older. The degree of stenosis does worsen with time in a few patients, so serial follow-up is important. Severe stenosis is rarely associated with sudden death but can cause right HF in patients as early as in their 20s and 30s. Pregnancy and exercise tend to be well tolerated except in severe stenosis.

The AHA/ACC guidelines and the ESC guidelines generally agree, though the ESC suggests severe pulmonic stenosis should be considered if the RV systolic pressure is greater than 80 mm Hg. Class I (definitive) indications for intervention include all symptomatic patients and all those with a resting peak-to-peak gradient greater than 64 mm Hg or a mean greater than 35 mm Hg, regardless of symptoms. Symptoms can include cyanosis due to right-to-left shunting via a patent foramen ovale (PFO) or atrial septal defect (ASD). Percutaneous balloon valvuloplasty is highly successful in domed valve patients and is the treatment of choice. Surgical commissurotomy can also be done, or pulmonary valve replacement (with either a bioprosthetic valve or homograft) when pulmonary valve regurgitation is too severe or the valve is dysplastic. Pulmonary outflow tract obstruction due to RV to PA conduit obstruction or to homograft pulmonary valve stenosis can often be relieved with a percutaneously implanted pulmonary valve (both the Medtronic Melody valve and the Edwards SAPIEN XT valve are FDA-approved). Frequently the seating of these valves is facilitated by placing a stent within the PA first, then the transcatheter device within this stent. Because the new catheter valve may result in compression of the coronary artery, *it is a class I requirement to assess the effect of the device on the coronary by use of a temporary balloon inflation prior to delivery of the device.* Percutaneous pulmonary valve replacement is also FDA-approved for those with conduit stenosis or following the Ross procedure. Percutaneous valve replacements have also been performed off-label for patients with native pulmonary valve disease, including those who have had tetralogy of Fallot repair (assuming the PA root size is small enough to seat a percutaneous valve).

Endocarditis prophylaxis is *unnecessary* for native valves even after valvuloplasty unless there has been prior pulmonary valve endocarditis (an unusual occurrence). It should be used if surgical or percutaneous valve replacement has occurred. Research has shown infective endocarditis following transcatheter pulmonary valve replacement occurs in 9.5% of cases at 5 years and 16.9% of cases at 8 years. However, multivariate analysis did not show an association between infective endocarditis and specific transcatheter valve type.

When to Refer

All symptomatic patients (regardless of gradient) and all asymptomatic patients whose peak pulmonary valve gradient is greater than 64 mm Hg or whose mean gradient is greater than 35 mm Hg should be referred to a cardiologist

with expertise in adult congenital heart disease. Patients also require intervention if cyanosis occurs due to a PFO or ASD or if there is exercise intolerance.

McElhinney DB et al. Multicenter study of endocarditis after transcatheter pulmonary valve replacement. J Am Coll Cardiol. 2021;78:575. [PMID: 34353535]

COARCTATION OF THE AORTA

ESSENTIALS OF DIAGNOSIS

- Usual presentation is systemic hypertension.
- Echocardiography/Doppler is diagnostic; a peak gradient of greater than 20 mm Hg may be significant due to collaterals around the coarctation reducing gradient despite severe obstruction.
- Associated bicuspid aortic valve in 50–80% of patients.
- Delayed pulse in femoral artery compared to brachial artery.
- Systolic pressure is higher in upper extremities than in lower extremities; diastolic pressures are similar.

General Considerations

Coarctation of the aorta consists of localized narrowing of the aortic arch just distal to the origin of the left subclavian artery. If the stenosis is severe, collateral circulation develops around the coarctation site through the intercostal arteries and the branches of the subclavian arteries and can result in a lower trans-coarctation gradient by enabling blood flow to bypass the obstruction. *Coarctation is a cause of secondary hypertension and should be considered in young patients with elevated blood pressure (BP).* The renin-angiotensin system is often abnormal, however, and contributes to the hypertension occasionally seen even after coarctation repair. A bicuspid valve is seen in approximately 50–80% of the cases, and there is an increased incidence of cerebral berry aneurysms. Significant native or recurrent aortic coarctation has been defined as follows: upper extremity/lower extremity resting peak-to-peak gradient greater than 20 mm Hg or mean Doppler systolic gradient greater than 20 mm Hg; upper extremity/lower extremity gradient greater than 10 mm Hg or mean Doppler gradient greater than 10 mm Hg when there is either decreased LV systolic function or aortic regurgitation; or upper extremity/lower extremity gradient greater than 10 mm Hg or mean Doppler gradient greater than 10 mm Hg when there is evidence for collateral flow around the coarctation. This should be coupled with anatomic evidence for coarctation of the aorta, typically defined by advanced imaging (cardiac magnetic resonance, CT angiography). The ESC guidelines have expanded the severity criteria and suggest stenting is appropriate if the patient is normotensive but has a peak gradient of greater than 20 mm Hg (class IIa) or if the stenosis by angiography is more than 50% (class IIb).

Clinical Findings

A. Symptoms and Signs

If cardiac failure does not occur in infancy, there are usually no symptoms until the hypertension produces LV failure. Cerebral hemorrhage, though rare, may occur. Approximately 10% of patients with coarctation of the aorta have intracranial aneurysms identified on magnetic resonance angiography or CT angiography. Increasing age has been identified as a risk factor. Strong arterial pulsations are seen in the neck and suprasternal notch. Hypertension is present in the arms, but the pressure is normal or low in the legs. This difference is exaggerated by exercise. Femoral pulsations are weak and are delayed in comparison with the brachial or radial pulse. A continuous murmur heard superiorly and midline in the back or over the left anterior chest may be present when large collaterals are present and is a clue that the coarctation is severe. The coarctation itself may result in systolic ejection murmurs heard in the left upper lung field anteriorly and near the spine on the left side posteriorly. There may be an aortic regurgitation or stenosis murmur due to an associated bicuspid aortic valve. Coarctation is associated with Turner syndrome (a sex chromosomal abnormality [XO]); a webbed neck may be present in these patients.

B. ECG and Chest Radiography

The ECG usually shows LVH. Radiography may show scalloping of the inferior portion of the ribs (**rib notching**) due to enlarged collateral intercostal arteries. Dilation of the left subclavian artery and poststenotic aortic dilation along with LV enlargement may be present. The coarctation region and the poststenotic dilation of the descending aorta may result in a **"3" sign** along the aortic shadow on the PA CXR (the notch in the "3" representing the area of coarctation).

C. Diagnostic Studies

Echocardiography/Doppler is usually diagnostic and may provide additional evidence for a bicuspid aortic valve. Both MRI and CT can provide excellent images of the coarctation anatomy, and one or the other should always be done to define the coarctation anatomic structure. MRI and echocardiography/Doppler can also provide estimates of the gradient across the lesion. Cardiac catheterization provides definitive gradient information and is obviously necessary if percutaneous stenting is to be considered.

Prognosis & Treatment

Cardiac failure is common in infancy and in older untreated patients when the coarctation is severe. Patients with a demonstrated peak gradient of greater than 20 mm Hg should be considered for intervention, especially if there is evidence of collateral blood vessels. As noted above, the ESC guidelines incorporate the stenosis severity (greater than 50%)

as defining severe coarctation as well. Many untreated patients with severe coarctation die of hypertension, rupture of the aorta, infective endarteritis, or cerebral hemorrhage before the age of 50. Aortic dissection also occurs with increased frequency. Coarctation of any significance may be poorly tolerated in pregnancy because of the inability to support the placental flow.

Resection of the coarctation site has a surgical mortality rate of 1–4% and includes risk of spinal cord injury. The percutaneous interventional procedure of choice is endovascular stenting; when anatomically feasible, self-expanding and balloon-expandable covered stents have been shown to be advantageous over bare metal stents. These covered stents are FDA-approved. Most coarctation repair in adults is percutaneous. Otherwise, surgical resection (usually with end-to-end anastomosis) should be performed. About 25–50% of surgically corrected patients continue to be hypertensive years after surgery because of permanent changes in the renin-angiotensin system, endothelial dysfunction, aortic stiffness, altered arch morphology, and increased ventricular stiffness. Whether the repair was by balloon dilatation, stenting, or surgical resection may make a difference in the development of hypertension. Recurrence of the coarctation stenosis following intervention requires long-term follow-up.

When to Refer

All patients with aortic coarctation and any detectable gradient should be referred to a cardiologist with expertise in adult congenital heart disease.

ATRIAL SEPTAL DEFECT & PATENT FORAMEN OVALE

ESSENTIALS OF DIAGNOSIS

- Often asymptomatic and discovered on routine physical examination.
- With an ASD and left-to-right shunt: RV lift; S2 widely split and fixed.
- Echocardiography/Doppler is diagnostic.
- ASDs should be closed if there is evidence of an RV volume overload regardless of symptoms.
- A PFO, present in 25% of the population, rarely can lead to paradoxical emboli.

General Considerations

The most common form of ASD (80% of cases) is persistence of the ostium secundum in the mid-septum. A less common abnormality is persistence of the ostium primum (low in the septum). In most patients with an ostium primum defect, there are mitral or tricuspid valve "clefts" as well as a ventricular septal defect (VSD) as part of the atrioventricular (AV) septal defect. A sinus venosus defect is a hole, usually at the upper (or rarely the lower) part of the atrial septum, due to failure of the embryonic superior vena cava or the inferior vena cava to merge with the atria properly. The superior vena cava sinus venosus defect is usually associated with an anomalous connection of the right upper pulmonary vein into the superior vena cava. The coronary sinus ASD is rare and is basically an unroofed coronary sinus that results in shunting from the left atrium (LA) to the coronary sinus and then to the RA.

In all cases, *normally oxygenated blood from the higher-pressure LA shunts into the RA, increasing RV output and pulmonary blood flow.* In children, the degree of shunting across these defects may be quite large (pulmonary to systemic blood flow ratios of 3:1 or so). As the RV compliance worsens from the chronic volume overload, the RA pressure may rise and the degree of left-to-right shunting may decrease over time. Eventually, if the RA pressure exceeds the LA, the shunt may reverse and be primarily right-to-left. When this happens, systemic cyanosis appears. The major factor in the direction of shunt flow is thus the compliance of the respective atrial chambers.

The pulmonary pressures are modestly elevated in most patients with an ASD due to the high pulmonary blood flow, but severe pulmonary hypertension with cyanosis (**Eisenmenger physiology**) is actually unusual, occurring in only about 15% of the patients with an ASD alone. Increased pulmonary vascular resistance (PVR) and pulmonary hypertension secondary to pulmonary vascular disease rarely occur in childhood or young adult life in secundum defects and are more common in primum defects, especially if there is an associated VSD. Eventual RV failure may occur with any atrial shunt of significant size, and most shunts should be corrected unless they are quite small (less than 1.5:1 left-to-right shunt). In adults, a large left-to-right shunt may have begun to reverse, so the absolute left-to-right shunt measurement (Qp/Qs, where Qp = pulmonary flow and Qs = systemic flow) at the time the patient is studied may underestimate the original shunt size. In addition, in most people the LV and LA compliance normally declines more over time than the RV and RA compliance; for this reason, the natural history of small atrial septal shunts is to increase the left-to-right shunting as the patient ages. There is generally only trivial shunting with a PFO compared to a true ASD. ASDs predispose to atrial fibrillation due to RA enlargement, and paradoxical right-to-left emboli do occur. If pulmonary hypertension does occur, the 2018 guidelines recommend that the shunt should still be closed as long as the left-to-right shunt is still greater than 1.5:1 and the systolic PA pressure is less than one-half the systemic arterial pressure and the PVR calculation is less than one-third systemic vascular resistance.

Interestingly, paradoxical emboli may be more common in patients with a PFO than a true ASD, especially when there is an atrial septal aneurysm. An aneurysm of the atrial septum is not a true aneurysm but rather simply a redundancy of the atrial septum that causes it to swing back and forth (greater than 10 mm). When present with a PFO, the back-and-forth swinging tends to pull open the PFO, encouraging shunting. This may help explain why more right-to-left shunting occurs in patients with an atrial

septal aneurysm and PFO than in those with a PFO alone. This creates the anatomic substrate for the occurrence of paradoxical emboli. Other factors may distort the atrial septum (such as an enlarged aorta) and result in an increased shunting in patients with a PFO. Right-to-left PFO shunting may be more prominent upright than supine, creating orthostatic hypoxemia **(platypnea orthodeoxia).** There may also be increased shunting in patients with a PFO and sleep apnea as the RA compliance may worsen during apneic spells when pulmonary pressures increase.

Clinical Findings

A. Symptoms and Signs

Patients with a small or moderate ASD or with a PFO are asymptomatic unless a complication occurs. There is only trivial shunting in a PFO unless the RA pressure increases for some other reason or the atrial septum is distorted. With larger ASD shunts, exertional dyspnea or HF may develop, most commonly in the fourth decade of life or later. Prominent RV and PA pulsations are then readily visible and palpable. A moderately loud systolic ejection murmur can be heard in the second and third interspaces parasternally as a result of increased flow through the pulmonary valve. S_2 is widely split and does not vary with respiration. The left-to-right shunt across the defect decreases with inspiration (as the RA pressure increases) and then increases with expiration (as the RA pressure decreases), thus keeping the RV stroke volume relatively constant in inspiration and expiration. A **"fixed" splitting** of the second sound results. In very large left-to-right shunts, a tricuspid rumble may be heard due to the high flow across the tricuspid valve in diastole.

B. ECG and Chest Radiography

Right axis deviation or RVH may be present depending on the size of the RV volume overload. Incomplete or complete right bundle branch block is present in nearly all cases of ASD, and superior axis deviation (left anterior fascicular block) is noted in the complete AV septal defect, where complete heart block is often seen as well. With sinus venosus defects, the P axis is leftward of +15° due to abnormal atrial activation with loss of the upper RA tissue from around the sinus node. This creates the negative P waves in the inferior leads. The CXR shows large pulmonary arteries, increased pulmonary vascularity, and an enlarged RA and RV as with all pre-tricuspid valve cardiac left-to-right shunts. The LA is not traditionally enlarged due to an ASD shunt because the chamber is being decompressed.

C. Diagnostic Studies

Echocardiography demonstrates evidence of RA and RV volume overload. The atrial defect is usually observed by echocardiography, although sinus venosus defects may be elusive since they are high in the atrial septum. Many patients with a PFO also have an atrial septal aneurysm (defined as greater than 10-mm excursion of the septum from the static position). Echocardiography with saline injection **(bubble contrast)** can demonstrate the right-to-left component of the shunt, and both pulsed and color flow Doppler flow studies can demonstrate shunting in either direction. In platypnea orthodeoxia, the shunt may primarily result from inferior vena cava blood, and a femoral vein saline injection may be required to demonstrate the shunt. Transesophageal echocardiography (TEE) is helpful when transthoracic echocardiography quality is not optimal because it improves the sensitivity for detection of small shunts and provides a better assessment of PFO or ASD anatomy. Both CT and MRI can elucidate the atrial septal anatomy, better detect multiple fenestrations, and demonstrate associated lesions such as anomalous pulmonary venous connections. Atrial septal anatomy can be complex, and either MRI, TEE, or CT can reveal whether there is an adequate rim around the defect to allow for safe positioning of an atrial septal occluder device. These studies can also help identify any anomalous pulmonary venous connections. Cardiac catheterization can define the size and location of the shunt and determine the pulmonary pressure and PVR.

Prognosis & Treatment

Patients with small atrial shunts live a normal life span with no intervention. Large shunts usually cause disability by age 40 years. Because left-to-right shunts and RV overload tend to increase with normal age-related reduction in LV (and subsequently LA) compliance, both AHA/ACC and the ESC guidelines suggest that *closure of all left-to-right shunts greater than 1.5:1 should be accomplished either by a percutaneous device or by surgery if any right heart structures are enlarged at all*. If the pulmonary systolic pressure is more than two-thirds the systemic systolic pressure, then pulmonary hypertension may preclude ASD closure. The ESC guidelines add the pulmonary vascular resistance to the criteria and consider it a class IIa indication if the PVR is between 3 and 5 Wood units, and the guidelines preclude the use of closure if the PVR is greater than or equal to 5 Wood units. Testing with transient balloon occlusion of the shunt, with pulmonary vasodilators, or with both may be required in the presence of pulmonary hypertension. Preservation of the cardiac output after transient balloon occlusion and evidence for preserved pulmonary vasoreactivity with pulmonary vasodilator testing all favor closure when pulmonary hypertension and at least a 1.5:1 left-to-right shunt are present. ESC guidelines favor bringing the patient back to the catheterization laboratory for retesting on pulmonary vasodilators, rather than using acute testing, to see if the PVR can be reduced below 5 Wood units. The ESC guidelines also suggest considering fenestrated closure in the face of pulmonary hypertension. The use of bosentan or sildenafil is recommended if the PVR is over 5 Wood units and there is a right-to-left shunt. After age 40 years, cardiac arrhythmias (especially atrial fibrillation) and HF occur with increased frequency due to the chronic right heart volume overload. Paradoxical systemic arterial embolization also becomes more of a concern as RV compliance is lost and the left-to-right shunt begins to reverse.

PFOs are usually *not* associated with significant shunting, and therefore, the patients are hemodynamically

asymptomatic and the heart size is normal. However, PFOs can be responsible for paradoxical emboli and are a possible cause of **cryptogenic strokes** in patients under age 55 years. Some shunting may occur with exercise if the right heart is enlarged or stiff. *Interestingly, the risk of recurrent paradoxical emboli is low regardless of whether the PFO is closed or not, and that observation has reduced the value of closing these defects in cryptogenic stroke.* Further confounding the advantage of PFO closure for cryptogenic stroke or transient ischemic attack (TIA) has been the discovery of frequent bouts of paroxysmal atrial fibrillation using **30-day monitoring** in these patients, suggesting atrial fibrillation is actually the real stroke/TIA risk factor in some patients.

Occasionally, a PFO that has not been pathologic may become responsible for cyanosis, especially if the RA pressure is elevated from pulmonary or RV hypertension or from severe tricuspid regurgitation.

Surgery involves stitching or patching of the foramen. For ostium secundum ASDs, percutaneous closure by use of a variety of devices is preferred over surgery when the anatomy is appropriate (usually this means there must be an adequate atrial septal rim around the defect to secure the occluder device).

Patients who have hypoxemia (especially upon standing or with exercise) should have the PFO closed if no other cause for hypoxemia is evident and there is right-to-left shunting demonstrated through the PFO. *For patients with cryptogenic stroke or TIA, it remains uncertain whether closure of the PFO, either by open surgical or percutaneous techniques, has any advantage over anticoagulation with either warfarin, a DOAC, or aspirin.*

From a practical standpoint, *patients younger than 55 years with cryptogenic stroke/TIA and no other identifiable cause except for the presence of a PFO should still be considered for PFO closure*. A 2020 update from the guideline subcommittee of the American Academy of Neurology reaffirms no change in this overall policy. The presence of an atrial septal aneurysm (with the septum appearing "floppy" on echocardiogram) has been associated with a higher risk of recurrent stroke/TIA in patients with cryptogenic stroke/TIA. A workup for any causes for hypercoagulability and a 30-day monitor should be part of the clinical assessment to exclude other potential causes for cryptogenic stroke/TIA. In meta-analysis of data in patients with cryptogenic stroke/TIA and PFO who have their PFO closed, ischemic stroke recurrence is less frequent compared with patients receiving medical treatment. Atrial fibrillation is more frequent but mostly transient in patients who have device closure. *There is no difference in TIA, all-cause mortality, or MI between those treated with medicine versus a closure device.* In a large, multicenter trial in France among patients who had had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of stroke recurrence was lower among those assigned to PFO closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone. PFO closure was associated with an increased risk of atrial fibrillation. Residual shunting after device closure is also present in up to 25% of patients. A report from Massachusetts General Hospital found a medium to large residual shunt increased the risk of a recurrent stroke or TIA threefold.

When to Refer

- All patients with an ASD should be evaluated by a cardiologist with expertise in adult congenital disease to ensure no other structural disease is present and to investigate whether the RV is enlarged.
- If the RA and RV sizes remain normal, serial echocardiography should be performed every 3–5 years.
- If the RA and RV volumes are increased, then referral to a cardiologist who performs percutaneous closure is warranted.
- Patients younger than 55 years with cryptogenic stroke when no other source is identified except for a PFO with right-to-left shunting should be considered for PFO closure or medical therapy. An associated atrial septal aneurysm or evidence for hypercoagulability increases risk. Aspirin alone appears *not* to be effective. DOACs with or without device closure of the PFO may have a role in preventing recurrent stroke.
- Patients with cyanosis and a PFO with evidence of a right-to-left shunt by agitated saline bubble contrast on echocardiography, especially if the cyanosis is worsened upon assuming the upright posture.

Deng W et al. Residual shunt after PFO closure and long-term stroke recurrence. Ann Intern Med. 2020;172:717. [PMID: 33253619]

Messé SR et al. Practice advisory update summary: patent foramen ovale and secondary stroke prevention: report of the Guideline Subcommittee of the American Academy of Neurology. Neurology. 2020;94:876. [PMID: 32350058]

Turc G et al. Atrial septal aneurysm, shunt size and recurrent stroke risk in patients with a PFO. J Am Coll Cardiol. 2020;75:2312. [PMID: 32381162]

VENTRICULAR SEPTAL DEFECT

ESSENTIALS OF DIAGNOSIS

- A restrictive VSD is small and makes a louder murmur than an unrestricted one, often with an accompanying thrill. The higher the gradient across the septum, the smaller the left-to-right shunt.
- Small defects may be asymptomatic.
- Larger defects result in pulmonary hypertension (Eisenmenger physiology) if not repaired or if the pulmonary circuit is not protected by RV outflow tract obstruction.
- Echocardiography/Doppler is diagnostic.

General Considerations

Congenital VSDs occur in various parts of the ventricular septum. Membranous and muscular septal defects may

spontaneously close in childhood as the septum grows and hypertrophies. A left-to-right shunt is present, with the degree depending on associated systolic RV pressure. The smaller the defect, the greater is the gradient from the LV to the RV and the louder the murmur. The presentation in adults depends on the size of the shunt and whether there is associated pulmonic or subpulmonic stenosis that has protected the lung from the systemic pressure and volume. Unprotected lungs with large shunts invariably lead to pulmonary vascular disease and severe pulmonary hypertension (Eisenmenger physiology). VSD sizes are defined by comparison to the aortic root size; a small or restrictive VSD diameter is less than 25% of the aortic root diameter, a moderately restrictive VSD diameter is 25–75% of the aorta, and an unrestricted VSD size is greater than 75% of the aortic diameter. The size can also be quantitated based on the Qp/Qs (left-to-right shunt), with a restrictive lesion being less than 1.5:1, moderately restrictive VSD being 1.5–2.2:1, and an unrestricted lesion being greater than 2.2:1. In rare cases of a VSD high in the ventricular septum, an aortic cusp (right coronary cusp) may prolapse into the VSD and reduce the VSD shunt but result in acute aortic regurgitation and acute HF.

Clinical Findings

A. Symptoms and Signs

The clinical features depend on the size of the defect and the presence or absence of RV outflow obstruction or increased PVR. Small shunts are associated with loud, harsh holosystolic murmurs in the left third and fourth interspaces along the sternum. A systolic thrill is common. Larger shunts may create both LV and RV volume and pressure overload. If pulmonary hypertension occurs, high-pressure pulmonary valve regurgitation may result. Right HF may gradually become evident late in the course, and the shunt will begin to balance or reverse as RV and LV systolic pressures equalize with the advent of pulmonary hypertension. Cyanosis from a developing right-to-left shunt may then occur. Cyanosis with pulmonary hypertension and an intracardiac shunt define the **Eisenmenger syndrome.**

B. ECG and Chest Radiography

The ECG may be normal or may show right, left, or biventricular hypertrophy, depending on the size of the defect and the PVR. With large shunts, the LV, the LA, and the pulmonary arteries are enlarged and pulmonary vascularity is increased on CXRs. The RV is often normal until late in the process. If an increased PVR (pulmonary hypertension) evolves, an enlarged PA with pruning of the distal pulmonary vascular bed is seen.

C. Diagnostic Studies

Echocardiography can demonstrate the size of the overloaded chambers and can usually define the defect anatomy. Doppler can qualitatively assess the magnitude of shunting by noting the gradient from LV to RV and, if some tricuspid regurgitation is present, the RV systolic pressure can be estimated. The septal leaflet of the tricuspid valve may be part of the VSD anatomy and the complex appears as a ventricular septal "aneurysm." These membranous septal aneurysms resemble a "windsock" and may fenestrate and result in a VSD shunt being present or they may remain intact. Color flow Doppler helps delineate the shunt severity and the presence of valvular regurgitation. MRI and cardiac CT can often visualize the defect and describe any other anatomic abnormalities. MRI can provide quantitative shunt data as well.

Cardiac catheterization is usually reserved for those with at least moderate shunting, to quantitate the PVR and the degree of pulmonary hypertension. The 2018 adult congenital heart disease guidelines suggest that if there is still at least a 1.5:1 left-to-right shunt and if the PVR is less than one-third that of the systemic vascular resistance, and the PA systolic pressure is more than one-half of the aortic systolic pressure, then the risk of VSD closure despite some pulmonary hypertension is acceptable and it should be done. If the PVR/systemic vascular resistance ratio or the systolic PA pressure/systolic aortic pressure ratio is greater than two-thirds or there is a net right-to-left shunt, then closure is contraindicated.

The vasoreactivity of the pulmonary circuit may be tested at catheterization using agents such as inhaled nitric oxide. The AHA/ACC guidelines suggest that if the pulmonary pressures can be lowered enough and the above ratios fall below the two-thirds value, then repair is reasonable as long as the left-to-right VSD shunt is greater than 1.5:1. The 2020 ESC guidelines focus not on the pulmonary to systemic systolic BP ratio, but on the pulmonary pressure and the PVR. A PVR of greater than or equal to 5 Wood units is considered inoperable unless pulmonary vasodilators can reduce the PVR to below that value. Bosentan, an endothelial receptor blocker that reduces pulmonary pressure in Eisenmenger syndrome, has been given a class I indication in these patients in both guidelines.

Prognosis & Treatment

Patients with a small VSD have a normal life expectancy except for the small risk of infective endocarditis. Antibiotic prophylaxis after dental work is recommended only when the VSD is residual from a prior patch closure or when there is associated pulmonary hypertension and cyanosis. With large VSD shunts, HF may develop early in life, and survival beyond age 40 years is unusual without intervention.

Small shunts (pulmonary to systemic flow ratio less than 1.5) in asymptomatic patients do not require surgery or other intervention. The presence of RV infundibular stenosis or pulmonary valve stenosis may protect the pulmonary circuit such that some patients, even with a large VSD, may still be surgical candidates as adults if there is no pulmonary hypertension.

Surgical repair of a VSD is generally a low-risk procedure unless there is significant Eisenmenger physiology. Devices for nonsurgical closure of muscular VSDs are approved and those for membranous VSDs are being implanted with promising results; however, conduction disturbance is a major complication. The percutaneous devices are also approved for closure of a VSD related to acute MI, although the results in this patient population

with very high risk have not been encouraging. In the acute MI setting, the devices have also been put across the ventricular septum at surgery to help provide a firm base on which to sew a pericardial patch, given the VSD in acute MI is often associated with widespread necrosis and multiple, serpiginous pathways. A percutaneous method, wherein the two sides of the device are sewn together using a subxiphoid approach, has been described. The medications used to treat pulmonary hypertension secondary to a VSD are similar to those used to treat idiopathic ("primary") pulmonary hypertension and at times can be quite effective in relieving symptoms and reducing the degree of cyanosis. *All patients who have a right-to-left shunt present should have filters placed on any intravenous lines to avoid any contamination or air bubbles from becoming systemic.*

When to Refer

All patients with a VSD should be referred to a cardiologist with expertise in adult congenital disease to decide if long-term follow-up or further studies are warranted.

TETRALOGY OF FALLOT

ESSENTIALS OF DIAGNOSIS

- Five features are characteristic:
  - –VSD.
  - –Concentric RVH.
  - –RV outflow obstruction due to infundibular stenosis.
  - –Septal overriding of the aorta in half the patients.
  - –A right-sided aortic arch in 25%.
- Most adult patients with tetralogy of Fallot have been operated on, usually with an RV outflow patch and VSD closure. If patch overrides the pulmonary valve annulus, pulmonary regurgitation is common.
- Physical examination may be deceptive after classic tetralogy repair, with severe pulmonary valve regurgitation difficult to detect.
- Echocardiography/Doppler may underestimate significant pulmonary valve regurgitation. Be wary if the RV is enlarged or enlarging.
- Arrhythmias are common; periodic ambulatory monitoring is recommended.
- Serious arrhythmias and sudden death may occur if the QRS is wide or the RV becomes quite large, or both.

General Considerations

Patients with tetralogy of Fallot have a VSD, RV infundibular stenosis, RVH, and a dilated aorta (in about half of patients it overrides the septum). If there is an associated ASD, the complex is referred to as **pentalogy of Fallot**. The basic lesion is a large VSD with migration of the septum above the VSD and under the pulmonary valve. There may be pulmonary valve stenosis as well, usually due to either a bicuspid pulmonary valve or RV outflow hypoplasia. The aorta can be quite enlarged and aortic regurgitation may occur. If more than 50% of the aorta overrides the ventricular septum, it is called **double outlet RV**. Two vascular abnormalities are common: a right-sided aortic arch (in 25%) and an anomalous left anterior descending coronary artery from the right cusp (7–9%). The latter is important in that surgical correction must avoid injuring the coronary artery when repairing the RV outflow obstruction. Pulmonary branch stenosis may also be present.

Most adult patients have undergone prior surgery. If significant RV outflow obstruction is present in the neonatal period, a systemic arterial to PA shunt may be the initial surgical procedure to improve pulmonary blood flow, though many infants undergo repair without this first step. Most adults will have had this initial palliative repair, however. The palliative procedure enables blood to reach the underperfused lung either by directly attaching one of the subclavian arteries to a main PA branch (**classic Blalock shunt**) or, more likely, by creating a conduit between the two (**modified Blalock shunt**). Total repair of the tetralogy of Fallot generally includes a VSD patch and usually an enlarging RV outflow tract patch, as well as a take-down of any prior arterial-PA shunt. If the RV outflow tract patch extends through the pulmonary valve into the PA (transannular patch), varying degrees of pulmonary valve regurgitation develop. Most surgeons approach the inside of the RV via the right atrium and through the tricuspid valve and try to avoid a transannular patch if possible. Over the years, the volume overload from residual severe pulmonary valve regurgitation becomes the major hemodynamic problem to deal with in adults. A large RV outflow patch contributes to a relative RV volume load. Ventricular arrhythmias can originate from the edge of either the VSD or outflow tract patch and tend to increase in frequency as the size of the RV increases.

Clinical Findings

Most adult patients in whom tetralogy of Fallot has been repaired are relatively asymptomatic unless right HF occurs or arrhythmias become an issue. Patients can be active and generally require no specific therapy.

A. Symptoms and Signs

Physical examination should include checking both arms for any loss of pulse from a prior shunt procedure in infancy. The jugular venous pulsations (JVP) may reveal an increased *a* wave from poor RV compliance or rarely a *c-v* wave due to tricuspid regurgitation. The right-sided arch has no consequence. The precordium may be active, often with a persistent pulmonary outflow murmur. P_2 may or may not be audible. A right-sided gallop may be heard. A residual VSD or an aortic regurgitation murmur may be present.

B. ECG and Chest Radiography

The ECG reveals RVH and right axis deviation; in repaired tetralogy, there is often a right bundle branch block pattern.

The CXR shows a classic boot-shaped heart with prominence of the RV and a concavity in the RV outflow tract. This may be less impressive following repair. The aorta may be enlarged and right-sided. *Importantly, the width of the QRS on ECG should be examined yearly because a QRS width of more than 180 msec is one of the risks for sudden death.* Most experts recommend ambulatory monitoring periodically (every 1–2 years) as well, especially if the patient experiences palpitations. Other identified risk factors for ventricular arrhythmias include having multiple prior cardiac surgeries, an elevated LVEDP, and older age at time of repair. In fact, it appears that the more the left side of the heart is involved, the higher the risk of sudden death.

C. Diagnostic Studies

Echocardiography/Doppler usually establishes the diagnosis by noting the unrestricted (large) VSD, the RV infundibular stenosis, and the enlarged aorta. In patients who have had tetralogy of Fallot repaired, echocardiography/Doppler also provides data regarding the amount of residual pulmonary valve regurgitation if a transannular patch is present, RV and LV function, and the presence of aortic regurgitation. Elevated N-terminal pro B-type natriuretic peptide (NT-proBNP) blood levels have also been correlated with increasing RV enlargement.

Cardiac MRI and CT can quantitate both the pulmonary regurgitation and the RV volumes. In addition, cardiac MRI and CT can identify whether there is either a native pulmonary arterial branch stenosis or a stenosis at the distal site of a prior arterial-to-PA shunt or other anomalies, such as an ASD. The ability of cardiac MRI to accurately quantitate the pulmonary regurgitation severity and provide more accurate RV volume measurements gives it an advantage over other imaging studies. Cardiac catheterization may be required to document the degree of pulmonary valve regurgitation because noninvasive studies depend on velocity gradients. Pulmonary angiography demonstrates the degree of pulmonary valve regurgitation, and RV angiography helps assess any postoperative outflow tract aneurysm.

The need for electrophysiologic studies with ventricular stimulation and potential ventricular tachycardia ablation has been suggested by some experts for patients who have had evidence for ventricular tachycardia, unexplained syncope, a wide QRS, are older, or who are about to undergo pulmonary valve replacement.

Prognosis & Treatment

A few patients with "just the right amount" of subpulmonic stenosis enter adulthood without having had surgical correction. However, most adult patients have had surgical repair, including VSD closure, resection of infundibular muscle, and insertion of an outflow tract patch to relieve the subpulmonic obstruction. Patients with pulmonary valve regurgitation should be monitored to ensure the RV volume does not progressively increase. In patients with tetralogy of Fallot, transthoracic echocardiogram monitoring of pulmonary valve regurgitation is recommended every 12–24 months based on the degree of regurgitation. Low-pressure pulmonary valve regurgitation is difficult to diagnose due to the fact that the RV diastolic pressures tend to be high and the pulmonary arterial diastolic pressure low. This means there is little gradient between the PA and the RV in diastole, so that there may be little murmur or evidence of turbulence on color flow Doppler. *If the RV begins to enlarge, it must be assumed that this is due to pulmonary valve regurgitation until proven otherwise.* Early surgical pulmonary valve replacement is increasingly being favored. The RV volumes from cardiac MRI are important in deciding when to intervene if the patient is not very symptomatic; an RV end-diastolic volume index of greater than 160 mm/m^2 or an RV end-systolic volume index of greater than 80 mm/m^2 is recommended as the cutoff. There are also a number of other triggers for intervention, details of which can be found in the AHA/ACC and ESC guidelines. A percutaneous approach to pulmonary valve regurgitation remains limited as the available percutaneous valve diameters are frequently too small for the size of the pulmonary annulus. The Melody valve is a bovine jugular vein prosthesis with the largest size being 22 mm in diameter. Percutaneous stented valves, particularly the Edwards SAPIEN XT, have been used successfully and can be used in patients with larger pulmonary root sizes. Often, a regular stent is placed within the PA first, with the stented valve then placed within this first stent. The expansion of the PA must not impede flow down any coronary artery; this is tested by a trial balloon expansion while imaging the coronary artery at the same time (class I requirement). There has been an increase in stented valve endocarditis noted after the placement of the Melody valve; this is being closely monitored.

If an anomalous coronary artery is present, then an extracardiac conduit around it from the RV to the PA may be necessary as part of the tetralogy repair. By 20-year follow-up, reoperation of the common tetralogy repair is needed in about 10–15%, not only for severe pulmonary valve regurgitation but also for residual infundibular stenosis. Usually the pulmonary valve is replaced with a pulmonary homograft, although a porcine bioprosthetic valve is also suitable. Percutaneous valve-in-valve stented bioprosthetic valves have successfully been used when there is surgical bioprosthetic valve dysfunction. Cryoablation of the tissue giving rise to arrhythmias is sometimes performed at the time of reoperation. Branch pulmonary stenosis may be percutaneously opened by stenting. If a conduit has been used already for repair of the RV outflow obstruction, a percutaneous approach with a stented pulmonary valve may be possible. All patients require endocarditis prophylaxis. Most adults with stable hemodynamics can be quite active, and most women can carry a pregnancy adequately if RV function is preserved.

Atrial fibrillation, reentrant atrial arrhythmias, and ventricular ectopy are common, especially after the age of 45. Left heart disease appears to cause arrhythmias more often than right heart disease. Biventricular dysfunction is not an uncommon consequence as the patient ages. The cause of associated LV dysfunction is often multifactorial and frequently unclear. Similarly, the aorta may enlarge with accompanying aortic regurgitation, and these lesions can become severe enough to warrant surgical intervention. Patients with RV or LV dysfunction or with dysfunction of both ventricles may require a prophylactic defibrillator.

When to Refer

All patients with tetralogy of Fallot should be referred to a cardiologist with expertise in adult congenital heart disease.

Ros D et al. Infectious endocarditis after percutaneous pulmonary valve implantation with a stent mounted bovine jugular vein valve. Clinical experience and the evaluation of the modified Duke criteria. Int J Cardiol. 2021;323;40. [PMID: 32860844]

VALVULAR HEART DISEASE

The typical findings of each native valve lesion are described in Table 10–2. Table 10–3 outlines bedside maneuvers to distinguish among the various systolic murmurs.

The 2017 ACC/AHA valvular heart disease guidelines suggest all lesions may be best classified clinically into one of six categories based on anatomy and symptoms.

Stage A: Patients at risk for valvular heart disease.

Stage B: Patients with progressive valvular heart disease (mild to moderate severity) and asymptomatic.

Stage C: Asymptomatic patients who have reached criteria for severe valvular heart disease.

C1: Severe valve lesion. Asymptomatic. Normal LV function.

C2: Severe valve lesion. Asymptomatic. Abnormal LV function.

Stage D: Symptomatic patients as a result of valvular heart disease.

In 2020, the ACC/AHA guideline for the management of patients with valvular heart disease was published, and this chapter will highlight the changes and additions from the prior guidelines, first published in 2014 and then updated in 2017.

Kronenberg F et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J. 2022;43:3925. [PMID: 36036785]

Otto CM et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease. J Am Coll Cardiol. 2021;77:450. [PMID: 33342587]

MITRAL STENOSIS

ESSENTIALS OF DIAGNOSIS

- Fatigue, exertional dyspnea, and orthopnea when the stenosis becomes severe.
- Symptoms often precipitated by onset of atrial fibrillation or pregnancy.
- Intervention indicated for symptoms, atrial fibrillation, or evidence of pulmonary hypertension. Most symptomatic patients have a mitral valve area of less than 1.5 cm^2.

General Considerations

Most patients with native valve mitral stenosis are presumed to have had rheumatic heart disease, although a history of rheumatic fever is noted in only about one-third. (Also see section on Rheumatic Fever.) Rheumatic mitral stenosis results in thickening of the leaflets, fusion of the mitral commissures, retraction, thickening and fusion of the chordae, and calcium deposition in the valve. Mitral stenosis can also occur due to congenital disease with chordal fusion or papillary muscle malposition. The papillary muscles may be abnormally close together, sometimes so close that they merge into a single papillary muscle (the **"parachute mitral valve"**). In these patients, the chordae or valvular tissue (or both) may also be fused. In older patients and in those undergoing dialysis, mitral annular calcification may stiffen the mitral valve and reduce its motion to the point where a mitral gradient is present. Calcium in the mitral annulus virtually invades the mitral leaflet from the annulus inward as opposed to the calcium buildup in the leaflets and commissures as seen in rheumatic heart disease. Mitral valve obstruction may also develop in patients who have had mitral valve repair with a mitral annular ring that is too small, or in patients who have had a surgical valve replacement (prosthetic valve-patient mismatch or degeneration of the prosthetic valve over time).

Clinical Findings

A. Symptoms and Signs

Two clinical syndromes classically occur in patients with mitral stenosis. In mild to moderate mitral stenosis, LA pressure and cardiac output may be essentially normal, and the patient is either asymptomatic or symptomatic only with extreme exertion. The measured valve area is usually between 1.5 cm^2 and 1.0 cm^2. In severe mitral stenosis (valve area less than 1.0 cm^2), severe pulmonary hypertension develops due to a "secondary stenosis" of the pulmonary vascular bed. In this condition, pulmonary edema is uncommon, but symptoms of low cardiac output and right HF predominate. Any measured valve area less than 1.5 cm^2 should be considered significant.

A characteristic finding of rheumatic mitral stenosis is an **opening snap** following A_2 due to the stiff mitral valve. The interval between the opening snap and aortic closure sound is long when the LA pressure is low but shortens as the LA pressure rises and approaches the aortic diastolic pressure. As mitral stenosis worsens, there is a localized low-pitched diastolic murmur whose duration increases with the severity of the stenosis as the mitral gradient continues throughout more of diastole. The diastolic murmur is best heard at the apex with the patient in the left lateral position (Table 10–2). Mitral regurgitation may be present as well.

Paroxysmal or chronic atrial fibrillation eventually develops in 50–80% of patients. Any increase in the heart rate reduces diastolic filling time and increases the mitral gradient. A sudden increase in heart rate may precipitate pulmonary edema. Therefore, *heart rate control is important*,

Table 10–2. Differential diagnosis of valvular heart disease.

	Mitral Stenosis	Mitral Regurgitation	Aortic Stenosis	Aortic Regurgitation	Tricuspid Stenosis	Tricuspid Regurgitation
Inspection	Malar flush, precordial bulge, and diffuse pulsation in young patients.	Usually prominent and hyperdynamic apical impulse to left of MCL.	Sustained PMI, prominent atrial filling wave.	Hyperdynamic PMI to left of MCL and downward. Visible carotid pulsations. Pulsating nailbeds (Quincke sign), head bob (deMusset sign).	Giant *a* wave in jugular pulse with sinus rhythm. Peripheral edema or ascites, or both.	Large *v* wave in jugular pulse; time with carotid pulsation. Peripheral edema or ascites, or both.
Palpation	"Tapping" sensation over area of expected PMI. RV pulsation in left third to fifth ICS parasternally when pulmonary hypertension is present. P_2 may be palpable.	Forceful, brisk PMI; systolic thrill over PMI. Pulse normal, small, or slightly collapsing.	Powerful, heaving PMI to left and slightly below MCL. Systolic thrill over aortic area, sternal notch, or carotid arteries in severe disease. Small and slowly rising carotid pulse. If bicuspid AS, check for delay at femoral artery to exclude coarctation.	Apical impulse forceful and displaced significantly to left and downward. Prominent carotid pulses. Rapidly rising and collapsing pulses (Corrigan pulse).	Pulsating, enlarged liver in ventricular systole.	RV pulsation. Systolic pulsation of liver.
Heart sounds, rhythm, and blood pressure	S_1 loud if valve mobile. Opening snap following S_2. The worse the disease, the closer the S_2-opening snap interval.	S_1 normal or buried in early part of murmur (exception in mitral prolapse where murmur may be late). Prominent third heart sound when severe MR. Atrial fibrillation common. Blood pressure normal. Midsystolic clicks may be present and may be multiple.	A_2 normal, soft, or absent. Prominent S_4. Blood pressure normal, or systolic pressure normal with high diastolic pressure.	S_1 normal or reduced, A_2 loud. Wide pulse pressure with diastolic pressure < 60 mm Hg. When severe, gentle compression of femoral artery with diaphragm of stethoscope may reveal diastolic flow (Duroziez) and pressure in leg on palpation > 40 mm Hg than in arm (Hill).	S_1 often loud.	Atrial fibrillation may be present.
Murmurs						
Location and transmission	Localized at or near apex. Diastolic rumble best heard in left lateral position; may be accentuated by having patient do sit-ups. Rarely, short diastolic murmur along lower left sternal border (Graham Steell) in severe pulmonary hypertension.	Loudest over PMI; posteriorly directed jets (ie, anterior mitral prolapse) transmitted to left axilla, left infrascapular area; anteriorly directed jets (ie, posterior mitral prolapse) heard over anterior precordium. Murmur unchanged after premature beat.	Right second ICS parasternally or at apex, heard in carotid arteries and occasionally in upper interscapular area. May sound like MR at apex (Gallaverdin phenomenon), but murmur occurs after S_1 and stops before S_2.	Diastolic: louder along left sternal border in third to fourth interspace. Heard over aortic area and apex. May be associated with low-pitched mid-diastolic murmur at apex (Austin Flint) due to functional mitral stenosis. If due to an enlarged aorta, murmur may radiate to right sternal border.	Third to fifth ICS along left sternal border out to apex. Murmur increases with inspiration.	Third to fifth ICS along left sternal border. Murmur hard to hear but increases with inspiration. Sit-ups can increase cardiac output and accentuate murmur.

Timing	Relation of opening snap to A_2 important. The higher the LA pressure, the earlier the opening snap. Presystolic accentuation before S_1 if in sinus rhythm. Graham Steell begins with P_2 (early diastole) if associated pulmonary hypertension.	Pansystolic: begins with S_1 and ends at or after A_2. May be late systolic in mitral valve prolapse.	Begins after S_1, ends before A_2. The more severe the stenosis, the later the murmur peaks.	Begins immediately after aortic second sound and ends before first sound (blurring both); helps distinguish from MR.	Rumble often follows audible opening snap.	At times, hard to hear. Begins with S_1 and fills systole. Increases with inspiration.
Character	Low-pitched, rumbling; presystolic murmur merges with loud S_1.	Blowing, high-pitched; occasionally harsh or musical.	Harsh, rough.	Blowing, often faint.	As for mitral stenosis.	Blowing, coarse, or musical.
Optimum auscultatory conditions	After exercise, left lateral recumbency. Use stethoscope bell, lightly applied.	After exercise; use stethoscope diaphragm. In prolapse, findings may be more evident while standing.	Use stethoscope diaphragm. Patient resting, leaning forward, breath held in full expiration.	Use stethoscope diaphragm. Patient leaning forward, breath held in expiration.	Use stethoscope bell. Murmur usually louder and at peak during inspiration. Patient recumbent.	Use stethoscope diaphragm. Murmur usually becomes louder during inspiration.
Radiography	Straight left heart border from enlarged LA appendage. Elevation of left mainstem bronchus. Large RV and pulmonary artery if pulmonary hypertension is present. Calcification in mitral valve in rheumatic mitral stenosis or in annulus in calcific mitral stenosis.	Enlarged LV and LA.	Concentric LVH. Prominent ascending aorta. Calcified aortic valve common.	Moderate to severe LV enlargement. Aortic root often dilated.	Enlarged right atrium with prominent SVC and azygous shadow.	Enlarged right atrium and RV.
ECG	Broad P waves in standard leads; broad negative phase of diphasic P in V_1. If pulmonary hypertension is present, tall peaked P waves, right axis deviation, or RVH appears.	Left axis deviation or frank LVH. P waves broad, tall, or notched in standard leads. Broad negative phase of diphasic P in V_1.	LVH.	LVH.	Tall, peaked P waves. Possible RVH.	Right axis usual.

(*continued*)

Table 10–2. Differential diagnosis of valvular heart disease. (continued)

	Mitral Stenosis	Mitral Regurgitation	Aortic Stenosis	Aortic Regurgitation	Tricuspid Stenosis	Tricuspid Regurgitation
Echocardiography						
Two-dimensional echocardiography	Thickened, immobile mitral valve with anterior and posterior leaflets moving together. "Hockey stick" shape to opened anterior leaflet in rheumatic mitral stenosis. Annular calcium with thin leaflets in calcific mitral stenosis. LA enlargement, normal to small LV. Orifice can be traced to approximate mitral valve orifice area.	Thickened mitral valve in rheumatic disease; mitral valve prolapse; flail leaflet or vegetations may be seen. Dilated LV in volume overload. Operate for LV end-systolic dimension < 4.5 cm.	Dense persistent echoes from the aortic valve with poor leaflet excursion. LVH late in the disease. Bicuspid valve in younger patients.	Abnormal aortic valve or dilated aortic root. Diastolic vibrations of the anterior leaflet of the mitral valve and septum. In acute aortic regurgitation, premature closure of the mitral valve before the QRS. When severe, dilated LV with normal or decreased contractility. Operate when LV end-systolic dimension > 5.0 cm.	In rheumatic disease, tricuspid valve thickening, decreased early diastolic filling slope of the tricuspid valve. In carcinoid, leaflets fixed, but no significant thickening.	Enlarged RV with paradoxical septal motion. Tricuspid valve often pulled open by displaced chordae.
Continuous and color flow Doppler and TEE	Prolonged pressure half-time across mitral valve allows estimation of gradient. MVA estimated from pressure half-time. Indirect evidence of pulmonary hypertension by noting elevated RV systolic pressure measured from the tricuspid regurgitation jet.	Regurgitant flow mapped into LA. Use of PISA helps assess MR severity. TEE important in prosthetic mitral valve regurgitation.	Increased transvalvular flow velocity; severe AS when peak jet > 4 m/sec (64 mm Hg). Valve area estimate using continuity equation is poorly reproducible.	Demonstrates regurgitation and qualitatively estimates severity based on percentage of LV outflow filled with jet and distance jet penetrates into LV. TEE important in aortic valve endocarditis to exclude abscess. Mitral inflow pattern describes diastolic dysfunction.	Prolonged pressure half-time across tricuspid valve can be used to estimate mean gradient. Severe tricuspid stenosis present when mean gradient > 5 mm Hg.	Regurgitant flow mapped into right atrium and venae cavae. RV systolic pressure estimated by tricuspid regurgitation jet velocity.

A_2, aortic second sound; AS, aortic stenosis; ICS, intercostal space; LA, left atrial; MCL, midclavicular line; MR, mitral regurgitation; MVA, measured valve area; P_2, pulmonary second sound; PISA, proximal isovelocity surface area; PMI, point of maximal impulse; S_1, first heart sound; S_2, second heart sound; S_4, fourth heart sound; SVC, superior vena cava; TEE, transesophageal echocardiography; V_1, chest ECG lead 1.

Table 10–3. Effect of various interventions on systolic murmurs. (Listed in alphabetical order)

Intervention	Hypertrophic Cardiomyopathy	Aortic Stenosis	Mitral Regurgitation	Mitral Prolapse
Exercise	↑	↑ or ×	↓	↑
Handgrip or squatting	↓	↓ or ×	↑	↓
Standing	↑	↑ or ×	↓ or ×	↑
Supine position with legs elevated	↓	↑ or ×	×	↓
Valsalva	↑	↓	↓ or ×	↑ or ↓

↑, increased; ↓, decreased; ×, unchanged.
Reproduced with permission from Paraskos JA. Combined valvular disease. In: Dalen JE, Alpert JS, Rahimtoola SH (ed). *Valvular Heart Disease*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2000.

with slow heart rates allowing for more diastolic filling of the LV.

B. Diagnostic Studies

Echocardiography is the most valuable technique for assessing mitral stenosis (Table 10–2). LA size can also be determined by echocardiography; increased size denotes an increased likelihood of atrial fibrillation and thrombus formation.

Because echocardiography and careful symptom evaluation provide most of the needed information, cardiac catheterization is used primarily to detect associated coronary or myocardial disease—usually after the decision to intervene has been made.

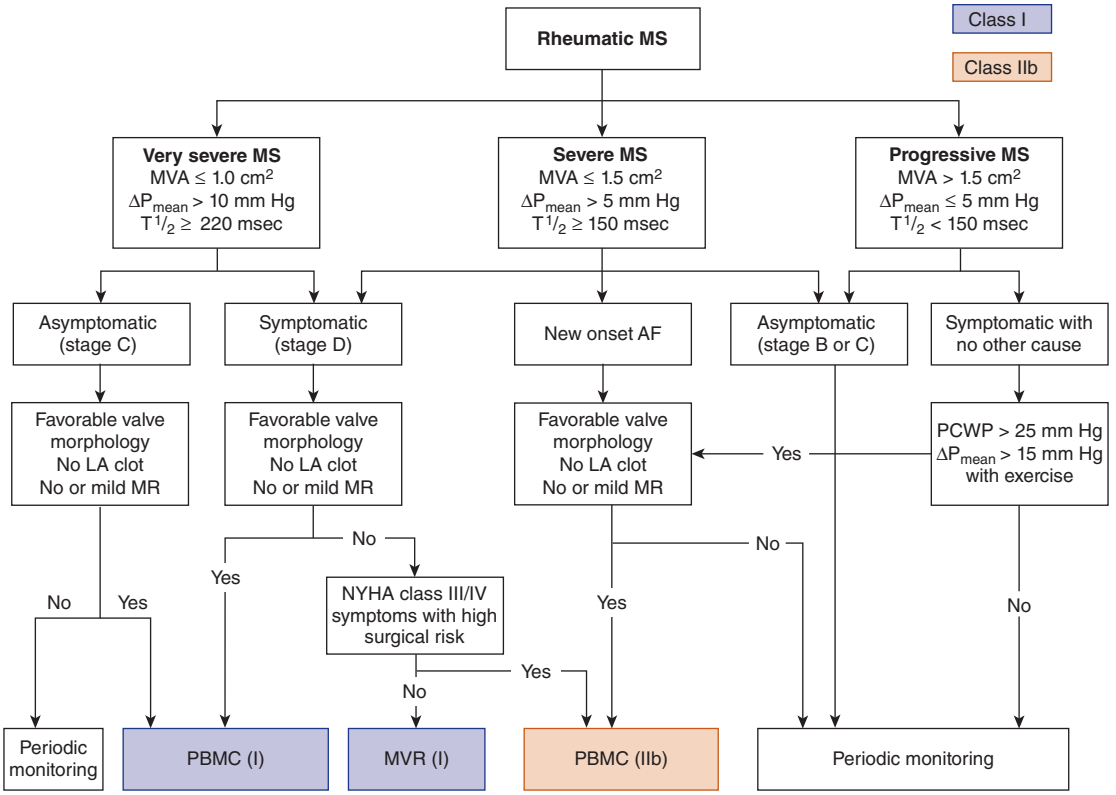
Treatment & Prognosis

In most cases, there is a long asymptomatic phase after the initial rheumatic infection, followed by subtle limitation of activity. Pregnancy and its associated increase in stroke volume and heart rate result in an increased transmitral pressure gradient and may precipitate symptoms. In particular, toward the end of pregnancy, the cardiac output continues to be maintained by an increase in heart rate, increasing the mitral gradient by shortening diastolic time. Patients with moderate to severe mitral stenosis should have the condition corrected prior to becoming pregnant if possible (when the measured valve area is about 2.0 cm^2). Pregnant patients who become symptomatic can undergo successful surgery, preferably in the third trimester, although balloon valvuloplasty is the treatment of choice if the echocardiography valve score is low enough.

The onset of atrial fibrillation often precipitates symptoms, which improve with control of the ventricular rate or restoration of sinus rhythm. Conversion to and subsequent maintenance of sinus rhythm are most commonly successful when the duration of atrial fibrillation is brief (less than 6–12 months) and the LA is not severely dilated (diameter less than 4.5 cm). *Once atrial fibrillation occurs, the patient should receive warfarin even if sinus rhythm is restored*, since atrial fibrillation often recurs even with antiarrhythmic therapy and 20–30% of these patients will have systemic embolization if untreated. Systemic embolization in the presence of only mild to moderate disease is not an indication for surgery but should be treated with warfarin. DOACs (dabigatran, apixaban, rivaroxaban, edoxaban) are *not* recommended by the most recent guidelines, since patients with atrial fibrillation were excluded from the approval trials. A randomized clinical trial published in 2022 supports this recommendation.

Indications for intervention focus on symptoms such as an episode of pulmonary edema, a decline in exercise capacity, or any evidence of pulmonary hypertension (peak systolic pulmonary pressure greater than 50 mm Hg). Some experts believe that the presence of atrial fibrillation should also be a consideration for an intervention. Most interventions are not pursued until the patient is symptomatic (stage D) (Figure 10–1). In some patients, symptoms develop with calculated mitral valve areas between 1.5 cm^2 and 1.0 cm^2. Symptoms or evidence of pulmonary hypertension should drive the decision to intervene in these patients, not the estimated valve area.

Open mitral commissurotomy is now rarely performed and has been replaced by percutaneous balloon valvuloplasty. Ten-year follow-up data comparing surgery to balloon valvuloplasty suggest no real difference in outcome between the two modalities. Replacement of the valve is indicated when combined stenosis and regurgitation are present or when the mitral valve echo score is much greater than 8–10. To determine the valve score, numbers 1 to 4 are assigned to four valve characteristics: mobility, calcification, thickening, and submitral scar. Thus, a maximum score is 16. Percutaneous balloon valvuloplasty has a very low mortality rate (less than 0.5%) and a low morbidity rate (3–5%). Operative mortality rates are also low: 1–3% in most institutions. Repeat balloon valvuloplasty can be done if the morphology of the valve remains suitable. At surgery, a **Maze procedure** may be done at the same time to reduce recurrent atrial arrhythmias. It involves a number of endocardial incisions across the right and left atria to disrupt the electrical activity that sustains atrial arrhythmias. In many institutions, the LA appendage is sewn closed to help remove a potential future source for thrombosis.



▲ **Figure 10–1.** The AHA/ACC guidelines for intervention in mitral stenosis. AF, atrial fibrillation; LA, left atrial; MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area; MVR, mitral valve replacement; NYHA, New York Heart Association; PBMC, percutaneous balloon mitral commissurotomy; PCWP, pulmonary capillary wedge pressure; ΔP_{mean}, mean pressure gradient; T½, half-life. (Reprinted with permission Circulation. 2014;129:e521–e643 ©2014 American Heart Association, Inc.)

Mechanical mitral prosthetic valves are more prone to thrombosis than mechanical aortic prosthetic valves. *The recommended INR range is thus higher (INR 2.5–3.5 or average of 3.0). Low-dose aspirin should be used in conjunction with warfarin if the bleeding risk is low. DOACs are not recommended as an anticoagulant.* It is a class IIa recommendation that warfarin be used for up to 6 months after implantation of a bioprosthetic mitral valve. Bioprosthetic valves tend to degenerate after about 10–15 years. Percutaneous balloon valvuloplasty is not effective when bioprosthetic valve stenosis occurs, but transcatheter valve-in-valve procedures have been successful. Transcatheter valve-in-valve procedures are becoming more common in patients at high risk for repeat cardiac surgical valve replacement. Reported early outcomes have been positive in patients with bioprosthetic valves, ring annuloplasty, and even in some patients with calcific mitral stenosis. Younger patients and those with ESKD are generally believed to do the poorest with bioprosthetic heart valves, although data have questioned the role of CKD as a major risk factor. Endocarditis prophylaxis is indicated for patients with prosthetic heart valves but is not indicated in native valve disease. Mitral stenosis due to calcific encroachment of the leaflets from mitral annular calcium can progress to severe mitral stenosis at times (estimated to be about 1 in 6 over 10 years). It does not lend itself to percutaneous valvuloplasty, and there are only case reports of using a percutaneous mitral valve replacement option.

When to Refer

- Patients with mitral stenosis should be monitored with yearly examinations, and echocardiograms should be performed more frequently as the severity of the obstruction increases.
- All patients should initially be seen by a cardiologist, who can then decide how often the patient needs cardiology follow-up and whether intervention is indicated.

Connolly SJ et al; INVICTUS Investigators. Rivaroxaban in rheumatic heart disease-associated atrial fibrillation. N Engl J Med. 2022;387:978. [PMID: 36036525]

Eng MH et al. Transcatheter mitral valve replacement in failed bioprosthetic surgical valves and surgical annuloplasty rings. Curr Cardiol Rep. 2022;24:1417. [PMID: 35980565]

MITRAL REGURGITATION

ESSENTIALS OF DIAGNOSIS

- May be asymptomatic for years (or for life).
- Severe mitral regurgitation may cause left-sided HF and lead to pulmonary hypertension and right-sided HF.
- For chronic primary mitral regurgitation, surgery is indicated for symptoms or when the LVEF is less than 60% or the echocardiographic LV end-systolic dimension is greater than 4.0 cm. Surgery also indicated in patients who have a progressive increase in LV size or decline in LVEF.
- In patients with mitral prolapse and severe mitral regurgitation, earlier surgery is indicated if mitral repair can be performed successfully with a high degree of certainty.
- Transcatheter edge-to-edge repair, if possible, can be done in symptomatic patients at higher surgical risk regardless of whether the mitral regurgitation is primary or secondary.
- Patients with functional chronic mitral regurgitation may improve with biventricular pacing and guideline-directed management and therapy.

General Considerations

Mitral regurgitation results in a volume load on the heart (increases preload) and reduces afterload. The result is an enlarged LV with an increased EF. Over time, the stress of the volume overload reduces myocardial contractile function; when this occurs, there is a drop in EF and a rise in end-systolic volume.

Clinical Findings

A. Symptoms and Signs

In **acute mitral regurgitation**, the LA size is not large, and LA pressure rises abruptly, leading to pulmonary edema if severe. When **chronic,** the LA enlarges progressively and the increased volume can be handled without a major rise in the LA pressure; the pressure in pulmonary veins and capillaries may rise only during exertion. Exertional dyspnea and fatigue progress gradually over many years.

Mitral regurgitation leads to chronic LA and LV enlargement and may result in subsequent atrial fibrillation and eventually LV dysfunction. Clinically, mitral regurgitation is characterized by a pansystolic murmur maximal at the apex, radiating to the axilla and occasionally to the base. The murmur does *not* change in intensity after a premature beat because the LV to LA gradient is unaffected. In addition, a hyperdynamic LV impulse and a brisk carotid upstroke may be present along with a prominent third heart sound due to the increased volume returning to the LV in early diastole (Tables 10–1 and 10–2). In acute mitral regurgitation, the murmur intensity may be modest due to little difference between the LA and LV systolic pressures during ventricular systole. The mitral regurgitation murmur due to mitral valve prolapse tends to radiate anteriorly in the presence of posterior leaflet prolapse and posteriorly when the prolapse is primarily of the anterior leaflet. Mitral regurgitation may not be pansystolic in these patients but occur only after the mitral click (until late in the disease process when it then becomes progressively more holosystolic).

B. Diagnostic Studies

Echocardiographic information demonstrating the underlying pathologic process (rheumatic, calcific, prolapse, flail leaflet, endocarditis, cardiomyopathy), LV size and function, LA size, PA pressure, and RV function can be invaluable in planning treatment as well as in recognizing associated lesions. The valvular heart disease guidelines provide details of the classification and measures of severity for primary and secondary mitral valve regurgitation. Doppler techniques provide qualitative and semiquantitative estimates of the severity of mitral regurgitation. TEE may help reveal the cause of regurgitation and is especially useful in patients who have had mitral valve replacement, in suspected endocarditis, and in identifying candidates for valvular repair. Echocardiographic dimensions and measures of systolic function are critical in deciding the timing of surgery. Asymptomatic patients with severe mitral regurgitation (stage C1) but preserved LV dimensions should undergo at least yearly echocardiography. Exercise hemodynamics with either Doppler echocardiography or cardiac catheterization may be useful when the symptoms do not fit the anatomic severity of mitral regurgitation. BNP or NT-proBNP is useful in the early identification of LV dysfunction in the presence of mitral regurgitation and asymptomatic patients, and values that trend upward over time appear to have prognostic importance.

Cardiac MRI is occasionally useful, especially if specific myocardial causes are being sought (such as amyloid or myocarditis) or if myocardial viability assessment is needed prior to deciding whether to add coronary artery bypass grafting to mitral valve surgery.

Cardiac catheterization provides a further assessment of regurgitation and its hemodynamic impact along with LV function, resting cardiac output, and PA pressure. *The guidelines recommend coronary angiography to determine the presence of incidental CAD prior to valve surgery in all men over age 40 years and in menopausal women with coronary risk factors.* In younger patients, no coronary angiography is needed unless there is a clinical suspicion of coronary disease. Cardiac multidetector coronary CT may be adequate to screen patients with valvular heart disease for asymptomatic CAD. A normal CT coronary angiogram has a high predictive value for patients with normal or insignificant disease.

Treatment & Prognosis

A. Primary Mitral Regurgitation

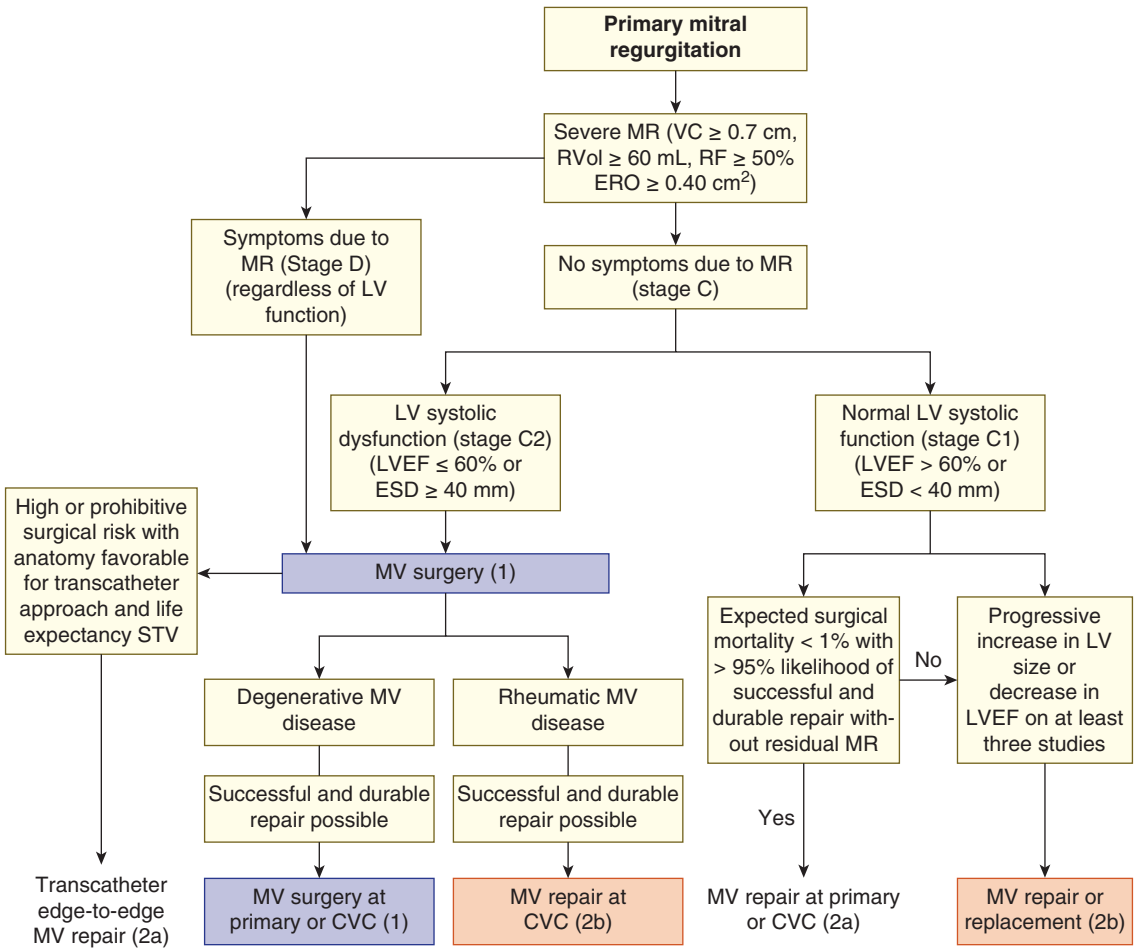
The degree of LV enlargement reflects the severity and chronicity of regurgitation. LV volume overload may

ultimately lead to LV failure and reduced cardiac output. LA enlargement may be considerable in **chronic mitral regurgitation** and a large amount of mitral regurgitation regurgitant volume may be tolerated. Patients with chronic lesions may thus remain asymptomatic for many years. Surgery is necessary when symptoms develop or when there is evidence for LV dysfunction, since progressive and irreversible deterioration of LV function can occur prior to the onset of symptoms. Early surgery is indicated even in asymptomatic patients with a reduced EF (less than 60%) or marked LV dilation with reduced contractility (end-systolic dimension greater than 4.0 cm) (Figure 10–2).

It is a class IIa indication for mitral valve surgery when the LVEF is greater than 60% and the LV end-systolic dimension is still less than 4.0 cm but serial imaging reveals a progressive increase in the LV end-systolic dimension or a serial decrease in the EF. Pulmonary hypertension development suggests the mitral regurgitation is severe and should prompt intervention.

Acute mitral regurgitation may develop abruptly, as with papillary muscle dysfunction following MI, valve perforation in infective endocarditis, in patients with hypertrophic cardiomyopathy (HCM), or when there are ruptured chordae tendineae in patients with mitral valve prolapse. Emergency surgery may be required.

Some patients may become hemodynamically unstable and require treatment with vasodilators or intra-aortic balloon counterpulsation that reduce the amount of retrograde regurgitant flow by lowering systemic vascular resistance and improving forward stroke volume. There is controversy regarding the role of afterload reduction in chronic mitral regurgitation, since the lesion inherently results in a reduction in afterload, and there are no data that chronic afterload reduction is effective in avoiding LV dysfunction or surgical intervention. A heightened sympathetic state has led some experts to suggest that beta-blockade be considered routinely, though this also remains speculative. The mitral regurgitation in patients with



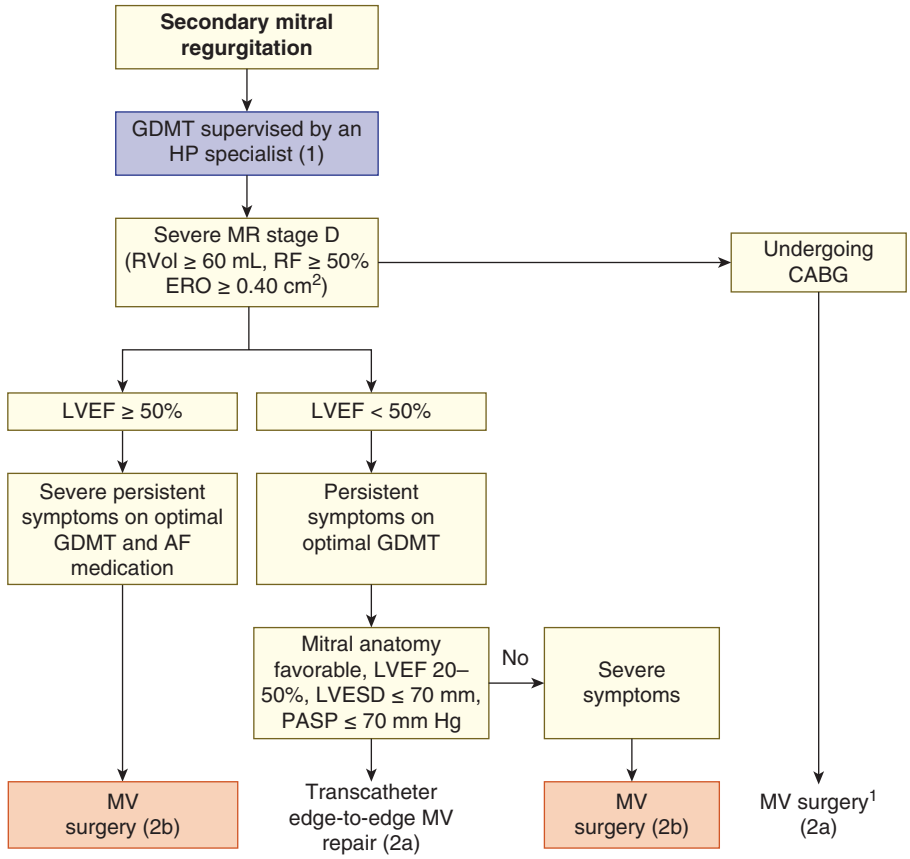
▲ **Figure 10–2.** Algorithm for intervention in primary mitral regurgitation. CVC, comprehensive valve center; ERO, effective regurgitant orifice; ESD, end-systolic dimension; MR, mitral regurgitation; MV, mitral valve; MVR, mitral valve replacement; RF, regurgitant fraction; RVol, regurgitant volume; VC, vena contracta. (Reprinted from Journal of the American College of Cardiology, 77, Otto CM et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, e25–e197, 2021, with permission from Elsevier.)

tachycardia-related cardiomyopathy may improve with normalization of the heart rate.

B. Myocardial Disease and Mitral Regurgitation (Secondary Mitral Regurgitation)

When mitral regurgitation is due to cardiac dysfunction, it may subside as the infarction heals or LV dilation diminishes. The cause of the regurgitation in most of these situations is displacement of the papillary muscles and an enlarged mitral annulus rather than papillary muscle ischemia. The fundamental problem is the lack of leaflet coaptation during systole (due to either leaflet prolapse or retraction). In acute MI, rupture of the papillary muscle may occur with catastrophic results. Transient—but sometimes severe—mitral regurgitation may occur during episodes of myocardial ischemia and contribute to flash pulmonary edema. Patients with dilated cardiomyopathies of any origin may have **secondary mitral regurgitation** due to the papillary muscle displacement or dilation of the mitral annulus, or both. If mitral valve replacement is performed, preservation of the chordae to the native valve helps prevent further ventricular dilation following surgery. Initially, several groups reported good results with mitral valve repair in patients with LVEF less than 30% and secondary mitral regurgitation. Guidelines advise that mitral valve repair/replacement can be attempted in severe mitral regurgitation patients with an EF less than 30% or an LV end-systolic dimension greater than 5.5 cm, or both, as long as repair and preservation of the chordae are possible. Figure 10–3 outlines the recommendations for intervention in secondary mitral regurgitation.

Mitral valve replacement with chordal preservation is preferred over mitral valve repair in patients with chronic ischemic cardiomyopathy. There may also be a role for cardiac resynchronization therapy with biventricular pacemaker insertion, which has been found to reduce mitral regurgitation related to cardiomyopathy in many patients. Guidelines recommend biventricular pacing prior to



[1]Chordal-sparing MV replacement may be reasonable to choose over downsized annuloplasty repair.

▲ **Figure 10–3.** Algorithm for intervention in secondary mitral regurgitation. AF, atrial fibrillation; CABG, coronary artery bypass graft; ERO, effective regurgitant orifice; GDMT, guideline-directed management and therapy; LVESD, LV end-systolic dimension; MR, mitral regurgitation; MV, mitral valve; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume. (Reprinted from Journal of the American College of Cardiology, 77, Otto CM et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, e25–e197, 2021, with permission from Elsevier.)

surgical repair in symptomatic patients who have functional mitral regurgitation as long as other criteria (eg, a QRS of greater than 150 msec or left bundle branch block or both) are present.

There are several ongoing trials of percutaneous approaches to reducing mitral regurgitation. These approaches include the use of a **mitral clip** (MitraClip) device to create a double-orifice mitral valve, various coronary catheter devices to reduce the mitral annular area, and devices to reduce the septal-lateral ventricular size and consequent mitral orifice size. Of these devices, the most success has been noted with the edge-to-edge MitraClip. Guidelines have accepted the use of the MitraClip in patients with secondary mitral regurgitation and high surgical risk. In addition, vascular plugging and occluder devices are being used in selected patients to occlude perivalvular leaks around prosthetic mitral valves. A transcatheter stented valve, which is used as a **transcatheter aortic valve replacement (TAVR)** device, can be used to open a degenerated mitral bioprosthetic valve in any position (aortic, mitral, tricuspid, or pulmonary). Transcatheter valve replacement has also been attempted in small series to repair mitral regurgitation following mitral valve repair with mixed results. Finally, the first cases of a stented mitral valve prosthesis to replace the entire mitral valve have been reported. Abbott has initiated the SUMMIT trial, a US-based pivotal trial utilizing the Tendyne percutaneous mitral valve replacement device. The mitral valve and aortic valve share a common "annulus" and some of the early attempts at percutaneous valve replacement have failed due to obstruction of the aortic outflow.

When to Refer

- All patients with more than mild mitral regurgitation should be referred to a cardiologist for an evaluation.
- Serial examinations and echocardiograms should be obtained and surgical referral made if there is an increase in the LV end-systolic dimensions, a fall in the LVEF to less than 60%, symptoms, evidence for pulmonary hypertension, or the new onset of atrial fibrillation.
- There is evidence that mitral valve repair should be done early in the course of the disease to improve mortality and morbidity.
- Treatment in severe mitral regurgitation in a patient with a dilated cardiomyopathy may be of benefit.

AORTIC STENOSIS

ESSENTIALS OF DIAGNOSIS

- Congenital bicuspid aortic valve (usually asymptomatic until middle or old age).
- "Degenerative" or calcific aortic stenosis; similar risk factors as atherosclerosis
- Visual observation of immobile aortic valve plus a valve area of less than 1.0 cm^2 define severe disease; low-gradient but severe aortic stenosis can thus be recognized when the stroke volume is reduced.
- Echocardiography/Doppler is diagnostic.
- Surgery typically indicated for symptoms. TAVR is approved for patients with calcific aortic stenosis.
- Intervention appropriate even in asymptomatic patients with super-severe aortic stenosis (mean gradient greater than 55 mm Hg) or when undergoing heart surgery for other reasons (eg, coronary artery bypass grafting [CABG]).
- BNP is a marker of early LV myocardial failure, and high levels (three times normal) suggest poor prognosis and can be an indication for intervention.

General Considerations

There are two common clinical scenarios in which aortic stenosis is prevalent. The first is due to a congenitally abnormal **unicuspid** or **bicuspid valve,** rather than tricuspid. Symptoms can occur in young or adolescent individuals if the stenosis is severe, but more often emerge at age 50–65 years when calcification and degeneration of the valve become manifest. A dilated ascending aorta, due to an intrinsic defect in the aortic root media and the hemodynamic effects of the eccentric aortic jet, may accompany the bicuspid valve in about half of these patients. Coarctation of the aorta is also seen in a number of patients with congenital aortic stenosis. Offspring of patients with a bicuspid valve have a much higher incidence of the disease in either the valve, the aorta, or both (up to 30% in some series).

A second, more common pathologic process, **degenerative** or **calcific aortic stenosis**, is thought to be related to calcium deposition due to processes similar to those that occur in atherosclerotic vascular disease. Approximately 25% of patients over age 65 years and 35% of those over age 70 years have echocardiographic evidence of aortic valve thickening (**sclerosis**). About 10–20% of these will progress to hemodynamically significant aortic stenosis over a period of 10–15 years.

Aortic stenosis has become the most common surgical valve lesion in developed countries, and many patients are older adults. The risk factors include hypertension, hypercholesterolemia, and smoking. HCM may also coexist with valvular aortic stenosis.

Clinical Findings

A. Symptoms and Signs

Slightly narrowed, thickened, or roughened valves **(aortic sclerosis)** or aortic dilation may contribute to the typical ejection murmur of aortic stenosis. In mild or moderate cases where the valve is still pliable, an ejection click may precede the murmur and the closure of the valve (S_2) is preserved. The characteristic systolic ejection murmur is heard at the aortic area and is usually transmitted to the neck and apex. In severe aortic stenosis, a palpable LV heave or thrill, a weak to absent aortic second sound, or

reversed splitting of the second sound is present (see Table 10–2). In some cases, only the high-pitched components of the murmur are heard at the apex, and the murmur may sound like mitral regurgitation (the so-called **Gallavardin phenomenon**). When the valve area is less than 0.8–1.0 cm^2 (normal, 3–4 cm^2), ventricular systole becomes prolonged and the typical carotid pulse pattern of delayed upstroke and low amplitude is present. A delayed upstroke, though, is an *unreliable* finding in older patients with extensive arteriosclerotic vascular disease and a stiff, noncompliant aorta. LVH increases progressively due to the pressure overload, eventually resulting in elevation of ventricular end-diastolic pressure. Cardiac output is maintained until the stenosis is severe. LV failure, angina pectoris, or syncope may be presenting symptoms of significant aortic stenosis; importantly, all symptoms tend to first occur with exertion.

B. Redefining Severe Aortic Stenosis

There are four different anatomic syndromes that occur in patients with severe aortic stenosis. The common underlying measure of **severe aortic stenosis** is an aortic valve area of less than 1.0 cm^2 and echocardiographic evidence of an immobile aortic valve. In patients with a normal LVEF and normal cardiac output, the threshold for intervention is a peak aortic gradient of greater than 64 mm Hg and mean aortic gradient of greater than 40 mm Hg. In the same situation, **super-severe aortic stenosis** is defined as a mean gradient of greater than 55 mm Hg or peak aortic velocity greater than 5 m/sec by Doppler.

In some patients with an aortic valve area of less than 1.0 cm^2 with a low cardiac output and stroke volume, the mean gradient may be less than 40 mm Hg. This can occur when the LV systolic function is poor (**low-gradient severe aortic stenosis with low LVEF**) or when the LV systolic function is normal **(paradoxical low-flow severe aortic stenosis with a normal LVEF).** Low flow (low output) in these situations is defined by an echocardiographic stroke volume index of less than 35 mL/min/m^2. Prognosis in patients with low gradient, low valve area, low output, and a normal LVEF aortic stenosis actually may be worse than in patients with the traditional high gradient, low valve area, normal output, and normal LVEF aortic stenosis. If low-flow severe aortic stenosis is present in the face of a low LVEF, provocative testing with dobutamine or nitroprusside is sometimes warranted to increase the stroke volume to discover if a mean aortic valve gradient of at least 40 mm Hg can be demonstrated without increasing the aortic valve area. If the aortic valve area can be made to increase and a mean gradient of greater than 40 mm Hg cannot be demonstrated by inotropic challenge, the presumption is that the low gradient is due to an associated cardiomyopathy and not the aortic valve stenosis. In this latter situation intervention is not indicated. The guidelines acknowledge these four situations (Table 10–4). Intervention is indicated in super-severe aortic stenosis even without demonstrable symptoms (grade C) and in any of the other situations when symptoms are present: D1 defines the symptomatic high-gradient patient; D2 the symptomatic low-flow, low-gradient patient with low LVEF; and D3 the symptomatic low-flow, low-gradient patient with normal LVEF.

Table 10–4. Summary of AHA/ACC guideline definitions of symptomatic severe aortic stenosis.

Category of Severe Aortic Stenosis[1]	Properties
High Gradient	
High gradient	> 4.0 m/sec Doppler jet velocity > 40 mm Hg mean gradient
Super-severe	> 5.0 m/sec Doppler jet velocity > 55 mm Hg mean gradient
Low Gradient	
Low flow	Reduced LVEF (< 50%)
Low flow	Paradoxical with normal LVEF (> 50%)

[1]All categories of severe aortic stenosis have abnormal systolic opening of the aortic valve and an aortic valve area < 1.0 cm^2.

Symptoms of LV failure may be sudden in onset or may progress gradually. Angina pectoris frequently occurs in aortic stenosis due to underperfusion of the endocardium. Of patients with calcific aortic stenosis and angina, half have significant associated CAD. Syncope, a late finding, occurs with exertion as the LV pressure rises, stimulating the LV baroreceptors to cause peripheral vasodilation. This vasodilation results in the need for an increase in stroke volume, which increases the LV systolic pressure again, creating a cycle of vasodilation and stimulation of the baroreceptors that eventually results in a drop in systemic BP, as the stenotic valve prevents further increase in stroke volume. Less commonly, syncope may be due to arrhythmias (usually ventricular tachycardia but sometimes AV block as calcific invasion of the conduction system from the aortic valve may occur).

C. Diagnostic Studies

The ECG reveals LVH or secondary repolarization changes in most patients but can be normal in up to 10%. The CXR may show (1) a normal or enlarged cardiac silhouette, (2) calcification of the aortic valve, and (3) dilation or calcification (or both) of the ascending aorta. The echocardiogram provides useful data about aortic valve calcification and leaflet opening, the severity of LV wall thickness, and overall ventricular function, while Doppler can provide an excellent estimate of the aortic valve gradient. *Valve area estimation by echocardiography is a critical component of the diagnosis of aortic stenosis due to issues such as paradoxical low-flow aortic stenosis (low-gradient, low-flow, normal LVEF patients).* Likewise, the echocardiography/Doppler can estimate the stroke volume index used to define the low-flow state when the valve area is small but the gradient is less than 40 mm Hg. Cardiac catheterization mostly provides an assessment of the hemodynamic consequence of the aortic stenosis, and the anatomy of the coronary arteries. Catheterization data can be important when there is a discrepancy between symptoms and the echocardiography/Doppler information of aortic stenosis severity. In younger

patients and in patients with high aortic gradients, the aortic valve need not be crossed at catheterization. Aortic regurgitation can be semiquantified by aortic root angiography. Either BNP or NT-proBNP may provide additional prognostic data in the setting of poor LV function and aortic stenosis. A BNP greater than 550 pg/mL has been associated with a poor outcome in these patients regardless of the results of dobutamine testing. Guidelines suggest intervention when the NT-proBNP is three times normal (class IIa indication). Stress testing can be done cautiously in patients in whom the aortic stenosis severity does not match the reported symptoms to confirm the reported clinical status. It should *not* be done in patients with super-severe aortic stenosis.

Prognosis & Treatment

Valve intervention is warranted in all patients who have symptomatic severe aortic stenosis (Figure 10–4). There are also times when asymptomatic aortic stenosis should undergo intervention. Asymptomatic patients with severe aortic stenosis (aortic valve area less than 1.0 cm^2) should generally undergo intervention according to the following guidelines: (1) they are undergoing other cardiac surgery (ie, CABG), (2) there is evidence for a reduced LVEF (less than 50%), (3) when the mean gradient exceeds 55 mm Hg (peak velocity greater than 5 m/sec), (4) when there is exercise intolerance or when the BP falls more than 10 mm Hg with exercise, (5) when there is severe valvular calcium,

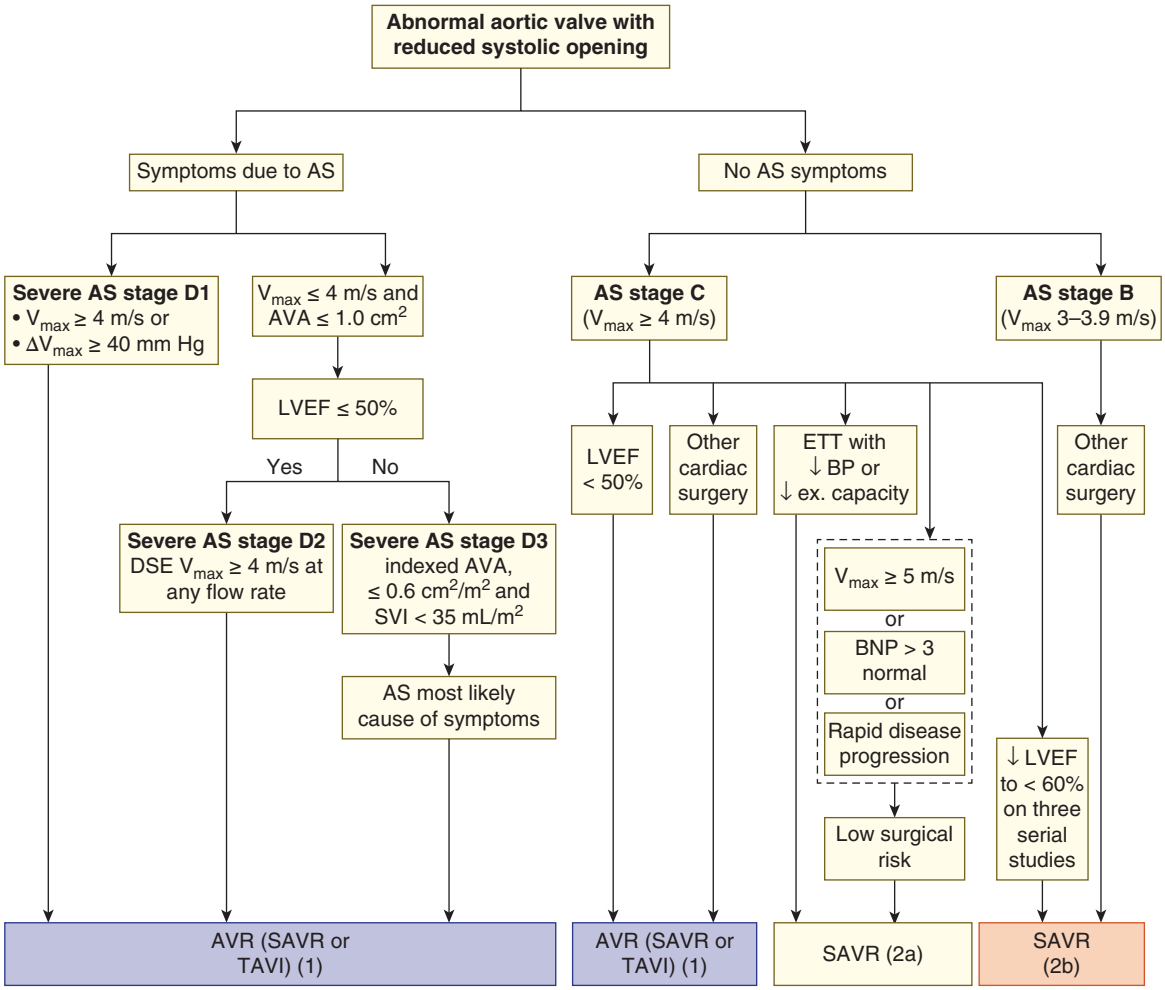


Figure 10–4. Algorithm for the timing of intervention in aortic valve stenosis. AS, aortic stenosis; AVA, aortic valve area; AVAi, aortic valve area index; AVR, aortic valve replacement; BP, blood pressure; DSE, dobutamine stress echocardiography; ETT, exercise treadmill test; ΔP_{mean}, mean systolic pressure gradient between LV and aorta; SAVR, surgical aortic valve replacement; SVI, stroke volume index; TAVI, transcatheter aortic valve implantation; TAVR, transcatheter aortic valve replacement; V_{max}, maximum velocity. (Reprinted from Journal of the American College of Cardiology, 77, Otto CM et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, e25–e197, 2021, with permission from Elsevier.)

(6) when there is evidence of a rapid increase in the peak aortic gradient (more than 0.3 m/sec/year), (7) when there has been a progressive decrease in the LVEF, or (8) when the NT-proBNP is three times normal. Following the onset of HF, angina, or syncope, the prognosis without surgery is poor (50% 3-year mortality rate). Medical treatment may stabilize patients in HF, but intervention is indicated for all symptomatic patients with evidence of significant aortic stenosis.

The surgical mortality rate for valve replacement is low, even in older adults, and ranges from 2% to 5%. This low risk is due to the dramatic hemodynamic improvement that occurs with relief of the increased afterload. Mortality rates are substantially higher when there is an associated ischemic cardiomyopathy. Severe coronary lesions are usually bypassed at the same time as aortic valve replacement (AVR), although there are few data to suggest this practice affects outcome. In some cases, a staged procedure with stenting of the coronaries prior to surgery may be considered, especially if a percutaneous AVR approach is being considered. Around one-third to one-half of all patients with aortic stenosis have significant CAD, so this is a common concern. With the success of **TAVR** or **transcatheter aortic valve implantation (TAVI),** the treatment options have greatly expanded for many patients with severe aortic stenosis. For this reason, a **Heart Valve Team** approach bringing together invasive and noninvasive cardiologists, radiologists, anesthesiologists, and cardiac surgeons is mandatory; clinical factors (such as frailty) and anatomic features (such as a calcified aorta, vascular access, etc) can affect the decision making.

Medical therapy to reduce the progression of disease has *not* been effective to date. Statins have been assessed in four major clinical trials. None revealed any benefit on the progression of aortic stenosis or on clinical outcomes despite the association of aortic stenosis with atherosclerosis. If patients with aortic stenosis have concomitant CAD, the guidelines for the use of statins should be followed. Efforts to reduce stenosis progression by blockage of the renin-angiotensin system have also been ineffective, although they are recommended for patients who have undergone TAVR. Control of systemic hypertension is an important adjunct, and inadequate systemic BP control is all too common due to unreasonable concerns about providing too much afterload reduction in patients with aortic stenosis. Normal systemic BP is important to maintain as the LV is affected by the total afterload (systemic BP plus the aortic valve gradient).

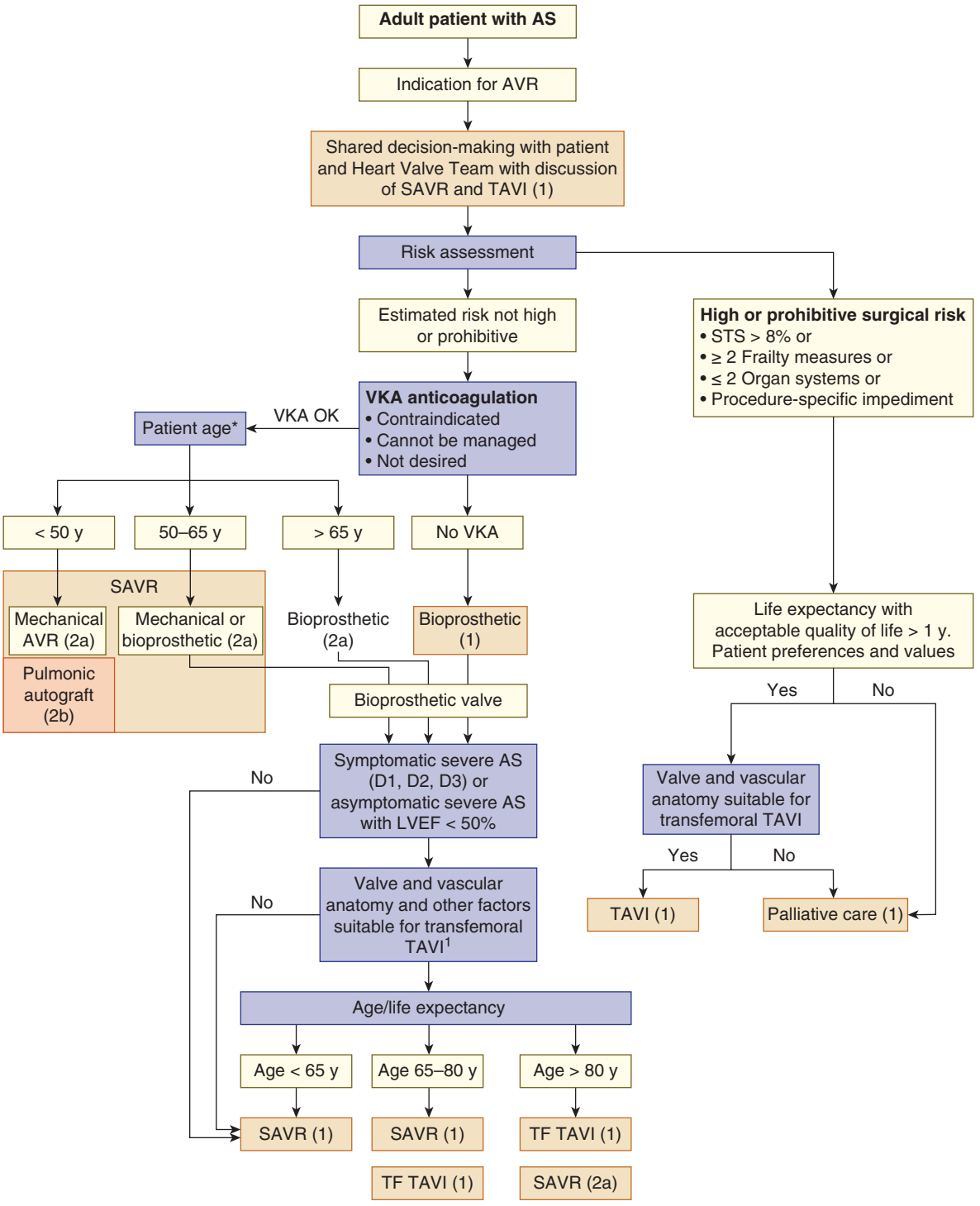
The interventional options in patients with aortic valve stenosis has expanded with the use of TAVR and depend on the patient's lifestyle and age. The algorithm to decide when an AVR is appropriate in various situations is outlined in Figure 10–5.

TAVR has been shown to be equivalent to surgical AVR (SAVR) in all the randomized trials of symptomatic patients, including those at low risk for surgery (less than 4%). Surgery is recommended for patients younger than 65 years or with a life expectancy of more than 20 years. TAVR is recommended for all patients older than 80 years. Either SAVR or TAVR can be considered for all patients between 65 and 80 years. The decision about whether to perform SAVR or TAVR should be made by the Heart Team; anatomic issues (such as an enlarged aorta, a coronary that might be trapped by a leaflet when the valve is inserted, an annulus too large or too small, extensive LV outflow tract calcium, etc) are often the deciding factors for whether TAVR can be done.

In young and adolescent patients, percutaneous balloon valvuloplasty still has a very small role. Balloon valvuloplasty is associated with early restenosis in older adults and, thus, is rarely used except as a temporizing measure prior to a more permanent SAVR or TAVR. Data suggest aortic balloon valvuloplasty in older adults has an advantage only in those with preserved LV function, and such patients are usually excellent candidates for SAVR or TAVR.

The **Ross procedure** is generally still considered a viable option in younger patients with a bicuspid valve, and it is performed by moving the patient's own pulmonary valve and a portion of its root to the aortic position and replacing the pulmonary valve with a homograft (or rarely a bioprosthetic valve). The coronaries require reimplantation. However, dilation of the pulmonary valve autograft and consequent aortic regurgitation, plus early stenosis of the pulmonary homograft in the pulmonary position, has reduced the enthusiasm for this approach in most institutions. Guidelines suggest the Ross procedure should only be considered in those younger than 50 years. Middle-aged and younger adults generally can tolerate the anticoagulation therapy necessary for the use of mechanical aortic valves, so patients younger than 50 years generally undergo AVR with a bileaflet mechanical valve. If the aortic root is severely dilated as well (greater than 4.5 cm), then the valve may be housed in a Dacron sheath (**Bentall procedure**) and the root replaced along with the aortic valve. Alternatively, a human homograft root and valve replacement can be used. In patients older than 50 years, bioprosthetic (either porcine or bovine pericardial) valves with a life expectancy of about 10–15 years are routinely used instead of mechanical valves to avoid need for anticoagulation. Data favor the bovine pericardial valve over the porcine aortic valve. Bioprosthetic valve degeneration in the larger valves can be potentially repaired by percutaneous valve-in-valve TAVR. If the aortic annulus is small, a bioprosthetic valve with a short sheath can be sewn to the aortic wall (the stentless AVR) rather than sewing the prosthetic annulus to the aortic annulus. ("Annulus" is a relative term when speaking of the aortic valve, since there is no true annulus.) Another popular surgical option when the aorta is enlarged is the use of the **Wheat procedure;** it involves aortic root replacement above the coronary arteries and replacement of the aortic valve below the coronary arteries. The coronary arteries thus remain attached to the native aorta between the new graft and prosthetic valve rather than being reimplanted onto an artificial sheath or homograft. Newer aortic valve replacements can be placed quickly through a small incision and often require only three stitches to anchor (ie, the **Perceval** or **Intuity valve replacements**). These can shorten pump times at surgery.

In patients with a bicuspid aortic valve, there is an associated ascending aortic aneurysm in about half. If the



▲ **Figure 10–5.** Algorithm for the type of valvular intervention in aortic valve stenosis. AS, aortic stenosis; AVR, aortic valve replacement; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation; TF, transfemoral; VKA, vitamin K antagonist. (Reprinted from Journal of the American College of Cardiology, 77, Otto CM et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, e25–e197, 2021, with permission from Elsevier.)

maximal dimension of the aortic root is greater than 5.5 cm, it is recommended to proceed with root replacement regardless of the severity of the aortic valve disease. It is also appropriate to intervene when the maximal aortic root size is greater than 5.0 cm in diameter if there is a family history of aortic dissection or the aortic root size increases by more than 0.5 cm in 1 year. The aortic valve may be replaced at the same time if at least moderate aortic stenosis is present or may be either left alone or repaired (valve sparing operation). If there is an indication for AVR and the root is greater than 4.5 cm in diameter, root replacement is also recommended at the time of SAVR.

The use of mechanical versus bioprosthetic AVR has changed over time. A bioprosthetic valve is acceptable for patients at any age for whom anticoagulant therapy is contraindicated, not desired, or cannot be managed, and is preferred in patients over the age of 65. An aortic mechanical valve should be used in patients younger than 50 years of age who can take warfarin. Shared decision making is key especially for patients 50–65 years old. **Anticoagulation** with warfarin is required with the use of mechanical aortic valves, and the INR should be maintained between 2.0 and 3.0 for bileaflet valves. In general, mechanical aortic valves are less subject to thrombosis than mechanical mitral valves and do *not* require bridging with enoxaparin unless there are other thromboembolic risk factors or it is an older generation AVR. Low-dose aspirin (eg, 81 mg daily) is recommended if there is a low bleeding risk. Some newer bileaflet mechanical valves (On-X) allow for a lower INR range from 1.5 to 2.0. Clopidogrel is recommended for the first 6 months after TAVR in combination with lifelong low-dose aspirin therapy (**dual antiplatelet therapy**). DOACs are *not* recommended for any mechanical valves but may be used in patients with a bioprosthetic AVR if treating atrial fibrillation or venous thrombosis.

The use of TAVR has grown dramatically. The Edwards SAPIEN valve is a balloon-expandable valvular stent, while the CoreValve is a valvular stent that self-expands when pushed out of the catheter sheath. Five-year outcome data comparing SAVR with TAVR show no difference in death or stroke at five years with lower rates of atrial fibrillation and shorter length of procedure stay observed in patients undergoing TAVR. Cost remains a major issue. The cost of TAVR is similar to SAVR, mostly due to the cost of the valve itself. All of the professional societies stress the importance of a Heart Valve Team when considering aortic stenosis intervention.

TAVR is also being used more frequently in **"valve-in-valve" procedures** to reduce the gradient with bioprosthetic valve dysfunction in patients at high risk of repeat cardiac surgical valve replacement (regardless of whether in the aortic, mitral, tricuspid, or pulmonary position). While the results of TAVR in patients with bicuspid aortic valves (as opposed to tricuspid) have been less impressive, newer modifications have improved the success rates in these anatomic situations as well. This is supported by data from the TVT registry showing similar procedural and 1-year outcomes for patients with bicuspid or tricuspid aortic valve stenosis.

When to Refer

- All patients with echocardiographic evidence for mild to moderate aortic stenosis (estimated peak valve gradient greater than 30 mm Hg by echocardiography/Doppler) should be referred to a cardiologist for evaluation and to determine the frequency of follow-up.
- Any patients with symptoms suggestive of aortic stenosis (ie, exertional symptoms of chest pressure, shortness of breath, or presyncope) should be seen by a cardiologist.

Halim SA et al. Outcomes of transcatheter aortic valve replacement in patients with bicuspid aortic valve disease: a report from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. Circulation. 2020;141:1071. [PMID: 32098500]

Mack MJ et al; PARTNER 3 Investigators. Transcatheter aortic-valve replacement in low-risk patients at five years. N Engl J Med. 2023;389:1949. [PMID: 37874020]

AORTIC REGURGITATION

ESSENTIALS OF DIAGNOSIS

- Usually asymptomatic until middle age; presents with left-sided failure or rarely chest pain.
- Echocardiography/Doppler is diagnostic.
- Surgery for symptoms, EF less than 50%, LV end-systolic dimension greater than 50 mm, or LV end-diastolic dimension greater than 65 mm.

General Considerations

Of all patients with isolated aortic valve disease, about 13% have predominately aortic regurgitation. Rheumatic aortic regurgitation has become much less common than in the preantibiotic era, and nonrheumatic causes now predominate. These include congenitally bicuspid valves, infective endocarditis, and hypertension. Many patients also have aortic regurgitation secondary to aortic root diseases, such as that associated with Marfan syndrome or aortic dissection. Rarely, inflammatory diseases, such as ankylosing spondylitis, may be implicated.

Clinical Findings

A. Symptoms and Signs

The clinical presentation is determined by the rapidity with which regurgitation develops. In **chronic aortic regurgitation,** the only sign for many years may be a soft aortic diastolic murmur. As the severity of the aortic regurgitation increases, diastolic BP falls, and the LV progressively enlarges. Most patients remain asymptomatic for long periods even at this point. LV failure is a late event and may be sudden in onset. Exertional dyspnea and fatigue are the most frequent symptoms, but paroxysmal nocturnal dyspnea and pulmonary edema may also occur. Angina pectoris

or atypical chest pain may occasionally be present. Associated CAD and presyncope or syncope are less common than in aortic stenosis.

Hemodynamically, because of compensatory LV dilation, patients eject a large stroke volume, which is adequate to maintain forward cardiac output until late in the course of the disease. LV diastolic pressure may rise when HF occurs. Abnormal LV systolic function as manifested by reduced EF (less than 50%) and increasing end-systolic LV volume (greater than 5.0 cm) are signs that surgical intervention is warranted.

The major physical findings in chronic aortic regurgitation relate to the high stroke volume being ejected into the systemic vascular system with rapid runoff as the regurgitation takes place (see Table 10–2). This results in a **wide arterial pulse pressure.** The pulse has a rapid rise and fall (**water-hammer pulse** or **Corrigan pulse**), with an elevated systolic and low diastolic pressure. The large stroke volume and flow back into the heart are also responsible for characteristic findings, such as **Quincke pulses** (nailbed capillary pulsations), **Duroziez sign** (to-and-fro murmur over a partially compressed femoral peripheral artery), and **Musset sign** (head bob with each pulse). In younger patients, the increased stroke volume may summate with the pressure wave reflected from the periphery and create a higher than expected systolic pressure in the lower extremities compared with the central aorta. Since the peripheral bed is much larger in the leg than the arm, the BP in the leg may be over 40 mm Hg higher than in the arm (**Hill sign**) in severe aortic regurgitation. The apical impulse is prominent, laterally displaced, usually hyperdynamic, and may be sustained. A systolic flow murmur is usually present and may be quite soft and localized; the aortic diastolic murmur is usually high-pitched and decrescendo. A mid or late diastolic low-pitched mitral murmur (**Austin Flint murmur**) may be heard in advanced aortic regurgitation, owing to relative obstruction of mitral inflow produced by partial closure of the mitral valve by the rapidly rising LV diastolic pressure due to the aortic regurgitation.

In **acute aortic regurgitation** (usually from aortic dissection or infective endocarditis), LV failure is manifested primarily as pulmonary edema and may develop rapidly; surgery is urgently required in such cases. Patients with acute aortic regurgitation do not have the dilated LV of chronic aortic regurgitation and the extra LV volume is handled poorly. For the same reason, the diastolic murmur is shorter, may be minimal in intensity, and the pulse pressure may not be widened—making clinical diagnosis difficult. The mitral valve may close prematurely even before LV systole has been initiated (**preclosure**) due to the rapid rise in the LV diastolic pressure, and the first heart sound is thus diminished or inaudible. Preclosure of the mitral valve can be readily detected on echocardiography and is considered an indication for urgent surgical intervention.

B. Diagnostic Studies

The ECG usually shows moderate to severe LVH. Radiographs show cardiomegaly with LV prominence and sometimes a dilated aorta.

Echocardiography demonstrates the major diagnostic features, including whether the lesion includes the proximal aortic root and what valvular pathology is present. *Annual assessments of LV size and function are critical in determining the timing for valve replacement when the aortic regurgitation is severe.* The 2020 ACC/AHA valvular guideline provides criteria for assessing the severity of aortic regurgitation. Cardiac MRI and CT can estimate aortic root size, particularly when there is concern for an ascending aneurysm. MRI can provide a regurgitant fraction to help confirm severity. Cardiac catheterization may be unnecessary in younger patients, particularly those with acute aortic regurgitation, but can help define hemodynamics, aortic root abnormalities, and associated CAD preoperatively in older patients. Increasing data are emerging that serum BNP or NT-proBNP may be an early sign of LV dysfunction, and it is possible that these data will be added to recommendations for surgical intervention in the future.

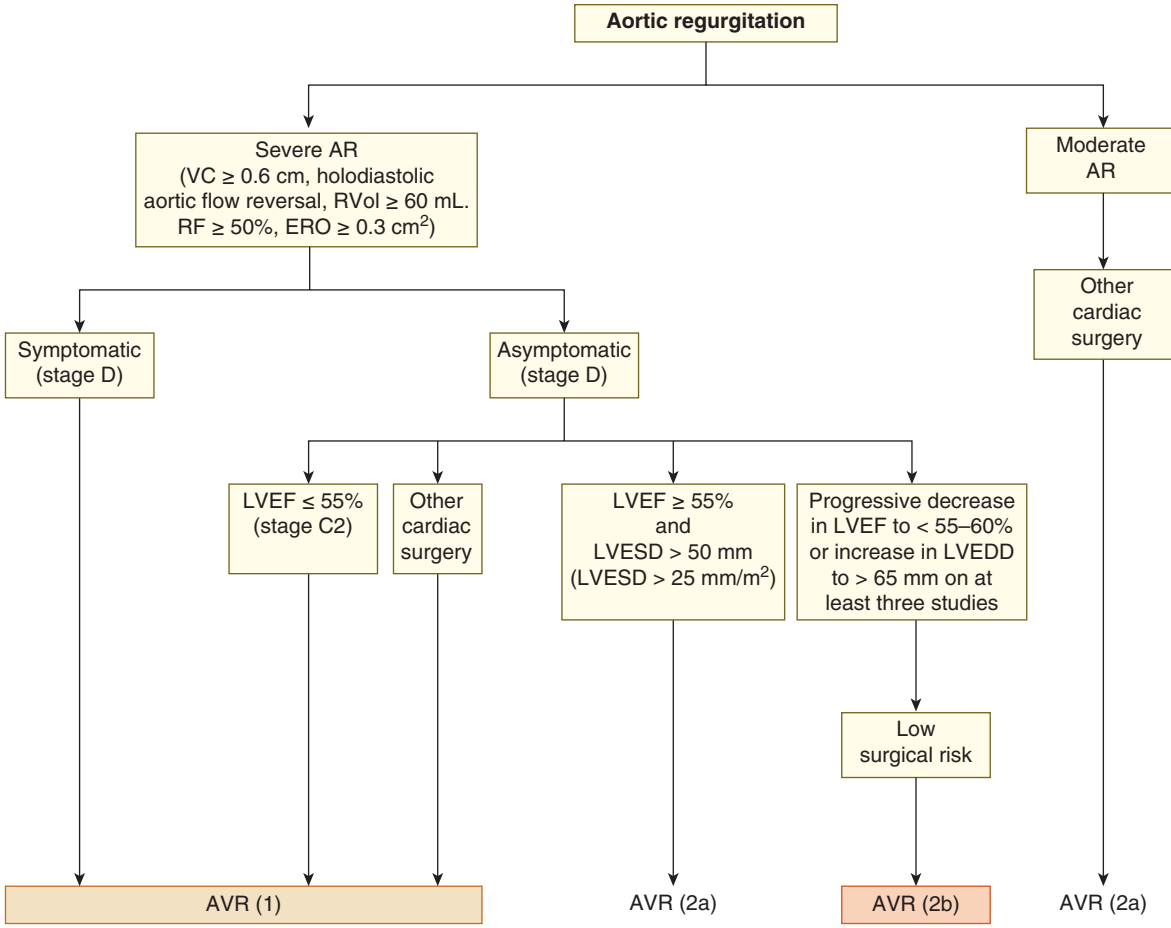
Treatment & Prognosis

Aortic regurgitation that appears or worsens during or after an episode of infective endocarditis or aortic dissection may lead to acute severe LV failure or subacute progression over weeks or months. The former usually presents as pulmonary edema; surgical replacement of the valve is indicated even during active infection. These patients may be transiently improved or stabilized by vasodilators.

Chronic aortic regurgitation may be tolerated for many years, but the prognosis without surgery becomes poor when symptoms occur. Since aortic regurgitation places both a preload (volume) and afterload increase on the LV, medications that decrease afterload can reduce regurgitation severity, although there are no convincing data that afterload reduction alters mortality. *Recommendations advocate afterload reduction in aortic regurgitation only when there is associated systolic hypertension (systolic BP greater than 140 mm Hg).* Afterload reduction in normotensive patients does not appear warranted. ARBs, rather than beta-blockers, are the preferred additions to the medical therapy in patients with an enlarged aorta, such as in Marfan syndrome, because of the theoretical ability of an ARB to reduce aortic stiffness (by blocking TGF-beta) and to slow the rate of aortic dilation. However, clinical trials evaluating the efficacy of ARBs to reduce aortic stiffness and slow the rate of aortic dilation have not yielded a positive outcome to support their use.

Surgery is indicated once symptoms emerge or for any evidence of LV dysfunction (as exhibited by a reduction in the LVEF to less than 55% or increase in the LV end-systolic diameter to greater than 50 mm by echocardiography). In addition, it is suggested that surgery should be considered even when the LV becomes excessively enlarged (LV end-diastolic diameter greater than 65 mm). Guidelines also suggest it be considered (class IIb) if serial imaging reveals a progressive increase in the size of the LV (Figure 10–6).

The issues with AVR covered in the above section concerning aortic stenosis pertain here. Early trials of TAVR had a high incidence of postprocedural residual aortic regurgitation (18.8% in one trial). Newer TAVR valves have



▲ **Figure 10–6.** Algorithm for intervention in aortic regurgitation. AR, aortic regurgitation; AVR, aortic valve replacement; EDD, end-diastolic dimension; ERO, effective regurgitant orifice; LVESD, LV end-systolic dimension; RF, regurgitant fraction; RVol, regurgitant volume; VC, vena contracta. (Reprinted from Journal of the American College of Cardiology, 77, Otto CM et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, e25-e197, 2021, with permission from Elsevier.)

greatly reduced residual aortic regurgitation when used in patients with pure native aortic regurgitation (4.2%). In multivariable analysis, postprocedural at least moderate aortic regurgitation was independently associated with 1-year all-cause mortality. Compared with the early-generation devices, TAVR using the new-generation devices was associated with improved procedural outcomes in treating patients with pure native aortic regurgitation. In patients with pure native aortic regurgitation, significant postprocedural aortic regurgitation was independently associated with increased mortality.

Aortic regurgitation due to a paravalvular prosthetic valve defect can occasionally be occluded with percutaneous occluder devices. *The choice of prosthetic valve for AVR depends on the patient's age and compatibility with warfarin anticoagulation similar to the choices for AVR in aortic stenosis.*

The operative mortality for AVR is usually in the 3–5% range. Aortic regurgitation due to aortic root disease requires repair or replacement of the root as well as surgical treatment of the aortic valve. Although valve-sparing operations have improved recently, most patients with root replacement undergo valve replacement at the same time. Root replacement in association with valve replacement may require anastomosis of the coronary arteries, and thus the procedure is more complex than valve replacement alone. The **Wheat procedure** replaces the aortic root but spares the area where the coronaries attach to avoid the necessity for their reimplantation. Following any aortic valve surgery, LV size usually decreases and LV function generally improves even when the baseline EF is depressed.

Repair of the aortic root in patients with a bicuspid valve should be done once the root diameter exceeds 5.5 cm regardless of aortic valve disease severity. There are data that dissection is much more prevalent when the aortic root diameter exceeds 6.0 cm, and the general sense is not to let it approach that size. Patients with risk factors (family history of dissection or an increase in the diameter of the

root greater than 0.5 cm in 1 year) should have the aorta repaired when the maximal dimension exceeds 5.0 cm. The following classifications summarize when to operate on the aortic root in patients with a bicuspid aortic valve based on the guidelines:

Class I indication (LOE C): aortic root diameter at sinuses or ascending aorta greater than 5.5 cm (regardless of need for AVR).

Class IIa indication (LOE C): aortic root diameter at sinuses or ascending aorta greater than 5.0 cm when there are associated risk factors (family history of dissection or increase in size more than 0.5 cm in 1 year).

Class IIa indication (LOE C): aortic root diameter greater than 4.5 cm if patient undergoing AVR for valvular reasons.

When to Refer

- Patients with audible aortic regurgitation should be seen, at least initially, by a cardiologist who can determine whether the patient needs follow-up.
- Patients with a dilated aortic root should be monitored by a cardiologist, since imaging studies other than the CXR or echocardiogram may be required to decide surgical timing.

TRICUSPID STENOSIS

ESSENTIALS OF DIAGNOSIS

- Female predominance.
- History of rheumatic heart disease most likely. Carcinoid disease and prosthetic valve degeneration are the most common etiologies in the United States.
- Echocardiography/Doppler is diagnostic.

General Considerations

Tricuspid stenosis is rare, affecting less than 1% of the population in developed countries and less than 3% worldwide. Native valve tricuspid valve stenosis is usually rheumatic in origin. In the United States, tricuspid stenosis is more commonly due to prior tricuspid valve repair or replacement or to the carcinoid syndrome. The incidence of tricuspid stenosis after tricuspid valve replacement increases considerably after 8 years post surgery. Tricuspid regurgitation frequently accompanies the lesion. It should be suspected when right HF appears in the course of mitral valve disease or in the postoperative period after tricuspid valve repair or replacement.

Clinical Findings

A. Symptoms and Signs

Tricuspid stenosis is characterized by right HF with hepatomegaly, ascites, and dependent edema. In sinus rhythm, a giant *a* wave is seen in the JVP, which is also elevated (see Table 10–2). The typical **diastolic rumble** along the lower left sternal border mimics mitral stenosis, though in tricuspid stenosis the rumble *increases with inspiration*. In sinus rhythm, a presystolic liver pulsation may be found. It should be considered when patients exhibit signs of carcinoid syndrome.

B. Diagnostic Studies

In the absence of atrial fibrillation, the ECG reveals RA enlargement. The CXR may show marked cardiomegaly with a normal PA size. A dilated superior vena cava and azygous vein may be evident.

The normal valve area of the tricuspid valve is 10 cm^2, so significant stenosis must be present to produce a gradient. Hemodynamically, a mean diastolic pressure gradient greater than 5 mm Hg is considered significant, although even a 2 mm Hg gradient can be considered abnormal. This can be demonstrated by echocardiography or cardiac catheterization. The 2017 update of the 2014 AHA/ACC guidelines suggests a tricuspid valve area of less than 1.0 cm^2 and a pressure half-time longer than 190 msec should be defined as significant because the gradient may vary depending on the heart rate.

Treatment & Prognosis

Tricuspid stenosis may be progressive, eventually causing severe right-sided HF. Initial therapy is directed at reducing the fluid congestion, with diuretics the mainstay (see Treatment, Heart Failure). When there is considerable bowel edema, torsemide or bumetanide may have an advantage over other loop diuretics, such as furosemide, because they are better absorbed from the gut. Aldosterone inhibitors also help, particularly if there is liver engorgement or ascites. Neither surgical nor percutaneous valvuloplasty is particularly effective for relief of tricuspid stenosis, as residual tricuspid regurgitation is common. Tricuspid valve replacement is the preferred surgical approach. Mechanical tricuspid valve replacement is rarely done because the low flow predisposes to thrombosis and because the mechanical valve cannot be crossed should the need arise for right heart catheterization or pacemaker implantation. Therefore, *bioprosthetic valves are almost always preferred.* Often tricuspid valve replacement is performed in conjunction with mitral valve replacement for rheumatic mitral stenosis or regurgitation. Percutaneous transcatheter valve replacement (stented valve) has been used in degenerative tricuspid prosthetic valve stenosis and a percutaneous tricuspid valve replacement device is being investigated. The indications for valve replacement in severe tricuspid stenosis are straightforward:

Class I indication (LOE C): at time of operation for left-sided valve disease.

Class I indication (LOE C): if symptomatic.

Class IIb indication (LOE C): rarely percutaneous balloon commissurotomy for isolated tricuspid stenosis in high-risk patients with no significant tricuspid regurgitation.

When to Refer

All patients with any evidence for tricuspid stenosis on an echocardiogram should be seen and monitored by a cardiologist to assess when intervention may be required.

TRICUSPID REGURGITATION

ESSENTIALS OF DIAGNOSIS

- Frequently occurs in patients with pulmonary or cardiac disease with pressure or volume overload on the RV.
- Tricuspid valve regurgitation from pacemaker lead placement is becoming more common.
- Echocardiography useful in determining cause (low- or high-pressure tricuspid regurgitation).

General Considerations

Tricuspid valvular regurgitation often occurs whenever there is RV dilation from any cause. As tricuspid regurgitation increases, the RV size increases further pulling the valve open due to chordal and papillary muscle displacement. This, in turn, worsens the severity of the tricuspid regurgitation. In addition, the tricuspid annulus is shaped like a horse's saddle. With RV failure, the annulus flattens and becomes elliptical, further distorting the relationship between the leaflets and chordal attachments. In most cases, the cause of the tricuspid regurgitation is the RV geometry (functional) and not primary tricuspid valve disease. An enlarged, dilated RV may be present if there is RV systolic hypertension from valvular or subvalvular pulmonary valve stenosis, pulmonary hypertension for any reason, in severe pulmonary valve regurgitation, or in cardiomyopathy. The RV may also be injured from an MI or may be inherently dilated due to infiltrative diseases (RV dysplasia or sarcoidosis). RV dilation often occurs secondary to left HF. Inherent abnormalities of the tricuspid valve include **Ebstein anomaly** (displacement of the septal and posterior, but not the anterior, leaflets into the RV), tricuspid valve prolapse, carcinoid plaque formation, collagen disease inflammation, valvular tumors, or tricuspid endocarditis. In addition, pacemaker lead valvular injury is an increasingly frequent iatrogenic cause.

Clinical Findings

A. Symptoms and Signs

The symptoms and signs of tricuspid regurgitation are identical to those resulting from RV failure due to any cause. As a generality, the diagnosis can be made by careful inspection of the JVP. The JVP waveform should decline during ventricular systole (the *x* descent). The timing of this decline can be observed by palpating the opposite carotid artery. As tricuspid regurgitation worsens, more and more of this *x* descent valley in the JVP is filled with the regurgitant wave until all of the *x* descent is obliterated and a positive systolic waveform will be noted in the JVP. An associated tricuspid regurgitation murmur may or may not be audible and can be distinguished from mitral regurgitation by the left parasternal location and an increase with inspiration (**Carvallo sign**). An S_3 may accompany the murmur and is related to the high flow returning to the RV from the RA. Cyanosis may be present if the increased RA pressure stretches the atrial septum and opens a PFO or there is a true ASD (eg, in about 50% of patients with Ebstein anomaly). Severe tricuspid regurgitation results in hepatomegaly, edema, and ascites.

B. Diagnostic Studies

The ECG is usually nonspecific, though atrial flutter or atrial fibrillation is common. The CXR may reveal evidence of an enlarged RA or dilated azygous vein and pleural effusion. The echocardiogram helps assess severity of tricuspid regurgitation (criteria available in the 2014 AHA/ACC valvular heart disease guidelines). In addition, echocardiography/Doppler provides RV systolic pressure as well as RV size and function. A paradoxically moving interventricular septum may be present due to the volume overload on the RV. Catheterization confirms the presence of the regurgitant wave in the RA and elevated RA pressures. If the PA or RV systolic pressure is less than 40 mm Hg, primary valvular tricuspid regurgitation should be suspected. In addition, in patients with severe tricuspid regurgitation and ascites, a hepatic wedge pressure can be performed at the time of the right heart catheterization. If there is a high gradient between the mean RA pressure and mean hepatic wedge, then cirrhosis is likely present. Normally, the gradient across the liver is less than 5 mm Hg. Mild cirrhosis is suspected if gradient is 5–10 mm Hg, moderate disease if 10–15 mm Hg, and significant cirrhosis if greater than 15 mm Hg.

Treatment & Prognosis

Mild tricuspid regurgitation is common and generally can be well managed with diuretics. When severe tricuspid regurgitation is present, bowel edema may reduce the effectiveness of diuretics, such as furosemide, and intravenous diuretics should be used initially. Torsemide or bumetanide is better absorbed in this situation when oral diuretics are added. Aldosterone antagonists have a role as well, particularly if ascites is present. At times, the efficacy of loop diuretics can be enhanced by adding a thiazide diuretic (see Treatment, Heart Failure).

Since most tricuspid regurgitation is secondary, definitive treatment usually requires elimination of the cause of the RV dysfunction. Surgical valve replacement in secondary (functional) tricuspid regurgitation is rarely if ever indicated until the cause of the RV dysfunction is resolved. If the problem is left heart disease, then treatment of the left heart issues may lower pulmonary pressures, reduce RV size, and resolve the tricuspid regurgitation. Treatment for primary and secondary causes of pulmonary hypertension will generally reduce the tricuspid regurgitation. Guidelines suggest that tricuspid valve surgery may be

considered when the tricuspid annular dilation at end-diastole exceeds 4.0 cm and the patient is symptomatic. It is a class I recommendation that tricuspid annuloplasty be performed when significant tricuspid regurgitation is present and mitral valve replacement or repair is being performed for mitral regurgitation. Annuloplasty without insertion of a prosthetic ring (**DeVega annuloplasty**) may also be effective in reducing the tricuspid annular dilation. The valve leaflet itself can occasionally be primarily repaired in tricuspid valve endocarditis. If there is an inherent defect in the tricuspid valve apparatus that cannot be repaired, then replacement of the tricuspid valve is warranted. A bioprosthetic valve rather than a mechanical valve, is almost always used because the risk of mechanical valve thrombosis is increased if the INR is not stable. Anticoagulation is *not* required for bioprosthetic valves unless there is associated atrial fibrillation or flutter. Tricuspid regurgitation due to bioprosthetic degeneration has been shown to respond to transcatheter valve replacement. There are early reports of percutaneous tricuspid valve replacement for native valve tricuspid regurgitation being successful. Furthermore, the concept of transcatheter edge-to-edge repair, as is commonly utilized to treat mitral valve regurgitation, was recently shown to be safe and effective at reducing the degree of tricuspid regurgitation and improving quality of life in patients with severe functional tricuspid regurgitation randomized to treatment with the TriClip device versus medical therapy.

When to Refer

- Anyone with moderate or severe tricuspid regurgitation should be seen at least once by a cardiologist to determine whether studies and intervention are needed.
- Severe tricuspid regurgitation requires regular follow-up by a cardiologist.

Sorajja P et al; TRILUMINATE Pivotal Investigators. Transcatheter repair for patients with tricuspid regurgitation. N Engl J Med. 2023;388:1833. [PMID: 36876753]

PULMONARY VALVE REGURGITATION

ESSENTIALS OF DIAGNOSIS

- Most cases are due to pulmonary hypertension resulting in high-pressure pulmonary valve regurgitation.
- Echocardiogram is definitive in high-pressure but may be less definitive in low-pressure pulmonary valve regurgitation.

General Considerations

Pulmonary valve regurgitation can be divided into **high-pressure causes** (due to pulmonary hypertension) and **low-pressure causes** (usually due to a dilated pulmonary annulus, a congenitally abnormal [bicuspid or dysplastic] pulmonary valve, plaque from carcinoid disease, surgical pulmonary valve replacement, or the residual physiology following a surgical transannular patch used to reduce the outflow gradient in tetralogy of Fallot). Because the RV tolerates a volume load better than a pressure load, it tends to tolerate low-pressure pulmonary valve regurgitation for long periods of time without dysfunction.

Clinical Findings

Most patients are asymptomatic. Those with marked pulmonary valve regurgitation may exhibit symptoms of right heart volume overload. On examination, a hyperdynamic RV can usually be palpated (**RV lift**). If the PA is enlarged, it also may be palpated along the left sternal border. P_2 will be palpable in pulmonary hypertension and both systolic and diastolic thrills are occasionally noted. On auscultation, the second heart sound may be widely split due to prolonged RV systole or an associated right bundle branch block. A pulmonary valve systolic click may be noted as well as a right-sided gallop. If pulmonic stenosis is also present, the ejection click may decline with inspiration, while any associated systolic pulmonary murmur will increase. In high-pressure pulmonary valve regurgitation, the pulmonary diastolic (**Graham Steell**) murmur is readily audible. It is often contributed to by a dilated pulmonary annulus. The murmur increases with inspiration and diminishes with the Valsalva maneuver. In low-pressure pulmonary valve regurgitation, the PA diastolic pressure may be only a few mm Hg higher than the RV diastolic pressure, and there is little diastolic gradient to produce a murmur or characteristic echocardiography/Doppler findings. At times, only contrast angiography or MRI of the main PA will show the free-flowing pulmonary valve regurgitation in low-pressure pulmonary valve regurgitation. This situation is common in patients following repair of tetralogy of Fallot where, despite little murmur, there may effectively be no pulmonary valve present. This can be suspected by noting an enlarging RV.

The ECG is generally of little value, although right bundle branch block is common, and there may be ECG criteria for RVH. The CXR may show only the enlarged RV and PA. Echocardiography may demonstrate evidence of RV volume overload (paradoxical septal motion and an enlarged RV), and Doppler can determine peak systolic RV pressure and reveal any associated tricuspid regurgitation. The interventricular septum may appear flattened if there is pulmonary hypertension. The size of the main PA can be determined and color flow Doppler can demonstrate the pulmonary valve regurgitation, particularly in the high-pressure situation. Cardiac MRI and CT can be useful for assessing the size of the PA, for estimating regurgitant flow, for excluding other causes of pulmonary hypertension (eg, thromboembolic disease, peripheral PA stenosis), and for evaluating RV function. Cardiac catheterization is confirmatory only.

Treatment & Prognosis

Pulmonary valve regurgitation rarely needs specific therapy other than treatment of the primary cause. In low-pressure

pulmonary valve regurgitation due to surgical transannular patch repair of tetralogy of Fallot, pulmonary valve replacement may be indicated if RV enlargement or dysfunction is present. In tetralogy of Fallot, the QRS will widen as RV function declines (a QRS greater than 180 msec, among other features, suggests a higher risk for sudden death) and increasing RV volumes should trigger an evaluation for potential severe pulmonary valve regurgitation. In carcinoid heart disease, pulmonary valve replacement with a porcine bioprosthesis may be undertaken, though the plaque from this disorder eventually coats the prosthetic pulmonary valve, limiting the life span of these valves. In high-pressure pulmonary valve regurgitation, treatment to control the cause of the pulmonary hypertension is key. High-pressure pulmonary valve regurgitation is poorly tolerated and is a serious condition that needs a thorough evaluation for cause and choice of therapy. Pulmonary valve replacement requires a bioprosthetic valve in most cases. Pulmonary valve regurgitation due to an RV to PA conduit or due to a pulmonary autograft replacement as part of the Ross procedure can be repaired with a percutaneous pulmonary valve (Melody valve). Bioprosthetic pulmonary valve regurgitation has also been treated using a percutaneous valve (Edwards SAPIEN). When the pulmonary valve is replaced percutaneously, the PA is often stented open to provide a platform for the percutaneous valve.

When to Refer

- Patients with pulmonary valve regurgitation that results in RV enlargement should be referred to a cardiologist regardless of the estimated pulmonary pressures.

MANAGEMENT OF ANTICOAGULATION FOR PATIENTS WITH PROSTHETIC HEART VALVES

The risk of thromboembolism is much lower with bioprosthetic valves than mechanical prosthetic valves. Mechanical mitral valve prostheses also pose a greater risk for thrombosis than mechanical aortic valves. For that reason, *the INR should be kept between 2.5 and 3.5 for mechanical mitral prosthetic valves but can be kept between 2.0 and 2.5 for most mechanical aortic prosthetic valves.* If there are additional risk factors in patients with a mechanical AVR (atrial fibrillation, previous thromboembolism, LV dysfunction, hypercoagulable state, or presence of older valve such as a ball-in-cage), then the INR for a mechanical AVR should be similar to a mechanical mitral valve replacement. Guidelines suggest the following as well: (1) a recommendation (class IIa) to expand the use of vitamin K antagonists (VKAs), such as warfarin, for up to 6 months after initial bioprosthetic valve replacement; (2) a lower target INR of 1.5–2.0 for a mechanical AVR using the On-X valve (class IIb); and (3) a consideration of VKA use with an INR of 2.5 for at least 3 months after TAVR (class IIa). Data from 2018 suggest that antiplatelet medications are inferior to warfarin for the prevention of thrombus in patients with the On-X mechanical valve. Concern regarding thrombus formation on bioprosthetic valves (including TAVR valves) also led to a class I recommendation to use multimodality imaging to identify such thrombus (class I). *The DOAC rivaroxaban has not been found to prevent stroke related to emboli from TAVR and it should not be used.* It is acceptable, though, to use DOACs for the treatment of atrial fibrillation in patients with bioprosthetic valves. For patients with a TAVR valve, it is reasonable to use dual antiplatelet therapy (clopidogrel and aspirin) for 3–6 months after the procedure. After that, lifelong low-dose aspirin should be used. As noted earlier, using warfarin for at least 3 months after TAVR is reasonable (class IIb), although that practice is widely variable. Randomized trials have *not* shown a benefit with DOACs after TAVR.

The European Registry of Pregnancy and Cardiac Disease (ROPAC) reported on a registry that compared pregnant persons who had undergone mechanical and bioprosthetic valve replacement to pregnant persons who had not. Maternal mortality was similar between the mechanical and bioprosthetic valve patients (1.5% and 1.4%, respectively) but was much higher than those without an artificial valve (0.2%). When patients with either mechanical or bioprosthetic valves were further assessed, it was found that pregnant persons with mechanical valves were more likely to suffer adverse events than women with bioprosthetic valves. Hemorrhagic events occurred in 23.1% versus 9.2%, miscarriage on warfarin occurred in 28.6% versus 9.2%, and late fetal death was noted in 7.1% versus 0.7%, respectively. These data suggest *a high risk for mortality and morbidity for pregnant patients with mechanical heart valves,* and in the WHO Classification of Maternal Cardiac Risk, the presence of a mechanical valve is considered a class III (out of IV) risk for pregnancy complications.

Stoppage of warfarin for noncardiac surgery is likewise dependent on which mechanical valve is involved, the patient-specific risk factors, and the procedure contemplated. The risk of thromboembolism is highest in the first few months after valve replacement. While the interruption of warfarin therapy is generally safe, most cases of valve thrombosis occur during periods of inadequate anticoagulation, so the time interval without coverage should be kept as short as possible. High-risk features include atrial fibrillation, a prior history of thromboembolism, HF or low LVEF, a hypercoagulable state, a mechanical valve in the mitral position, a known high-risk valve (ball-in-cage), or concomitant hypercoagulable state (such as with an associated cancer). The use of *bridging VKAs*, unfractionated heparin, low-molecular-weight heparin (LMWH), and antifibrinolytics in various clinical situations in patients with valvular heart disease is summarized in Table 10–5. In general, low-risk procedures (eg, pacemaker implantation, cataract removal, and routine dental work) require no stoppage of VKAs, while in other situations the warfarin can be stopped 3 days ahead of the procedure and resumed the night after the procedure (ie, in patients with bileaflet aortic valves) without any bridging unfractionated heparin or LMWH. It is reasonable to consider bridging based on the CHA2DS2-VASc score in patients with bioprosthetic heart valves or annuloplasty rings who take anticoagulants for atrial fibrillation. In high-risk patients, principally just those with a mechanical mitral valve, the warfarin should be stopped and bridging with either unfractionated heparin or LMWH begun once the INR falls below therapeutic levels.

Table 10–5. Recommendations for administering vitamin K antagonist (VKA) therapy in patients undergoing procedures or patients with certain clinical conditions. (Listed in alphabetical order, within categories.)

Procedures	Recommendations
Bridging for mechanical heart valves	Required only for those at high risk for thromboembolism (generally only those with a mechanical mitral [not aortic] valve) Bridge with UFH or LMWH and stop UFH 4–6 hours before procedure or stop LMWH 24 hours before procedure Resume 48–72 hours after the procedure
General	Stop VKA 5 days prior and resume 12–24 hours after procedure
Clinical Situations	**Recommendations**
Aspirin use in patients with a bioprosthetic valve	
Bioprosthetic aortic or mitral valve replacement	Aspirin (50–100 mg) indefinitely. Reasonable to consider VKA to achieve INR 2.5 for first 3 months
Transcatheter valve replacement	Aspirin (50–100 mg) indefinitely
Mitral or aortic repair	Aspirin (50–100 mg) indefinitely
Atrial fibrillation and moderate or severe mitral stenosis	VKA (target INR 2.0–3.0) If patient prefers not to receive VKA, aspirin (50–100 mg) plus clopidogrel (75 mg)
Endocarditis	
Native valve or bioprosthetic valve endocarditis	No anticoagulation recommended
Mechanical valve endocarditis	Hold VKA until "safe to resume" (generally when mycotic aneurysm is ruled out or there is no need for urgent surgery)
Intermittent atrial fibrillation or history of systemic embolus and mitral stenosis	VKA (target INR 2.0–3.0)
Long-term anticoagulation after valve replacement	
Bioprosthetic valve in normal sinus rhythm	Aspirin (50–100 mg). Anticoagulation with a VKA to achieve an INR of 2.5 is reasonable for the first 3 months after surgical bioprosthetic MVR or AVR in patients at low risk for bleeding
Mechanical valve replacement	VKA (target INR 2.0–3.0 for mechanical aortic valve, target INR 1.5–2.5 for On-X aortic valve after the first 3 months with an initial target INR of 2.0–3.0, target INR 2.5–3.5 for mechanical mitral valve)
Pregnancy and a mechanical heart valve	Add aspirin (50–100 mg) for persons at high risk VKA may be used during first trimester and throughout pregnancy if dose of warfarin is ≤ 5 mg/day If VKA dosage normally > 5 mg/day, then adjusted dose LMWH twice daily throughout pregnancy (follow anti-Xa 4 hours after dose, with target of 0.8 U/mL to 1.2 U/mL) or LMWH may be used only during the first trimester, then resume VKA during second and third trimesters ***or*** Adjusted dose UFH every 12 hours throughout pregnancy (aPTT > 2 times control) or UFH may be used only during the first trimester, then resume VKA during second and third trimester Discontinuation of VKA with initiation of UFH (2 times normal PTT) recommended before planned vaginal delivery
Prosthetic valve thrombosis	
Right-sided valve Left-sided valve	Slow-infusion fibrinolytic therapy or intravenous heparin Early surgery if thrombus large (> 0.8 cm^2), symptomatic from valvular obstruction, high surgical risk, or LA thrombus. Thrombolysis with heparin or slow-infusion fibrinolytic therapy may be tried initially if patient is stable If thrombus evident on bioprosthetic valve creating increased gradient, use of VKA reasonable to assess whether obstructive gradient can be improved
Sinus rhythm and mitral stenosis	If left atrial size > 5.5 cm, then consider VKA (target 2.0–3.0)

aPTT, activated partial thromboplastin time; AVR, aortic valve replacement; LMWH, low-molecular-weight heparin; MVR, mitral valve replacement; PTT, partial thromboplastin time. UFH, unfractionated heparin.

Adapted from Nishimura RA et al. 2014 AHA/ACC guidelines for the management of patients with valvular heart disease: executive summary. Circulation. 2014;129:2440–92; and Nishimura RA et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease. J Am Coll Cardiol. 2017;70:252–289.

Fresh frozen plasma or prothrombin complex concentrate is reasonable in an emergency situation for acute reversal if serious bleeding occurs. *Most patients with a mechanical valve should not have the warfarin reversed with vitamin K, if it can be avoided, because this can result in a transient hypercoagulable state, and it may take many days to reach a therapeutic INR again.*

Warfarin causes fetal skeletal abnormalities in up to 2% of patients who become pregnant while taking the medication, so every effort is made to defer mechanical valve replacement in women until after childbearing age. However, if an individual with a mechanical valve becomes pregnant while taking warfarin, the risk of stopping warfarin may be higher for the mother than the risk of continuing warfarin for the fetus. The risk of warfarin to the fetal skeleton is greatest during the first trimester and, remarkably, is more related to dose than to the INR level. Guidelines suggest it is reasonable to continue warfarin for the first trimester if the dose is 5 mg/day or less. If the dose is more than 5 mg/day, it is appropriate to consider either LMWH (as long as the anti-Xa is being monitored [range: 0.8 U/mL to 1.2 U/mL 4–6 hours post-dose]) or continuous intravenous unfractionated heparin (if the activated partial thromboplastin time [aPTT] can be monitored and is at least two times control). Guidelines suggest warfarin and low-dose aspirin are safe during the second and third trimester, and then should be stopped upon anticipation of delivery. At time of vaginal delivery, unfractionated intravenous heparin with aPTT at least two times control is desirable. DOACs (antithrombin or Xa inhibitors) should *not* be used in place of warfarin for mechanical prosthetic valves since there are no data that they are safe during pregnancy or safe for mechanical valves in general.

Management of suspected mechanical valve thrombosis depends on whether a left-sided or right-sided valve is involved, the size of the thrombus, and the patient's clinical condition. Simple fluoroscopy can help assess mechanical valve motion, although a TEE is indicated to assess thrombus size. *Therapeutic unfractionated heparin should be given to all patients with a thrombosed valve,* and this alone is generally effective. Fibrinolytic therapy is indicated if heparin therapy is ineffective and the clinical onset has been less than 2 weeks, the thrombus is smaller than 0.8 cm^2, New York Heart Association (NYHA) class symptoms are mild (functional class I or II), or the valve is right-sided. Surgery is rarely indicated; it is reserved for those with left-sided mechanical valves in NYHA functional class III or IV HF or in whom TEE demonstrates a mobile thrombus larger than 0.8 cm^2. The use of urgent initial therapy for a thrombosed mechanical valve should include low-dose, slow-infusion fibrinolytic therapy or urgent surgery if the patient is symptomatic.

CORONARY HEART DISEASE (Atherosclerotic CAD, Ischemic Heart Disease)

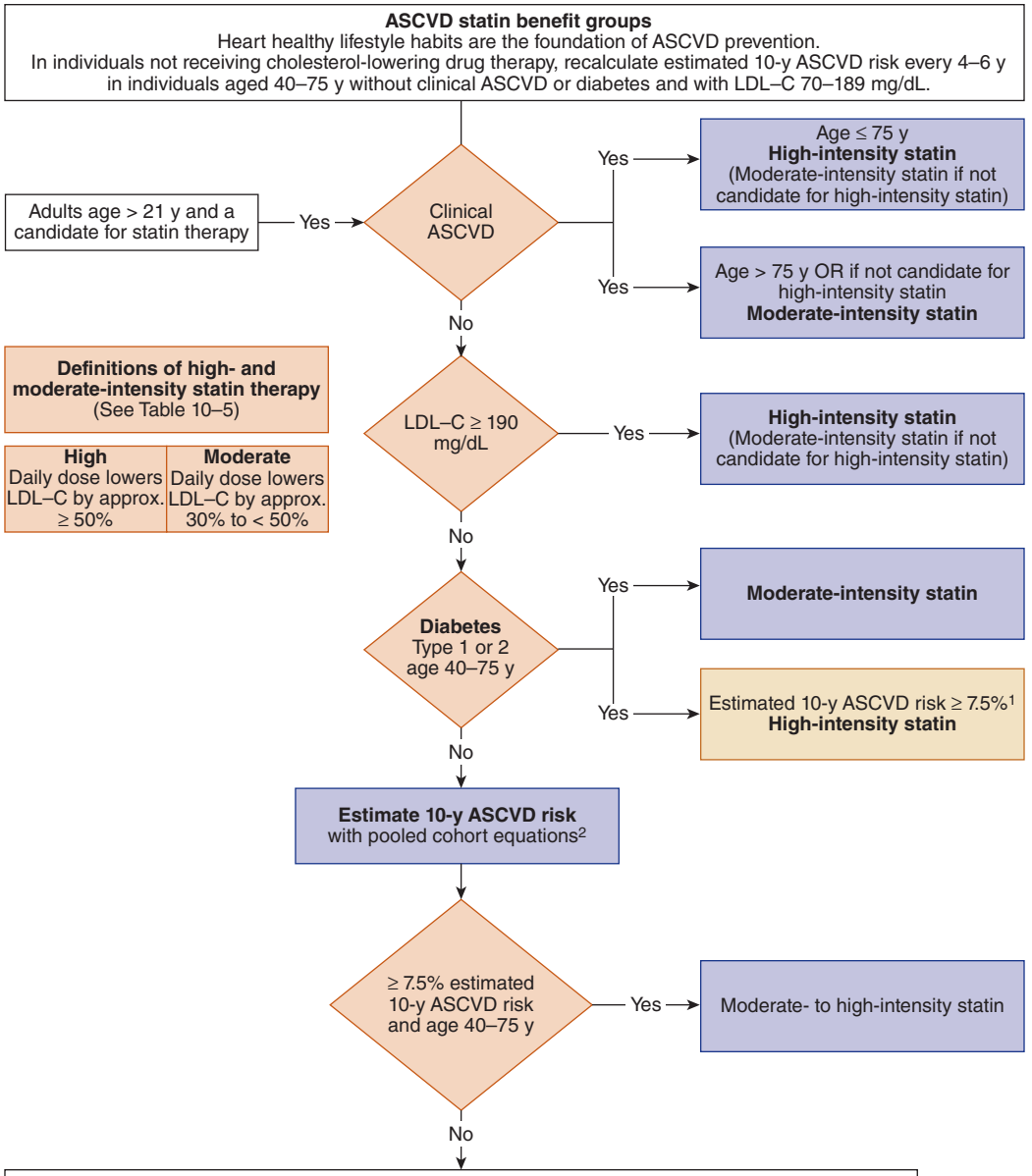
CHD, or atherosclerotic CAD, is the number one cause of death in the United States and worldwide. Every minute in the United States, a person dies of CHD. About 37% of people who experience an acute coronary event, either angina or MI, will die of it in the same year. Death rates of CHD have declined every year since 1968, with about half of the decline from 1980 to 2000 due to treatments and half due to improved risk factors. CHD is still responsible for 1 in 4 of all deaths in the United States, totaling over 659,000 deaths annually. Each year, 805,000 individuals have a heart attack in the United States. CHD afflicts nearly 18.2 million Americans, and the prevalence rises steadily with age; thus, the aging of the US population promises to increase the overall burden of CHD.

Risk Factors for CAD

Most patients with CHD have some identifiable risk factor. These include a **positive family history** (the younger the onset in a first-degree relative, the greater the risk), **male sex, blood lipid abnormalities, diabetes mellitus, hypertension, physical inactivity, abdominal obesity, cigarette smoking, psychosocial factors,** and consumption of **too few fruits and vegetables** and **too much alcohol**. Many of these risk factors are modifiable. *Smoking remains the number one preventable cause of death and illness in the United States.* Although cigarette smoking rates have declined in the United States in recent decades, 11.5% of adults smoked cigarettes in 2021. According to the WHO, 1 year after quitting, the risk of CHD decreases by 50%. Various interventions have been shown to increase the likelihood of successful smoking cessation (see Chapter 1).

Hypercholesterolemia is an important modifiable risk factor for CHD. Risk increases progressively with higher levels of LDL cholesterol and declines with higher levels of HDL cholesterol. Composite risk scores, such as the **Framingham score** and the **10-year atherosclerotic CVD risk calculator** (http://my.americanheart.org/cvriskcalculator), provide estimates of the 10-year probability of development of CHD that can guide primary prevention strategies. The 2018 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults suggests statin therapy in four populations: patients with (1) clinical atherosclerotic disease, (2) LDL cholesterol 190 mg/dL or higher, (3) diabetes who are aged 40–75 years, and (4) an estimated 10-year atherosclerotic risk of 7.5% or more aged 40–75 years (Figure 10–7). Importantly, *the guidelines do not recommend treating to a target LDL cholesterol.* Patients in these categories should be treated with a moderate- or high-intensity statin, with high-intensity statin for populations with higher risk. Moderate-intensity statins are rosuvastatin 5–10 mg, atorvastatin 10–20 mg, simvastatin 20–40 mg, or pravastatin 40–80 mg. High-intensity statins are rosuvastatin 20–40 mg or atorvastatin 40–80 mg. The ACC/AHA atherosclerotic CVD estimator allows clinicians to determine the 10-year ASCVD risk to determine treatment decisions (http://tools.acc.org/ascvd-risk-estimator-plus/). The 2022 USPSTF Lipid Recommendations suggest statin therapy for primary prevention of CVD in those 40 to 75 years of age with one or more risk factors and a 10-year estimated CVD risk of 10% or greater.

The **metabolic syndrome** is defined as a constellation of three or more of the following: abdominal obesity,



[1]Percent reduction in LDL–C can be used as an indication of response and adherence to therapy but is not in itself a treatment goal.

[2]The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes. A downloadable spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a web-based calculator are available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/science-and-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx.

[3]Primary LDL–C ≥ 160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset < 55 years of age in a first-degree male relative or < 65 years of age in a first-degree female relative, high-sensitivity C-reactive protein > 2 mg/L, CAC score ≥ 300 Agatston units or ≥ 75 percentile for age, sex, and ethnicity, ankle-brachial index < 0.9, or elevated lifetime risk of ASCVD.

▲ **Figure 10–7.** Major recommendations for statin therapy for atherosclerotic CVD prevention. ASCVD, atherosclerotic CVD; CAC, coronary artery calcium; LDL–C, LDL cholesterol. (Adapted from Stone NJ et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1.)

triglycerides 150 mg/dL or higher, HDL cholesterol less than 40 mg/dL for men or less than 50 mg/dL for women, fasting glucose 110 mg/dL or higher, and hypertension. This syndrome is increasing in prevalence at an alarming rate. Related to the metabolic syndrome, the **epidemic of obesity** in the United States is likewise a major factor contributing to CHD risk.

Myocardial Hibernation & Stunning

Areas of myocardium that are persistently underperfused but still viable may develop sustained contractile dysfunction. This phenomenon, which is termed **myocardial hibernation,** appears to represent an adaptive response that may be associated with depressed LV function. It is important to recognize this phenomenon, since this form of dysfunction is reversible following coronary revascularization. Hibernating myocardium can be identified by radionuclide testing, PET, contrast-enhanced MRI, or its retained response to inotropic stimulation with dobutamine. A related phenomenon, termed **myocardial stunning,** is the occurrence of persistent contractile dysfunction following prolonged or repetitive episodes of myocardial ischemia. Clinically, myocardial stunning is often seen after reperfusion of acute MI and is defined with improvement following revascularization.

de Cabo R et al. Effects of intermittent fasting on health, aging, and disease. N Engl J Med. 2019;381:2541. Erratum in: N Engl J Med. 2020;382:298. Erratum in: N Engl J Med. 2020;382:978. [PMID: 31881139]

US Preventive Services Task Force; Mangione CM et al. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2022;328:746. [PMID: 35997723]

Virani SS et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. Circulation. 2021;143:e254. [PMID: 33501848]

Primary & Secondary Prevention of CHD

Although many risk factors for CHD are not modifiable, it is now clear that interventions, such as smoking cessation, treatment of dyslipidemia, and lowering of BP can both prevent coronary disease and delay its progression and complications after it is manifest.

Lowering LDL levels delays the progression of atherosclerosis and in some cases may produce *regression*. Even in the absence of regression, fewer new lesions develop, endothelial function may be restored, and coronary event rates are markedly reduced in patients with clinical evidence of vascular disease.

A series of clinical trials has demonstrated the efficacy of **hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins)** in preventing death, coronary events, and strokes. Beneficial results have been found in patients who have already experienced coronary events (secondary prevention), those at particularly high risk for events (patients with diabetes and patients with peripheral artery disease), those with elevated cholesterol without multiple risk factors, and those without vascular disease or diabetes with elevated high-sensitivity CRP (hsCRP) with normal LDL levels. The benefits of statin therapy at moderate and high doses (see previous section on risk factors for coronary artery disease-hyperlipidemia) are recommended by the cholesterol treatment guidelines. The IMPROVE-IT study showed that **ezetimibe**, 10 mg daily, combined with simvastatin was modestly better than simvastatin alone in reducing the risk of MI and ischemic stroke, but *not* mortality, in stabilized patients following an ACS. This was associated with a reduction of LDL to 53.7 mg/dL compared to 69.7 mg/dL. With this data, ezetimibe can be used in combination with statin therapy in patients who are not at target cholesterol level for secondary prevention (for individuals at high risk for cardiovascular events with an LDL greater than 70 on maximal intensity statin therapy [IIa recommendation]) or cannot tolerate high-dose statin therapy.

Benefits occurred regardless of age, race, baseline cholesterol levels, or the presence of hypertension. It is clear that for patients with vascular disease, statins provide benefit for those with normal cholesterol levels, and that more aggressive statin use is associated with greater benefits. *All patients at significant risk for vascular events should receive a statin regardless of their cholesterol levels, and many experts recommend that with those who have prior cardiovascular events should have their LDL lowered below 70 mg/dL.*

Monoclonal antibodies that inhibit **proprotein convertase subtilisin/kexin type 9 (PCSK9)** reduce LDL cholesterol levels significantly beyond levels associated with traditional statin therapy. These therapies have been studied in randomized trials of patients with maximally tolerated statin therapy (and for patients with statin intolerance) and have lowered LDL with signals of improved cardiovascular outcomes. The FOURIER trial showed that the PCSK9 inhibitor evolocumab, added to a statin, reduced the composite of atherothrombotic outcomes by 20% but did *not* reduce mortality. The ODYSSEY Outcomes trial demonstrated alirocumab reduced cardiovascular events in patients with ACSs. *Alirocumab and evolocumab have been approved by the FDA for patients on maximally tolerated statin therapy with familial hypercholesterolemia and atherosclerotic vascular disease, or both, and who require additional lowering of LDL.* These medications cost several thousand dollars per year in the United States. Alirocumab has also been approved by the FDA for secondary prevention of cardiovascular events. Inclisiran (a small interfering RNA that goes to the liver and prevents the production of PCSK9) has been studied as a twice yearly injection showing reduction in LDL and was approved by the FDA in early 2022.

The placebo-controlled, double-blind CLEAR Outcomes trial randomized 13,970 patients with a history of or at high-risk of ASCVD and an LDL-C greater than 100 mg/dL to bempedoic acid therapy or placebo. Treatment with bempedoic acid, an ATP citrate lyase inhibitor, resulted in reduction in the composite primary end-point of cardiovascular death, nonfatal MI, nonfatal stroke, or coronary revascularization procedure. This important investigation provides another option to reduce major adverse cardiac

events in at-risk patients who cannot tolerate or prefer not to take statin therapy.

Fish oil supplements have *not* been shown consistently to provide benefit for reducing risk. The AHA does *not* recommend omega-3 fatty acids for primary prevention of CVD in high-risk patients or in primary prevention of stroke. The AHA states treatment is reasonable for secondary prevention of CHD and sudden cardiac death among patients with prevalent CHD. Icosapent ethyl, a concentrated eicosapentaenoic acid at a high dose, was shown to be beneficial in the REDUCE-IT trial. Patients with established CVD or with diabetes and other risk factors, with fasting triglyceride level of 135–499 mg/dL, who were on statins were randomized to 2 g of icosapent ethyl twice daily or placebo. There was a 26% relative risk reduction in cardiovascular death, MI, and stroke, as well as a 20% relative risk reduction in cardiovascular death. Icosapent ethyl is approved by the FDA as an adjunct to maximally tolerated statin therapy to reduce the risk of MI, stroke, coronary revascularization, or unstable angina requiring hospitalization in patients with triglycerides of 150 mg/dL or more and either established CVD or diabetes mellitus and two or more additional risk factors. The role of high-dose omega-3 fatty acids was studied compared to corn oil and not shown to reduce cardiovascular events, leading to increased interest in comparative studies.

Treatment to raise HDL levels has failed to show benefit. The AIM High trial found no benefit from the addition of niacin in patients with vascular disease and a serum LDL near 70 mg/dL who were receiving statin therapy. The HPS2-THRIVE trial found no benefit but rather substantial harm of extended-release niacin (2 g) plus laropiprant (an antiflushing agent) for preventing vascular events in a population of over 25,000 patients with vascular disease who were taking simvastatin.

For primary prevention*, aspirin has little overall benefit, including for patients with established diabetes, and is* not *recommended for most patients.* In 2022, the USPSTF issued guidance on the use of aspirin for primary prevention of cardiovascular events. The document recommended that patient aged 40–59 years with a 10-year ASCVD risk of 10% or greater should have a shared-decision making conversation regarding the potential risk and benefits of initiating aspirin therapy for primary prevention. In addition, the document recommended that patients 60 years of age and older should not initiate aspirin for primary prevention of CVD.

Antiplatelet therapy is a very effective measure for secondary prevention *and patients with established vascular disease should be treated with aspirin.* The exact dose of aspirin in chronic CAD (81 mg vs 325 mg) was evaluated in a large pragmatic trial (ADAPTABLE). The unique pragmatic clinical trial design demonstrated that 81 mg aspirin was associated with a favorable cardiovascular event risk and bleeding risk compared with 325 mg daily.

While clopidogrel was found to be effective at preventing vascular events for 9–12 months after ACSs, and there are some benefits in prolonging dual antiplatelet therapy after coronary stenting, clopidogrel was *not* found to be effective at preventing vascular events in combination with aspirin with longer-term treatment in the CHARISMA trial. This trial included patients with clinically evident stable atherothrombosis or with multiple risk factors; all were treated with aspirin and observed for a median of 28 months.

In the COMPASS trial, rivaroxaban, a direct factor Xa inhibitor, at a dose of 2.5 mg twice daily in addition to 100 mg of aspirin, was shown to reduce cardiovascular death, MI, and stroke by a relative risk reduction of 24% compared to 100 mg aspirin monotherapy in stable patients with CAD and peripheral artery disease. Bleeding was modestly increased. All-cause mortality was also reduced by 18%. This regimen is approved by the FDA and is used for long-term management of patients with CAD and peripheral artery disease and should be considered in this group at high risk for adverse cardiac events with a low bleeding risk profile.

The HOPE and the EUROPA trials demonstrated that ACE inhibitors (ramipril 10 mg/day and perindopril 8 mg/day, respectively) reduced fatal and nonfatal vascular events (cardiovascular deaths, nonfatal MIs, and nonfatal strokes) by 20–25% in patients at high risk, including patients with diabetes with additional risk factors or patients with clinical coronary, cerebral, or peripheral arterial atherosclerotic disease. An overview of these trials has demonstrated that while low-risk patients may *not* derive substantial benefits from ACE inhibitors, *most patients with vascular disease, even in the absence of HF or LV dysfunction, should be treated with an ACE inhibitor.*

An interesting approach to secondary prevention of cardiovascular events was investigated in the SECURE trial. Utilizing a polypill (aspirin, ramipril, and atorvastatin) or standard medical therapy with multiple agents, 2499 patients with a history of an MI in the prior 6 months were randomized to polypill treatment or a standard approach with multiple agents and followed for 3 years. Medication adherence was statistically higher in the polypill cohort and this was associated with a statistically significant lower rate of major adverse cardiac events.

Over one-third of patients with vascular disease have type 2 diabetes. In addition to controlling risk factors, using high-intensity statins and ACE inhibitors or ARBs, *there is proven benefit to reduce cardiovascular events by using oral SGLT-2 inhibitors (specifically, empagliflozin, dapagliflozin, or canagliflozin) or injectable GLP1-receptor agonists (liraglutide, semaglutide, dulaglutide).* The cardiovascular benefits appear to be independent from the modest glucose lowering effects, and SGLT-2 inhibitors have benefits for patients with HF regardless of whether they have diabetes or HF with reduced versus preserved EF (see Heart Failure section). Importantly, the SELECT RCT enrolled 17,604 patients with *a BMI greater than 27 and no history of diabetes mellitus* and showed a statistically significant decrease in the composite primary end-point of cardiovascular death, nonfatal MI, or nonfatal stroke in the group treated with semaglutide.

Another approach to secondary prevention of cardiovascular events has evolved from clinical trials evaluating colchicine, which is commonly utilized to treat gout, at a lower dose of 0.5 mg daily. This regimen resulted in a 23%

reduction in major adverse cardiac events in post-MI patients and 31% in stable CAD patients. The European Society of Cardiology adopted colchicine into the secondary prevention guidelines in 2021. The US FDA approved colchicine for secondary prevention in June 2023.

Anker SD et al; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385:1451. [PMID: 34449189]
Castellano JM et al; SECURE Investigators. Polypill strategy in secondary cardiovascular prevention. N Engl J Med. 2022;387:967. [PMID: 36018037]
Jones WS et al; ADAPTABLE Team. Comparative effectiveness of aspirin dosing in cardiovascular disease. N Engl J Med. 2021;384:1981. [PMID: 33999548]
Lincoff AM et al; SELECT Trial Investigators. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023;389:2221. [PMID: 37952131]
Nelson K et al. Low-dose colchicine for secondary prevention of coronary artery disease: JACC Review Topic of the Week. J Am Coll Cardiol. 2023;82:648. [PMID: 37558377]
Nicholls SJ et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. JAMA. 2020;324:2268. [PMID: 33190147]
Nissen SE et al; CLEAR Outcomes Investigators. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. N Engl J Med. 2023;388:1353. [PMID: 36876740]
US Preventive Services Task Force; Davidson KW et al. Aspirin use to prevent cardiovascular disease: US Preventive Services Task Force recommendation statement. JAMA. 2022;327:1577. [PMID: 35471505]

CHRONIC STABLE ANGINA PECTORIS (Chronic Coronary Syndromes)

ESSENTIALS OF DIAGNOSIS

- Precordial chest pain, usually precipitated by stress or exertion, relieved rapidly by rest or nitrates.
- ECG or scintigraphic evidence of ischemia during pain or stress testing.
- Angiographic demonstration of significant obstruction of major coronary vessels.

General Considerations

Angina pectoris is the manifestation of stable CAD or chronic coronary syndromes, and it is usually due to atherosclerotic heart disease. Coronary vasospasm may occur at the site of a lesion or, less frequently, in apparently normal vessels. Other unusual causes of coronary artery obstruction, such as congenital anomalies, emboli, arteritis, or dissection, may cause ischemia or infarction. Angina may also occur in the absence of coronary artery obstruction as a result of severe myocardial hypertrophy, severe aortic stenosis or regurgitation, or in response to increased metabolic demands, as in hyperthyroidism, marked anemia, or paroxysmal tachycardias with rapid ventricular rates.

Clinical Findings

A. Symptoms

The diagnosis of angina pectoris principally depends on the history, which should specifically include the following information: circumstances that precipitate and relieve angina, characteristics of the discomfort, location and radiation, duration of attacks, and effect of nitroglycerin.

1. Circumstances that precipitate and relieve angina— Angina occurs most commonly during activity and is relieved by resting. Patients may prefer to remain upright rather than lie down, as increased preload in recumbency increases myocardial work. The amount of activity required to produce angina may be relatively consistent under comparable physical and emotional circumstances or may vary from day to day. The threshold for angina is usually lower after meals, during excitement, or on exposure to cold. It is often lower in the morning or after strong emotion; the latter can provoke attacks in the absence of exertion. In addition, discomfort may occur during sexual activity, at rest, or at night as a result of coronary spasm.

2. Characteristics of the discomfort— Patients often do not refer to angina as "pain" but as a sensation of tightness, squeezing, burning, pressing, choking, aching, bursting, "gas," indigestion, or an ill-characterized discomfort. It is often characterized by *clenching a fist* over the mid chest. The distress of angina is rarely sharply localized and is not spasmodic.

3. Location and radiation— The distribution of the distress may vary widely in different patients but is usually the same for each patient unless unstable angina or MI supervenes. In most cases, the discomfort is felt behind or slightly to the left of the mid sternum. When it begins farther to the left or, uncommonly, on the right, it characteristically moves centrally substernally. Although angina may radiate to any dermatome from C8 to T4, it radiates most often to the left shoulder and upper arm, frequently moving down the inner volar aspect of the arm to the elbow, forearm, wrist, or fourth and fifth fingers. It may also radiate to the right shoulder or arm, the lower jaw, the neck, or even the back.

4. Duration of attacks— Angina is generally of short duration and subsides completely without residual discomfort. If the attack is precipitated by exertion and the patient promptly stops to rest, it usually lasts under 3 minutes. Attacks following a heavy meal or brought on by anger often last 15–20 minutes. Attacks lasting more than 30 minutes are unusual and suggest the development of an ACS with unstable angina, MI, or an alternative diagnosis.

5. Effect of nitroglycerin— The diagnosis of angina pectoris is supported if sublingual nitroglycerin promptly and invariably shortens an attack and if prophylactic nitrates permit greater exertion or prevent angina entirely.

B. Signs

Examination during angina frequently reveals a significant elevation in systolic and diastolic BP, although hypotension

may also occur, and may reflect more severe ischemia or inferior ischemia (especially with bradycardia) due to a **Bezold-Jarisch reflex**. Occasionally, a gallop rhythm and an apical systolic murmur due to transient mitral regurgitation from papillary muscle dysfunction are present during pain only. Supraventricular or ventricular arrhythmias may be present, either as the precipitating factor or as a result of ischemia.

It is important to detect signs of diseases that may contribute to or accompany atherosclerotic heart disease, eg, diabetes mellitus (retinopathy or neuropathy), xanthelasma tendinous xanthomas, hypertension, thyrotoxicosis, myxedema, or peripheral artery disease. Aortic stenosis or regurgitation, HCM, and mitral valve prolapse should be sought, since they may produce angina or other forms of chest pain.

C. Laboratory Findings

Other than standard laboratory tests to evaluate for ACS (troponin and CK-MB) and factors contributing to ischemia (such as anemia) and to screen for risk factors that may increase the probability of true CHD (such as hyperlipidemia and diabetes mellitus), blood tests are not helpful to diagnose chronic angina.

D. ECG

The resting ECG is often normal in patients with a history of angina. In the remainder, abnormalities include old MI, nonspecific ST–T changes, and changes of LVH. During anginal episodes, as well as during asymptomatic ischemia, *the characteristic ECG change is horizontal or downsloping ST-segment depression that reverses after the ischemia disappears.* T wave flattening or inversion may also occur. Less frequently, transient ST-segment elevation is observed; this finding suggests severe (transmural) ischemia from coronary occlusion, and it can occur with coronary spasm.

E. Pretest Probability

The history as detailed above, the physical examination findings, and laboratory and ECG findings are used to develop a pretest probability of CAD as the cause of the clinical symptoms. Other important factors to include in calculating the pretest probability of CAD are patient age, sex, and clinical symptoms. Patients with low to intermediate pretest probability for CAD should undergo noninvasive stress testing whereas patients with high pretest probability are generally referred for cardiac catheterization. National review of diagnostic cardiac catheterization findings in patients without known CAD undergoing angiography has shown that between 38% and 40% of patients do not have obstructive disease.

F. Exercise ECG

Exercise ECG testing is the most commonly used noninvasive procedure for evaluating inducible ischemia in the patient with angina. Exercise ECG testing is often combined with imaging studies (nuclear or echocardiography), but in low-risk patients without baseline ST-segment abnormalities or in whom anatomic localization is not necessary, the exercise ECG remains the recommended initial procedure because of considerations of cost, convenience, and long-standing prognostic data.

Exercise testing can be done on a motorized treadmill or with a bicycle ergometer. A variety of exercise protocols are utilized, the most common being the **Bruce protocol,** which increases the treadmill speed and elevation every 3 minutes until limited by symptoms. At least two ECG leads should be monitored continuously.

1. Precautions and risks—The risk of exercise testing is about one infarction or death per 1000 tests, but individuals who have pain at rest or minimal activity are at higher risk and should not be tested. *Many of the traditional exclusions, such as recent MI or HF, are no longer used if the patient is stable and ambulatory, but symptomatic aortic stenosis remains a relative contraindication.*

2. Indications—Exercise testing is used (1) to confirm the diagnosis of angina; (2) to determine the severity of limitation of activity due to angina; (3) to assess prognosis in patients with known coronary disease, including those recovering from MI, by detecting groups at high or low risk; and (4) to evaluate responses to therapy. Because false-positive tests often exceed true positives, leading to much patient anxiety and self-imposed or mandated disability, *exercise testing of asymptomatic individuals should be done only for those whose occupations place them or others at special risk (eg, airline pilots).*

3. Interpretation—The usual ECG criterion for a positive test is 1-mm (0.1-mV) *horizontal or downsloping ST-segment depression* (beyond baseline) measured 80 msec after the J point. By this criterion, 60–80% of patients with anatomically significant coronary disease will have a positive test, but 10–30% of those without significant disease will also be positive. False positives are uncommon when a 2-mm depression is present. Additional information is inferred from the time of onset and duration of the ECG changes, their magnitude and configuration, BP and heart rate changes, the duration of exercise, and the presence of associated symptoms. In general, patients exhibiting more severe ST-segment depression (more than 2 mm) at low workloads (less than 6 minutes on the Bruce protocol) or heart rates (less than 70% of age-predicted maximum)—especially when the duration of exercise and rise in BP are limited or when hypotension occurs during the test—have more severe disease and a poorer prognosis. Depending on symptom status, age, and other factors, such patients should be referred for coronary arteriography and possible revascularization. On the other hand, less impressive positive tests in asymptomatic patients are often "false positives." Therefore, exercise testing results that do not conform to the clinical suspicion should be confirmed by stress imaging.

G. Myocardial Stress Imaging

Myocardial stress imaging (scintigraphy, echocardiography, or MRI) is indicated (1) when the resting ECG makes an exercise ECG difficult to interpret (eg, left bundle

branch block, baseline ST–T changes, low voltage); (2) for confirmation of the results of the exercise ECG when they are contrary to the clinical impression (eg, a positive test in an asymptomatic patient); (3) to localize the region of ischemia; (4) to distinguish ischemic from infarcted myocardium; (5) to assess the completeness of revascularization following bypass surgery or coronary angioplasty; or (6) as a prognostic indicator in patients with known coronary disease. Published criteria summarize these indications for stress testing.

1. Myocardial perfusion scintigraphy—This test, also known as **radionuclide imaging,** provides images in which radionuclide uptake is proportionate to blood flow at the time of injection. Isotopes used include thallium-201, technetium-99m sestamibi, and tetrafosmin.

Stress imaging is positive in about 75–90% of patients with anatomically significant coronary disease and in 20–30% of those without it. Occasionally, other conditions, including infiltrative diseases (sarcoidosis, amyloidosis), left bundle branch block, and dilated cardiomyopathy, may produce resting or persistent perfusion defects. False-positive radionuclide tests may occur as a result of diaphragmatic attenuation or, in women, attenuation through breast tissue. Tomographic imaging (single-photon emission CT [SPECT]) can reduce the severity of artifacts.

2. Radionuclide angiography—This procedure, also known as **multi-gated acquisition scan,** or **MUGA scan,** uses radionuclide tracers to image the LV and measures its EF and wall motion. In coronary disease, resting abnormalities usually represent infarction, and those that occur only with exercise usually indicate stress-induced ischemia. Exercise radionuclide angiography has approximately the same sensitivity as myocardial perfusion scintigraphy, but it is less specific in older individuals and those with other forms of heart disease. In addition, because of the precision around LVEF, the test is also used for monitoring patients exposed to cardiotoxic therapies (such as some chemotherapeutic agents).

3. Stress echocardiography—Echocardiograms performed during supine exercise or immediately following upright exercise may demonstrate exercise-induced *segmental wall motion abnormalities* as an indicator of ischemia. In experienced laboratories, the test accuracy is comparable to that obtained with scintigraphy—though a higher proportion of tests is technically inadequate. While exercise is the preferred stress because of other information derived, pharmacologic stress with **high-dose dobutamine** (20–40 mcg/kg/min) can be used as an alternative to exercise.

H. Other Imaging

1. PET—PET and SPECT scanning can accurately distinguish transiently dysfunctional ("stunned") myocardium from scar tissue.

2. CT and MRI scanning—CT scanning can image the heart and, with contrast medium and multislice technology, the coronary arteries. *Multislice CT angiography may be useful in evaluating patients with low likelihood of significant CAD to rule out disease.* Its use has been associated with lower 5-year mortality compared to standard care in patients with stable chest pain. With lower radiation exposure than radionuclide SPECT imaging, CT angiography may also be useful for evaluating chest pain and suspected ACS. In the large randomized comparative effectiveness PROMISE trial, patients with stable chest pain undergoing anatomic imaging with CT angiography had similar outcomes to patients undergoing functional testing (stress ECG, stress radionuclide, or stress echocardiography). CT angiography with noninvasive functional assessment of coronary stenosis (fractional flow reserve), termed **CT-FFR,** has also been evaluated in patients with low-intermediate likelihood of CAD. CT-FFR has been shown to reduce the number of patients without coronary disease requiring invasive angiography. CT-FFR has been approved for clinical use and is being used in clinical practice in the United States and Europe. The use of CT-FFR has been endorsed with a level IIa recommendation for intermediate-risk patients with chest pain and no prior history of CAD with a 40–90% stenosis on CT imaging to guide need for revascularization in the 2021 ACC/AHA Guideline for the Evaluation and Diagnosis of Chest Pain.

Electron beam CT (EBCT) (coronary calcium score) can quantify coronary artery calcification, which is highly correlated with atheromatous plaque and has high sensitivity, but low specificity, for obstructive coronary disease. This test has not traditionally been used in symptomatic patients. According to the AHA, persons who are at low risk (less than 10% 10-year risk) or at high risk (greater than 20% 10-year risk) for obstructive coronary disease do not benefit from coronary calcium assessment (class III, level of evidence: B). However, in clinically selected, intermediate-risk patients (5–7.5% atherosclerotic CVD), it may be reasonable to determine the atherosclerosis burden using EBCT in order to refine clinical risk prediction and to select patients for more aggressive target values for lipid-lowering therapies (class IIb, level of evidence: B).

Cardiac MRI using gadolinium provides high-resolution images of the heart and great vessels without radiation exposure or use of iodinated contrast media. Gadolinium has been associated with a rare but fatal complication in patients with severe kidney disease, called **necrotizing systemic fibrosis.** Gadolinium can demonstrate perfusion using dobutamine or adenosine to produce *pharmacologic stress*. Advances have been made in imaging the proximal coronary arteries. Perhaps the most clinically used indication of cardiac MRI is for identification of **myocardial fibrosis,** either from MI or infiltration, done with gadolinium contrast. This allows high-resolution imaging of myocardial viability and infiltrative cardiomyopathies.

I. Ambulatory ECG Monitoring

Ambulatory ECG recorders can monitor for ischemic ST-segment depression, but this modality is rarely used for ischemia detection. In patients with CAD, these episodes usually signify ischemia, even when asymptomatic ("silent").

J. Coronary Angiography

Selective coronary arteriography is the definitive diagnostic procedure for CAD. It can be performed with low mortality (about 0.1%) and morbidity (1–5%), but due to the invasive nature and cost, it is recommended only in patients with a high pretest probability of CAD.

Coronary arteriography should be performed in the following circumstances if percutaneous transluminal coronary angioplasty or bypass surgery is a consideration:

1. Life-limiting stable angina despite an adequate medical regimen.
2. Clinical presentation (unstable angina, postinfarction angina, etc) or noninvasive testing suggests high-risk disease (see Indications for Revascularization).
3. Concomitant aortic valve disease and angina pectoris, to determine whether the angina is due to accompanying coronary disease.
4. Asymptomatic older patients undergoing valve surgery so that concomitant bypass may be done if the anatomy is propitious.
5. Recurrence of symptoms after coronary revascularization to determine whether bypass grafts or native vessels are occluded.
6. Cardiac failure where a surgically correctable lesion, such as LV aneurysm, mitral regurgitation, or reversible ischemic dysfunction, is suspected.
7. Persons who have experienced sudden death, symptomatic, or life-threatening arrhythmias when CAD may be a correctable cause.
8. Chest pain of uncertain cause or cardiomyopathy of unknown cause.
9. Emergently performed cardiac catheterization with intention to perform primary percutaneous coronary intervention (PCI) in patients with suspected acute MI.

A narrowing of more than 50% of the luminal diameter is considered hemodynamically (and clinically) significant, although most lesions producing ischemia are associated with narrowing in excess of 70%. In those with strongly positive exercise ECGs or scintigraphic studies, three-vessel or left main disease may be present in 75–95% depending on the criteria used. **Intravascular ultrasound (IVUS)** is useful as an adjunct for assessing the results of angioplasty or stenting. In addition, IVUS is the invasive diagnostic method of choice for ostial left main lesions and coronary dissections. In **fractional flow reserve (FFR),** a pressure wire is used to measure the relative change in pressure across a coronary lesion after adenosine-induced hyperemia. Revascularization based on abnormal FFR improves clinical outcomes compared to revascularization of all angiographically stenotic lesions. Fractional flow reserve is an important invasive tool to aid with ischemia-driven revascularization and has become the standard tool to evaluate borderline lesions in cases in which the clinical team is evaluating the clinical and hemodynamic significance of a coronary stenosis. Additionally, pressures distally/pressures proximally during a wave-free period in diastole have been shown to demonstrate similar clinical outcomes to fractional flow reserve, without the use of adenosine.

LV angiography is usually performed at the same time as coronary arteriography. Global and regional LV function are visualized, as well as mitral regurgitation if present. LV function is a major determinant of prognosis in CHD.

Differential Diagnosis

When atypical features are present—such as prolonged duration (hours or days) or darting, or knifelike pains at the apex or over the precordium—ischemia is less likely.

Anterior chest wall syndrome is characterized by a sharply localized tenderness of the intercostal muscles. Inflammation of the chondrocostal junctions may result in diffuse chest pain that is also reproduced by local pressure **(Tietze syndrome).** Intercostal neuritis (due to herpes zoster or diabetes mellitus, for example) also mimics angina.

Cervical or thoracic spine disease involving the dorsal roots produces sudden sharp, severe chest pain suggesting angina in location and "radiation" but related to specific movements of the neck or spine, recumbency, and straining or lifting. Pain due to cervical or thoracic disk disease involves the outer or dorsal aspect of the arm and the thumb and index fingers rather than the ring and little fingers.

Reflux esophagitis, peptic ulcer, chronic cholecystitis, esophageal spasm, and functional GI disease may produce pain suggestive of angina pectoris. The picture may be especially confusing because ischemic pain may also be associated with upper GI symptoms, and esophageal motility disorders may be improved by nitrates and calcium channel blockers. Assessment of esophageal motility may be helpful.

Degenerative and inflammatory lesions of the left shoulder and thoracic outlet syndromes may cause chest pain due to nerve irritation or muscular compression; the symptoms are usually precipitated by movement of the arm and shoulder and are associated with paresthesias.

Pneumonia, PE, and spontaneous pneumothorax may cause chest pain as well as dyspnea. Dissection of the thoracic aorta can cause severe chest pain that is commonly felt in the back; it is sudden in onset, reaches maximum intensity immediately, and may be associated with changes in pulses. Other cardiac disorders, such as mitral valve prolapse, HCM, myocarditis, pericarditis, aortic valve disease, or RVH, may cause atypical chest pain or even myocardial ischemia.

Treatment

Sublingual nitroglycerin is the medication of choice for acute management; it acts in about 1–2 minutes. As soon as the attack begins, one fresh tablet is placed under the tongue. This may be repeated at 3- to 5-minute intervals, but if pain is not relieved or improving after 5 minutes, the patient should call 9-1-1; *pain not responding to three tablets or lasting more than 20 minutes may represent evolving infarction*. The dosage (0.3, 0.4, or 0.6 mg) and the number of tablets to be used before seeking further medical

attention must be individualized. Nitroglycerin buccal spray is also available as a metered (0.4 mg) delivery system. It has the advantage of being more convenient for patients who have difficulty handling the pills and of being more stable.

Prevention of Further Attacks

A. Aggravating Factors

Angina may be aggravated by hypertension, LV failure, arrhythmia (usually tachycardias), strenuous activity, cold temperatures, and emotional states. These factors should be identified and treated when possible.

B. Nitroglycerin

Nitroglycerin, 0.3–0.6 mg sublingually or 0.4–0.8 mg translingually by spray, should be taken 5 minutes before any activity likely to precipitate angina. Sublingual isosorbide dinitrate (2.5–5 mg) is only slightly longer-acting than sublingual nitroglycerin.

C. Long-Acting Nitrates

Longer-acting nitrate preparations include isosorbide dinitrate, 10–40 mg orally three times daily; isosorbide mononitrate, 10–40 mg orally twice daily or 60–120 mg once daily in a sustained-release preparation; oral sustained-release nitroglycerin preparations, 6.25–12.5 mg two to four times daily; nitroglycerin ointment, 2% ointment, 0.5–2 inches (7.5–30 mg in the morning and 6 hours later); and transdermal nitroglycerin patches that deliver nitroglycerin at rates of 0.2, 0.4, and 0.6 mg/hour rate (0.1–0.8 mg/hour), and should be taken off after 12–14 hours of use for a 10–12 hour patch-free interval daily. The main limitation to long-term nitrate therapy is *tolerance*, which can be limited by using a regimen that includes a minimum 8- to 10-hour period per day without nitrates. Isosorbide dinitrate can be given three times daily, with the last dose after dinner, or longer-acting isosorbide mononitrate once daily. Transdermal nitrate preparations should be removed overnight in most patients.

Nitrate therapy is often limited by headache. Other side effects include nausea, light-headedness, and hypotension. Importantly, phosphodiesterase inhibitors used commonly for erectile dysfunction should not be taken within 24 hours of nitrate use.

D. Beta-Blockers

Beta-blockers are the only antianginal agents that have been demonstrated to prolong life in patients with coronary disease (post-MI). *Beta-blockers should be considered for first-line therapy in most patients with chronic angina* and are recommended as such by the stable ischemic heart disease guidelines.

Beta-blockers with intrinsic sympathomimetic activity, such as pindolol, are less desirable because they may exacerbate angina in some individuals and have not been effective in secondary prevention trials. Otherwise, despite differences in cardioselectivity, vasodilation, and lipid solubility all beta-blockers seem to be equally efficacious in the treatment of stable ischemic heart disease. The pharmacology and side effects of the beta-blockers are discussed in Chapter 13 (see Tables 13–10 and 13–11). The dosages of all these medications when given for angina are similar. The major contraindications are severe bronchospastic disease, bradyarrhythmias, and decompensated HF.

E. Ranolazine

Ranolazine is indicated for chronic angina. Ranolazine has no effect on heart rate and BP, and it has been shown in clinical trials to prolong exercise duration and time to angina, both as monotherapy and when administered with conventional antianginal therapy. It is safe to use with erectile dysfunction medications. The usual dose is 500 mg orally twice a day. Because it can cause QT prolongation, it is contraindicated in patients with existing QT prolongation; in patients taking QT prolonging medications, such as class I or III antiarrhythmics (eg, quinidine, dofetilide, sotalol); and in those taking potent and moderate CYP450 3A inhibitors (eg, clarithromycin and rifampin). Of interest, in spite of the QT prolongation, there is a significantly lower rate of ventricular arrhythmias with its use following ACSs, as shown in the MERLIN trial.

F. Calcium Channel Blocking Agents

Unlike the beta-blockers, calcium channel blockers have *not* been shown to reduce mortality postinfarction and in some cases have increased ischemia and mortality rates. This appears to be the case with some dihydropyridines (eg, nifedipine) and with diltiazem and verapamil in patients with clinical HF or moderate to severe LV dysfunction. Meta-analyses have suggested that short-acting nifedipine in moderate to high doses causes an *increase* in mortality. It is uncertain whether these findings are relevant to longer-acting dihydropyridines. Nevertheless, considering the uncertainties and the lack of demonstrated favorable effect on outcomes, calcium channel blockers should be considered third-line anti-ischemic medications in the postinfarction patient. Similarly, these agents, with the exception of amlodipine (which proved safe in patients with HF in the PRAISE-2 trial), should be avoided in patients with HF or low EFs.

The pharmacologic effects and side effects of the calcium channel blockers are discussed in Chapter 13 and summarized in Table 13–8. Diltiazem, amlodipine, and verapamil are preferable because they produce less reflex tachycardia and because the former, at least, may cause fewer side effects. Nifedipine, nicardipine, and amlodipine are also approved agents for angina. Isradipine, felodipine, and nisoldipine are not approved for angina but probably are as effective as the other dihydropyridines.

G. Ivabradine

Ivabradine selectively blocks the I_f current and specifically lowers heart rate. It has been shown to reduce angina in patients with chronic stable angina and is approved in Europe. However, the SIGNIFY trial found no overall

difference in clinical outcomes in patients without HF and angina and that there may have been harm for patients with significant angina with regard to outcomes of cardiovascular death and MI.

H. Alternative and Combination Therapies

Patients who do not respond to one class of antianginal medication often respond to another. It may, therefore, be worthwhile to use an alternative agent before progressing to combinations. *The stable ischemic heart disease guidelines recommend starting with a beta-blocker as initial therapy, followed by long-acting nitrates, calcium channel blockers, or ranolazine.* A few patients will have further response to a regimen including all four agents.

I. Platelet-Inhibiting Agents

Several studies have demonstrated the benefit of antiplatelet medications for patients with stable and unstable vascular disease. Therefore, *unless contraindicated, aspirin (81 mg orally daily) should be prescribed for all patients with angina.* A $P2Y_{12}$ inhibitor **clopidogrel,** 75 mg orally daily, reduces vascular events in patients with stable vascular disease (as an alternative to aspirin) and in patients with ACSs (in addition to aspirin). Thus, it is also a good alternative in aspirin-intolerant patients. Clopidogrel in addition to aspirin did not reduce MI, stroke, or cardiovascular death in the CHARISMA trial of patients with CVD or multiple risk factors, with about a 50% increase in bleeding. However, it might be reasonable to use combination clopidogrel and aspirin for certain high-risk patients with established coronary disease, as tested in the Dual Antiplatelet Therapy (DAPT) trial. Specifically, *prolonged use of dual antiplatelet therapy with aspirin and clopidogrel may be beneficial in patients post–percutaneous stenting with drug-eluting stents who have a low bleeding risk.*

Ticagrelor, a $P2Y_{12}$ inhibitor, has been shown to reduce cardiovascular events in patients with ACSs. Additionally, in patients with prior MI, long-term treatment with ticagrelor plus aspirin reduced cardiovascular events compared to aspirin alone. In patients with peripheral artery disease, ticagrelor monotherapy did *not* reduce cardiovascular events compared to clopidogrel.

Vorapaxar is an inhibitor of the protease-activated receptor-1. It was shown to reduce cardiovascular events for patients with stable atherosclerosis with a history of MI or peripheral artery disease in the TRA 2P trial. It is contraindicated for patients with a history of stroke or TIA due to increased risk of intracranial hemorrhage.

Rivaroxaban, a direct factor Xa inhibitor, when used at a dose of 2.5 mg twice daily in addition to low-dose aspirin, was found to reduce cardiovascular events including cardiovascular death, MI, or stroke when compared to aspirin monotherapy in patients with known CAD or peripheral artery disease. This agent is approved and provides another option for patients.

Guidelines recommend *dual antiplatelet therapy (aspirin and $P2Y_{12}$ therapy) in patients with recent MI (within 1 year) or recent stenting (within 6 months) and for prolonged therapy (more than 1 year) in patients at high ischemic risk (multivessel coronary disease or polyvascular disease) and low bleeding risk.*

J. Risk Reduction

Patients with coronary disease should undergo aggressive **risk factor modification.** This approach, with a particular focus on statin treatment, treating hypertension, stopping smoking, and exercise and weight control (especially for patients with metabolic syndrome or at risk for diabetes), may markedly improve outcomes. For patients with diabetes and CVD, there is uncertainty about the optimal target blood sugar control. The ADVANCE trial suggested some benefit for tight blood sugar control with target HbA_{1C} of 6.5% or less, but the ACCORD trial found that routine aggressive targeting for blood sugar control to HbA_{1C} to less than 6.0% in patients with diabetes and coronary disease was associated with *increased* mortality. Therefore, *tight blood sugar control should be avoided particularly in patients with a history of severe hypoglycemia, long-standing diabetes, and advanced vascular disease.* Aggressive BP control (target systolic BP less than 120 mm Hg) in the ACCORD trial was *not* associated with reduction in CHD events despite reducing stroke. In contrast, the SPRINT trial, which did not include patients with diabetes, demonstrated a reduction in cardiovascular events in patients with a reduction in death from any cause and reduction in MI with a goal systolic BP of less than 120 mm Hg versus of goal of less than 140 mm Hg. Some increase in adverse events was noted. Based on this and the totality of results, *the AHA has recommended defining hypertension at the 130 mm Hg level.*

K. Revascularization

1. Indications—There is general agreement that otherwise healthy patients in the following groups should undergo revascularization: (1) patients with unacceptable symptoms despite medical therapy to its tolerable limits; (2) patients with left main coronary artery stenosis greater than 50% with or without symptoms; (3) patients with three-vessel disease with LV dysfunction (EF less than 50% or previous transmural infarction); (4) patients with unstable angina who after symptom control by medical therapy continue to exhibit ischemia on exercise testing or monitoring; and (5) post-MI patients with continuing angina or severe ischemia on noninvasive testing. The use of revascularization for patients with ACSs and acute ST-segment elevation MI (STEMI) is discussed below.

Data from the COURAGE trial have shown that for patients with chronic angina and disease suitable for PCI, PCI in addition to stringent guideline-directed medical therapy aimed at both risk reduction and anti-anginal care offers no mortality benefit beyond excellent medical therapy alone, and relatively moderate long-term symptomatic improvement. Therefore, *for patients with mild to moderate CAD and limited symptoms, revascularization may not provide significant functional status quality-of-life benefit.* For patients with moderate to significant coronary stenosis, such as those who have two-vessel disease associated with underlying LV dysfunction, anatomically critical lesions

(greater than 90% proximal stenoses, especially of the proximal left anterior descending artery), or physiologic evidence of severe ischemia (early positive exercise tests, large exercise-induced thallium scintigraphic defects, or frequent episodes of ischemia on ambulatory monitoring), a heart team consisting of revascularization physicians (interventional cardiologists and surgeons) may be required to review and provide patients with the best revascularization options. More recently, another study examined the role of PCI revascularization along with optimal guideline-directed medical therapy versus optimal guideline-directed medical therapy alone in 700 randomized patients with ischemic cardiomyopathy (EF less than 35%) and myocardial viability. Compared with optimal medical therapy alone, PCI did *not* improve mortality, rate of hospitalization for HF, or EF.

The ISCHEMIA trial found that for patients with moderate to severe ischemia on stress testing, coronary angiography and revascularization did not reduce the risk of cardiovascular death, MI, hospitalization for unstable angina, HF, or resuscitated cardiac arrest. Thus, in the context of optimal medical therapy to prevent cardiovascular events, a higher threshold for whom to evaluate with stress tests and coronary angiography may be reasonable.

2. Type of procedure—

A. Percutaneous coronary intervention including stenting—PCI, including balloon angioplasty and coronary stenting, can effectively open stenotic coronary arteries. Coronary stenting, with either bare metal stents or drug-eluting stents, has substantially reduced restenosis. Stenting can also be used selectively for left main coronary stenosis, particularly when CABG is contraindicated or deemed high risk.

PCI is possible but often less successful in bypass graft stenoses. Experienced operators are able to successfully dilate more than 90% of lesions attempted. The major early complication is intimal dissection with vessel occlusion, although this is rare with coronary stenting. The use of intravenous platelet glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) substantially reduces the rate of periprocedural MI, and placement of intracoronary stents markedly improves initial and long-term angiographic results, especially with complex and long lesions. After PCI, all patients should have CK-MB and troponin measured. The definition of a *periprocedural infarction* has been debated, with many experts advocating for a clinical definition that incorporates different enzyme cutpoints, angiographic findings, and electrocardiographic evidence. Acute thrombosis after stent placement can largely be prevented by aggressive antithrombotic therapy (long-term aspirin, 81–325 mg, plus clopidogrel, 300–600 mg loading dose followed by 75 mg daily, for between 30 days and 1 year, and with acute use of platelet glycoprotein IIb/IIIa inhibitors).

A major limitation with PCI has been restenosis, which occurs in the first 6 months in less than 10% of vessels treated with drug-eluting stents, 15–30% of vessels treated with bare metal stents, and 30–40% of vessels without stenting. Factors associated with higher restenosis rates include diabetes, small luminal diameter, longer and more complex lesions, and lesions at coronary ostia or in the left anterior descending coronary artery. Drug-eluting stents that elute antiproliferative agents, such as sirolimus, everolimus, zotarolimus, or paclitaxel, have substantially reduced restenosis. In-stent restenosis is often treated with restenting with drug-eluting stents, and rarely with brachytherapy. The nearly 2 million PCIs performed worldwide per year far exceed the number of CABG operations, but the rationale for many of the procedures performed in patients with stable angina should be for angina symptom reduction. Moreover, data published in 2021 reported that 706,263 PCIs were performed in the United States from 2018 to 2019.

The role of routine functional stress testing following PCI to improve patient outcomes was analyzed in a randomized study of 1706 patients. There was no difference in all-cause death, MI, or hospitalization for unstable angina between the those assigned to surveillance stress testing at 1 year following PCI or those receiving standard care, strongly arguing *against* a role for routine stress testing in asymptomatic patients post-PCI.

The COURAGE trial and the ORBITA sham-controlled trial have confirmed earlier studies in showing that, even for patients with moderate anginal symptoms and positive stress tests, PCI provides no benefit over medical therapy with respect to death or MI. PCI was more effective at relieving angina, although most patients in the medical group had improvement in symptoms. PCI was also not more effective than optimal medical therapy for exercise time in patients with one vessel coronary disease. Thus, *in patients with mild or moderate stable symptoms, aggressive lipid-lowering and antianginal therapy may be a preferable initial strategy, reserving PCI for patients with significant and refractory symptoms or for those who are unable to take the prescribed medicines.*

Several studies of PCI, including those with drug-eluting stents, versus CABG in patients with multivessel disease have been reported. The SYNTAX trial as well as previously performed trials with drug-eluting stent use in PCI patients show comparable mortality and infarction rates over follow-up periods of 1–3 years but a high rate (approximately 40%) of repeat procedures following PCI. Stroke rates are higher with CABG. As a result, the choice of revascularization procedure may depend on details of coronary anatomy and is often a matter of patient preference. However, it should be noted that less than 20% of patients with multivessel disease meet the entry criteria for the clinical trials, so these results cannot be generalized to all multivessel disease patients. Outcomes with percutaneous revascularization in patients with diabetes have generally been inferior to those with CABG. The FREEDOM trial demonstrated that *CABG surgery was superior to PCI with regard to death, MI, and stroke for patients with diabetes and multivessel coronary disease* at 5 years across all subgroups of SYNTAX score anatomy.

B. Coronary artery bypass grafting—CABG can be accomplished with a very low mortality rate (1–3%) in otherwise healthy patients with preserved cardiac function. However, the mortality rate of this procedure rises to 4–8%

in older individuals and in patients who have had a prior CABG.

Grafts using one or both **internal mammary arteries** (usually to the left anterior descending artery or its branches) provide the best long-term results in terms of patency and flow. Segments of the saphenous vein (or, less optimally, other veins) or the radial artery interposed between the aorta and the coronary arteries distal to the obstructions are also used. One to five distal anastomoses are commonly performed.

Minimally invasive surgical techniques may involve a limited sternotomy, lateral thoracotomy (MIDCAB), or thoracoscopy (port-access). They are more technically demanding, usually not suitable for more than two grafts, and do not have established durability. Bypass surgery can be performed both on circulatory support (on-pump) and without direct circulatory support (off-pump). Randomized trial data have not shown a benefit with off-pump bypass surgery, but minimally invasive surgical techniques allow earlier postoperative mobilization and discharge.

The operative mortality rate is increased in patients with poor LV function (LVEF less than 35%) or those requiring additional procedures (valve replacement or ventricular aneurysmectomy). Patients over 70 years of age, patients undergoing repeat procedures, or those with important noncardiac disease (especially CKD and diabetes) or poor general health also have higher operative mortality and morbidity rates, and full recovery is slow. Thus, CABG should be reserved for more severely symptomatic patients in this group. Early (1–6 months) graft patency rates average 85–90% (higher for internal mammary grafts), and subsequent graft closure rates are about 4% annually. Early graft failure is common in vessels with poor distal flow, while late closure is more frequent in patients who continue smoking and those with untreated hyperlipidemia. Antiplatelet therapy with aspirin improves graft patency rates. Smoking cessation and vigorous treatment of blood lipid abnormalities (particularly with statins) are necessary. Repeat revascularization may be necessary because of recurrent symptoms due to progressive native vessel disease and graft occlusions. Reoperation is technically demanding and less often fully successful than the initial operation. In addition, in patients with ischemic mitral regurgitation, mitral repair at the time of a CABG does *not* offer any clinical benefit.

L. Mechanical Extracorporeal Counterpulsation

Extracorporeal counterpulsation entails repetitive inflation of a high-pressure chamber surrounding the lower half of the body during the diastolic phase of the cardiac cycle for daily 1-hour sessions over a period of 7 weeks. Randomized trials have shown that extracorporeal counterpulsation reduces angina, thus it may be considered for relief of refractory angina in patients with stable coronary disease.

M. Neuromodulation

Spinal cord stimulation can be used to relieve chronic refractory angina. Spinal cord stimulators are subcutaneously implantable via a minimally invasive procedure under local anesthesia.

Prognosis

The prognosis of angina pectoris has improved with development of therapies aimed at secondary prevention. Mortality rates vary depending on the number of vessels diseased, the severity of obstruction, the status of LV function, and the presence of complex arrhythmias. Mortality rates are progressively higher in patients with one-, two-, and three-vessel disease and those with left main coronary artery obstruction (ranging from 1% per year to 25% per year). *The outlook in individual patients is unpredictable, and nearly half of the deaths are sudden.* Therefore, risk stratification is attempted. Patients with accelerating symptoms have a poorer outlook. Among stable patients, those whose exercise tolerance is severely limited by ischemia (less than 6 minutes on the Bruce treadmill protocol) and those with extensive ischemia by exercise ECG or scintigraphy have more severe anatomic disease and a poorer prognosis. The **Duke Treadmill Score,** based on a standard Bruce protocol exercise treadmill test, provides an estimate of risk of death at 1 year. The score uses time on the treadmill, amount of ST-segment depression, and presence of angina (Table 10–6).

When to Refer

All patients with new or worsening symptoms believed to represent progressive angina or a positive stress test for myocardial ischemia with continued angina despite medical therapy (or both) should be referred to a cardiologist.

When to Admit

- Patients with elevated cardiac biomarkers, ischemic ECG findings, or hemodynamic instability.
- Patients with new or worsened symptoms, possibly thought to be ischemic, but who lack high-risk features can be observed with serial ECGs and biomarkers and discharged if stress testing shows low-risk findings.

Castro-Dominguez YS et al. Predicting in-hospital mortality in patients undergoing percutaneous coronary intervention. J Am Coll Cardiol. 2021;78:216. [PMID: 33957239]

Table 10–6. Duke Treadmill Score: calculation and interpretation.

Time in minutes on Bruce protocol		= _____
–5 × amount of depression (in mm)		= _____
–4 × angina index 0 = no angina on test 1 = angina, not limiting 2 = limiting angina		= _____
Total Summed Score	**Risk Group**	**Annual Mortality**
≥ 5	Low	0.25%
–10 to 4	Intermediate	1.25%
≤ –11	High	5.25%

Knuuti J et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020; 41:407. [PMID: 31504439]
Park DW et al; POST-PCI Investigators. Routine functional testing or standard care in high-risk patients after PCI. N Engl J Med. 2022;387:905. [PMID: 36036496]
Perera D et al; REVIVED-BCIS2 Investigators. Percutaneous revascularization for ischemic left ventricular dysfunction. N Engl J Med. 2022;387:1351. [PMID: 36027563]
Writing Committee Members; Gulati M et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2021;78:e187. [PMID: 34756653]

CORONARY VASOSPASM & ANGINA OR MI WITH NORMAL CORONARY ARTERIOGRAMS

ESSENTIALS OF DIAGNOSIS

- Precordial chest pain, often occurring at rest during stress or without known precipitant, relieved rapidly by nitrates.
- ECG evidence of ischemia during pain, sometimes with ST-segment elevation.
- Angiographic demonstration of:
  - –No significant obstruction of major coronary vessels.
  - –Coronary spasm that responds to intracoronary nitroglycerin or calcium channel blockers.

General Considerations

Although most symptoms of myocardial ischemia result from fixed stenosis of the coronary arteries, intraplaque hemorrhage, or thrombosis at the site of lesions, some ischemic events may be precipitated or exacerbated by coronary vasoconstriction.

Spasm of the large coronary arteries with resulting decreased coronary blood flow may occur spontaneously or may be induced by exposure to cold, emotional stress, or vasoconstricting medications, such as ergot-derivative medications. Spasm may occur both in normal and in stenosed coronary arteries. Even MI may occur as a result of spasm in the absence of visible obstructive CHD, although most instances of such coronary spasm occur in the presence of coronary stenosis.

Cocaine can induce myocardial ischemia and infarction by causing coronary artery vasoconstriction or by increasing myocardial energy requirements. It also may contribute to accelerated atherosclerosis and thrombosis. The ischemia in **Prinzmetal (variant) angina** usually results from coronary vasoconstriction. It tends to involve the right coronary artery and there may be no fixed stenoses. Myocardial ischemia may also occur in patients with normal coronary arteries as a result of disease of the coronary microcirculation or abnormal vascular reactivity. MI without obstructive coronary disease is more frequent in women and has been shown to be due to atherosclerosis or ruptured plaques in 80% of cases. The 2020 ESC guidelines recommend cardiac MRI to aid in determining the cause of MI without obstructive coronary disease.

Clinical Findings

Ischemia may be silent or result in angina pectoris.

Prinzmetal (variant) angina is a clinical syndrome in which chest pain occurs without the usual precipitating factors and is associated with ST-segment elevation rather than depression. It often affects women under 50 years of age. It characteristically occurs in the early morning, awakening patients from sleep, and is apt to be associated with arrhythmias or conduction defects. It may be diagnosed by challenge with ergonovine (a vasoconstrictor), although the results of such provocation are not specific and it entails risk.

Treatment

Patients with chest pain associated with ST-segment elevation should undergo coronary arteriography to determine whether fixed stenotic lesions are present. If they are, aggressive medical therapy or revascularization is indicated, since the presence of these lesions may represent an unstable phase of the disease. If significant lesions are not seen, there may still be endothelial disruption and plaque rupture. If spasm is suspected, avoidance of precipitants, such as cigarette smoking and cocaine, is the top priority. Episodes of coronary spasm generally respond well to nitrates, and both nitrates and calcium channel blockers (including long-acting nifedipine, diltiazem, or amlodipine [see Table 13–8]) are effective prophylactically. By allowing unopposed alpha-1-mediated vasoconstriction, beta-blockers have exacerbated coronary vasospasm, but they may have a role in management of patients in whom spasm is associated with fixed stenoses.

When to Refer

All patients with persistent symptoms of chest pain that may represent spasm should be referred to a cardiologist.

ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

ESSENTIALS OF DIAGNOSIS

- Distinction in ACS between patients with and without ST-segment elevation at presentation is essential to determine need for reperfusion therapy.
- Fibrinolytic therapy is harmful in ACS without ST-segment elevation, unlike with ST-segment elevation, where acute reperfusion saves lives.
- Antiplatelet and anticoagulation therapies and coronary intervention are mainstays of treatment.

General Considerations

***ACSs** comprise the spectrum of unstable cardiac ischemia from unstable angina to acute MI.* ACSs are classified based on the presenting ECG as either **ST-segment elevation MI (STEMI)** or **non–ST-segment elevation MI (NSTEMI)**. This allows for immediate classification and guides determination of whether patients should be considered for acute reperfusion therapy. The evolution of cardiac biomarkers then allows determination of whether MI has occurred.

ACSs represent a *dynamic state* in which patients frequently shift from one category to another, as new ST elevation can develop after presentation and cardiac biomarkers can become abnormal with recurrent ischemic episodes.

Clinical Findings

A. Symptoms and Signs

Patients with ACSs generally have symptoms and signs of myocardial ischemia either at rest or with minimal exertion. These symptoms and signs are similar to the chronic angina symptoms described above, consisting of substernal chest pain or discomfort that may radiate to the jaw, left shoulder or arm. Dyspnea, nausea, diaphoresis, or syncope may either accompany the chest discomfort or may be the only symptom of ACS. *About one-third of patients with MI have no chest pain per se*—these patients tend to be older, female, have diabetes, and be at higher risk for subsequent mortality. Patients with ACSs have signs of HF in about 10% of cases, and this is also associated with higher risk of death.

Many hospitals have developed **chest pain observation units** to provide a systematic approach toward serial risk stratification to improve the triage process. In many cases, those who have not experienced new chest pain and have insignificant ECG changes and no cardiac biomarker elevation undergo treadmill exercise tests or imaging procedures to exclude ischemia at the end of an 8- to 24-hour period and are discharged directly from the emergency department if these tests are negative.

B. Laboratory Findings

Depending on the time from symptom onset to presentation, initial laboratory findings may be normal. The markers of cardiac myocyte necrosis (**myoglobin**, **CK-MB,** and **troponin I and T**) may all be used to identify acute MI, although *high-sensitivity troponin is the recommended biomarker to diagnose acute MI* (see Laboratory Findings, Acute Myocardial Infarction with ST-Segment Elevation). In patients with STEMI, these initial markers are often within normal limits as the patient is being rushed to immediate reperfusion. In patients without ST-segment elevation, it is the presence of abnormal CK-MB or troponin values that are associated with myocyte necrosis and the diagnosis of MI. High-sensitivity troponin assays allow rapid assessment of MI in emergency departments by using 1- or 2-hour rule out algorithms. The universal definition of MI is a rise of cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least one of the following: symptoms of ischemia, ECG changes of new ischemia, new Q waves, or imaging evidence of new loss of viable myocardium or new wall motion abnormality.

Serum creatinine is an important determinant of risk, and estimated creatinine clearance is important to guide dosing of certain antithrombotics, including eptifibatide and enoxaparin.

C. ECG

Many patients with ACSs will exhibit ECG changes during pain—either ST-segment elevation, ST-segment depression, or T wave flattening or inversion. Dynamic ST-segment shift is the most specific for ACS. ST-segment elevation in lead AVR suggests left main or three-vessel disease.

Treatment

A. General Measures

Treatment of ACSs without ST elevation should be multifaceted. Patients who are at medium or high risk should be hospitalized, maintained at bed rest or at very limited activity for the first 24 hours, monitored, and given supplemental oxygen. Sedation with a benzodiazepine agent may help if anxiety is present.

B. Specific Measures

Figure 10–8 provides an algorithm for initial management of NSTEMI.

C. Antiplatelet and Anticoagulation Therapy

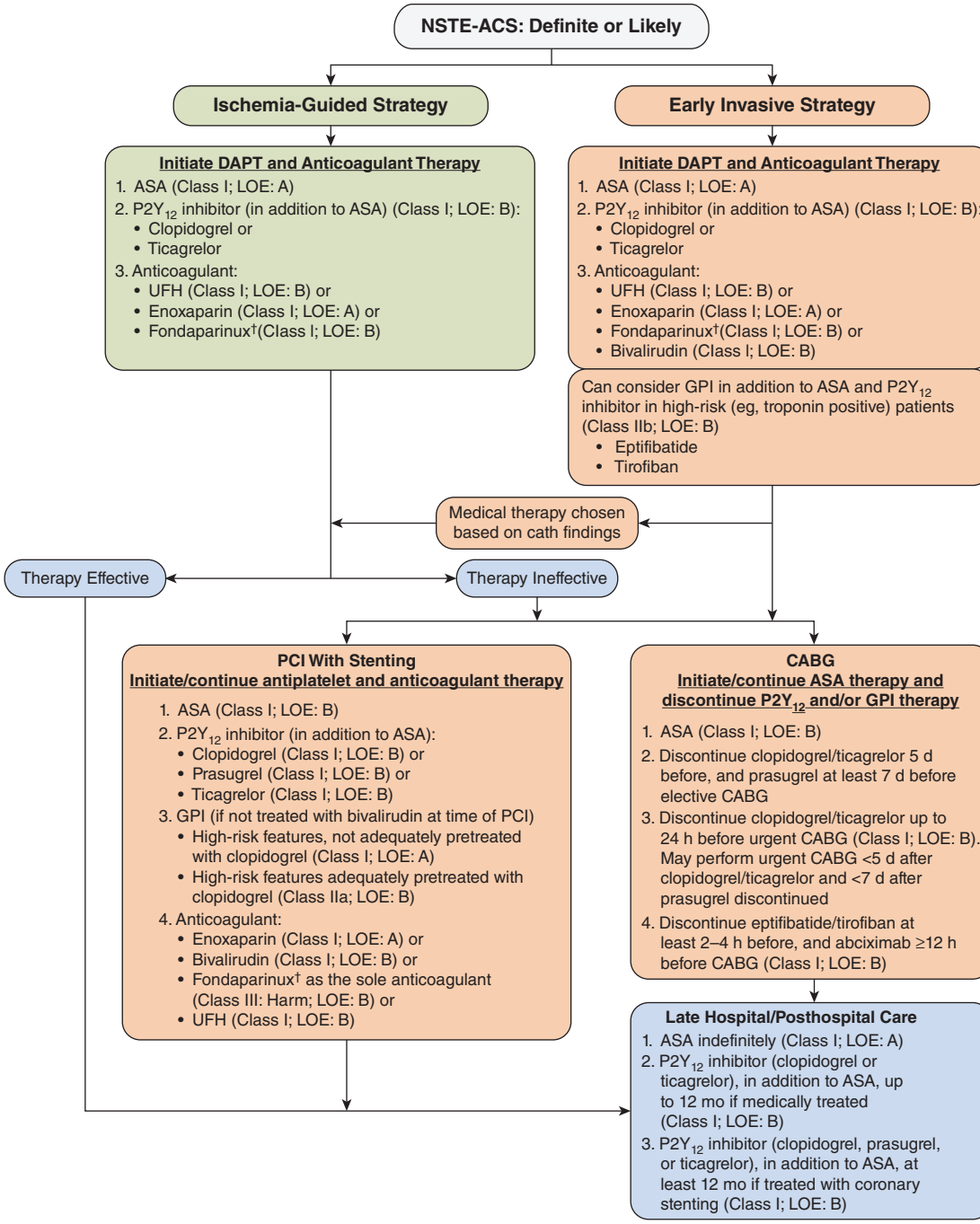
Patients should receive a combination of antiplatelet and anticoagulant agents on presentation. *Fibrinolytic therapy should be avoided in patients without ST-segment elevation since they generally do not have an acute coronary occlusion, and the risk of such therapy appears to outweigh the benefit.*

1. Antiplatelet therapy—

a. Aspirin—Aspirin, 162–325 mg loading dose, then 81 mg daily, should be commenced immediately and continued for the first month. The 2020 ESC guidelines for longer-term aspirin treatment recommend aspirin 75–100 mg/day as preferable to higher doses with or without coronary stenting.

b. P2Y12 inhibitors—ACC/AHA guidelines call for either a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel [at the time of PCI], or ticagrelor) as a class I recommendation. The ESC guidelines provide a stronger recommendation for a $P2Y_{12}$ inhibitor upfront, as a class IA recommendation for all patients. Both sets of guidelines recommend postponing elective CABG surgery for at least 5 days after the last dose of clopidogrel or ticagrelor and at least 7 days after the last dose of prasugrel, due to risk of bleeding.

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial demonstrated a 20% reduction in



▲ **Figure 10–8.** Algorithm for management of patients with definite or likely NSTE-ACS.*
*See corresponding full-sentence recommendations and their explanatory footnotes.
†In patients who have been treated with fondaparinux (as upfront therapy) who are undergoing PCI, an additional anticoagulant with anti-IIa activity should be administered at the time of PCI because of the risk of catheter thrombosis. ASA indicates aspirin; CABG, coronary artery bypass graft; cath, catheter; COR, Class of Recommendation; DAPT, dual antiplatelet therapy; GPI, glycoprotein IIb/IIIa inhibitor; LOE, Level of Evidence; NSTE-ACS, non–ST-elevation ACS; PCI, percutaneous coronary intervention; pts, patients; and UFH, unfractionated heparin. (Reproduced with permission from Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in J Am Coll Cardiol. 2014 Dec 23;64(24):2713-4. Dosage error in article text]. J Am Coll Cardiol. 2014;64(24):e139-e228.)

the composite end point of cardiovascular death, MI, and stroke with the addition of clopidogrel (300-mg loading dose, 75 mg/day for 9–12 months) to aspirin in patients with non–ST-segment elevation ACSs. The large CURRENT trial showed that "double-dose" clopidogrel (600-mg initial oral loading dose, followed by 150 mg orally daily) for 7 days reduced stent thrombosis with a modest increase in major (but not fatal) bleeding and, therefore, it is an option for patients with ACS undergoing PCI.

The ESC guidelines recommend ticagrelor for all patients at moderate to high risk for ACS (class I recommendation). Prasugrel is recommended for patients who have not yet received another $P2Y_{12}$ inhibitor, for whom a PCI is planned, and who are not at high risk for life-threatening bleeding. Clopidogrel is reserved for patients who cannot receive either ticagrelor or prasugrel. Some studies have shown an association between assays of residual platelet function and thrombotic risk during $P2Y_{12}$ inhibitor therapy, and both the European and the US guidelines do not recommend routine platelet function testing to guide therapy (class IIb recommendation).

Prasugrel is both more potent and has a faster onset of action than clopidogrel. The TRITON trial compared prasugrel with clopidogrel in patients with STEMI or NSTEMI in whom PCI was planned; prasugrel resulted in a 19% relative reduction in death from cardiovascular causes, MI, or stroke, at the expense of an increase in serious bleeding (including fatal bleeding). Stent thrombosis was reduced by half. Because patients with prior stroke or TIA had higher risk of intracranial hemorrhage, prasugrel is contraindicated in such patients. Bleeding was also higher in patients with low body weight (less than 60 kg) and age 75 years or older, and caution should be used in these populations. For patients with STEMI treated with PCI, prasugrel appears to be especially effective (compared to clopidogrel) without a substantial increase in bleeding. For patients who will not receive revascularization, prasugrel, when compared to clopidogrel, had no overall benefit in the TRILOGY trial (the dose of prasugrel was lowered for older adults). Prasugrel appears to be at least comparable to ticagrelor for patients with STEMI regarding safety and efficacy based on the ISAR-REACT 5 trial.

Ticagrelor has a faster onset of action than clopidogrel and a more consistent and potent effect. The PLATO trial showed that when ticagrelor was started at the time of presentation in ACS patients (UA/NSTEMI and STEMI), it reduced cardiovascular death, MI, and stroke by 16% when compared with clopidogrel. In addition, there was a 22% relative risk reduction in mortality with ticagrelor. The overall rates of bleeding were similar between ticagrelor and clopidogrel, although non–CABG-related bleeding was modestly higher. The finding of a lesser treatment effect in the United States may have been related to use of higher-dose aspirin, and thus when using ticagrelor, low-dose aspirin (81 mg/day) is recommended.

c. Glycoprotein IIB/IIIA inhibitors—Small-molecule inhibitors of the platelet glycoprotein IIb/IIIa receptor are useful adjuncts in high-risk patients (usually defined by fluctuating ST-segment depression or positive biomarkers) with ACSs, particularly when they are undergoing PCI. Tirofiban, 25 mcg/kg over 3 minutes, followed by 0.15 mcg/kg/min, and eptifibatide, 180 mcg/kg bolus followed by a continuous infusion of 2 mcg/kg/min, have both been shown to be effective. Downward dose adjustments of the infusions are required in patients with reduced kidney function. The bolus or loading dose remains unadjusted. For example, if the estimated creatinine clearance is below 50 mL/min, the eptifibatide infusion should be cut in half to 1 mcg/kg/min.

2. Anticoagulant therapy—

a. Heparin—Several trials have shown that LMWH (enoxaparin 1 mg/kg subcutaneously every 12 hours) is somewhat more effective than unfractionated heparin in preventing recurrent ischemic events in the setting of ACSs. However, the SYNERGY trial showed that unfractionated heparin and enoxaparin had similar rates of death or (re)infarction in the setting of frequent early coronary intervention.

b. Fondaparinux—Fondaparinux, a specific factor Xa inhibitor given in a dose of 2.5 mg subcutaneously once a day, was found in the OASIS-5 trial to be equally effective as enoxaparin among 20,000 patients at preventing early death, MI, and refractory ischemia, and resulted in a 50% reduction in major bleeding. This reduction in major bleeding translated into a significant reduction in mortality (and in death or MI) at 30 days. While catheter-related thrombosis was more common during coronary intervention procedures with fondaparinux, the FUTURA trial found that it can be controlled by adding unfractionated heparin (in a dose of 85 U/kg without glycoprotein IIb/IIIa inhibitors, and 60 U/kg with glycoprotein IIb/IIIa inhibitors) during the procedure. Guidelines recommend fondaparinux, describing it as especially favorable for patients who are initially treated medically and who are at high risk for bleeding, such as older adults.

c. Direct thrombin inhibitors—The ACUITY trial showed that bivalirudin appears to be a reasonable alternative to heparin (unfractionated heparin or enoxaparin) plus a glycoprotein IIb/IIIa antagonist for many patients with ACSs who are undergoing early coronary intervention. Bivalirudin (without routine glycoprotein IIb/IIIa inhibitor) is associated with substantially less bleeding than heparin plus glycoprotein IIb/IIIa inhibitor, although it may have numerically increased cardiovascular events. The ISAR-REACT-4 trial showed that bivalirudin has similar efficacy compared to abciximab but better bleeding outcomes in NSTEMI patients. Bivalrudin does not have an FDA-approved indication for NSTEMI care.

D. Temporary Discontinuation of Antiplatelet Therapy for Procedures

Patients who have had recent coronary stents are at risk for thrombotic events, including stent thrombosis, if $P2Y_{12}$ inhibitors are discontinued for procedures (eg, dental procedures or colonoscopy). If possible, these procedures should be delayed until the end of the necessary treatment period with $P2Y_{12}$ inhibitors, which generally is at least 1 month with bare metal stents and 3–6 months with

drug-eluting stents. With current generation drug-eluting stents, elective stenting patients with bleeding risk may have $P2Y_{12}$ inhibitors stopped before 3 months. Before that time, if a procedure is necessary, risk and benefit of continuing the antiplatelet therapy through the time of the procedure should be assessed. Aspirin should generally be continued throughout the period of the procedure. Patients with polymer-free drug coated stents who are at high risk for bleeding and receiving a short course of dual antiplatelet therapy had fewer cardiovascular and bleeding events. Likewise, in the MASTER-DAPT trial, patients at high risk for bleeding treated for 1 month with DAPT had noninferior outcomes with respect to major adverse cardiac events compared with longer duration DAPT with lower rates of bleeding. *A cardiologist should be consulted before temporary discontinuation of these agents.*

E. Nitroglycerin

Nitrates are first-line therapy for patients with ACSs presenting with chest pain. Nonparenteral therapy with sublingual or oral agents or nitroglycerin ointment is usually sufficient. If pain persists or recurs, intravenous nitroglycerin should be started. The usual initial dosage is 10 mcg/min. The dosage should be titrated upward by 10–20 mcg/min (to a maximum of 200 mcg/min) until angina disappears or mean arterial pressure drops by 10%. Careful—usually continuous—BP monitoring is required when intravenous nitroglycerin is used. Avoid hypotension (systolic BP less than 100 mm Hg). Tolerance to continuous nitrate infusion is common.

F. Beta-Blockers

Beta-blockers are an important part of the initial treatment of unstable angina unless otherwise contraindicated. The pharmacology of these agents is discussed in Chapter 13 and summarized in Tables 13–10 and 13–11. Use of agents with intrinsic sympathomimetic activity should be avoided in this setting. Oral medication is adequate in most patients, but intravenous treatment with metoprolol, given as three 5-mg doses 5 minutes apart as tolerated and in the absence of HF, achieves a more rapid effect. Oral therapy should be titrated upward as BP permits.

G. Calcium Channel Blockers

Calcium channel blockers have *not* been shown to favorably affect outcome in unstable angina, and they should be used primarily as third-line therapy in patients with continuing angina who are taking nitrates and beta-blockers or those who are not candidates for these medications. In the presence of nitrates and without accompanying beta-blockers, diltiazem or verapamil is preferred, since nifedipine and the other dihydropyridines are more likely to cause reflex tachycardia or hypotension. The initial dosage should be low, but upward titration should proceed steadily (see Table 13–8).

H. Statins

The PROVE-IT trial provides evidence for starting a statin in the days immediately following an ACS. In this trial, more intensive therapy with atorvastatin 80 mg/day, regardless of total or LDL cholesterol level, improved outcome compared to pravastatin 40 mg/day, with the curves of death or major cardiovascular event separating as early as 3 months after starting therapy. *High-intensity statins are recommended for all patients with ACSs.*

Indications for Coronary Angiography

For patients with ACS, including NSTEMI, *risk stratification* is important for determining intensity of care. Several therapies, including glycoprotein IIb/IIIa inhibitors, LMWH heparin, and early invasive catheterization, have been shown to have the greatest benefit in higher-risk patients with ACS. As outlined in the ACC/AHA guidelines, patients with any high-risk feature (Table 10–7) generally warrant an early invasive strategy with catheterization and revascularization. For patients without these high-risk features, either an invasive or noninvasive approach, using exercise (or pharmacologic stress for patients unable to exercise) stress testing to identify patients who have residual ischemia, are at high risk, or both, can be used. Moreover, based on the ICTUS trial, a strategy based on selective coronary angiography and revascularization for instability or inducible ischemia, or both, even for patients with positive troponin, is acceptable (ACC/AHA class IIb recommendation).

Two risk-stratification tools are available that can be used at the bedside, the **GRACE Risk Score** (http://www.outcomes-umassmed.org/grace) and the **TIMI Risk Score** (http://www.timi.org). The GRACE Risk Score, which applies to patients with or without ST elevation, was developed in a more generalizable registry population and has better discrimination of risk. It includes age (as a continuous variable), Killip class, BP, ST-segment deviation, cardiac arrest at presentation, serum creatinine, elevated creatine kinase (CK)-MB or troponin, and heart rate. The TIMI Risk Score includes seven variables: age 65 years or older, three or more cardiac risk factors, prior coronary stenosis of 50% or more, ST-segment deviation, two anginal events in prior 24 hours, aspirin in prior 7 days, and elevated cardiac markers.

When to Refer

- All patients with acute MI should be referred to a cardiologist.
- Patients who are taking a $P2Y_{12}$ inhibitor following coronary stenting should consult a cardiologist before discontinuing treatment for nonemergency procedures.

Collet JP et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021;42:1289. [PMID: 32860058]

Valgimigli M et al; MASTER DAPT Investigators. Dual antiplatelet therapy after PCI in patients at high bleeding risk. N Engl J Med. 2021;385:1643. [PMID: 34449185]

Writing Committee Members; Lawton JS et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022;79:e21. Erratum in: J Am Coll Cardiol. 2022;79:1547. [PMID: 34895950]

Table 10–7. Indications for catheterization and percutaneous coronary intervention.[1]

ACSs (unstable angina and non–ST-elevation MI)	
Class I	Early invasive strategy for any of the following high-risk indicators:
	Recurrent angina/ischemia at rest or with low-level activity
	Elevated troponin
	ST-segment depression
	Recurrent ischemia with evidence of HF
	High-risk stress test result
	EF < 40%
	Hemodynamic instability
	Sustained ventricular tachycardia
	PCI within 6 months
	Prior CABG
	In the absence of these findings, either an early conservative or early invasive strategy
Class IIa	Early invasive strategy for patients with repeated presentations for ACS despite therapy
Class III	Extensive comorbidities in patients in whom benefits of revascularization are not likely to outweigh the risks
	Acute chest pain with low likelihood of ACS
Acute MI after fibrinolytic therapy	
Class I	Cardiogenic shock or acute severe HF that develops after initial presentation
	Intermediate- or high-risk findings on predischarge noninvasive ischemia testing
	Spontaneous or easily provoked myocardial ischemia
Class IIa	Failed reperfusion or reocclusion after fibrinolytic therapy
	Stable[2] patients after successful fibrinolysis, before discharge and ideally between 3 and 24 hours

[1]Class I indicates treatment is useful and effective, IIa indicates weight of evidence is in favor of usefulness/efficacy, class IIb indicates weight of evidence is less well established, and class III indicates intervention is not useful/effective and may be harmful. Level of evidence A recommendations are derived from large-scale randomized trials, and B recommendations are derived from smaller randomized trials or carefully conducted observational analyses.
[2]Although individual circumstances will vary, clinical stability is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.
ACCF/AHA, American College of Cardiology Foundation/American Heart Association; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.
Data from O'Gara PT et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127: e362–e425.

ACUTE MI WITH ST-SEGMENT ELEVATION

ESSENTIALS OF DIAGNOSIS

- Sudden but not instantaneous development of prolonged (greater than 30 minutes) anterior chest discomfort (sometimes felt as "gas" or pressure).
- Sometimes painless, masquerading as acute HF, syncope, stroke, or shock.
- ECG: ST-segment elevation or left bundle branch block.
- Immediate reperfusion treatment is warranted.
- Primary PCI within 90 minutes of first medical contact is the goal and is superior to fibrinolytic therapy.
- Fibrinolytic therapy within 30 minutes of hospital presentation is the goal and reduces mortality if given within 12 hours of onset of symptoms.

General Considerations

STEMI results, in most cases, from an occlusive coronary thrombus at the site of a preexisting (though not necessarily severe) atherosclerotic plaque. More rarely, infarction may result from prolonged vasospasm, inadequate myocardial blood flow (eg, hypotension), or excessive metabolic demand. Very rarely, MI may be caused by embolic occlusion, vasculitis, aortic root or coronary artery dissection, or aortitis. Cocaine, a cause of infarction, should be considered in young individuals without risk factors. A condition that may mimic STEMI is stress cardiomyopathy (also referred to as **tako-tsubo** or **apical ballooning syndrome**). *ST elevation connotes an acute coronary occlusion and warrants immediate reperfusion therapy with activation of emergency services.*

Clinical Findings

A. Symptoms

1. Premonitory pain—There is usually a worsening in the pattern of angina preceding the onset of symptoms of MI; classically the onset of angina occurs with minimal exertion or at rest.

2. Pain of infarction—Unlike anginal episodes, most infarctions occur *at rest*, and more commonly in the early morning. The pain is similar to angina in location and radiation but it may be more severe, and it builds up rapidly or in waves to maximum intensity over a few minutes or longer. Nitroglycerin has little effect; even opioids may not relieve the pain.

3. Associated symptoms—Patients may break out in a cold sweat, feel weak and apprehensive, and move about, seeking a position of comfort. They prefer not to lie quietly. Light-headedness, syncope, dyspnea, orthopnea, cough,

wheezing, nausea and vomiting, or abdominal bloating may be present singly or in any combination.

4. Painless infarction—One-third of patients with acute MI present *without* chest pain, and these patients tend to be undertreated and have poor outcomes. Older patients, women, and patients with diabetes mellitus are more likely to present without chest pain. As many as 25% of infarctions are detected on routine ECG without any recallable acute episode.

5. Sudden death and early arrhythmias—Of all deaths from MI, about half occur before the patients arrive at the hospital, with death presumably caused by ventricular fibrillation.

B. Signs

1. General—Patients may appear anxious and sometimes are sweating profusely. The heart rate may range from marked bradycardia (most commonly in inferior infarction) to tachycardia, low cardiac output, or arrhythmia. The BP may be high, especially in patients with previous hypertension, or low in patients with shock. Respiratory distress usually indicates HF. Fever, usually low grade, may appear after 12 hours and persist for several days.

2. Chest—The **Killip classification** is the standard way to classify HF in patients with acute MI and has powerful prognostic value. Killip class I is absence of rales and S_3, class II is rales that do not clear with coughing over one-third or less of the lung fields or presence of an S_3, class III is rales that do not clear with coughing over more than one-third of the lung fields, and class IV is cardiogenic shock (rales, hypotension, and signs of hypoperfusion).

3. Heart—The cardiac examination may be unimpressive or very abnormal. Jugular venous distention reflects RA hypertension, and a Kussmaul sign (failure of decrease of jugular venous pressure with inspiration) is suggestive of RV infarction. Soft heart sounds may indicate LV dysfunction. Atrial gallops (S_4) are the rule, whereas ventricular gallops (S_3) are less common and indicate significant LV dysfunction. Mitral regurgitation murmurs are not uncommon and may indicate papillary muscle dysfunction or, rarely, rupture. Pericardial friction rubs are uncommon in the first 24 hours but may appear later.

4. Extremities—Edema is usually not present. Cyanosis and cold temperature indicate low output. The peripheral pulses should be noted, since later shock or emboli may alter the examination.

C. Laboratory Findings

Cardiac-specific markers of myocardial damage include quantitative determinations of CK-MB, highly sensitive and conventional troponin I, and troponin T. Each of these tests may become positive as early as 4–6 hours after the onset of an MI and should be abnormal by 8–12 hours. Troponins are more sensitive and specific than CK-MB. "Highly sensitive" or "fourth-generation" troponin assays were approved in 2017. They are the standard assays in most of Europe, with a 10- to 100-fold lower limit of detection, allowing MI to be detected earlier, using the change in value over 3 hours.

Circulating levels of troponins may remain elevated for 5–7 days or longer and therefore are generally not useful for evaluating suspected early reinfarction. Elevated CK-MB generally normalizes within 24 hours, thus being more helpful for evaluation of reinfarction. Low-level elevations of troponin in patients with severe CKD may not be related to acute coronary disease but rather a function of the physiologic washout of the marker. While many conditions including chronic HF are associated with elevated levels of the high-sensitivity troponin assays, these assays may be especially useful when negative to exclude MI in patients reporting chest pain.

D. ECG

The extent of the ECG abnormalities, especially the sum of the total amount of *ST-segment deviation*, is a good indicator of the extent of acute infarction and risk of subsequent adverse events. The classic evolution of changes is from peaked ("hyperacute") T waves, to ST-segment elevation, to Q wave development, to T wave inversion. This may occur over a few hours to several days. *The evolution of new Q waves (longer than 30 msec in duration and 25% of the R wave amplitude) is diagnostic, but Q waves do not occur in 30–50% of acute infarctions* (**non–Q wave infarctions,** which are typically *not* associated with ST elevation). Left bundle branch block, especially when new (or not known to be old), in a patient with symptoms of an acute MI is considered to be a **"STEMI equivalent"**; reperfusion therapy is indicated for the affected patient. Concordant ST elevation (ie, ST elevation in leads with an overall positive QRS complex) with left bundle branch block is a specific finding indicating STEMI.

E. Chest Radiography

The CXR may demonstrate signs of HF, but these changes often lag behind the clinical findings. Signs of aortic dissection, including mediastinal widening, should be sought as a possible alternative diagnosis.

F. Echocardiography

Echocardiography provides convenient *bedside assessment* of LV global and regional function. This can help with the diagnosis and management of infarction; echocardiography has been used successfully to make judgments about admission and management of patients with suspected infarction, including in patients with ST-segment elevation or left bundle branch block of uncertain significance, since normal wall motion makes an infarction unlikely. Doppler echocardiography is generally the most convenient procedure for diagnosing postinfarction mitral regurgitation or VSD.

G. Other Noninvasive Studies

Diagnosis of MI and extent of MI can be assessed by various imaging studies in addition to echocardiography. **MRI with gadolinium contrast enhancement** is the most

sensitive test to detect and quantitate extent of infarction, with the ability to detect as little as 2 g of MI. **Technetium-99m pyrophosphate scintigraphy,** when injected at least 18 hours postinfarction, complexes with calcium in necrotic myocardium to provide a "hot spot" image of the infarction. This test is insensitive to small infarctions, and false-positive studies occur, so its use is limited to patients in whom the diagnosis by ECG and enzymes is not possible—principally those who present several days after the event or have intraoperative infarctions. **Scintigraphy with thallium-201** or **technetium-based perfusion tracers** will demonstrate "cold spots" in regions of diminished perfusion, which usually represent infarction when the radiotracer is administered at rest, but abnormalities do not distinguish recent from old damage. All of these tests may be considered after the patient has had revascularization.

H. Hemodynamic Measurements

These can be helpful in managing the patient with suspected cardiogenic shock. Use of PA catheters, however, has generally *not* been associated with better outcomes and should be limited to patients with severe hemodynamic compromise for whom the information would be anticipated to change management.

Treatment

A. Aspirin, $P2Y_{12}$ Inhibitors (Prasugrel, Ticagrelor, and Clopidogrel)

All patients with definite or suspected acute MI should receive aspirin at a dose of 162 mg or 325 mg at once regardless of whether fibrinolytic therapy is being considered or the patient has been taking aspirin. Chewable aspirin provides more rapid blood levels. Patients with a definite aspirin allergy should be treated with a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor).

$P2Y_{12}$ inhibitors, in combination with aspirin, have been shown to provide important benefits in patients with acute STEMI. Thus, guidelines call for a *$P2Y_{12}$ inhibitor to be added to aspirin for all patients with STEMI, regardless of whether reperfusion is given, and continued for at least 14 days, and generally for 1 year.* The preferred $P2Y_{12}$ inhibitors are prasugrel (60 mg orally on day 1, then 10 mg daily) or ticagrelor (180 mg orally on day 1, then 90 mg twice daily). Both of these medications demonstrated superior outcomes to clopidogrel in clinical studies of primary PCI. Clopidogrel should be administered as a loading dose of 300–600 mg orally for faster onset of action than the 75 mg maintenance dose. With fibrinolytic therapy, ticagrelor appears to be a reasonable alternative to clopidogrel, at least after an initial clopidogrel dose. Prasugrel is contraindicated in patients with a history of stroke or who are older than 75 years.

B. Reperfusion Therapy

Patients with STEMI who seek medical attention within 12 hours of the onset of symptoms should be treated with reperfusion therapy, either primary PCI or fibrinolytic therapy. Patients without ST-segment elevation (previously labeled "non–Q wave" infarctions) do not *benefit, and may derive harm, from thrombolysis.*

1. Primary percutaneous coronary intervention— Immediate coronary angiography and primary PCI (including stenting) of the infarct-related artery have been shown to be *superior* to thrombolysis when done by experienced operators in high-volume centers with rapid time from first medical contact to intervention ("door-to-balloon"). US and European guidelines call for first medical contact or *door-to-balloon times of 90 minutes or less.* Several trials have shown that if efficient transfer systems are in place, transfer of patients with acute MI from hospitals without primary PCI capability to hospitals with primary PCI capability with first door-to-device times of 120 minutes or less can improve outcome compared with fibrinolytic therapy at the presenting hospital, although this requires sophisticated systems to ensure rapid identification, transfer, and expertise in PCI. Because PCI also carries a lower risk of hemorrhagic complications, including intracranial hemorrhage, it may be the preferred strategy in many older patients and others with contraindications to fibrinolytic therapy (see Table 10–8 for factors to consider in choosing fibrinolytic therapy or primary PCI).

A. Stenting—*PCI with stenting is standard for patients with acute MI.* Although randomized trials have shown a benefit with regard to fewer repeat interventions for restenosis with the use of **drug-eluting stents** in STEMI patients, and current generation drug-eluting stents have similar or lower rates of stent thrombosis than bare metal stents, **bare metal stents** may still be used for selected patients without the ability to obtain and comply with $P2Y_{12}$ inhibitor therapy. In the subgroup of patients with cardiogenic shock, early catheterization and percutaneous or surgical revascularization are the preferred management and have been shown to reduce mortality.

Glycoprotein IIb/IIIa inhibitors, and specifically abciximab, have been shown to reduce major thrombotic events, and possibly mortality, when added to heparin for patients undergoing primary PCI.

"Facilitated" PCI, whereby a combination of medications (full- or reduced-dose fibrinolytic agents, with or without glycoprotein IIb/IIIa inhibitors) is given followed by immediate PCI, is *not* recommended. *Patients should be treated either with primary PCI or with fibrinolytic agents (and immediate rescue PCI for reperfusion failure), if it can be done promptly* as outlined in the ACC/AHA and European guidelines. Timely access to most appropriate reperfusion, including primary PCI, can be expanded with development of regional systems of care, including emergency medical systems and networks of hospitals. Patients treated with fibrinolytic therapy appear to have improved outcomes if transferred for routine coronary angiography and PCI within 24 hours. The AHA has a program called "Mission: Lifeline" to support the development of regional systems of care (http://www.heart.org/missionlifeline).

B. Antiplatelet therapy after drug-eluting or bare metal stents—In patients with an ACS, **dual antiplatelet therapy** is indicated for 1 year in all patients (including those with medical therapy and those patients

Table 10–8. Fibrinolytic therapy for acute MI.

	Alteplase; Tissue Plasminogen Activator (t-PA)	Reteplase	Tenecteplase (TNK-t-PA)	Streptokinase
Source	Recombinant DNA	Recombinant DNA	Recombinant DNA	Group C *Streptococcus*
Half-life	5 minutes	15 minutes	20 minutes	20 minutes
Usual dose	100 mg	20 units	40 mg	1.5 million units
Administration	Initial bolus of 15 mg, followed by 50 mg infused over the next 30 minutes and 35 mg over the following 60 minutes	10 units as a bolus over 2 minutes, repeated after 30 minutes	Single weight-adjusted bolus, 0.5 mg/kg	750,000 units over 20 minutes followed by 750,000 units over 40 minutes
Anticoagulation after infusion	Aspirin, 325 mg daily; heparin, 5000 units as bolus, followed by 1000 units/hour infusion, subsequently adjusted to maintain PTT 1.5–2 times control	Aspirin, 325 mg; heparin as with t-PA	Aspirin, 325 mg daily	Aspirin, 325 mg daily; there is no evidence that adjunctive heparin improves outcome following streptokinase
Clot selectivity	High	High	High	Low
Fibrinogenolysis	+	+	+	+++
Bleeding	+	+	+	+
Hypotension	+	+	+	+++
Allergic reactions	+	+	+	++
Reocclusion	10–30%	—	5–20%	5–20%
Approximate cost[1]	$10,560.43	$5964.98	$7462.63	Not available in the United States

[1]Average wholesale price (AWP, for AB-rated generic when available) for quantity listed.
PTT, partial thromboplastin time.
Source: IBM Micromedex, Red Book (electronic version). IBM Watson Health, Greenwood Village, CO, USA. Available at https://www.micromedexsolutions.com (accessed April 8, 2020). AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

undergoing revascularization irrespective of stent type). The DAPT (Dual Antiplatelet Therapy) study showed fewer death, MI, and stroke events with longer (up to 30 months) dual antiplatelet therapy for patients who had received drug-eluting stents, but it also showed more bleeding and a tendency for higher mortality. Treatment with clopidogrel for longer than 1 year after drug-eluting stents, therefore, should be individualized based on thrombotic and bleeding risks. For patients undergoing elective or stable PCI (not in the context of ACS), the duration of dual antiplatelet therapy is recommended for at least 1 month for patients receiving bare metal stents and for at least 3 months for patients receiving drug-eluting stents. These recommendations are based both on the durations of therapies during the studies evaluating the stents, and the pathophysiologic understanding of the timing of endothelialization following bare metal versus drug-eluting stent implantation.

2. Fibrinolytic therapy—

A. Benefit—Fibrinolytic therapy reduces mortality and limits infarct size in patients with STEMI (defined as 0.1 mV or more in two inferior or lateral leads or two contiguous precordial leads), or with left bundle branch block (not known to be old). The greatest benefit occurs if treatment is initiated within the first 3 hours after the onset of presentation, when up to a 50% reduction in mortality rate can be achieved. The magnitude of benefit declines rapidly thereafter, but a 10% relative mortality reduction can be achieved up to 12 hours after the onset of chest pain. The survival benefit is greatest in patients with large—usually anterior—infarctions. *Primary PCI (including stenting) of the infarct-related artery, however, is superior to thrombolysis when done by experienced operators with rapid time from first medical contact to intervention ("door-to-balloon").*

B. Contraindications—Major bleeding complications occur in 0.5–5% of patients, the most serious of which is intracranial hemorrhage. The major risk factors for intracranial bleeding are age 75 years or older, hypertension at presentation (especially over 180/110 mm Hg), low body weight (less than 70 kg), and the use of fibrin-specific fibrinolytic agents (alteplase, reteplase, tenecteplase). Although patients over age 75 years have a much higher mortality rate with acute MI and therefore may derive greater benefit, the risk of severe bleeding is also higher, particularly among patients with risk factors for intracranial hemorrhage, such as severe hypertension or recent stroke. Patients presenting more than 12 hours after the onset of chest pain may also derive a small benefit, particularly if pain and

ST-segment elevation persist, but rarely does this benefit outweigh the attendant risk.

Absolute contraindications to fibrinolytic therapy include previous hemorrhagic stroke, other strokes or cerebrovascular events within 1 year, known intracranial neoplasm, recent head trauma (including minor trauma), active internal bleeding (excluding menstruation), or suspected aortic dissection. *Relative contraindications* are BP greater than 180/110 mm Hg at presentation, other intracerebral pathology not listed above as a contraindication, known bleeding diathesis, trauma within 2–4 weeks, major surgery within 3 weeks, prolonged (more than 10 minutes) or traumatic CPR, recent (within 2–4 weeks) internal bleeding, noncompressible vascular punctures, active diabetic retinopathy, pregnancy, active peptic ulcer disease, a history of severe hypertension, current use of anticoagulants (INR greater than 2.0–3.0), and (for streptokinase) prior allergic reaction or exposure to streptokinase or anistreplase within 2 years.

c. Fibrinolytic agents—Four fibrinolytic agents are available for acute MI and are characterized in Table 10–8.

(1) Selection of a fibrinolytic agent—In the United States, most patients are treated with alteplase, reteplase, or tenecteplase. The differences in efficacy between them are small compared with the potential benefit of treating a greater proportion of appropriate candidates in a more prompt manner. The principal objective should be to administer a thrombolytic agent within 30 minutes of presentation—or even during transport. The ability to administer tenecteplase as a single bolus is an attractive feature that may facilitate earlier treatment. The combination of a reduced-dose thrombolytic given with a platelet glycoprotein IIb/IIIa inhibitor does not reduce mortality but does cause a modest increase in bleeding complications.

(2) Postfibrinolytic management—After completion of the fibrinolytic infusion, aspirin (81–325 mg/day) and anticoagulation should be continued until revascularization or for the duration of the hospital stay (or up to 8 days). Anticoagulation with LMWH (enoxaparin or fondaparinux) is preferable to unfractionated heparin.

(a) Low-molecular-weight heparin—In the EXTRACT trial, enoxaparin significantly reduced death and MI at day 30 (compared with unfractionated heparin), at the expense of a modest increase in bleeding. In patients younger than age 75, enoxaparin was given as a 30-mg intravenous bolus and 1 mg/kg subcutaneously every 12 hours; in patients aged 75 years and older, it was given with no bolus and 0.75 mg/kg subcutaneously every 12 hours. This appeared to attenuate the risk of intracranial hemorrhage in older adults that had been seen with full-dose enoxaparin. Another antithrombotic option is fondaparinux, given at a dose of 2.5 mg subcutaneously once a day. There is no benefit of fondaparinux among patients undergoing primary PCI, and fondaparinux is *not* recommended as a sole anticoagulant during PCI due to risk of catheter thrombosis.

(b) Unfractionated heparin—Anticoagulation with intravenous heparin (initial dose of 60 U/kg bolus to a maximum of 4000 units, followed by an infusion of 12 U/kg/hour to a maximum of 1000 U/hour, then adjusted to maintain an aPTT of 50–75 seconds beginning with an aPTT drawn 3 hours after thrombolytic) is continued for at least 48 hours after alteplase, reteplase, or tenecteplase, and with continuation of an anticoagulant until revascularization (if performed) or until hospital discharge (or day 8).

The VALIDATE trial found no benefit to bivalirudin compared to unfractionated heparin regarding the outcome of death, MI, or major bleeding.

(c) Prophylactic therapy against bleeding—For all patients with STEMI treated with intensive antithrombotic therapy, prophylactic treatment with PPIs, or antacids and an H_2-blocker, is advisable. However, certain PPIs, such as omeprazole and esomeprazole, may decrease the clinical effect of clopidogrel; in such cases, pantoprazole, lansoprazole, and dexlansoprazole may be better PPI options.

3. Assessment of myocardial reperfusion, recurrent ischemic pain, reinfarction—Myocardial reperfusion can be recognized clinically by the early cessation of pain and the resolution of ST-segment elevation. Although at least 50% resolution of ST-segment elevation by 90 minutes may occur without coronary reperfusion, *ST resolution is a strong predictor of better outcome*. Even with anticoagulation, 10–20% of reperfused vessels will reocclude during hospitalization, although reocclusion and reinfarction appear to be reduced following intervention. **Reinfarction**, indicated by recurrence of pain and ST-segment elevation, can be treated by readministration of a thrombolytic agent or immediate angiography and PCI.

C. General Measures

Cardiac care unit monitoring should be instituted as soon as possible. Patients without complications can be transferred to a telemetry unit after 24 hours. Activity should initially be limited to bed rest but can be advanced within 24 hours. Progressive ambulation should be started after 24–72 hours if tolerated. For patients without complications, discharge by day 4 appears to be appropriate. Low-flow oxygen therapy (2–4 L/min) should be given if oxygen saturation is reduced, but there is no value to routine use of oxygen.

D. Analgesia

An initial attempt should be made to relieve pain with sublingual nitroglycerin. However, if no response occurs after two or three tablets, intravenous opioids provide the most rapid and effective analgesia and may also reduce pulmonary congestion. Morphine sulfate, 4–8 mg, or meperidine, 50–75 mg, should be given. Subsequent small doses can be given every 15 minutes until pain abates.

NSAIDs, other than aspirin, should be avoided during hospitalization for STEMI due to increased risk of mortality, myocardial rupture, hypertension, HF, and kidney injury with their use.

E. Beta-Adrenergic Blocking Agents

Trials have shown modest short-term benefit from beta-blockers started during the first 24 hours after acute MI if there are no contraindications (metoprolol 25–50 mg orally

twice daily). Aggressive beta-blockade can increase shock, with overall harm in patients with HF. Thus, early beta-blockade should be avoided in patients with any degree of HF, evidence of low-output state, increased risk of cardiogenic shock, or other relative contraindications to beta-blockade. Carvedilol (beginning at 6.25 mg twice a day, titrated to 25 mg twice a day) was shown to be beneficial in the CAPRICORN trial following the acute phase of large MI.

F. Nitrates

Nitroglycerin is the agent of choice for continued or recurrent ischemic pain and is useful in lowering BP or relieving pulmonary congestion. However, routine nitrate administration is *not* recommended, since no improvement in outcome has been observed in the ISIS-4 or GISSI-3 trials. Nitrates should be avoided in patients who received phosphodiesterase inhibitors (sildenafil, vardenafil, and tadalafil) in the prior 24 hours.

G. ACE Inhibitors

A series of trials (SAVE, AIRE, SMILE, TRACE, GISSI-III, and ISIS-4) have shown both short- and long-term improvement in survival with ACE inhibitor therapy. The benefits are greatest in patients with an EF of 40% or less, large infarctions, or clinical evidence of HF. Because substantial amounts of the survival benefit occur on the first day, ACE inhibitor treatment should be commenced early in patients without hypotension, especially patients with large or anterior MI. Given the benefits of ACE inhibitors for patients with vascular disease, it is reasonable to *use ACE inhibitors for all patients following STEMI who do not have contraindications.*

H. Angiotensin Receptor Blockers

Although there has been inconsistency in the effects of different ARBs on mortality for patients post-MI with HF, LV dysfunction, or both, the VALIANT trial showed that valsartan 160 mg orally twice a day is *equivalent* to captopril in reducing mortality. Thus, valsartan should be used for all patients with ACE inhibitor intolerance, and is a reasonable, albeit more expensive, alternative to captopril. The combination of captopril and valsartan (at a reduced dose) was *no better than either agent alone* and resulted in more side effects.

I. Aldosterone Antagonists

The RALES trial showed that 25 mg of spironolactone can reduce the mortality rate of patients with advanced HF, and the EPHESUS trial showed a 15% relative risk reduction in mortality with eplerenone 25 mg daily for patients post-MI with LV dysfunction (LVEF of 40% or less) and either clinical HF or diabetes. Kidney dysfunction or hyperkalemia are contraindications, and patients must be monitored carefully for development of hyperkalemia.

J. Calcium Channel Blockers

There are no studies to support the routine use of calcium channel blockers in most patients with acute MI—and indeed, they have the potential to exacerbate ischemia and cause death from reflex tachycardia or myocardial depression. *Long-acting calcium channel blockers should generally be reserved for management of hypertension or ischemia as second- or third-line medications after beta-blockers and nitrates.*

K. Long-Term Antithrombotic Therapy

Discharge on aspirin, 81–325 mg/day, since it is highly effective, inexpensive, and well tolerated, is a key quality indicator of MI care. Patients who received a coronary stent should also receive a $P2Y_{12}$ inhibitor (see Antiplatelet therapy after drug-eluting or bare metal stents, above).

Patients who have received a coronary stent and who require warfarin anticoagulation present a particular challenge, since **"triple therapy"** with aspirin, clopidogrel, and warfarin has a high risk of bleeding. Triple therapy should be (1) limited to patients with a clear indication for warfarin (such as $CHADS_2$ score of 2 or more or a mechanical prosthetic valve), (2) used for the shortest period of time (such as 1 month after placement of bare metal stent; drug-eluting stents that would require longer clopidogrel duration should be avoided if possible), (3) used with low-dose aspirin and with strategies to reduce risk of bleeding (eg, PPIs for patients with a history of GI bleeding), and (4) used with consideration of a lower target anticoagulation intensity (INR 2.0–2.5, at least for the indication of atrial fibrillation) during the period of concomitant treatment with aspirin and $P2Y_{12}$ therapy. The PIONEER trial studied three treatment regimens for patients with atrial fibrillation who had coronary stent placement with a primary outcome of bleeding: (1) rivaroxaban 2.5 mg twice daily plus clopidogrel, (2) rivaroxaban 15 mg once daily plus clopidogrel, and (3) warfarin plus aspirin plus clopidogrel. There was less bleeding in the patients who received rivaroxaban plus clopidogrel than in those who received "triple therapy," although the trial was not powered to assess efficacy, and thus the low dose of rivaroxaban may be inadequate. Consensus statements recommend oral anticoagulation (with either warfarin or a DOAC) be combined with clopidogrel and with a relatively short duration of aspirin (1–4 weeks) for the typical patient with atrial fibrillation and coronary stents. Dabigatran, 110 mg and 150 mg, was also studied in patients with atrial fibrillation who underwent PCI. Dual therapy with dabigatran and clopidogrel was shown to be beneficial for bleeding compared to triple therapy, with similar rates of thrombotic cardiovascular events. However, there were too few thrombotic events to be certain about efficacy of discontinuing the aspirin, and there was a suggestion that MI and stent thrombosis occurred more often with the 110-mg dose of dabigatran than with clopidogrel alone. *Given the trial evidence to date, for a typical patient, it is reasonable to use a DOAC and clopidogrel and to discontinue aspirin at the time of hospital discharge or 1–4 weeks after stenting.*

The AUGUSTUS trial, which tested apixaban versus warfarin and aspirin versus placebo in a factorial trial, found that apixaban resulted in 31% less major and clinically relevant nonmajor bleeding than warfarin for patients with atrial fibrillation and coronary stents or ACSs or both.

Avoiding aspirin, after an average of 6 days after the PCI, resulted in less bleeding and a nonsignificant increase in stent thrombosis. It is reasonable to stop aspirin at hospital discharge or at day 7 for patients with atrial fibrillation who are taking apixaban or warfarin at the time of discharge, although continuing aspirin for 1 month may reduce stent thrombosis.

L. Coronary Angiography

For patients who do not reperfuse based on lack of at least 50% resolution of ST elevation, **rescue angioplasty** should be performed and has been shown to reduce the composite risk of death, reinfarction, stroke, or severe HF. Patients treated with coronary angiography and PCI 3–24 hours after fibrinolytic therapy showed improved outcomes. Patients with recurrent ischemic pain prior to discharge should undergo catheterization and, if indicated, revascularization. PCI of a totally occluded infarct-related artery more than 24 hours after STEMI should generally not be performed in asymptomatic patients with one- or two-vessel disease without evidence of severe ischemia.

When to Refer

All patients with acute MI should be referred to a cardiologist.

Writing Committee Members; Lawton JS et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022;79:e21. Erratum in: J Am Coll Cardiol. 2022;79:1547. [PMID: 34895950]

Complications

A variety of complications can occur after MI even when treatment is initiated promptly.

A. Postinfarction Ischemia

In clinical trials of thrombolysis, recurrent ischemia occurred in about one-third of patients, was more common following NSTEMI than after STEMI, and had important short- and long-term prognostic implications. Vigorous medical therapy should be instituted, including nitrates and beta-blockers as well as aspirin 81–325 mg/day, anticoagulant therapy (unfractionated heparin, enoxaparin, or fondaparinux), and clopidogrel (75 mg orally daily). Most patients with postinfarction angina—and all who are refractory to medical therapy—should undergo early catheterization and revascularization by PCI or CABG.

B. Arrhythmias

Abnormalities of rhythm and conduction are common.

1. Sinus bradycardia—This is most common in inferior infarctions or may be precipitated by medications. Observation or withdrawal of the offending agent is usually sufficient. If accompanied by signs of low cardiac output, atropine intravenously is usually effective. Temporary pacing is rarely required.

2. Supraventricular tachyarrhythmias—Sinus tachycardia is common and may reflect either increased adrenergic stimulation or hemodynamic compromise due to hypovolemia or pump failure. In the latter, beta-blockade is contraindicated. Supraventricular premature beats are common and may be premonitory for atrial fibrillation. Electrolyte abnormalities and hypoxia should be corrected and causative agents (especially aminophylline) stopped. *Atrial fibrillation should be rapidly controlled or converted to sinus rhythm.* Intravenous beta-blockers, such as metoprolol (2.5–5 mg intravenously every 2–5 minutes, maximum 15 mg over 10–minutes) or short-acting esmolol (50–200 mcg/kg/min), are the agents of choice if cardiac function is adequate. Intravenous diltiazem (5–15 mg/hour) may be used if beta-blockers are contraindicated or ineffective. Electrical cardioversion (commencing with 100 J) may be necessary if atrial fibrillation is complicated by hypotension, HF, or ischemia, but the arrhythmia often recurs. Amiodarone (150 mg intravenous bolus and then 15–30 mg/hour intravenously, or rapid oral loading dose for cardioversion of 400 mg three times daily) may be helpful to restore or maintain sinus rhythm.

3. Ventricular arrhythmias—Ventricular arrhythmias are most common in the first few hours after infarction and are a marker of high risk. Ventricular premature beats may be premonitory for ventricular tachycardia or fibrillation, but generally should *not* be treated in the absence of frequent or sustained ventricular tachycardia. Lidocaine is *not* recommended as a prophylactic measure.

Sustained ventricular tachycardia should be treated with a 1 mg/kg bolus of lidocaine if the patient is stable or by electrical cardioversion (100–200 J) if not. If the arrhythmia cannot be suppressed with lidocaine, procainamide (100 mg boluses over 1–2 minutes every 5 minutes to a cumulative dose of 750–1000 mg) or intravenous amiodarone (150 mg over 10 minutes, which may be repeated as needed, followed by 360 mg over 6 hours and then 540 mg over 18 hours) should be initiated, followed by an infusion of 0.5 mg/min (720 mg/24 hours). Ventricular fibrillation is treated electrically (300–400 J). All patients taking antiarrhythmics should be monitored with telemetry or ECGs during initiation. Unresponsive ventricular fibrillation should be treated with additional amiodarone and repeat cardioversion while CPR is administered.

Accelerated idioventricular rhythm is a regular, wide-complex rhythm at a rate of 60–120/min. It may occur with or without reperfusion and should *not* be treated with antiarrhythmics, which could cause asystole.

4. Conduction disturbances—All degrees of AV block may occur in the course of acute MI. Block at the level of the AV node is more common than infranodal block and occurs in approximately 20% of inferior MIs. First-degree block is the most common and requires no treatment. Second-degree block is usually of the Mobitz type I form (Wenckebach), is often transient, and requires treatment only if associated with a heart rate slow enough to cause symptoms. Complete AV block occurs in up to 5% of acute inferior infarctions, usually is preceded by Mobitz I second-degree block, and generally resolves spontaneously, though

it may persist for hours to several weeks. The escape rhythm originates in the distal AV node or AV junction and hence has a narrow QRS complex and is reliable, albeit often slow (30–50 beats/min). Treatment is often necessary because of resulting hypotension and low cardiac output. Intravenous atropine (1 mg) usually restores AV conduction temporarily, but if the escape complex is wide or if repeated atropine treatments are needed, temporary ventricular pacing is indicated. The prognosis for these patients is only slightly worse than for patients in whom AV block does not develop.

In anterior infarctions, the site of block is distal, below the AV node, and usually a result of extensive damage of the His-Purkinje system and bundle branches. New first-degree block (prolongation of the PR interval) is unusual in anterior infarction; Mobitz type II AV block or complete heart block may be preceded by intraventricular conduction defects or may occur abruptly. The escape rhythm, if present, is an unreliable wide-complex idioventricular rhythm. Urgent ventricular pacing is mandatory, but even with successful pacing, morbidity and mortality are high because of the extensive myocardial damage. New conduction abnormalities, such as right or left bundle branch block or fascicular blocks, may presage progression, often sudden, to second- or third-degree AV block. Temporary ventricular pacing is recommended for new-onset alternating bilateral bundle branch block, bifascicular block, or bundle branch block with worsening first-degree AV block. Patients with anterior infarction who progress to second- or third-degree block even transiently should be considered for insertion of a prophylactic permanent ventricular pacemaker before discharge.

C. Myocardial Dysfunction

Persons with hypotension not responsive to fluid resuscitation or refractory HF or cardiogenic shock should be considered for urgent echocardiography to assess left and right ventricular function and for mechanical complications, right heart catheterization, and continuous measurements of arterial pressure. These measurements permit the accurate assessment of volume status and may facilitate decisions about volume resuscitation, selective use of vasopressors and inotropes, and mechanical support.

1. Acute LV failure—Dyspnea, diffuse rales, and arterial hypoxemia usually indicate LV failure. General measures include supplemental oxygen to increase arterial saturation to above 95% and elevation of the trunk. Diuretics are usually the initial therapy unless RV infarction is present. Intravenous furosemide (10–40 mg) or bumetanide (0.5–1 mg) is preferred because of the reliably rapid onset and short duration of action of these medications. Higher dosages can be given if an inadequate response occurs. Morphine sulfate (4 mg intravenously followed by increments of 2 mg) is valuable in acute pulmonary edema.

Diuretics are usually effective; however, because most patients with acute infarction are not volume overloaded, the hemodynamic response may be limited and may be associated with hypotension. In mild HF, sublingual isosorbide dinitrate (2.5–10 mg every 2 hours) or nitroglycerin ointment (6.25–25 mg every 4 hours) may be adequate to lower pulmonary capillary wedge pressure (PCWP). In more severe failure, especially if cardiac output is reduced and BP is normal or high, sodium nitroprusside may be the preferred agent. It should be initiated only with arterial pressure monitoring; the initial dosage should be low (0.25 mcg/kg/min) to avoid excessive hypotension, but the dosage can be increased by increments of 0.5 mcg/kg/min every 5–10 minutes up to 5–10 mcg/kg/min until the desired hemodynamic response is obtained. Excessive hypotension (mean BP less than 65–75 mm Hg) or tachycardia (greater than 10/min increase) should be avoided.

Intravenous nitroglycerin (starting at 10 mcg/min) also may be effective but may lower PCWP with less hypotension. Oral or transdermal vasodilator therapy with nitrates or ACE inhibitors is often necessary after the initial 24–48 hours.

Inotropic agents should be avoided if possible, because they often increase heart rate and myocardial oxygen requirements and worsen clinical outcomes. Dobutamine has the best hemodynamic profile, increasing cardiac output and modestly lowering PCWP, usually without excessive tachycardia, hypotension, or arrhythmias. The initial dosage is 2.5 mcg/kg/min, and it may be increased by similar increments up to 15–20 mcg/kg/min at intervals of 5–10 minutes. Dopamine is more useful in the presence of hypotension, since it produces peripheral vasoconstriction, but it has a less beneficial effect on PCWP. Digoxin has not been helpful in acute infarction except to control the ventricular response in atrial fibrillation, but it may be beneficial if chronic HF persists.

2. Hypotension and shock—*Patients with hypotension (systolic BP less than 90 mm Hg, individualized depending on prior BP) and signs of diminished perfusion (low urinary output, confusion, cold extremities) that does not respond to fluid resuscitation should be presumed to have cardiogenic shock and should be considered for urgent catheterization and revascularization.* Sparing use of **intra-aortic balloon pump (IABP)** support and hemodynamic monitoring with a **PA catheter** can be considered, although these later measures have *not* been shown to improve outcome. Up to 20% will have findings indicative of intravascular hypovolemia (due to diaphoresis, vomiting, decreased venous tone, medications—such as diuretics, nitrates, morphine, beta-blockers, calcium channel blockers, and thrombolytic agents—and lack of oral intake). These should be treated with successive boluses of 100 mL of normal saline until PCWP reaches 15–18 mm Hg to determine whether cardiac output and BP respond. Pericardial tamponade due to hemorrhagic pericarditis (especially after thrombolytic therapy or CPR) or ventricular rupture should be considered and excluded by echocardiography if clinically indicated. RV infarction, characterized by a normal PCWP but elevated RA pressure, can produce hypotension. This is discussed below.

Most patients with cardiogenic shock will have moderate to severe LV systolic dysfunction, with a mean EF of 30% in the SHOCK trial. If hypotension is only modest (systolic pressure higher than 90 mm Hg) and the PCWP is elevated, diuretics should be administered. If the BP falls,

inotropic support will need to be added. A large randomized trial showed *no benefit* of IABP support in cardiogenic shock.

Norepinephrine (0.1–0.5 mcg/kg/min) is generally considered to be the most appropriate inotrope/vasopressor for cardiogenic shock based on limited randomized clinical trial evidence suggesting less arrhythmias and improved outcomes compared with dopamine. Dopamine is nonetheless also an option and can be initiated at a rate of 2–4 mcg/kg/min and increased at 5-minute intervals to the appropriate hemodynamic end point. At dosages lower than 5 mcg/kg/min, it improves renal blood flow; at intermediate dosages (2.5–10 mcg/kg/min), it stimulates myocardial contractility; at higher dosages (greater than 8 mcg/kg/min), it is a potent alpha-1-adrenergic agonist. In general, BP and cardiac index rise, but PCWP does not fall. Dopamine may be combined with nitroprusside or dobutamine (see above for dosing), or the latter may be used in its place if hypotension is not severe.

Patients with cardiogenic shock not due to hypovolemia have a poor prognosis, with 30-day mortality rates of 40–80%. The IABP-SHOCK II trial found that the use of an IABP does *not* offer a mortality benefit at 30 days or 1 year, compared with routine care with rapid revascularization, and is likely not helpful. Surgically implanted (or percutaneous) ventricular assist devices may be used in refractory cases. Emergent cardiac catheterization and coronary angiography followed by percutaneous or surgical revascularization offer the best chance of survival. Additionally, revascularization in shock should be aimed at the culprit artery only, avoiding multivessel PCI.

D. RV Infarction

RV infarction is present in one-third of patients with inferior wall infarction but is clinically significant in less than 50% of these. It presents as hypotension with relatively preserved LV function and *should be considered whenever patients with inferior infarction exhibit low BP, raised venous pressure, and clear lungs*. Hypotension is often exacerbated by medications that decrease intravascular volume or produce venodilation, such as diuretics, nitrates, and opioids. RA pressure and JVP are high, while PCWP is normal or low and the lungs are clear. The diagnosis is suggested by ST-segment elevation in right-sided anterior chest leads, particularly RV_4. The diagnosis can be confirmed by echocardiography or hemodynamic measurements. Treatment consists of fluid loading beginning with 500 mL of 0.9% saline over 2 hours to improve LV filling, and inotropic agents only if necessary.

E. Mechanical Defects

Partial or complete rupture of a papillary muscle or of the interventricular septum occurs in less than 1% of acute MIs and carries a poor prognosis. These complications occur in both anterior and inferior infarctions, *usually 3–7 days after the acute event*. They are detected by the appearance of a new systolic murmur and clinical deterioration, often with pulmonary edema. The two lesions are distinguished by the location of the murmur (apical versus parasternal) and by Doppler echocardiography. Hemodynamic monitoring is essential for appropriate management and demonstrates an increase in oxygen saturation between the RA and PA in VSD and, often, a large *v* wave with mitral regurgitation. Treatment by nitroprusside and, preferably, **intra-aortic balloon counterpulsation (IABC)** reduces the regurgitation or shunt, but surgical correction is mandatory. In patients remaining hemodynamically unstable or requiring continuous parenteral pharmacologic treatment or counterpulsation, early surgery is recommended, though mortality rates are high (15% to nearly 100%, depending on residual ventricular function and clinical status). Patients who are stabilized medically can have delayed surgery with lower risks (10–25%), although this may be due to the death of sicker patients, some of whom may have been saved by earlier surgery.

F. Myocardial Rupture

Complete rupture of the LV free wall occurs in less than 1% of patients and usually results in immediate death. It occurs 2–7 days postinfarction, usually involves the anterior wall, and is more frequent in older women. Incomplete or gradual rupture may be sealed off by the pericardium, creating a pseudoaneurysm. This may be recognized by echocardiography, radionuclide angiography, or LV angiography, often as an incidental finding. It demonstrates a narrow-neck connection to the LV. Early surgical repair is indicated, since delayed rupture is common.

G. LV Aneurysm

An LV aneurysm, a sharply delineated area of scar that bulges paradoxically during systole, develops in 10–20% of patients surviving an acute infarction. This usually follows anterior ST-segment elevation infarctions. Aneurysms are recognized by persistent ST-segment elevation (beyond 4–8 weeks), and a wide neck from the LV can be demonstrated by echocardiography, scintigraphy, or contrast angiography. They rarely rupture but may be associated with arterial emboli, ventricular arrhythmias, and HF. Surgical resection may be performed for these indications if other measures fail. The best results (mortality rates of 10–20%) are obtained when the residual myocardium contracts well and when significant coronary lesions supplying adjacent regions are bypassed.

H. Pericarditis

The pericardium is involved in approximately 50% of infarctions, but pericarditis is often not clinically significant. Twenty percent of patients with ST-segment elevation infarctions will have an audible friction rub if examined repetitively. Pericardial pain occurs in approximately the same proportion after 2–7 days and is recognized by its variation with respiration and position (improved by sitting). Often, no treatment is required, but aspirin (650 mg every 4–6 hours) will usually relieve the pain. Indomethacin and corticosteroids can cause impaired infarct healing and predispose to myocardial rupture, and therefore should generally be *avoided* in the early post-MI period. Likewise,

anticoagulation should be used cautiously, since hemorrhagic pericarditis may result.

One week to 12 weeks after infarction, **Dressler syndrome** (post-MI syndrome) occurs in less than 5% of patients. This is an autoimmune phenomenon and presents as pericarditis with associated fever, leukocytosis, and, occasionally, pericardial or pleural effusion. It may recur over months. Treatment is the same as for other forms of pericarditis. A short course of nonsteroidal agents or corticosteroids may help relieve symptoms, but the use of nonsteroidal agents in the first several weeks after MI may impair infarct healing.

I. Mural Thrombus

Mural thrombi are common in large anterior infarctions but not in infarctions at other locations. Arterial emboli occur in approximately 2% of patients with known infarction, usually within 6 weeks. Anticoagulation with heparin followed by short-term (3-month) warfarin therapy (or DOAC therapy based on limited case report experience) results in clot resolution and prevents most emboli and should be considered in all patients with large anterior infarctions and evidence of LV thrombi. Mural thrombi can be detected by echocardiography or cardiac MRI. If the thrombus is resolved at 3 months, then anticoagulation can be discontinued.

Postinfarction Management

After the first 24 hours, the focus of patient management is to prevent recurrent ischemia, improve infarct healing and prevent remodeling, and prevent recurrent vascular events. Patients with hemodynamic compromise, who are at high risk for death, need careful monitoring and management of volume status.

A. Risk Stratification

Risk stratification is important for the management of STEMI. GRACE and TIMI risk scores can be helpful tools. Patients with recurrent ischemia (spontaneous or provoked), hemodynamic instability, impaired LV function, HF, or serious ventricular arrhythmias should undergo cardiac catheterization (see Table 10–7). ACE inhibitor (or ARB) therapy is indicated in patients with clinical HF or LVEF of 40% or less. Aldosterone blockade is indicated for patients with an LVEF of 40% or less and either HF or diabetes mellitus.

For patients not undergoing cardiac catheterization, **submaximal** exercise (or pharmacologic stress testing for patients unable to exercise) before discharge or a **maximal** test after 3–6 weeks (the latter being more sensitive for ischemia) helps patients and clinicians plan the return to normal activity. Imaging in conjunction with stress testing adds additional sensitivity for ischemia and provides localizing information. Both exercise and pharmacologic stress imaging have successfully predicted subsequent outcomes. One of these tests should be used prior to discharge in patients who have received thrombolytic therapy as a means of selecting appropriate candidates for coronary angiography.

B. Secondary Prevention

Postinfarction management should begin with identification and modification of risk factors. Treatment of hyperlipidemia and smoking cessation both prevent recurrent infarction and death. Statin therapy should be started before the patient is discharged from the hospital to reduce recurrent atherothrombotic events. BP control as well as cardiac rehabilitation and exercise are also recommended. They can be of considerable psychological benefit and appear to improve prognosis.

Beta-blockers improve survival rates, primarily by reducing the incidence of sudden death in high-risk subsets of patients, though their value may be less in patients without complications with small infarctions and normal exercise tests. While a variety of beta-blockers have been shown to be beneficial, for patients with LV dysfunction managed with contemporary treatment, carvedilol titrated to 25 mg orally twice a day has been shown to reduce mortality. Beta-blockers with intrinsic sympathomimetic activity have *not* proved beneficial in postinfarction patients.

Antiplatelet agents are beneficial; aspirin (75–100 mg daily, after the initial dose) and $P2Y_{12}$ inhibitor therapy for 1 year are recommended. Prasugrel provides further reduction in thrombotic outcomes compared with clopidogrel, at the cost of more bleeding, but is contraindicated for patients with prior stroke. Likewise, ticagrelor provides benefit over clopidogrel. Calcium channel blockers have *not* been shown to improve prognoses overall and should not be prescribed purely for secondary prevention. Antiarrhythmic therapy other than with beta-blockers has *not* been shown to be effective except in patients with symptomatic arrhythmias. Amiodarone has been studied in several trials of postinfarct patients with either LV dysfunction or frequent ventricular ectopy. Although survival was not improved, amiodarone was not harmful—unlike other agents in this setting. Therefore, it is the *agent of choice for individuals with symptomatic postinfarction supraventricular arrhythmias*. While implantable defibrillators improve survival for patients with postinfarction LV dysfunction and HF, the DINAMIT trial found *no benefit to implantable defibrillators implanted in the 40 days following acute MI*.

C. ACE Inhibitors and ARBs in Patients with LV Dysfunction

Patients who sustain substantial myocardial damage often experience subsequent progressive LV dilation and dysfunction, leading to clinical HF and reduced long-term survival. In patients with EFs less than 40%, long-term ACE inhibitor (or ARB) therapy prevents LV dilation and the onset of HF and prolongs survival. The HOPE trial, as well as an overview of trials of ACE inhibitors for secondary prevention, also demonstrated a reduction of approximately 20% in mortality rates and the occurrence of nonfatal MI and stroke with ramipril treatment of patients with coronary or peripheral vascular disease and without confirmed LV systolic dysfunction. Therefore, ACE inhibitor therapy should be strongly considered in this broader group of patients—and especially in patients with diabetes

and those with even mild systolic hypertension, in whom the greatest benefit was observed (see Table 13–6).

D. Revascularization

The indications for CABG are similar to those for patients with chronic coronary syndromes, including left main stenosis and multivessel disease (particularly with type 2 diabetes or LV dysfunction, or both). For patients who have undergone primary PCI and have residual left main or multivessel disease, CABG may be appropriate, but the timing needs to take into account the high risk of stent thrombosis if $P2Y_{12}$ inhibitor therapy is interrupted. For patients with noninfarct-related CAD, stenting should generally be performed on these lesions prior to hospital discharge.

RHEUMATIC FEVER

ESSENTIALS OF DIAGNOSIS

- More common in developing countries (100 cases/100,000 population) than in the United States (~2 cases/100,000 population).
- Peak incidence between ages 5 and 15 years.
- Presence of two major Jones criteria or one major and two minor.
- May involve mitral and other valves acutely, rarely leading to HF.

General Considerations

Rheumatic fever is a systemic immune process that is a sequela of a beta-hemolytic streptococcal infection of the pharynx. It is a major scourge in developing countries and responsible for 320,000 deaths in young people worldwide each year. Over 15 million people have evidence for rheumatic heart disease. Signs of **acute rheumatic fever** usually commence 2–3 weeks after infection but may appear as early as 1 week or as late as 5 weeks. The disease has become quite uncommon in the United States, except in immigrants. The peak incidence is between ages 5 and 15 years; rheumatic fever is rare before age 4 years or after age 40 years. Rheumatic carditis and valvulitis may be self-limited or may lead to slowly progressive valvular deformity. The characteristic lesion is a perivascular granulomatous reaction with valvulitis. The mitral valve is acutely attacked in 75–80% of cases, the aortic valve in 30% (but rarely as the sole valve involved), and the tricuspid and pulmonary valves in under 5% of cases.

The clinical profile of the infection includes carditis in 50–70% and arthritis in 35–66%, followed by chorea (10–30%, predominantly in girls) then subcutaneous nodules (0–10%) and erythema marginatum (in less than 6%). Echocardiography has been found to be superior to auscultation, and the 2015 guidelines introduced **subclinical carditis** to the Jones criteria to represent abnormal echocardiographic findings when auscultatory findings were either not present or not recognized.

Chronic rheumatic heart disease results from single or repeated attacks of rheumatic fever that produce rigidity and deformity of valve cusps, fusion of the commissures, or shortening and fusion of the chordae tendineae. Valvular stenosis or regurgitation results, and the two often coexist. In chronic rheumatic heart disease, the mitral valve alone is abnormal in 50–60% of cases; combined lesions of the aortic and mitral valves occur in 20%; pure aortic lesions are less common. Tricuspid involvement occurs in about 10% of cases, but only in association with mitral or aortic disease and is thought to be more common when recurrent infections have occurred. The pulmonary valve is rarely affected long term. *A history of rheumatic fever is obtainable in only 60% of patients with rheumatic heart disease.* While there has been progress against this disease, it remains a major cardiovascular problem in the poorest regions of the world.

Clinical Findings

The presence of two major criteria—or one major and two minor criteria—establishes the diagnosis. While India, New Zealand, and Australia have all published revised guidelines since 2001, the 2015 recommendations have revised the Jones criteria in a scientific statement from the AHA where subclinical carditis is now recognized with the advent of echocardiography. The revised criteria also recognize that a lower threshold should be used to diagnosis acute rheumatic fever in populations with high risk.

A. Major Criteria

1. Carditis—Carditis is most likely to be evident in children and adolescents. Any of the following suggests the presence of carditis: (1) pericarditis; (2) cardiomegaly, detected by physical signs, radiography, or echocardiography; (3) HF, right- or left-sided—the former perhaps more prominent in children, with painful liver engorgement due to tricuspid regurgitation; and (4) mitral or aortic regurgitation murmurs, indicative of dilation of a valve ring with or without associated valvulitis or morphologic findings on echocardiography of rheumatic valvulitis. The **Carey–Coombs** short mid-diastolic mitral murmur may be present due to inflammation of the mitral valve. It is a class I (LOE B) indication to perform echocardiography/Doppler studies on all cases of suspected or confirmed acute rheumatic fever.

2. Erythema marginatum and subcutaneous nodules—Erythema marginatum begins as rapidly enlarging macules that may be less notable on darker skin tones and that assume the shape of rings or crescents with clear centers. They may be raised, confluent, and either transient or persistent and usually on the trunk or proximal extremities. Subcutaneous nodules are uncommon except in children. They are small (2 cm or less in diameter), firm, and nontender and are attached to fascia or tendon sheaths over bony prominences. They persist for days or weeks, are

recurrent, and are indistinguishable from rheumatoid nodules. Neither the rash nor nodules ever occur as the sole manifestation of acute rheumatic fever.

3. Sydenham chorea—This is the most definitive manifestation of acute rheumatic fever. Defined as involuntary choreoathetoid movements primarily of the face, tongue, and upper extremities, Sydenham chorea may be the sole manifestation of rheumatic fever. Girls are more frequently affected than boys, and occurrence in adults is rare.

4. Polyarthritis—This is a migratory polyarthritis that involves the large joints sequentially. In adults and in certain populations with moderate to high risk, only a single joint may be affected. The arthritis lasts 1–5 weeks and subsides without residual deformity. Prompt response of arthritis to therapeutic doses of salicylates or nonsteroidal agents is characteristic.

B. Minor Criteria

These include fever, polyarthralgia, reversible prolongation of the PR interval, and an elevated ESR or CRP. A lower threshold is set for patients at high risk. The 2015 guidelines stipulate that evidence for a preceding streptococcal infection can be defined by an increase in or rising anti-streptolysin O titer or streptococcal antibodies (anti-DNAase B), a positive throat culture for group A beta-hemolytic *Streptococcus,* or a positive rapid group A streptococcal carbohydrate antigen test in a child with a high pretest probability of streptococcal pharyngitis.

Treatment

A. General Measures

The patient should be kept at strict bed rest until the temperature returns to normal (without the use of antipyretic medications) and the ESR, plus the resting pulse rate, and the ECG have all returned to baseline.

B. Medical Measures

1. Salicylates—The salicylates markedly reduce fever and relieve joint pain and swelling. They have no effect on the natural course of the disease. Adults may require large doses of aspirin, 0.6–0.9 g every 4 hours; children are treated with lower doses.

2. Penicillin—Penicillin (benzathine penicillin, 1.2 million units intramuscularly once, or procaine penicillin, 600,000 units intramuscularly daily for 10 days) is used to eradicate streptococcal infection if present. Erythromycin may be substituted (40 mg/kg/day). A 2022 randomized study demonstrated reduced progression of latent rheumatic heart disease with benzathine penicillin during 2 years of follow-up.

3. Corticosteroids—There is no proof that cardiac damage is prevented or minimized by corticosteroids. A short course of corticosteroids (prednisone, 40–60 mg orally daily, with tapering over 2 weeks) usually causes rapid improvement of the joint symptoms and is indicated when response to salicylates has been inadequate.

Prevention of Recurrent Rheumatic Fever

Improvements in socioeconomic conditions and public health are critical to reducing bouts of rheumatic fever. The initial episode of rheumatic fever can usually be prevented by early treatment of streptococcal pharyngitis with penicillin (see Chapter 34). Prevention of recurrent episodes of rheumatic fever is critical. Recurrences of rheumatic fever are most common in patients who have had carditis during their initial episode and in children, 20% of whom will have a second episode within 5 years. The preferred method of prophylaxis is with benzathine penicillin G, 1.2 million units intramuscularly every 4 weeks. Oral penicillin (250 mg twice daily) is less reliable.

If the patient is allergic to penicillin, sulfadiazine (or sulfisoxazole), 1 g daily, or erythromycin, 250 mg orally twice daily, may be substituted. The macrolide azithromycin is similarly effective against group A streptococcal infection. If the patient has not had an immediate hypersensitivity (anaphylactic-type) reaction to penicillin, then cephalosporin may also be used.

Recurrences are uncommon after 5 years following the first episode and in patients over 21 years of age. Prophylaxis is usually discontinued after these times except in groups with a high risk of streptococcal infection—parents or teachers of young children, nurses, military recruits, etc. Secondary prevention of rheumatic fever depends on whether carditis has occurred. Guidelines suggest that if there is no evidence for carditis, preventive therapy can be stopped at age 21 years. If carditis has occurred but there is no residual valvular disease, it can be stopped at 10 years after the acute rheumatic fever episode. If carditis has occurred with residual valvular involvement, it should be continued for 10 years after the last episode or until age 40 years if the patient is in a situation in which reexposure would be expected.

Prognosis

Initial episodes of rheumatic fever may last months in children and weeks in adults. The immediate mortality rate is 1–2%. Persistent rheumatic carditis with cardiomegaly, HF, and pericarditis implies a poor prognosis; 30% of children thus affected die within 10 years after the initial attack. After 10 years, two-thirds of patients will have detectable valvular abnormalities (usually thickened valves with limited mobility), but significant symptomatic valvular heart disease or persistent cardiomyopathy occurs in less than 10% of patients with a single episode. In developing countries, acute rheumatic fever occurs earlier in life and recurs more frequently; thus, the evolution to chronic valvular disease is both accelerated and more severe.

Beaton A et al. Secondary antibiotic prophylaxis for latent rheumatic heart disease. N Engl J Med. 2022;386:230. [PMID: 34767321]

Dooley LM et al. Rheumatic heart disease: a review of the current status of global research activity. Autoimmun Rev. 2021;20:102740. [PMID: 33333234]

DISEASES OF THE PERICARDIUM

ACUTE INFLAMMATORY PERICARDITIS

ESSENTIALS OF DIAGNOSIS

- Anterior pleuritic chest pain that is worse supine than upright.
- Pericardial rub.
- Fever common.
- ESR or inflammatory CRP usually elevated.
- ECG reveals diffuse ST-segment elevation with associated PR depression.

General Considerations

Acute (less than 2 weeks) inflammation of the pericardium may be infectious in origin or may be due to systemic diseases (autoimmune syndromes, uremia), neoplasm, radiation, drug toxicity, hemopericardium, postcardiac surgery, or contiguous inflammatory processes in the myocardium or lung. In many of these conditions, the pathologic process involves both the pericardium and the myocardium. Overall pericarditis accounts for 0.2% of hospital admissions and about 5% of patients with nonischemic chest pain seen in the emergency department. The ESC in 2015 proposed four categories of pericarditis: acute, incessant, current, and chronic. Each category has its own diagnostic criteria. In **acute pericarditis,** there are four criteria: (1) pericardial chest pain, (2) pericardial rub, (3) new widespread ST elevation or PR depression, and (4) new or worsening pericardial effusion. To establish the diagnosis of acute pericarditis, at least two of these four criteria must be present. **Incessant pericarditis** is defined by its duration; it lasts longer than 4–6 weeks but less than 3 months without remission. **Recurrent pericarditis** can be diagnosed in a patient with one reported episode of pericarditis who has been symptom free for at least 4–6 weeks. Finally, **chronic pericarditis** is diagnosed when it persists for more than 3 months.

Viral infections (especially infections with coxsackieviruses and echoviruses but also influenza, Epstein-Barr, varicella, hepatitis, mumps, and HIV viruses) are the most common cause of acute pericarditis and probably are responsible for many cases classified as idiopathic. COVID-19 has been associated with both acute pericarditis and even cardiac tamponade. Males—usually under age 50 years—are most commonly affected. The differential diagnosis primarily requires exclusion of acute MI. **Tuberculous pericarditis** is rare in developed countries but remains common in certain areas of the world. It results from direct lymphatic or hematogenous spread; clinical pulmonary involvement may be absent or minor, although associated pleural effusions are common. **Bacterial pericarditis** is equally rare and usually results from direct extension from pulmonary infections. Pneumococci, though, can cause a primary pericardial infection. *Borrelia burgdorferi,* the organism responsible for Lyme disease, can also cause myopericarditis (and occasionally heart block). **Uremic pericarditis** is a common complication of CKD. The pathogenesis is uncertain; it occurs both with untreated uremia and in otherwise stable dialysis patients. Spread of adjacent lung cancer as well as invasion by breast cancer, renal cell carcinoma, Hodgkin disease, and lymphomas are the most common **neoplastic processes** involving the pericardium and have become the most frequent causes of pericardial tamponade in many countries. Pericarditis may occur 2–5 days after infarction due to an inflammatory reaction to transmural myocardial necrosis **(post-MI** or **postcardiotomy pericarditis [Dressler syndrome]). Radiation** can initiate a fibrinous and fibrotic process in the pericardium, presenting as subacute pericarditis or constriction. Radiation pericarditis usually follows treatments of more than 4000 cGy delivered to ports including more than 30% of the heart.

Other causes of pericarditis include **connective tissue diseases,** such as SLE and rheumatoid arthritis, **drug-induced pericarditis** (minoxidil, penicillins, clozapine), and **myxedema.** In addition, pericarditis may result from **pericardial injury** from invasive cardiac procedures (such as cardiac pacemaker and defibrillator perforation and intracardiac ablation, especially atrial fibrillation ablation), and the implantation of intracardiac devices (such as ASD occluder devices).

Pericarditis and myocarditis may coexist in 20–30% of patients. Myocarditis is often suspected when there is an elevation of serum troponins, although there are no data that suggest troponin elevations are associated with a poor prognosis.

Clinical Findings

A. Symptoms and Signs

The presentation and course of inflammatory pericarditis depend on its cause, but most syndromes have associated chest pain, which is usually pleuritic and postural (relieved by sitting). The pain is substernal but may radiate to the neck, shoulders, back, or epigastrium. Dyspnea may also be present and the patient is often febrile. A pericardial **friction rub** is characteristic, with or without evidence of fluid accumulation or constriction. The presentation of tuberculous pericarditis tends to be subacute, but nonspecific symptoms (fever, night sweats, fatigue) may be present for days to months. Pericardial involvement develops in 1–8% of patients with pulmonary tuberculosis. Symptoms and signs of bacterial pericarditis are similar to those of other types of inflammatory pericarditis, but patients appear toxic and are often critically ill. Uremic pericarditis can present with or without symptoms; fever is absent. Often neoplastic pericarditis is painless, and the presenting symptoms relate to hemodynamic compromise or the primary disease. At times the pericardial effusion is very large, consistent with its chronic nature. Post-MI or postcardiotomy pericarditis (Dressler syndrome) usually presents as a recurrence of pain with pleural-pericardial features. A rub is often audible, and repolarization changes on the ECG

may be confused with ischemia. Large effusions are uncommon, and spontaneous resolution usually occurs in a few days. Dressler syndrome occurs days to weeks to several months after MI or open heart surgery, may be recurrent, and probably represents an autoimmune syndrome. Patients present with typical pain, fever, malaise, and leukocytosis. Rarely, other symptoms of an autoimmune disorder, such as joint pain and fever, may occur. *Tamponade is rare with Dressler syndrome after MI but not when it occurs postoperatively.* The clinical onset of radiation pericarditis is usually within the first year but may be delayed for many years; often a full decade or more may pass before constriction becomes evident.

B. Laboratory Findings and Diagnostic Studies

The diagnosis of viral pericarditis is usually clinical, and leukocytosis is often present. Rising viral titers in paired sera may be obtained for confirmation but are rarely done. Cardiac enzymes may be slightly elevated, reflecting an epicardial myocarditis component. The echocardiogram is often normal or reveals only a trivial amount of extra fluid during the acute inflammatory process. The diagnosis of tuberculous pericarditis can be inferred if acid-fast bacilli are found elsewhere. The tuberculous pericardial effusions are usually small or moderate but may be large when chronic. The yield of mycobacterial organisms by pericardiocentesis is low; pericardial biopsy has a higher yield but may also be negative, and pericardiectomy may be required. If bacterial pericarditis is suspected on clinical grounds, diagnostic pericardiocentesis can be confirmatory. In uremic patients not on dialysis, the incidence of pericarditis correlates roughly with the level of BUN and creatinine. The pericardium is characteristically "shaggy" in uremic pericarditis, and the effusion is hemorrhagic and exudative. The diagnosis of neoplastic pericarditis can occasionally be made by cytologic examination of the effusion or by pericardial biopsy, but it may be difficult to establish clinically if the patient has received mediastinal radiation within the previous year. Neoplastic pericardial effusions develop over a long period of time and may become quite huge (more than 2 L). The ESR is high in post-MI or postcardiotomy pericarditis and can help confirm the diagnosis. Large pericardial effusions and accompanying pleural effusions are frequent. Myxedema pericardial effusions due to hypothyroidism usually are characterized by the presence of cholesterol crystals within the fluid.

C. Other Studies

The ECG usually shows generalized ST and T wave changes and may manifest a characteristic progression beginning with diffuse ST elevation, followed by a return to baseline and then to T wave inversion. Atrial injury is often present and manifested by PR depression, especially in the limb leads. The CXR is frequently normal but may show cardiac enlargement (if pericardial fluid is present), as well as signs of related pulmonary disease. Mass lesions and enlarged lymph nodes may suggest a neoplastic process. About 60% of patients have a pericardial effusion (usually mild) detectable by echocardiography. MRI and CT scan can visualize neighboring tumor in neoplastic pericarditis. A screening chest CT or MRI is often recommended to ensure there are no extracardiac diseases contiguous to the pericardium. A consensus statement from the American Society of Echocardiography proposes adding an elevated CRP and late gadolinium enhancement of the pericardium to confirmatory criteria for the diagnosis of pericarditis. There are data that the degree of quantitative delayed enhancement of the pericardium is associated with a higher rate of recurrent pericarditis. PET scanning can also be used to help define pericardial inflammation.

Treatment

For acute pericarditis, experts suggest a restriction in activity until symptom resolution. For athletes, the duration of exercise restriction should be until resolution of symptoms and normalization of all laboratory tests (generally 3 months). The 2015 ESC guidelines recommend aspirin 750–1000 mg every 8 hours for 1–2 weeks with a taper by decreasing the dose 250–500 mg every 1–2 weeks or ibuprofen 600 mg every 8 hours for 1–2 weeks with a taper by decreasing the dose by 200–400 mg every 1–2 weeks. Gastroprotection should be included. Studies support initial treatment of the acute episode with colchicine to prevent recurrences. Colchicine should be added to the NSAID at 0.5–0.6 mg once (for patients less than 70 kg) or twice (for patients more than 70 kg) daily and continued for at least 3 months. Tapering of colchicine is not mandatory; however, in the last week of treatment, the dosage can be reduced every other day for patients less than 70 kg or once a day for those more than 70 kg. *Aspirin and colchicine should be used instead of NSAIDs in post-MI pericarditis (Dressler syndrome)*, since NSAIDs and corticosteroids may have an adverse effect on myocardial healing. Aspirin in doses of 750–1000 mg three times daily for 1–2 weeks plus 3 months of colchicine is the recommended treatment for Dressler syndrome. Despite initial treatment, recurrence has been reported in about 30%.

Colchicine should be used for at least 6 months as therapy in all refractory cases and in recurrent pericarditis. At times a longer duration of therapy is required. The CRP is used to assess the effectiveness of treatment, and once it is normalized, tapering is initiated. Indomethacin in doses of 25–50 mg every 8 hours can also be considered in recurrent pericarditis in place of ibuprofen. Systemic corticosteroids can be added in patients with severe symptoms, in refractory cases, or in patients with immune-mediated etiologies, but such therapy may entail a higher risk of recurrence and may actually prolong the illness. Colchicine is recommended in addition to corticosteroids, again for at least 3 months, to help prevent recurrences. Prednisone in doses of 0.25–0.5 mg/kg/day orally is generally suggested with tapering over a 4- to 6-week period. Studies have confirmed the advantage of adding anakinra, an interleukin-1 receptor antagonist, for the treatment of recurrent pericarditis, especially for corticosteroid-dependent and colchicine-resistant pericarditis.

As a rule, symptoms subside in several days to weeks. The major early complication is **tamponade,** which occurs in less than 5% of patients. There may be recurrences in the

first few weeks or months. Rarely, when colchicine therapy alone fails or cannot be tolerated (usually due to GI symptoms), the pericarditis may require more significant immunosuppression, such as cyclophosphamide, azathioprine, intravenous human immunoglobulins, interleukin-1 receptor antagonists (anakinra), or methotrexate. If colchicine plus more significant immunosuppression fails, surgical pericardial stripping may be considered in recurrent cases even without clinical evidence for constrictive pericarditis.

Standard antituberculous medication therapy is usually successful for tuberculous pericarditis (see Chapter 9), but constrictive pericarditis can occur. Uremic pericarditis usually resolves with the institution of—or with more aggressive—dialysis. Tamponade is somewhat common, and partial pericardiectomy (**pericardial window**) may be necessary. Whereas anti-inflammatory agents may relieve the pain and fever associated with uremic pericarditis, indomethacin and systemic corticosteroids do *not* affect its natural history. The prognosis with neoplastic effusion is poor, with only a small minority surviving 1 year. If it is compromising the clinical comfort of the patient, the effusion is initially drained percutaneously. A pericardial window, either by a subxiphoid approach or via video-assisted thoracic surgery, allows for partial pericardiectomy. Installation of chemotherapeutic agents or tetracycline may be used to reduce the recurrence rate. Symptomatic therapy is the initial approach to radiation pericarditis, but recurrent effusions and constriction often require surgery.

Prognosis

Patients with acute pericarditis and any of the following criteria have the poorest prognosis: fever higher than 38°C, subacute onset, large effusion with or without tamponade, lack of response to anti-inflammatory medication after 1 week, myopericarditis, traumatic pericarditis, and those on oral anticoagulation. About 15% of patients have at least one of these high-risk findings.

When to Refer

Patients who do not respond initially to conservative management, who have recurrences, or who appear to be developing constrictive pericarditis should be referred to a cardiologist for further assessment.

Imazio M et al. Anakinra for corticosteroid-dependent and colchicine-resistant pericarditis. The IRAP (International Registry of Anakinra for Pericarditis) study. Eur J Prev Cardiol 2020;27:956. [PMID: 31610707]

PERICARDIAL EFFUSION & TAMPONADE

ESSENTIALS OF DIAGNOSIS

Pericardial effusion

- Clinical impact determined by the speed of accumulation.
- May or may not cause pain.

Tamponade

- Tachycardia with an elevated JVP and either hypotension or a paradoxical pulse.
- Low voltage or electrical alternans on ECG.
- Echocardiography is diagnostic.

Pericardial effusion can develop during any of the acute pericarditis processes. Because the pericardium covers the ascending aorta and arch, aortic dissection, rupture, or both can lead to tamponade as well. The *speed of accumulation* determines the physiologic importance of the effusion. Because of pericardial stretch, effusions larger than 1000 mL that develop slowly may produce no hemodynamic effects. Conversely, smaller effusions that appear rapidly can cause tamponade due to the curvilinear relationship between the volume of fluid and the intrapericardial pressure. *Tamponade is characterized by elevated intrapericardial pressure (greater than 15 mm Hg)*, which restricts venous return and ventricular filling. As a result, the stroke volume and arterial pulse pressure fall, and the heart rate and venous pressure rise. Shock and death may result.

Clinical Findings

A. Symptoms and Signs

Pericardial effusions may be associated with pain if they occur as part of an acute inflammatory process or may be painless, as is often the case with neoplastic or uremic effusion. Dyspnea and cough are common, especially with tamponade. Cardiac tamponade can be a life-threatening syndrome evidenced by tachycardia, hypotension, pulsus paradoxicus, raised JVP, muffled heart sounds, and decreased ECG voltage or electrical alternans. Other symptoms may result from the primary disease. The prognosis is a function of the cause. Large idiopathic chronic effusions (over 3 months) have a 30–35% risk of progression to cardiac tamponade.

A pericardial friction rub may be present even with large effusions. In cardiac tamponade, tachycardia, tachypnea, a narrow pulse pressure, and a relatively preserved systolic pressure are characteristic. **Pulsus paradoxus** is defined as a decline of greater than 10 mm Hg in systolic pressure during inspiration. Since the RV and LV share the same pericardium, when there is significant pericardial effusion, as the RV enlarges with inspiratory filling, septal motion toward the LV chamber reduces LV filling and results in an accentuated drop in the stroke volume and systemic BP with inspiration (the **paradoxical pulse**). CVP is elevated and, since the intrapericardial, and thus intracardiac, pressures are high even at the initiation of diastole, there is no evident *y* descent in the RA, RV, or LV hemodynamic tracings because the pericardial pressure prevents early ventricular filling. This differs from constriction where most of the initial filling of the RV and LV occurs during early diastole (rapid *y* descent), and it is only in mid to late diastole that the ventricles can no longer fill. In tamponade, ventricular filling is inhibited throughout diastole. Edema or ascites are rarely present in tamponade; these signs favor a more chronic process.

B. Laboratory Findings

Laboratory tests tend to reflect the underlying processes (see causes of pericarditis under General Considerations above).

C. Diagnostic Studies

CXR can suggest chronic effusion by an enlarged cardiac silhouette with a globular configuration but may appear normal in acute situations. The ECG often reveals nonspecific T wave changes and reduced QRS voltage. **Electrical alternans** is present only occasionally but is pathognomonic and is believed to be due to the heart swinging within the large effusion. Echocardiography is the primary method for demonstrating pericardial effusion and is quite sensitive. If tamponade is present, the high intrapericardial pressure may collapse lower pressure cardiac structures, such as the RA and RV. Cardiac CT and MRI also demonstrate pericardial fluid, pericardial thickening, and any associated contiguous lesions within the chest. Diagnostic pericardiocentesis or biopsy may be indicated for microbiologic and cytologic studies; a pericardial biopsy may be performed relatively simply through a small subxiphoid incision or by use of a video-assisted thoracoscopic surgical procedure. Unfortunately, *the quality of the pericardial fluid itself rarely leads to a diagnosis*, and any type of fluid (serous, serosanguinous, bloody, etc) can be seen in most diseases. Pericardial fluid analysis is most useful in excluding a bacterial cause and is occasionally helpful in malignancies. Effusions due to hypothyroidism or lymphatic obstruction may contain cholesterol or be chylous in nature, respectively.

Treatment

Small effusions can be followed clinically by careful observations of the JVP and by testing for a change in the paradoxical pulse. The most common cause of a paradoxical pulse is severe pulmonary disease, especially asthma, where marked changes in intrapleural pressures occur with inspiration and expiration. Serial echocardiograms are indicated if no intervention is immediately contemplated. Vasodilators and diuretics should be avoided. **When tamponade is present, urgent pericardiocentesis or cardiac surgery is required.** Because the pressure–volume relationship in the pericardial fluid is curvilinear and upsloping, removal of even a small amount of fluid often produces a dramatic fall in the intrapericardial pressure and immediate hemodynamic benefit; but complete drainage with a catheter is preferable. Continued or repeat drainage may be indicated, especially in malignant effusions. Pericardial windows via video-assisted thoracoscopy have been particularly effective in preventing recurrences when the underlying cause of the effusion continues to be present and are more effective than needle pericardiocentesis, subxiphoid surgical windows, or percutaneous balloon pericardiotomy. Effusions related to recurrent inflammatory pericarditis can be treated as noted above (see Acute Inflammatory Pericarditis). The presence of pericardial fluid in patients with pulmonary hypertension is a poor prognostic sign.

When to Refer

- Any unexplained pericardial effusion should be referred to a cardiologist.
- Trivial pericardial effusions are common, especially in HF, and need not be referred unless symptoms of pericarditis are evident.
- Hypotension or a paradoxical pulse suggesting the pericardial effusion is hemodynamically compromising the patient is a medical emergency and requires immediate drainage.
- Any echocardiographic signs of tamponade.

CONSTRICTIVE PERICARDITIS

ESSENTIALS OF DIAGNOSIS

- Clinical evidence of right HF.
- No fall or an elevation of the JVP with inspiration (Kussmaul sign).
- Echocardiographic evidence for septal bounce and reduced mitral inflow velocities with inspiration.
- At times may be difficult to differentiate from restrictive cardiomyopathy.
- Cardiac catheterization may be necessary when clinical and echocardiographic features are equivocal.

General Considerations

Pericardial inflammation can lead to a thickened, fibrotic, adherent pericardium that restricts diastolic filling and produces chronically elevated venous pressures. In the past, tuberculosis was the most common cause of constrictive pericarditis, but while it remains so in underdeveloped countries, it is rare now in the rest of the world. Constrictive pericarditis rarely occurs following recurrent pericarditis. The risk of constrictive pericarditis due to viral or idiopathic pericarditis is less than 1%. Its occurrence increases following immune-mediated or neoplastic pericarditis (2–5%) and is highest after purulent bacterial pericarditis (20–30%). Other causes include post cardiac surgery, radiation therapy, and connective tissue disorders. A small number of cases are drug-induced or secondary to trauma, asbestosis, sarcoidosis, or uremia. At times, both pericardial tamponade and constrictive pericarditis may coexist, a condition referred to as **effusive-constrictive pericarditis**. The only definitive way to diagnose this condition is to reveal the underlying constrictive physiology once the pericardial fluid is drained. The differentiation of constrictive pericarditis from a restrictive cardiomyopathy may require cardiac catheterization and the utilization of all available noninvasive imaging methods.

Clinical Findings

A. Symptoms and Signs

The principal symptoms are slowly progressive dyspnea, fatigue, and weakness. Chronic edema, hepatic congestion, and ascites are usually present. Ascites often seems out of proportion to the degree of peripheral edema.

The examination reveals these signs and a characteristically elevated jugular venous pressure with a rapid *y* descent. This can be detected at bedside by careful observation of the jugular pulse and noting an apparent increased pulse wave at the end of ventricular systole (due to the relative accentuation of the *v* wave by the rapid *y* descent). **Kussmaul sign**—a failure of the JVP to fall with inspiration—is also a frequent finding. The apex may actually retract with systole and a pericardial "knock" may be heard in early diastole. Pulsus paradoxus is unusual. Atrial fibrillation is common.

B. Diagnostic Studies

At times, constrictive pericarditis is extremely difficult to differentiate from restrictive cardiomyopathy and the two may coexist. When unclear, the use of both noninvasive testing and cardiac catheterization is required to sort out the difference.

1. Radiographic findings—The CXR may show normal heart size or cardiomegaly. Pericardial calcification is best seen on the lateral view and is uncommon. It rarely involves the LV apex, and finding of calcification at the LV apex is more consistent with LV aneurysm.

2. Echocardiography—Echocardiography rarely demonstrates a thickened pericardium. A **septal "bounce"** reflecting the rapid early filling is common, though. RV/LV interaction may be demonstrated by an inspiratory reduction in the mitral inflow Doppler pattern of greater than 25%, much as in tamponade. Usually, the initial mitral inflow into the LV is very rapid, and this can be demonstrated as well by the Doppler inflow (E wave) pattern. Other echocardiographic features, such as the ratio of the medial and lateral mitral annular motion (e' velocity), the respiration-related septal shift, and hepatic vein expiratory diastolic reversal ratio, also suggest constrictive physiology.

3. Cardiac CT and MRI—These imaging tests are only occasionally helpful. Pericardial thickening of more than 4 mm must be present to establish the diagnosis, but no pericardial thickening is demonstrable in 20–25% of patients with constrictive pericarditis. Some MRI techniques demonstrate the septal bounce and can provide further evidence for ventricular interaction.

4. Cardiac catheterization—This procedure is often confirmatory or can be diagnostic in difficult cases where the echocardiographic features are unclear or mixed. As a generality, the pulmonary pressure is low in constriction (as opposed to restrictive cardiomyopathy). In constrictive pericarditis, because of the need to demonstrate RV/LV interaction, cardiac catheterization should include simultaneous measurement of both the LV and RV pressure tracings with inspiration and expiration. This interaction can be demonstrated by cardiac MRI. Hemodynamically, patients with constriction have equalization of end-diastolic pressures throughout their cardiac chambers, there is rapid early filling then an abrupt increase in diastolic pressure (**"square-root" sign**), the RV end-diastolic pressure is more than one-third the systolic pressure, simultaneous measurements of RV and LV systolic pressure reveal a discordance with inspiration (the RV rises as the LV falls), and there is usually a Kussmaul sign (failure of the RA pressure to fall with inspiration). In restrictive cardiomyopathy, there is concordance of RV and LV systolic pressures with inspiration.

Treatment

Therapy should be aimed at the specific etiology initially. If there is laboratory evidence of ongoing inflammation, then anti-inflammatory medications may have a role. Once the hemodynamics are evident, the mainstay of treatment is diuresis. As in other disorders of right HF, the diuresis should be aggressive, using loop diuretics (oral torsemide or bumetanide if bowel edema is suspected or intravenous furosemide), thiazides, and aldosterone antagonists (especially in the presence of ascites and liver congestion). Surgical pericardiectomy should be recommended when diuretics are unable to control symptoms. Pericardiectomy removes only the pericardium between the phrenic nerve pathways, however, and most patients still require diuretics after the procedure, though symptoms are usually dramatically improved. Morbidity and mortality after pericardiectomy are high (up to 15%) and are greatest in those with the most disability prior to the procedure. Poor prognostic predictors include prior radiation, kidney dysfunction, higher pulmonary systolic pressures, abnormal LV systolic function, a lower serum sodium level, liver dysfunction, and older age. Pericardial calcium has no impact on survival.

When to Refer

If the diagnosis of constrictive pericarditis is unclear or the symptoms of fluid retention resist medical therapy, then referral to a cardiologist is warranted to both establish the diagnosis and recommend therapy.

Anasari-Gilani K et al. Multimodality approach to the diagnosis and management of constrictive pericarditis. Echocardiography. 2020;30:632. [PMID: 32240548]

Goldstein JA et al. Hemodynamics of constrictive pericarditis and restrictive cardiomyopathy. Catheter Cardiovasc Interv. 2020;95:1240. [PMID: 31904891]

PULMONARY HYPERTENSION

ESSENTIALS OF DIAGNOSIS

- Mean PA pressure 25 mm Hg or greater.
- Dyspnea and often cyanosis.
- Enlarged pulmonary arteries on CXR.
- Elevated JVP and RV heave.
- Echocardiography is often diagnostic.

General Considerations

The normal pulmonary bed offers about one-tenth as much resistance to blood flow as the systemic arterial system. Based on the 2019 Sixth World Symposium on Pulmonary Hypertension, the definition of pulmonary hypertension was changed. It was defined by a mean PA pressure of 20 mm Hg with a PVR of greater than or equal to 3 Wood units. Three categories were then defined:

1. **Precapillary pulmonary hypertension**: mean PA pressure greater than 20 mm Hg, PVR greater than or equal to 3.0 Wood units, PCWP less than or equal to 15 mm Hg
2. **Isolated post-capillary pulmonary hypertension**: mean PA pressure greater than 20 mm Hg, PVR less than 3.0 Wood units, PCWP greater than 15 mm Hg
3. **Combined pre- and post-pulmonary hypertension**: mean PA pressure greater than 20 mm Hg, PVR greater than or equal to 3.0 Wood units, PCWP greater than 15 mm Hg

The Sixth World Symposium on Pulmonary Hypertension developed a clinical classification of pulmonary hypertension.

Group I includes **pulmonary arterial hypertension (PAH)** related to an underlying pulmonary vasculopathy. It includes the former "primary pulmonary hypertension" under the term "idiopathic pulmonary hypertension" and is defined as pulmonary hypertension and elevated PVR in the absence of other disease of the lungs or heart. Its cause is unknown. About 6–10% have heritable PAH. Drug and toxic pulmonary hypertension have been described as associated with the use of anorexigenic agents that increase serotonin release and block its uptake. These include aminorex fumarate, fenfluramine, and dexfenfluramine. In some cases, there is epidemiologic linkage to ingestion of rapeseed oil or L-tryptophan and use of recreational drugs, such as amphetamines and cocaine. Pulmonary hypertension associated with connective tissue disease includes cases associated with systemic sclerosis—up to 8–12% of patients with systemic sclerosis may be affected. Pulmonary hypertension has also been associated with HIV infection, portal hypertension, congenital heart disease (Eisenmenger syndrome), schistosomiasis, and chronic hemolytic anemia (eg, sickle cell anemia). In rare instances, obstruction of the pulmonary venous circulation may occur (pulmonary veno-occlusive disease and capillary hemangiomatosis).

Group II includes all cases related to left heart disease. **Group III** includes cases due to parenchymal lung disease, impaired control of breathing, or living at high altitude. This group encompasses those with idiopathic pulmonary fibrosis and COPD. **Group IV** represents patients with chronic thromboembolic disease or other PA obstruction. **Group V** includes multifactorial causes such as hematologic, systemic, and metabolic disorders.

Clinical Findings

A. Symptoms and Signs

Common to all is exertional dyspnea, chest pain, fatigue, and light-headedness as early symptoms; later symptoms include syncope, abdominal distention, ascites, and peripheral edema as RV function worsens. Chronic lung disease, especially sleep apnea, often is overlooked as a cause for pulmonary hypertension as is chronic thromboembolic disease. Patients with idiopathic pulmonary hypertension are characteristically young women who have evidence of right HF that is usually progressive, leading to death in 2–8 years without therapy. This is a decidedly different prognosis than patients with Eisenmenger physiology due to a left-to-right shunt; 40% of patients with Eisenmenger physiology are alive 25 years after the diagnosis has been made. Patients have manifestations of low cardiac output, with weakness and fatigue, as well as edema and ascites as right HF advances. Peripheral cyanosis is present, and syncope on effort may occur.

B. Diagnostic Studies

The ESC and European Respiratory Society updated guidelines for the diagnosis and treatment of pulmonary hypertension in 2019. *All patients with a high risk for PAH should undergo confirmatory right heart catheterization.*

The laboratory evaluation of idiopathic pulmonary hypertension must exclude a secondary cause. A hypercoagulable state should be sought by measuring protein C and S levels, the presence of a lupus anticoagulant, the level of factor V Leiden, prothrombin gene mutations, and D-dimer. Chronic pulmonary emboli must be excluded (usually by ventilation-perfusion lung scan or contrast spiral CT); the ventilation-perfusion scan is the more sensitive test but not specific. If it is normal, then chronic thromboembolic pulmonary hypertension is very unlikely. The CXR helps exclude a primary pulmonary etiology—evidence for patchy pulmonary edema may raise the suspicion of pulmonary veno-occlusive disease due to localized obstruction in pulmonary venous drainage. A sleep study may be warranted if sleep apnea is suspected. The ECG is generally consistent with RVH and RA enlargement. Echocardiography with Doppler helps exclude an intracardiac shunt and usually demonstrates an enlarged RV and RA—at times they may be huge and hypocontractile. Severe pulmonic or tricuspid valve regurgitation may be present. Interventricular septal flattening seen on the echocardiogram is consistent with pulmonary hypertension. Doppler interrogation of the tricuspid regurgitation jet provides an estimate of RV systolic pressure. PFTs help exclude other disorders, though primary pulmonary hypertension may present with only a reduced carbon monoxide DL_{CO} or severe desaturation (particularly if a PFO has been stretched open and a right-to-left shunt is present). A declining DL_{CO} may precede the development of pulmonary hypertension in a patient with systemic sclerosis. Chest CT demonstrates enlarged pulmonary arteries and excludes other causes (such as emphysema or interstitial lung disease). Pulmonary angiography (or magnetic resonance angiography or CT angiography) reveals loss of the smaller acinar pulmonary vessels and tapering of the larger ones. Catheterization allows measurement of pulmonary pressures and testing for vasoreactivity using a variety of agents, but nitric oxide is the preferred testing agent due to its ease of use and short half-life. A positive response is

defined as one that decreases the pulmonary mean pressure by greater than 10 mm Hg, with the final mean PA pressure less than 40 mm Hg. Abdominal ultrasound is recommended to exclude portal hypertension. A lung biopsy is no longer suggested as relevant for the diagnosis.

Treatment & Prognosis

The treatment of PAH continues to evolve and depends on the etiology. For group I patients with a normal PCWP, treatment is related to the response to nitric oxide challenge with those responsive being initially treated with calcium channel blockers. The vast majority of patients, unfortunately, do not respond to the acute vasoreactivity testing. Specific PAH therapy is therefore recommended in this situation. This begins with monotherapy but expands to the use of sequential medication therapy when pulmonary pressures are not improved. In critically ill hypotensive patients inotropic support may be required and eventually lung transplantation considered. Balloon atrial septostomy is considered a IIb recommendation (on the notion that increased right-to-left shunting will improve cardiac output), but it is very rarely utilized.

Medication monotherapy varies in effectiveness depending on the etiologic classification. Only those in class I who respond to nitric oxide should get calcium channel blockers. Medication therapies include endothelin-receptor blockers (ambrisentan, bosentan, macitentan), phosphodiesterase type-5 inhibitors (sildenafil, tadalafil, and vardenafil), a guanylate cyclase stimulator (riociquat), prostanoids (epoprostenol, iloprost, teprostinil, and beraprost), and an IP-receptor agonist (selexipag). Various medication combinations have been approved and, when ineffective, sequential medication therapies may be used. Many medications interfere with HIV treatment, and this needs to be assessed if relevant. Due to inherent lung disease or left heart disease, there are no therapies that are specific to PAH. Bosentan, an endothelin-receptor blocker, has received a class I indication for patients with Eisenmenger syndrome. Anticoagulation is often recommended and is required lifelong in chronic thromboembolic pulmonary hypertension. The number of patients with inoperable chronic thromboembolic pulmonary hypertension being treated with balloon pulmonary angioplasty has increased dramatically since favorable results have been reported. Riociguat remains the only approved medical therapy for chronic thromboembolic pulmonary hypertension patients in this latter group.

Counseling and patient education are also important. Aerobic exercise is recommended but no heavy physical exertion or isometric exercise. Routine immunizations are advised. Pregnancy should be strongly discouraged and preventive measures taken to ensure it does not occur. Maternal mortality in severe PAH may be up to 50%.

Warfarin anticoagulation is recommended in all patients with idiopathic PAH and no contraindication. Diuretics are useful for the management of right-sided HF; clinical experience suggests loop diuretics (torsemide or bumetanide, which are absorbed even if bowel edema is present) plus spironolactone are preferable. Oxygen should be used to maintain oxygen saturation greater than 90%. Acute vasodilator testing (generally with nitric oxide) should be performed in all patients with idiopathic PAH who may be potential candidates for long-term therapy with calcium channel blockers. Patients with PAH caused by conditions other than idiopathic PAH respond poorly to oral calcium channel blockers, and there is little value of acute vasodilator testing in these patients.

When to Refer

All patients with suspected pulmonary hypertension should be referred to either a cardiologist or pulmonologist who specializes in pulmonary hypertension.

NEOPLASTIC DISEASES OF THE HEART

PRIMARY CARDIAC TUMORS

Primary cardiac tumors are rare and constitute only a small fraction of all tumors that involve the heart or pericardium. The most common primary tumor is **atrial myxoma**; it comprises about 50% of all tumors in adult case series. It is generally attached to the atrial septum and is more likely to grow on the LA side of the septum rather than the RA. Patients with myxoma can rarely present with the characteristics of a systemic illness, with obstruction of blood flow at the mitral valve level, or with signs of peripheral embolization. The syndrome includes fever, malaise, weight loss, leukocytosis, elevated ESR, and emboli (peripheral or pulmonary, depending on the location of the tumor). This is sometimes confused with infective endocarditis, lymphoma, other cancers, or autoimmune diseases. In most cases, the tumor may grow to considerable size and produce symptoms by simply obstructing mitral inflow. Episodic pulmonary edema (classically occurring when an upright posture is assumed) and signs of low output may result. Physical examination may reveal a diastolic sound related to motion of the tumor ("tumor plop") or a diastolic murmur similar to that of mitral stenosis. Right-sided myxomas may cause symptoms of right-sided failure. Familial myxomas occur as part of the Carney complex, which consists of myxomas, pigmented skin lesions, and endocrine neoplasia.

The diagnosis of atrial myxoma is established by echocardiography or by pathologic study of embolic material. Cardiac MRI is useful as an adjunct. Contrast angiography is frequently unnecessary, although it may demonstrate a "tumor blush" when the mass is vascular. Surgical excision is usually curative, though recurrences do occur and serial echocardiographic follow-up is recommended.

The second most common primary cardiac tumors are **valvular papillary fibroelastomas** and **atrial septal lipomas.** These tend to be benign and usually require no therapy. Papillary fibroelastomas are usually on the pulmonary or aortic valves, may embolize or cause valvular dysfunction, and should be removed if large and mobile. Other primary cardiac tumors include rhabdomyomas (that often appear multiple in both the RV and LV), fibrous histiocytomas, hemangiomas, and a variety of unusual sarcomas. Some sarcomas may be of considerable size

before discovery. Primary pericardial tumors, such as mesotheliomas related to asbestos exposure, may also occur. The diagnosis may be supported by an abnormal cardiac contour on radiograph. Echocardiography is usually helpful but may miss tumors infiltrating the ventricular wall. Cardiac MRI is the diagnostic procedure of choice along with gated CT imaging for all cardiac tumors.

SECONDARY CARDIAC TUMORS

Metastases from malignant tumors can also affect the heart. *Most often this occurs in malignant melanoma*, but other tumors that are known to metastasize to the heart include bronchogenic carcinoma; carcinoma of the breast; lymphoma; renal cell carcinoma; sarcomas; and, in patients with AIDS, Kaposi sarcoma. These are often clinically silent but may lead to pericardial tamponade, arrhythmias and conduction disturbances, HF, and peripheral emboli. The ECG may reveal regional Q waves. The diagnosis is often made by echocardiography, but cardiac MRI and CT scanning can often better delineate the extent of involvement. Metastatic tumors, especially lung or breast, may invade the pericardium and result in very large pericardial effusions as they result in slow accumulation of fluid. The prognosis is poor for all secondary cardiac tumors and treatment is generally palliative. On occasion, surgical resection for debulking or removal and chemotherapy may be effective in relieving symptoms.

Treatment

Many primary tumors may be resectable. Atrial myxomas should be removed surgically due to the high incidence of embolization from these friable tumors. Recurrences require lifelong monitoring with echocardiography. Papillary fibroelastomas are usually benign but they should be removed if they appear mobile and are larger than 10 mm in size or if there is evidence of embolization at the time of discovery. Large pericardial effusions from metastatic tumors may be drained for comfort, but the fluid invariably recurs. Rhabdomyomas may be surgically cured if the tumor is accessible and can be removed while still leaving enough functioning myocardium intact.

When to Refer

All patients with suspected cardiac tumors should be referred to a cardiologist or cardiac surgeon for evaluation and possible therapy.

Rahouma M et al. Cardiac tumors prevalence and mortality: a systematic review and meta-analysis. Int J Surg. 2020;76:178. [PMID: 32169566]

TRAUMATIC HEART DISEASE

Trauma is the leading cause of death in patients aged 1–44 years; cardiac and vascular trauma is second only to neurologic injury as the reason for these deaths. Penetrating wounds to the heart are often lethal unless immediately surgically repaired. In a 20-year review of penetrating trauma at a single institution, it was found that gunshot wounds were fatal 13 times more often than stab wounds and that factors such as hypotension, Glasgow Coma Score less than 8, Revised Trauma Score less than 7.84, associated injuries, and the more severe the injuries (Injury Severity Score greater than 25) all added to the mortality and morbidity risk.

Blunt trauma is a more frequent cause of cardiac injuries. This type of injury is common in motor vehicle accidents and may occur with any form of chest trauma, including CPR efforts. The most common injuries are myocardial contusions or hematomas. The RV is particularly prone to contusion as it sits directly under the sternum. Other forms of nonischemic cardiac injury include metabolic injury due to burns, electrical current, or sepsis. These may be asymptomatic (particularly in the setting of more severe injuries) or may present with chest pain of a nonspecific nature or, not uncommonly, with a pericardial component. Elevations of cardiac enzymes are frequent, and can be quite high, but the levels do not correlate with prognosis. There are some data that the presence of certain other cardiac biomarkers, such as NT-proBNP, correlate better with significant myocardial injury. Echocardiography may reveal an akinetic myocardial segment or pericardial effusion. Cardiac MRI may also suggest acute injury. Coronary CT angiography or angiography can reveal a coronary dissection or acute occlusion if that is a concern. Pericardiocentesis is warranted if tamponade is evident. As noted above, tako-tsubo transient segmental myocardial dysfunction can occur due to the accompanying stress.

Severe trauma may also cause myocardial or valvular rupture. Cardiac rupture can involve any chamber, but survival is most likely if injury is to one of the atria or the RV. Hemopericardium or pericardial tamponade is the usual clinical presentation, and surgery is almost always necessary. Mitral and aortic valve rupture may occur during severe blunt trauma—the former presumably if the impact occurs during systole and the latter if during diastole. Patients reach the hospital in shock or severe HF. Immediate surgical repair is essential. The same types of injuries may result in transection of the aorta, either at the level of the arch or distal to the takeoff of the left subclavian artery at the ligamentum arteriosum. Transthoracic echocardiography and TEE are the most helpful and immediately available diagnostic techniques. CT and MRI may also be required to better define the injury before surgical intervention.

Blunt trauma may also result in damage to the coronary arteries. Acute or subacute coronary thrombosis is the most common presentation. The clinical syndrome is one of acute MI with attendant ECG, enzymatic, and contractile abnormalities. Emergent revascularization is sometimes feasible, either by the percutaneous route or by coronary artery bypass surgery. LV aneurysms are common outcomes of traumatic coronary occlusions, likely due to sudden occlusion with no collateral vascular support. Coronary artery dissection or rupture may also occur in the setting of blunt cardiac trauma.

As expected, patients with severe preexisting conditions fare the least well after cardiac trauma. Data from

ReCONECT, a trauma consortium, reveal that mortality is linked to volume of cases seen at various centers, preexisting coronary disease or HF, intubation, age, and a severity scoring index.

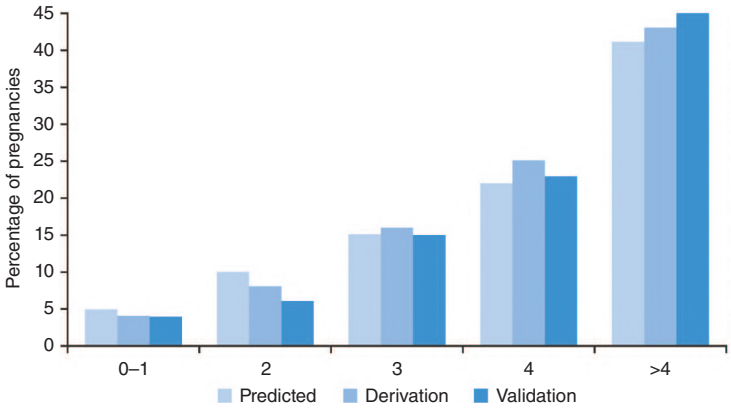
Qamar SR et al. State of the art imaging review of blunt and penetrating cardiac trauma. Can Assoc Radiol J. 2020;71:301. [PMID: 32066272]

HEART DISEASE & PREGNANCY

General principles to discuss with the patient include preconceptual counseling, pregnancy risk assessment, genetic risks, environmental risks, and pregnancy management. For some patients, it may also include a discussion regarding contraception, termination of a pregnancy, and a conversation about not only the delivery but what will happen post-pregnancy (including issues such as an eventual need for heart surgery or transplantation). In a review of 1315 pregnancies in patients with heart disease, 3.6% had serious cardiovascular complications and half were found to be preventable. Two-thirds of the complications occurred in the antepartum period. Adverse fetal and neonatal events, as expected, were much more common in those pregnancies with cardiovascular events.

The **Cardiac Disease in Pregnancy Investigation (CARPREG I)** scoring system for risk from cardiac events for women with heart disease noted four major risk factors: (1) NYHA FC III or IV HF, (2) prior cardiac events, (3) mitral or aortic obstruction, and (4) LVEF less than 40%. One point is assigned to each. Patients with no points had a 5% risk, those with 1 point had a complication rate of 27%, while for those with 2 or more points, the risk was 74%. Other reviews have suggested that the major risk for adverse outcomes or death to either the mother or fetus include pulmonary hypertension (with pulmonary pressure greater than three-quarters of systemic pressure), maternal cyanosis, systemic ventricular dysfunction, poor maternal functional class, severe left-sided valvular obstruction, aortic coarctation, significantly dilated aortic root, significant unrepaired heart defects, and warfarin therapy in patients with mechanical valves. In 2018, this group reported the results from a follow-up study (**CARPREG II**). Cardiac complications occurred in 16% of pregnancies and were primarily related to arrhythmias and HF. Although the overall rates of cardiac complications during pregnancy did not change over the years, the frequency of pulmonary edema decreased (8% from 1994 to 2001 vs. 4% from 2001 to 2014). Ten predictors of maternal cardiac complications were identified: five general predictors (prior cardiac events or arrhythmias, poor functional class or cyanosis, high-risk valve disease/LV outflow tract obstruction, systemic ventricular dysfunction, no prior cardiac interventions); four lesion-specific predictors (mechanical valves, high-risk aortopathies, pulmonary hypertension, CAD); and one delivery of care predictor (late pregnancy assessment). These 10 predictors were incorporated into a new risk index (CARPREG II) shown in Figure 10–9.

The WHO offers guidelines for the management of pregnancy in patients with congenital heart disease. This 2011 guideline also outlines risks to the fetus. Table 10–9 summarizes the observations and recommendations. Medication usage during pregnancy is always a difficult decision since *most have not been studied*. ACE inhibitors and amiodarone are contraindicated. Beta-blockers (including labetalol, metoprolol, and sotalol), digoxin, and calcium channel blockers are generally well tolerated (especially nifedipine, amlodipine, or verapamil, although there is controversy with diltiazem). There are concerns about the use of atenolol and premature birth, and it should not be used. Labetalol has been found to be particularly useful for treating hypertension as has methyldopa (though this is rarely used). Diuretics can generally be given safely. Pregnancy is a hypercoagulable state; the use of warfarin is



PREDICTOR	POINTS
Prior cardiac events or arrhythmias	3
Baseline NYHA III-IV or cyanosis	3
Mechanical valve	3
Ventricular dysfunction	2
High-risk left-sided valve disease/ left ventricular outflow tract obstruction	2
Pulmonary hypertension	2
Coronary artery disease	2
High-risk aortopathy	2
No prior cardiac intervention	1
Late pregnancy assessment	1

▲ **Figure 10–9.** Risk index for material cardiac complications in pregnancy (CARPREG II). The risk index is divided into five categories based on the sum of the points for a given pregnancy: 0 to 1 point; 2 points; 3 points; 4 points; and more than 4 points. The predicted risks for primary cardiac events stratified according to point score were 0 to 1 point (5%), 2 points (10%), 3 points (15%), 4 points (22%), and more than 4 points (41%). NYHA, New York Heart Association. (Reproduced with permission from Silversides CK, Grewal J, Mason J, et al. Pregnancy outcomes in women with heart disease: the CARPREG II Study. J Am Coll Cardiol. 2018;71(21):2419–2430.)

Table 10–9. Management strategies for women with valve disease, complex congenital heart disease, pulmonary hypertension, aortopathy, and dilated cardiomyopathy.

High-Risk Heart Disease in Pregnancy
- Preconception counseling and pregnancy risk stratification for all women with high-risk heart disease of childbearing age
- In women considering pregnancy: Switch to safer cardiac medications and emphasize importance of close monitoring
- In women avoiding pregnancy: Discuss safe and effective contraception choices or termination in early pregnancy

	Management Strategy		
Disease	Pregnancy Not Advised	Pregnancy Management	Delivery
Valve disease	• Severe mitral and aortic valve disease • Mechanical prosthetic valves if effective anticoagulation not possible	• Close follow-up • Medication therapy for HF or arrhythmias • Balloon valvuloplasty or surgical valve replacement in refractory cases	• Vaginal delivery preferred • C-section in case of fetal or maternal instability • Early delivery for clinical and hemodynamic deterioration • Consider hemodynamic monitoring during labor and delivery
Complex congenital heart disease	• Significant ventricular dysfunction • Severe AV valve dysfunction • Falling Fontan circulation • Oxygen saturation < 85%	• Close follow-up	• Vaginal delivery preferred • C-section in case of fetal or maternal instability • Consider hemodynamic monitoring during labor and delivery
Pulmonary hypertension	• Established pulmonary arterial hypertension	• Close follow-up • Early institution of pulmonary vasodilators	• Vaginal delivery preferred • C-section in case of fetal or maternal instability • Timing of delivery depends on clinical and RV function • Early delivery advisable • Diuresis after delivery to prevent RV volume overload • Extended hospital stay after delivery
Aortopathy	***For some women—*** • Marfan syndrome • Bicuspid aortic valve • Turner syndrome • Rapid growth of aortic diameter or family history of premature aortic dissection	• Treat hypertension • Beta-blockers to reduce heart rate • Frequent echocardiographic assessment • Surgery during pregnancy or after C-section if large increase in aortic diameter	• C-section in cases of significant aortic dilation –Marfan syndrome > 40 mm –Bicuspid aortic valve > 45 mm –Turner syndrome: aortic size index > 20 mm/m^2
Dilated cardiomyopathy	• LVEF < 40% • History of peripartum cardiomyopathy	• Close follow-up • Beta-blockers • Diuretic agents for volume overload • Vasodilators for hemodynamic and symptomatic improvement	• Vaginal delivery preferred • C-section in case of fetal or maternal instability • Consider hemodynamic monitoring during labor and delivery • Early delivery for clinical and hemodynamic deterioration

AV, atrioventricular; C-section, cesarean section.
Reproduced with permission from Elkayam U et al. High-risk cardiac disease in pregnancy: part I. J Am Coll Cardiol. 2016;68(4):396–410.

discussed above under valvular disease and congenital heart disease, but fundamentally the risk is dose related (not INR related) and warfarin can be used during the first trimester if the dose is 5 mg or less. For many patients, the most common potential complication is an atrial arrhythmia or systemic hypertension (systemic BP greater than 140/90 mm Hg). Patients should be hospitalized if BP exceeds 170/110 mm Hg.

Patients with adult congenital heart disease are at risk not only for cardiovascular events but also for obstetric events such as hypertension, preeclampsia, placenta previa or abruption, and early delivery.

Pfaller B et al. Preventing complications in pregnant women with cardiac disease. J Am Coll Cardiol. 2020;75:1443. [PMID: 32216913]

Tita AT et al; Chronic Hypertension and Pregnancy (CHAP) Trial Consortium. Treatment for mild chronic hypertension during pregnancy. N Engl J Med. 2022;386:1781. [PMID: 35363951]

CARDIOVASCULAR COMPLICATIONS OF PREGNANCY

Pregnancy-related hypertension (eclampsia and preeclampsia) is discussed in Chapter 21.

1. Cardiomyopathy of Pregnancy (Peripartum Cardiomyopathy)

In approximately 1 in 3000 to 4000 live births, dilated cardiomyopathy develops in the mother in the final month of pregnancy or within 6 months after delivery. Risk factors include preeclampsia, twin pregnancies, and Black race (likely via racism, social marginalization). The course of the disease is variable; most cases improve or resolve completely over several months, but others progress to refractory HF. About 60% of patients make a complete recovery. Serum BNP levels are routinely elevated in pregnancy, but serial values may be useful in predicting who may be at increased risk for a worse outcome. Beta-blockers have been administered judiciously to these patients, with at least anecdotal success. Diuretics, hydralazine, and nitrates help treat the HF with minimal risk to the fetus. Sotalol is acceptable for ventricular or atrial arrhythmias if other beta-blockers are ineffective. Some experts advocate anticoagulation because of an increased risk of thrombotic events, and both warfarin and heparin have their proponents. In severe cases, transient use of extracorporeal membrane oxygenation (ECMO) has been lifesaving. Recurrence in subsequent pregnancies is common, particularly if cardiac function has not completely recovered, and subsequent pregnancies are to be discouraged if the EF remains less than 55%. The risk of recurrent HF in a subsequent pregnancy has been estimated to be 21%. Delivery of the baby is important, though the peak incidence of the problem is in the first week after delivery and a few cases appear up to 5 weeks after delivery. Since an anti-angiogenic cleaved prolactin fragment is considered causal for peripartum cardiomyopathy, bromocriptine (a prolactin release inhibitor) has been reported to be beneficial. A multicenter trial in Europe found LVEF improved to a greater extent in patients with peripartum cardiomyopathy who were given bromocriptine than those who were not given bromocriptine. In addition, bromocriptine treatment was associated with high rate of full LV recovery and low morbidity and mortality in peripartum cardiomyopathy patients compared with other peripartum cardiomyopathy cohorts not treated with bromocriptine.

For a complete review of the current issues surrounding peripartum cardiomyopathy, the reader is referred to the state-of-art article noted below.

Davis MB et al. Peripartum cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75:207. [PMID: 31948651]

2. Coronary Artery & Aortic Vascular Abnormalities During Pregnancy

An ACS occurs in 2.8–8.1 per 1,000,000 pregnancies. Many are women over 35 years. It is known that pregnancy predisposes to dissection of the aorta and other arteries, perhaps because of the accompanying connective tissue changes. The risks are particularly high in patients with Marfan, Ehlers-Danlos, or Loeys-Dietz syndromes. The risk is highest in the third trimester, and coronary dissection, thrombosis, and atherosclerosis have about equal prevalence. The most frequent cause in one study was coronary dissection, and it has a peak incidence in the early postpartum period. Paradoxical emboli through a PFO to the coronary arteries have been implicated in a few instances. Clinical management is essentially similar to that of other patients with acute infarction, unless there is a connective tissue disorder. If nonatherosclerotic dissection is present, coronary intervention may be risky, as further dissection can be aggravated. In most instances, conservative management is warranted. At times, extensive aortic dissection requires surgical intervention. Marfan patients are particularly susceptible to further aortic expansion during pregnancy when the aortic diameter is more than 4.5 cm (greater or equal to 27 mm/m^2), and pregnancy should be discouraged in these situations. Some data, however, suggest that there is an increased risk of dissection during pregnancy even when the elective repair is reasonable (ie, when the aortic root is greater than 4.0 cm in women with Marfan syndrome contemplating pregnancy). Acute infarction during pregnancy is associated with an 8% maternal mortality and 56% incidence of premature delivery. If PCI is required, it is now recommended that a drug-eluting stent be considered rather than a bare metal stent. Medications that appear to be safe during pregnancy include aspirin, beta-blockers, clopidogrel, heparin or enoxaparin, and nitrates. Medications that are not safe include aldosterone inhibitors, ACE inhibitors or ARBs, DOACs, and statins. If need be, fibrinolytics, GP IIb/IIIa inhibitors, bivalirudin, and calcium channel blockers can be used.

Tweet MS et al. Pregnancy-associated myocardial infarction: prevalence, causes, and interventional management. Circ Cardiovasc Interv. 2020;13:e008687. [PMID: 32862672]

3. Management of Labor

Although vaginal delivery is usually well tolerated, unstable patients (including patients with severe hypertension and worsening HF) should have planned cesarean section. Spinal anesthesia results in a large drop in the systemic vascular resistance and can worsen right-to-left shunting. An increased risk of aortic rupture has been noted during delivery in patients with coarctation of the aorta and severe aortic root dilation with Marfan syndrome, and vaginal delivery should be avoided in these patients. For most patients, even those with complex congenital heart disease, vaginal delivery is the preferred method, however. Immediately following delivery, there are numerous fluid shifts that occur with the initial blood loss, reducing preload and accompanied by the loss of afterload reduction that had been provided by the placenta. Quickly, however, venous return increases as the uterus is no longer compressing the inferior vena cava and there is an infusion of fluid into the vascular system as the uterus quickly shrinks back toward its normal size. The sudden increase in preload and loss of afterload following delivery can result in HF during the first 48–72 hours after the delivery and that remains the high-risk time for susceptible patients.

CARDIOVASCULAR SCREENING OF ATHLETES

The sudden death of a competitive athlete inevitably becomes an occasion for local, if not national, publicity. On each occasion, the public and the medical community ask whether such events could be prevented by more careful or complete screening. Although each event is tragic, it must be appreciated that there are approximately 5 million competitive athletes at the high school level or above in any given year in the United States. The number of cardiac deaths occurring during athletic participation is unknown but estimates at the high school level range from one in 100,000 to one in 300,000 participants. Death rates among more mature athletes increase as the prevalence of CAD rises. These numbers highlight the problem of how best to screen individual participants. Even an inexpensive test such as an ECG would generate an enormous cost if required of all athletes, and it is likely that only a few individuals with high risk for sudden death would be detected. Echocardiography, either as a routine test or as a follow-up examination for abnormal ECGs, would be prohibitively expensive except for the elite professional athlete. Thus, *the most feasible approach is that of a careful medical history and cardiac examination performed by personnel aware of the conditions responsible for most sudden deaths in competitive athletes*.

It is important to point out that sudden death is much more common in the older than the younger athlete. Older athletes will generally seek advice regarding their fitness for participation. These individuals should recognize that strenuous exercise is associated with an increase in risk of sudden cardiac death and that appropriate training substantially reduces this risk. Preparticipation screening for risk of sudden death in the older athlete is a complex issue and at present is largely focused on identifying inducible ischemia due to significant coronary disease.

In a series of 158 athletic deaths in the United States between 1985 and 1995, *hypertrophic cardiomyopathy (36%) and coronary anomalies (19%) were by far the most frequent underlying conditions*. LVH was present in another 10%, ruptured aorta (presumably due to Marfan syndrome or cystic medial necrosis) in 6%, myocarditis or dilated cardiomyopathy in 6%, aortic stenosis in 4%, and arrhythmogenic RV dysplasia in 3%. In addition, commotio cordis, or sudden death due to direct myocardial injury, may occur. More common in children, ventricular tachycardia or ventricular fibrillation may occur even after a minor direct blow to the heart; it is thought to be due to the precipitation of a PVC just prior to the peak of the T wave on ECG.

A careful family and medical history and cardiovascular examination will identify most individuals at risk. An update in 2014 recommends that *all middle school and higher athletes undergo a medical screen questionnaire and examination*. The 12 elements in the examination are outlined in Table 10–10.

A family history of premature sudden death or CVD, or of any of these predisposing conditions should mandate further workup, including an ECG and echocardiogram.

Table 10–10. 12-element AHA recommendations for preparticipation cardiovascular screening of competitive athletes.

Medical History
Personal History
1. Exertional chest pain/discomfort
2. Unexplained syncope/near-syncope
3. Excessive exertional and unexplained dyspnea/fatigue
4. Prior recognition of a heart murmur
5. Elevated systemic blood pressure
Family History
6. Premature death (sudden and unexpected, or otherwise) before age of 50 years due to heart disease in one or more relatives
7. Disability from heart disease in a close relative before age of 50 years
8. Specific knowledge of certain cardiac conditions in family members: hypertrophic cardiomyopathy, dilated cardiomyopathy, long QT syndrome or other ion channelopathies, Marfan syndrome, or other important arrhythmias
Physical Examination
9. Heart murmur
10. Diminished femoral pulse (to exclude coarctation)
11. Phenotype of Marfan syndrome
12. Brachial artery blood pressure (sitting position)

AHA, American Heart Association.
Reproduced with permission from Lawless CE, Asplund C, Asif IM, et al. Protecting the heart of the American athlete: proceedings of the American College of Cardiology Sports and Exercise Cardiology Think Tank October 18, 2012, Washington, DC. J Am Coll Cardiol. 2014;64(20):2146–2171.

Symptoms of unexplained fatigue or dyspnea, exertional chest pain, syncope, or near syncope also warrant further evaluation. A Marfan-like appearance, significant elevation of BP, abnormalities of heart rate or rhythm, and pathologic heart murmurs or heart sounds should also be investigated before clearance for athletic participation is given. Such an evaluation is recommended before participation at the high school and college levels and every 2 years during athletic competition.

Stress-induced syncope or chest pressure may be the first clue to an anomalous origin of a coronary artery. Anatomically, this lesion occurs most often when the left anterior descending artery or left main coronary arises from the right coronary cusp and traverses between the aorta and pulmonary trunks. The "slit-like" orifice that results from the angulation at the vessel origin is thought to cause ischemia when the aorta and pulmonary arteries enlarge during vigorous exercise and tension is placed on the coronary.

The toughest distinction may be in sorting out the healthy athlete with LVH from the athlete with hypertrophic cardiomyopathy. In general, the healthy athlete's heart is *less* likely to have an unusual pattern of LVH (such as asymmetric septal hypertrophy), or to have LA enlargement, an abnormal ECG, an LV cavity less than 45 mm in diameter at end-diastole, an abnormal diastolic filling pattern, or a family history of hypertrophic cardiomyopathy. The athlete is more likely to be male than the individual with

hypertrophic cardiomyopathy, where women are equally at risk. Cardiac MRI is emerging as a useful means to separate the athlete's heart from hypertrophic obstructive cardiomyopathy. Increased risk is also evident in patients with the WPW syndrome, a prolonged QTc interval, or those who demonstrate the abnormal ST changes in leads V1 and V2 consistent with the Brugada syndrome.

Selective use of routine ECG and stress testing is recommended in men above age 40 years and women above age 50 years who continue to participate in vigorous exercise and at earlier ages when there is a positive family history for premature CAD, hypertrophic cardiomyopathy, or multiple risk factors. Because at least some of the risk features (long QT, LVH, Brugada syndrome, WPW syndrome) may be evident on routine ECG screening, several cost-effectiveness studies have been done. Most suggest that preparticipation ECGs are of potential value, though what to do when the QTc is mildly increased is unclear. Many experts feel the high incidence of false-positive ECG studies makes it very ineffective as a screening tool. With the low prevalence of cardiac anomalies in the general public, it has been estimated that 200,000 individual athletes would need to be screened to identify the single individual who would die suddenly. A report from Canada reviewing 74 sudden cardiac arrests during sports activity noted that the vast majority occurred during noncompetitive sports. The incidence during competitive sports was 0.76 per 100,000 athlete-years, and there was not a clear association with structural heart disease in most. Genetic testing of all athletes who demonstrate T wave inversions on their ECG also has been shown to be ineffective; the genetic testing contributed an additional diagnosis in only 2.5% of subjects over that obtained by routine clinical means.

The issue of routine screening, therefore, remains controversial. A report from the United Kingdom in 2018, screening adolescent soccer players from 1996 to 2016 (that included ECG and echocardiography), identified diseases associated with sudden death in only 0.38% of the 11,168 athletes screened for a total of 118,351 person-years. The incidence of sudden death was about 7 per 100,000 athletes and most were related to cardiomyopathies that had not been detected on the screening procedures.

In 2017, a position paper from a number of European societies presented arguments regarding the use of a number of preparticipation screening options. The manuscript also provided input from a number of international sports organizations. They concluded that there were data to support obtaining the clinical history, performing a physical examination, and performing a 12-lead ECG on all participants. They did *not* recommend echocardiography as a screening tool.

In 2017, a consensus statement from the American Medical Society for Sports Medicine was published summarizing the recommendations for the appropriate screening options in the various clinical scenarios. Once an individual with high risk has been identified, guidelines from the Bethesda conference and the ESC can be used to help determine whether the athlete may continue to participate in sporting events. Table 10–11 summarizes these recommendations.

Table 10–11. Recommendations for competitive sports participation among athletes with potential causes of SCD.

Condition	36th Bethesda Conference	European Society of Cardiology
Structural Cardiac Abnormalities		
HCM	Exclude athletes with a probable or definitive clinical diagnosis from all competitive sports. Genotype-positive/phenotype-negative athletes may still compete.	Exclude athletes with a probable or definitive clinical diagnosis from all competitive sports. Exclude genotype-positive/phenotype-negative individuals from competitive sports.
ARVC	Exclude athletes with a probable or definitive diagnosis from competitive sports.	Exclude athletes with a probable or definitive diagnosis from competitive sports.
CCAA	Exclude from competitive sports.	Not applicable.
	Participation in all sports 3 months after successful surgery would be permitted for an athlete with ischemia, ventricular arrhythmia or tachyarrhythmia, or LV dysfunction during maximal exercise testing.	
Electrical Cardiac Abnormalities		
WPW	Athletes without structural heart disease, without a history of palpitations, or without tachycardia can participate in all competitive sports. In athletes with symptoms, electrophysiological study and ablation are recommended. Return to competitive sports is allowed after corrective ablation, provided that the ECG has normalized.	Athletes without structural heart disease, without a history of palpitations, or without tachycardia can participate in all competitive sports. In athletes with symptoms, electrophysiological study and ablation are recommended. Return to competitive sports is allowed after corrective ablation, provided that the ECG has normalized.

(*continued*)

Table 10–11. Recommendations for competitive sports participation among athletes with potential causes of SCD. (continued)

Condition	36th Bethesda Conference	European Society of Cardiology
LQTS	Exclude any athlete with a previous cardiac arrest or syncopal episode from competitive sports. Asymptomatic patients restricted to competitive low-intensity sports. Genotype-positive/phenotype-negative athletes may still compete.	Exclude any athlete with a clinical or genotype diagnosis from competitive sports.
BrS	Exclude from all competitive sports except those of low intensity.	Exclude from all competitive sports.
CPVT	Exclude all patients with a clinical diagnosis from competitive sports. Genotype-positive/phenotype-negative patients may still compete in low-intensity sports.	Exclude all patients with a clinical diagnosis from competitive sports. Genotype-positive/phenotype-negative patients are also excluded.
Acquired Cardiac Abnormalities		
Commotio cordis	Eligibility for returning to competitive sport in survivors is a matter of individual clinical judgment. Survivors must undergo a thorough cardiovascular workup including 12-lead ECG, ambulatory ECG monitoring, and echocardiography.	Not applicable.
Myocarditis	Exclude from all competitive sports. Convalescent period of 6 months. Athletes may return to competition when test results normalize.	Exclude from all competitive sports. Convalescent period of 6 months. Athletes may return to competition when test results normalize.

ARVC, arrhythmogenic RV cardiomyopathy; BrS, Brugada syndrome; CCAA, congenital coronary artery anomalies; CPVT, catecholaminergic polymorphic ventricular tachycardia; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; SCD, sudden cardiac death; WPW, Wolff-Parkinson-White syndrome.

Reproduced with permission from Chandra N et al. Sudden cardiac death in young athletes: practical challenges and diagnostic dilemmas. J Am Coll Cardiol. 2013;61(10):1027–1040.

Screening for return to play after myocardial/pericardial involvement with COVID-19 is an important issue (see Infectious Myocarditis in Chapter 11). An expert consensus statement from the ACC suggests the following:

1. In the athlete who has had COVID-19, the ECG and high-sensitivity troponin should be normal. If any clinical concerns remain, then a transthoracic echocardiogram should be obtained.
2. Point-of-care echocardiography is not recommended, as the most common echocardiogram abnormalities may be missed by point-of-care echocardiography. These include RV dysfunction, diastolic LV abnormalities, and early signs of LV dysfunction (including abnormal global longitudinal strain). These are "red flags."
3. If any "red flags" from echocardiogram are present, then cardiac MRI should be obtained. MRI provides better assessment of RV function and abnormalities of myocardial edema (T2 imaging), intracellular and extracellular signaling (T1 imaging), and late gadolinium enhancement. The long-term significance of these findings is unknown.
4. Other imaging modalities can include coronary CT, chest CTA (looking for PE, given the hypercoagulable state COVID-19 creates), and rarely PET imaging.
5. Cardiopulmonary exercise testing is to be avoided during the acute phase but is valuable at 3–6 months after the illness if symptoms persist and as part of return to play guidelines.

Phelan D et al. Screening of potential cardiac involvement in competitive athletes recovering from COVID-19: an expert consensus statement. JACC Cardiovasc Imaging. 2020;13:2635. [PMID: 33303102]

11 Heart Failure & Cardiomyopathy

Christopher B. Granger, MD

HEART FAILURE

ESSENTIALS OF DIAGNOSIS

- LV failure: Either due to systolic or diastolic dysfunction. Predominant symptoms are those of low cardiac output and congestion, including dyspnea.
- RV failure: Symptoms of fluid overload predominate; usually RV failure is secondary to LV failure.
- Assessment of LV function is a crucial part of diagnosis and management.
- Optimal management of chronic HF includes combination medical therapies, such as ACE inhibitors, aldosterone antagonists, and beta-blockers.

General Considerations

HF is a common syndrome that is increasing in incidence and prevalence. Approximately 6.7 million patients in the United States have HF, with 8 million or more patients projected to have HF by 2030. Each year in the United States, 1,297,000 patients are discharged from the hospital with a diagnosis of HF. It is primarily a disease of aging, with over 75% of existing and new cases occurring in individuals over 65 years of age. Seventy-five percent of HF patients have antecedent hypertension. The prevalence of HF rises from less than 1% in individuals below 60 years to nearly 10% in those over 80 years of age.

HF may be right-sided, left-sided, or both. Patients with **left HF** may have symptoms of low cardiac output and elevated pulmonary venous pressure; dyspnea is the predominant feature. Signs of fluid retention predominate in **right HF.** Most patients exhibit symptoms or signs of both right- and left-sided failure, and LV dysfunction is the primary cause of RV failure. Approximately half of patients with HF have **preserved LV systolic function** and usually have some degree of **diastolic dysfunction.** Patients with reduced or preserved systolic function may have similar symptoms and it may be difficult to distinguish clinically between the two based on signs and symptoms. In developed countries, CAD with resulting MI and loss of functioning myocardium (**ischemic cardiomyopathy**) is the most common cause of systolic HF. Systemic hypertension remains an important cause of HF and, even more commonly in the United States, an exacerbating factor in patients with cardiac dysfunction due to other causes, such as CAD. Several processes may present with **dilated** or **congestive cardiomyopathy,** which is characterized by LV or biventricular dilation and generalized systolic dysfunction. These are discussed elsewhere in this chapter, but the most common are alcoholic cardiomyopathy, viral myocarditis (including infections by HIV; see also the COVID-19 section in Chapter 34), and dilated cardiomyopathies with no obvious underlying cause **(idiopathic cardiomyopathy).** Rare causes of dilated cardiomyopathy include infiltrative diseases (hemochromatosis, sarcoidosis, amyloidosis, etc), other infectious agents, metabolic disorders, cardiotoxins, and medication toxicity. **Valvular heart diseases**—particularly degenerative aortic stenosis and chronic aortic or mitral regurgitation—are not infrequent causes of HF. Persistent tachycardia, often related to atrial arrhythmias, can cause systolic dysfunction that may be reversible with controlling the rate. Diastolic cardiac dysfunction is associated with aging and related myocardial stiffening, as well as LVH, commonly resulting from hypertension. Conditions such as **hypertrophic** or **restrictive cardiomyopathy,** diabetes, and pericardial disease can produce the same clinical picture. Atrial fibrillation with or without rapid ventricular response may contribute to impaired LV filling.

HF is often preventable by early detection of patients at risk and by early intervention. The importance of these approaches is emphasized by US guidelines that have incorporated a classification of HF that includes four stages. **Stage A** includes patients at risk for developing HF (such as patients with hypertension). In the majority of these patients, development of HF can be prevented with interventions such as the aggressive treatment of hypertension, modification of coronary risk factors, and reduction of excessive alcohol intake. **Stage B** includes patients who have structural heart disease, increased filling pressures, risk factors and elevated biomarkers, but no current or

previously recognized symptoms of HF. Examples include patients with previous MI, other causes of reduced systolic function, LVH, or asymptomatic valvular disease. Both ACE inhibitors and beta-blockers prevent HF in the first two of these conditions, and more aggressive treatment of hypertension and early surgical intervention are effective in the latter two. **Stages C** and **D** include patients with clinical HF (current or previous) and the relatively small group of patients who have become refractory to the usual therapies, respectively.

Clinical Findings

A. Symptoms

The most common symptom of patients with **left HF** is shortness of breath, chiefly exertional dyspnea at first and then progressing to orthopnea, paroxysmal nocturnal dyspnea, and rest dyspnea. Chronic nonproductive cough, which is often worse in the recumbent position, may occur. Nocturia due to excretion of fluid retained during the day and increased renal perfusion in the recumbent position is a common nonspecific symptom of HF, as is fatigue and exercise intolerance. *These symptoms correlate poorly with the degree of cardiac dysfunction.* Patients with **right HF** have predominate signs of fluid retention, with the patient exhibiting edema, hepatic congestion and, on occasion, loss of appetite and nausea due to edema of the gut or impaired GI perfusion and ascites. Surprisingly, some individuals with severe LV dysfunction will display few signs of left HF and appear to have isolated right HF. Indeed, they may be clinically indistinguishable from patients with right HF secondary to pulmonary disease.

Patients with acute HF from MI, myocarditis, and acute valvular regurgitation due to endocarditis or other conditions usually present with pulmonary edema. Patients with episodic symptoms may be having LV dysfunction due to intermittent ischemia. Patients may also present with acute exacerbations of chronic, stable HF. Exacerbations may be caused by alterations in therapy (or patient noncompliance), excessive salt and fluid intake, arrhythmias, excessive activity, pulmonary emboli, intercurrent infection, or progression of the underlying disease.

Patients with HF are often categorized by the NYHA classification as **class I** (asymptomatic), **class II** (symptomatic with moderate activity), **class III** (symptomatic with mild activity), or **class IV** (symptomatic at rest). This classification is important since some of the treatments are indicated based on NYHA classification.

B. Signs

Many patients with HF, including some with severe symptoms, appear comfortable at rest. Others will be dyspneic during conversation or minor activity, and those with long-standing severe HF may appear cachectic or cyanotic. The vital signs may be normal, but tachycardia, hypotension, and reduced pulse pressure may be present. Patients often show signs of increased sympathetic nervous system activity, including cold extremities and diaphoresis. Important peripheral signs of HF can be detected by examination of the neck, the lungs, the abdomen, and the extremities. *RA pressure may be estimated through the height of the pulsations in the jugular venous system*. With the patient at 45 degrees, measure the height of the pulsation about the sternal angle, and add 5 cm to estimate the height above the left atrium, with a pressure greater than 8 cm being abnormal. In addition to the height of the venous pressure, abnormal pulsations, such as regurgitant *v* waves, should be sought. Examination of the carotid pulse may allow estimation of pulse pressure as well as detection of aortic stenosis. Thyroid examination may reveal occult hyperthyroidism or hypothyroidism, which are readily treatable causes of HF. Crackles at the lung bases reflect transudation of fluid into the alveoli. Pleural effusions may cause bibasilar dullness to percussion. Expiratory wheezing and rhonchi may be signs of HF. Patients with severe right HF may have hepatic enlargement—tender or nontender—due to passive congestion. Systolic pulsations may be felt in tricuspid regurgitation. Sustained moderate pressure on the liver may increase jugular venous pressure (JVP) (a positive **hepatojugular reflux** is an increase of greater than 1 cm, which correlates with elevated pulmonary capillary wedge pressure [PCWP]). Ascites may also be present. Peripheral pitting edema is a common sign in patients with right HF and may extend into the thighs and abdominal wall.

Cardinal cardiac examination signs are a parasternal lift, indicating pulmonary hypertension; an enlarged and sustained LV impulse, indicating LV dilation and hypertrophy; a diminished first heart sound, suggesting impaired contractility; and an S_3 gallop originating in the LV and sometimes the RV. An S_4 is usually present in diastolic HF. Murmurs should be sought to exclude primary valvular disease; secondary mitral regurgitation and tricuspid regurgitation murmurs are common in patients with dilated ventricles. In chronic HF, many of the expected signs of HF may be absent despite markedly abnormal cardiac function and hemodynamic measurements.

C. Laboratory Findings

A blood count may reveal anemia and a high red-cell distribution width (RDW), both of which are associated with poor prognosis in chronic HF through poorly understood mechanisms. Kidney function tests can determine whether cardiac failure is associated with impaired kidney function that may reflect poor kidney perfusion. CKD is another poor prognostic factor in HF and may limit certain treatment options. Serum electrolytes may disclose hypokalemia, which increases the risk of arrhythmias; hyperkalemia, which may limit the use of inhibitors of the renin–angiotensin system; or hyponatremia, an indicator of marked activation of the renin–angiotensin system and a poor prognostic sign. Thyroid function should be assessed to detect occult thyrotoxicosis or myxedema, and iron studies should be checked to test for hemochromatosis. In unexplained cases, appropriate biopsies may lead to a diagnosis of amyloidosis. Myocardial biopsy may exclude specific causes of dilated cardiomyopathy but rarely reveals specific reversible diagnoses.

Serum BNP is a powerful prognostic marker that adds to clinical assessment in differentiating dyspnea due to HF from noncardiac causes. Two markers—**BNP** and

NT-proBNP—provide similar diagnostic and prognostic information. BNP is expressed primarily in the ventricles and is elevated when ventricular filling pressures are high. It is quite sensitive in patients with symptomatic HF—whether due to systolic or to diastolic dysfunction—but less specific in older patients, women, and patients with COPD. Studies have shown that BNP can help in emergency department triage in the diagnosis of acute decompensated HF, such that an *NT-proBNP less than 300 pg/mL or BNP less than 100 pg/mL, combined with a normal ECG, makes HF unlikely.* BNP is less sensitive and specific to diagnose HF in the chronic setting. BNP may be helpful in guiding the intensity of diuretic and a more consistent use of disease-modifying therapies, such as ACE inhibitors and beta-blockers, for the management of chronic HF. BNP, but not NT-proBNP, is increased by neprilysin inhibitors, since neprilysin degrades BNP. Thus, while NT-proBNP is still reliable, BNP should *not* be used to monitor degree of HF when patients are treated with sacubitril/valsartan. Worsening breathlessness or weight associated with a rising BNP (or both) might prompt increasing the dose of diuretics. However, *there is no proven value in using serial natriuretic peptide measurements to guide therapy*, as shown in the GUIDE-IT trial. Elevation of serum troponin, and especially of high-sensitivity troponin, is common in both chronic and acute HF, and it is associated with higher risk of adverse outcomes.

D. ECG and Chest Radiography

ECG may indicate an underlying or secondary arrhythmia, MI, or nonspecific changes that often include low voltage, intraventricular conduction defects, LVH, and nonspecific repolarization changes. CXRs provide information about the size and shape of the cardiac silhouette. Cardiomegaly is an important finding and is a poor prognostic sign. Evidence of pulmonary venous hypertension includes relative dilation of the upper lobe veins, perivascular edema (haziness of vessel outlines), interstitial edema, and alveolar fluid. In acute HF, these findings correlate moderately well with pulmonary venous pressure. However, patients with chronic HF may show relatively normal pulmonary vasculature despite markedly elevated pressures. Pleural effusions are common and tend to be bilateral or right-sided.

E. Additional Studies

The clinical diagnosis of systolic myocardial dysfunction is often inaccurate. The primary confounding conditions are diastolic dysfunction of the heart with decreased relaxation and filling of the LV (particularly in hypertension and in hypertrophic states) and pulmonary disease.

The most useful test is the echocardiogram because it can differentiate HF with and without preserved LV systolic function. The echocardiogram can define the size and function of both ventricles and of the atria. LVEF is the most commonly used measurement to define systolic function. RV function is assessed by contractility and other measures, such as tricuspid annular plane systolic excursion. Echocardiography will also allow detection of pericardial effusion, valvular abnormalities, intracardiac shunts, and segmental wall motion abnormalities suggestive of old MI as opposed to more generalized forms of dilated cardiomyopathy.

Radionuclide angiography as well as cardiac MRI also measure LVEF and permit analysis of regional wall motion. These tests are especially useful when echocardiography is technically suboptimal, such as in patients with severe pulmonary disease. MRI can assess for presence of scar tissue and of infiltrative disease. When myocardial ischemia is suspected as a cause of LV dysfunction, as it should be unless there is another clear cause, stress testing or coronary angiography should be performed.

F. Cardiac Catheterization

In most patients with HF, clinical examination and noninvasive tests can determine LV size and function and valve function to support and refine the diagnosis. Left heart catheterization may be helpful to define the presence and extent of CAD, although CT angiography may also be appropriate, especially when the likelihood of coronary disease is low. Evaluation for coronary disease is particularly important when LV dysfunction may be partially reversible by revascularization. The combination of angina or noninvasive evidence of significant myocardial ischemia with symptomatic HF is often an indication for coronary angiography if the patient is a potential candidate for revascularization. Right heart catheterization may be useful to select and monitor therapy in patients refractory to standard therapy.

Treatment: Heart Failure With Reduced LVEF

The treatment of HF is aimed at relieving symptoms, improving functional status, and preventing death and hospitalizations. *The evidence of clinical benefit, including reducing death and hospitalization, as well as reducing sudden cardiac death, of most therapies is limited to patients with HF with reduced LVEF (40% or less).* The SGLT-2 inhibitors, which reduce HF hospitalization for patients with preserved EF, are the one exception to this general finding. ***Using angiotensin receptor-neprilysin inhibitor, beta-blockers, mineralocorticoid receptor antagonists, and SGLT-2 inhibitor medication at appropriate doses for HF with reduced LVEF is estimated to reduce mortality by over 70%. Thus, this goal is as important as any in all of cardiology.*** It is now recognized that patients with mildly reduced EF (41–49%) may derive benefit from mineralocorticoid receptor antagonist and angiotensin receptor-neprilysin inhibitor (ARNI) (sacubitril/valsartan). Treatment of HF with preserved LVEF is aimed at improving symptoms and treating comorbidities. *Achieving target (or maximally tolerated up to target) dosing to obtain the benefits of these treatments that have been shown in clinical trials is important* (Table 11–1).

A. Correction of Reversible Causes

The major reversible causes of HF with reduced LVEF, also called **chronic systolic HF,** include valvular lesions, myocardial ischemia, uncontrolled hypertension, arrhythmias (especially persistent tachycardias), alcohol- or drug-induced myocardial depression, hypothyroidism, intracardiac shunts, and high-output states. Calcium

Table 11–1. Evidence-based doses of disease-modifying medications in key randomized trials in HFrEF or after MI (medications listed in alphabetical order within classes).

Medications	Starting Dose	Target Dose
ACE Inhibitors		
Captopril	6.25 mg three times daily	50 mg three times daily
Enalapril	2.5 mg twice daily	10–20 mg twice daily
Lisinopril	2.5–5.0 mg once daily	20–35 once daily
Ramipril	2.5 mg once daily	10 mg once daily
Trandolapril	0.5 mg once daily	4 mg once daily
Beta-Blockers		
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice daily
Metoprolol succinate (CR/XL)	12.5–25 mg once daily	200 mg once daily
Nebivolol	1.25 once daily	10 mg once daily
ARBs		
Candesartan	4–8 mg once daily	32 mg once daily
Losartan	50 mg once daily	150 mg once daily
Valsartan	40 mg twice daily	160 mg twice daily
Aldosterone Antagonists		
Eplerenone	25 mg once daily	50 mg once daily
Spironolactone	25 mg once daily	50 mg once daily
ARNI		
Sacubitril/valsartan	49/51 mg twice daily	97/103 mg twice daily
I_f Channel Blocker		
Ivabradine	5 mg twice daily	7.5 mg twice daily
SGLT-2 inhibitors		
Dapagliflozin	10 mg once daily	10 mg once daily
Empagliflozin	10 mg once daily	10 mg once daily

ARNI, angiotensin receptor-neprilysin inhibitor; HFrEF, HF with reduced EF.

channel blockers with negative inotropy (specifically verapamil or diltiazem), antiarrhythmic medications, thiazolidinediones, and NSAIDs may be important contributors to worsening HF. Some metabolic and infiltrative cardiomyopathies may be partially reversible, or their progression may be slowed; these include hemochromatosis, sarcoidosis, and amyloidosis. Once possible reversible components are being addressed, the measures outlined below are appropriate.

B. Pharmacologic Treatment

See also the following section Acute Heart Failure & Pulmonary Edema.

1. Diuretic therapy—Diuretics are the most effective means of providing symptomatic relief to patients with moderate to severe HF with dyspnea and fluid overload, for HF with either reduced or preserved LVEF. Few patients with symptoms or signs of fluid retention can be optimally managed without a diuretic. However, excessive diuresis can lead to electrolyte imbalance and neurohormonal activation. *A combination of a diuretic and an ACE inhibitor or ARNI, along with the early addition of a beta-blocker and SGLT-2 inhibitor, should be the initial treatment in most symptomatic patients with HF and reduced LVEF.*

When fluid retention is mild, **thiazide diuretics** or a similar type of agent (hydrochlorothiazide, 25–100 mg; metolazone, 2.5–5 mg; chlorthalidone, 25–50 mg; etc) may be sufficient. Thiazide or related diuretics often provide better control of hypertension than short-acting loop agents. The thiazides are generally *ineffective* when the GFR falls below 30–40 mL/min/1.73 m^2, a not infrequent occurrence in patients with severe HF. *Metolazone maintains its efficacy down to a GFR of approximately 20–30 mL/min/1.73 m^2.* Adverse reactions include hypokalemia and intravascular volume depletion with resulting prerenal azotemia, skin rashes, neutropenia and thrombocytopenia, hyperglycemia, hyperuricemia, and hepatic dysfunction.

Patients with more severe HF should be treated with one of the oral **loop diuretics.** These include furosemide (20–320 mg daily), bumetanide (1–8 mg daily), and torsemide (20–200 mg daily). These agents have a rapid onset and a relatively short duration of action. In patients with preserved kidney function, two or more daily doses are preferable to a single larger dose. In acute situations or when GI absorption is in doubt, they should be given intravenously. Torsemide may be effective when furosemide is not, related to better absorption and a longer half-life, although a large randomized trial has shown no difference in clinical outcomes between these diuretics. Larger doses (up to 500 mg of furosemide or equivalent) may be required with severe renal impairment. The major adverse reactions include intravascular volume depletion, prerenal azotemia, and hypotension. Hypokalemia, particularly with accompanying digitalis therapy, is a major problem. Less common side effects include skin rashes, GI distress, and ototoxicity (the latter more common with ethacrynic acid and possibly less common with bumetanide).

The **oral potassium-sparing agents** are often useful in combination with the loop diuretics and thiazides, with the first choice being the aldosterone inhibitors spironolactone (12.5–100 mg daily) or eplerenone (25–100 mg daily), which reduce mortality in addition to the diuretic effect. Aldosterone is often increased in HF. These medications spare loss of potassium, they have some diuretic effect (especially at higher doses), and they also improve clinical outcomes, including survival. Their onsets of action are slower than the other potassium-sparing agents, and spironolactone's side effects include gynecomastia and hyperkalemia. Combinations of potassium supplements or ACE inhibitors and potassium-sparing medications can increase the risk of hyperkalemia but have been used with success in patients with persistent hypokalemia.

Patients with refractory edema may respond to combinations of a loop diuretic and thiazide-like agents. Metolazone, because of its maintained activity with CKD, is the most useful agent for such a combination. Extreme caution must be observed with this approach, since massive diuresis and electrolyte imbalances often occur; 2.5 mg of metolazone orally should be added to the previous dosage of loop diuretic. In many cases this is necessary only once or twice a week, but dosages up to 10 mg daily have been used in some patients.

2. Inhibitors of the renin–angiotensin–aldosterone system—Inhibition of the renin–angiotensin–aldosterone system with ACE inhibitors should be part of the initial therapy of this syndrome based on their mortality benefits.

A. ACE INHIBITORS—At least seven ACE inhibitors have been shown to be effective for the treatment of HF or the related indication of postinfarction LV dysfunction (see Table 13–6). ACE inhibitors reduce mortality by approximately 20% in patients with symptomatic HF and have also been shown to prevent hospitalizations, increase exercise tolerance, and reduce symptoms in these patients. As a result, *ACE inhibitors generally should be part of first-line treatment of patients with symptomatic LV systolic dysfunction (EF less than 40%), usually in combination with a diuretic. They are also indicated for the management of patients with reduced EFs without symptoms because they prevent the progression to clinical HF.*

Because ACE inhibitors may induce significant hypotension, particularly following the initial doses, they must be *started with caution*. Hypotension is most prominent in patients with already low BPs (systolic pressure less than 100 mm Hg), hypovolemia, prerenal azotemia (especially if it is diuretic induced), and hyponatremia (an indicator of activation of the renin–angiotensin system). These patients should generally be started at low dosages (captopril 6.25 mg orally three times daily, enalapril 2.5 mg orally daily, or the equivalent), but other patients may be started at twice these dosages. Within several days (for those with the markers of higher risk) or at most 2 weeks, patients should be questioned about symptoms of hypotension, and both kidney function and potassium levels should be monitored.

ACE inhibitors should be titrated to the dosages proved effective in clinical trials (captopril 50 mg three times daily, enalapril 10 mg twice daily, ramipril 10 mg daily, lisinopril 20 mg daily, or the equivalent) over a period of 1–3 months. Most patients will tolerate these doses. *Asymptomatic hypotension is not a contraindication to up-titrating or continuing ACE inhibitors.* Some patients exhibit increases in serum creatinine or potassium, but they do *not* require discontinuation if the levels stabilize—even at values as high as 3 mg/dL and 5.5 mEq/L, respectively. Kidney dysfunction is more frequent in patients with diabetes, older patients, and those with low systolic pressures, and these groups should be monitored more closely. The most common side effects of ACE inhibitors in HF patients are dizziness (often not related to the level of BP) and cough, though the latter is often due as much to HF or intercurrent pulmonary conditions as to the ACE inhibitor. ACE inhibitor–induced cough is more common in women than in men.

B. ANGIOTENSIN II RECEPTOR BLOCKERS—Another approach to inhibiting the renin–angiotensin–aldosterone system is the use of specific ARBs (see Table 13–6), which will decrease adverse effects of angiotensin II by blocking the AT_1 receptor.

However, these agents do *not* share the effects of ACE inhibitors on other potentially important pathways that produce increases in bradykinin, prostaglandins, and nitric oxide in the heart, blood vessels, and other tissues. ARBs, specifically candesartan or valsartan, provide important benefits as an alternative to ACE inhibitors in chronic HF with reduced LVEF. (A large trial of patients with chronic HF and preserved LVEF found no benefit from the ARB irbesartan.) While they have the same level of recommendation in the guidelines, *generally ACE inhibitors are preferred over ARBs for patients who tolerate them, although starting an ARB will avoid the need for a washout period when transitioning to sacubitril/valsartan.*

C. SPIRONOLACTONE AND EPLERENONE—Inhibiting aldosterone has become a mainstay of management of symptomatic HF with reduced LVEF. The RALES trial compared spironolactone 25 mg daily with placebo in patients with advanced HF (current or recent class IV) already receiving ACE inhibitors and diuretics and showed a 29% reduction in mortality as well as similar decreases in other clinical end points. Based on the EMPHASIS-HF trial, the efficacy and safety of aldosterone antagonism—in the form of eplerenone, 25–50 mg orally daily—is established for patients with mild or moderate HF. Hyperkalemia was uncommon in severe HF clinical trial patients who received high doses of diuretic as maintenance therapy; however, hyperkalemia in patients taking spironolactone appears to be common in general practice. Potassium levels must be monitored closely during initiation of spironolactone (after 1 and 4 weeks of therapy) and periodically thereafter, particularly for patients with even mild degrees of kidney injury, and in patients receiving ACE inhibitors.

D. COMBINATION SACUBITRIL AND VALSARTAN—The combination of valsartan and sacubitril is called an **ARNI.** Compared to the ACE inhibitor enalapril, the ARNI was shown to reduce cardiovascular death and hospitalization for HF by 20% for patients with HF and reduced LVEF in a large randomized trial (PARADIGM-HF) of patients who had been taking an ACE inhibitor or ARB. Cardiovascular death itself was also reduced by 20%.

This evidence led to a class I recommendation by the ACC/AHA and the European Society of Cardiology (ESC) guidelines for the use of *sacubitril/valsartan as a replacement for ACE inhibitors for patients with HF with reduced EF who remain symptomatic on an ACE inhibitor, beta-blocker, and mineralocorticoid inhibitor.* Patients with baseline systolic BP less than 100 mm Hg were not included in the PARADIGM trial, and symptomatic hypotension is more common with sacubitril/valsartan than ACE inhibitor. Sacubitril/valsartan can be safely started in the hospital

for patients admitted with decompensated failure, once they are stable with systolic BP of at least 100 mm Hg and there has been a 36-hour washout period since the last dose of ACE inhibitor.

While there was some evidence of benefit, sacubitril/valsartan did not result in significant improvement in the primary outcome of total HF hospitalizations and cardiovascular death in the PARAGON-HF trial studying a population of patients with HF and preserved LVEF (45% or greater). However, the FDA has approved sacubitril/valsartan in this population, particularly for patients with EF "below normal," that is for EF less than 50% including patients with *mildly reduced EF (41–49%)*.

3. Beta-blockers—Beta-blockers are part of the foundation of care of chronic HF based on their life-saving benefits. The mechanism of this benefit remains unclear, but it is likely that chronic elevations of catecholamines and sympathetic nervous system activity cause progressive myocardial damage, leading to worsening LV function and dilation. The primary evidence for this hypothesis is that over a period of 3–6 months, beta-blockers produce consistent substantial rises in EF (averaging 10% absolute increase) and reductions in LV size and mass.

Three medications have strong evidence of reducing mortality: **carvedilol** (a nonselective beta-1- and beta-2-receptor blocker), the beta-1-selective **extended-release agent metoprolol succinate** (but not short-acting metoprolol tartrate), and **bisoprolol** (beta-1-selective agent).

There is a strong recommendation that *stable patients (defined as having no recent deterioration or evidence of volume overload) with mild, moderate, and even severe HF should be treated with a beta-blocker unless there is a noncardiac contraindication.* In the COPERNICUS trial, carvedilol was both well tolerated and highly effective in reducing both mortality and HF hospitalizations in a group of patients with severe (NYHA class III or IV) symptoms, but care was taken to ensure that they were free of fluid retention at the time of initiation. In this study, one death was prevented for every 13 patients treated for 1 year—as dramatic an effect as has been seen with a pharmacologic therapy in the history of cardiovascular medicine. One trial comparing carvedilol and (short-acting) metoprolol tartrate (COMET) found significant reductions in all-cause mortality and cardiovascular mortality with carvedilol. Thus, patients with chronic HF should be treated with extended-release metoprolol succinate, bisoprolol, or carvedilol but *not* short-acting metoprolol tartrate.

Because even apparently stable patients may deteriorate when beta-blockers are initiated, initiation must be done *gradually and with great care*. Carvedilol is initiated at a dosage of 3.125 mg orally twice daily and may be increased to 6.25, 12.5, and 25 mg twice daily at intervals of approximately 2 weeks. The protocols for sustained-release metoprolol use were started at 12.5 or 25 mg orally daily and doubled at intervals of 2 weeks to a target dose of 200 mg daily (using the Toprol XL sustained-release preparation). Bisoprolol was administered at a dosage of 1.25, 2.5, 3.75, 5, 7.5, and 10 mg orally daily, with increments at 1- to 4-week intervals. More gradual up-titration is often more convenient and may be better tolerated.

Patients should be instructed to monitor their weight at home as an indicator of fluid retention and to report any increase or change in symptoms immediately. Before each dose increase, patients should be seen and examined to ensure that there has not been fluid retention or worsening of symptoms. If HF worsens, this can usually be managed by increasing diuretic doses and delaying further increases in beta-blocker doses, though downward adjustments or discontinuation is sometimes required. Carvedilol, because of its beta-blocking activity, may cause dizziness or hypotension. This can usually be managed by reducing the doses of other vasodilators and by slowing the pace of dose increases.

4. SGLT-2 inhibitors—Four large clinical trials, two with patients with HF and reduced LVEF and two with preserved LVEF, have shown that *dapagliflozin and empagliflozin, inhibitors of SGLT-2, substantially reduce the risk of cardiovascular death and hospitalization for HF for patients with reduced or preserved LVEF, as well as with or without diabetes.* Each medication is used in a single dose, 10 mg a day, and each results in rapid benefits (within 2 weeks) and is well tolerated with respect to blood pressure and renal function. SGLT-2 inhibitors also reduced kidney disease progression, and patients with eGFR of 20 mL/min/1.73 m^2 have been included in these trials.

5. Digitalis glycosides—The efficacy of digitalis glycosides in reducing the symptoms of HF has been established in at least four multicenter trials that have demonstrated that digoxin withdrawal is associated with worsening symptoms and signs of HF, more frequent hospitalizations for decompensation, and reduced exercise tolerance. Digoxin should be considered for patients who remain symptomatic when taking diuretics and ACE inhibitors as well as for patients with HF who are in atrial fibrillation and require rate control. However, there is uncertainty about the safety of digoxin in this population with atrial fibrillation, especially with higher digoxin concentrations.

Digoxin has a half-life of 24–36 hours and is eliminated almost entirely by the kidneys. The oral maintenance dose may range from 0.125 mg three times weekly to 0.5 mg daily. It is lower in patients with kidney dysfunction, in older patients, and in those with smaller lean body mass. Although an oral loading dose of 0.75–1.25 mg (depending primarily on lean body size) over 24–48 hours may be given if an early effect is desired, in most patients with chronic HF it is sufficient to begin with the expected maintenance dose (usually 0.125–0.25 mg daily). Amiodarone, quinidine, propafenone, and verapamil are among the medications that may increase digoxin levels up to 100%. It is prudent to measure a blood level after 7–14 days (and at least 6 hours after the last dose was administered). Optimum serum digoxin levels are 0.7–1.2 ng/mL. Digoxin may induce ventricular arrhythmias, especially when hypokalemia or myocardial ischemia is present. Digoxin toxicity is discussed in Chapter 40.

6. Nitrates and hydralazine—The combination of hydralazine and isosorbide dinitrate has been shown to *improve outcomes in self-identified Black persons*. ARBs or ARNIs have largely supplanted the use of the hydralazine–isosorbide

dinitrate combination in patients with intolerance to ACE inhibitors.

See section Acute MI with ST-Segment Elevation for a discussion on the intravenous vasodilating medications and their dosages.

A. Nitrates—Intravenous vasodilators (sodium nitroprusside or nitroglycerin) are used primarily for acute or severely decompensated chronic HF, especially when accompanied by hypertension or myocardial ischemia. If neither of the latter is present, therapy is best initiated and adjusted based on hemodynamic measurements. The starting dosage for nitroglycerin is generally about 10 mcg/min, which is titrated upward by 10–20 mcg/min (to a maximum of 200 mcg/min) until mean arterial pressure drops by 10%. Hypotension (BP less than 100 mm Hg systolic) should be avoided. For sodium nitroprusside, the starting dosage is 5–10 mcg/min, with upward titration to a maximum dose of 400 mcg/min.

Isosorbide dinitrate, 20–40 mg orally three times daily, and nitroglycerin ointment, 2%, 15–16 mg (1.4 inches; 1 inch=15 mg) every 6–8 hours, appear to be equally effective, although the ointment is generally reserved for inpatient use only. The nitrates are moderately effective in relieving shortness of breath, especially in patients with mild to moderate symptoms, but less successful—probably because they have little effect on cardiac output—in advanced HF. Nitrate therapy is generally well tolerated, but headaches and hypotension may limit the dose of all agents. The development of *tolerance* to long-term nitrate therapy occurs. This is minimized by intermittent therapy, especially if a daily 8- to 12-hour nitrate-free interval is used, but probably develops to some extent in most patients receiving these agents. Transdermal nitroglycerin patches have no sustained effect in patients with HF and should *not* be used for this indication.

B. Hydralazine—Oral hydralazine is a potent arteriolar dilator; when used as a single agent, it has *not* been shown to improve symptoms or exercise tolerance during long-term treatment. The combination of nitrates and oral hydralazine produces greater hemodynamic effects as well as clinical benefits.

7. Ivabradine—Ivabradine inhibits the I_f channel in the sinus node and has the specific effect of slowing sinus rate. Ivabradine is approved by the FDA for use in stable patients with HF and heart rate of 70 beats/min who are taking the maximally tolerated dose of beta-blockers or in patients in whom beta-blockers are contraindicated. It is approved by the European Medicines Agency for use in patients with a heart rate of 75 beats/min or more. Both the US and the European guidelines give it a class IIa recommendation for patients in sinus rhythm with a heart rate of 70 beats/min or more with an EF of 35% or less, and persisting symptoms despite treatment with an evidence-based dose of beta-blocker (or a maximum tolerated dose below that), ACE inhibitor (or ARB), and an aldosterone antagonist (or ARB). In a trial of patients with chronic angina, ivabradine did not reduce cardiovascular events, and there may have been more events with ivabradine (than placebo) in patients with symptomatic angina.

8. Vericiguat (a soluble guanylate cyclase stimulator)—Vericiguat is FDA-approved to reduce the risk of cardiovascular death and HF hospitalization following a hospitalization for HF in patients with chronic HF and LVEF less than 45%. The VICTORIA trial showed a modest but significant reduction in cardiovascular death and HF hospitalization with vericiguat, *added to other effective therapies*, in this population with high-risk population.

9. Combination of medical therapies—Optimal management of chronic HF involves using combinations of proven life-saving therapies. *Patients with HF and reduced LVEF should be treated with all four life-saving medications: beta-blockers, mineralocorticoid (aldosterone) receptor antagonists, sacubitril/valsartan, and SGLT-2 inhibitors.* This combination, titrated to full tolerated doses, with careful monitoring of kidney function and potassium, will provide the greatest pharmacologic benefit to the majority of patients with HF with reduced LVEF. Achieving this goal has been shown to be more effective using a systematic approach with care pathways and frequent clinic visits. There are advantages to starting all of these medications before hospital discharge for patients hospitalized with HF, when possible.

10. Treatments that may cause harm in HF with reduced LVEF—Several therapies should be *avoided,* when possible, in patients with systolic HF. These include thiazolidinediones (glitazones) that cause worsening HF, most calcium channel blockers (with the exception of amlodipine and felodipine), NSAIDs, and cyclooxygenase-2 inhibitors that cause sodium and water retention and renal impairment, and the combination of an ACE inhibitor, ARB, and aldosterone blocker that increases the risk of hyperkalemia.

11. Anticoagulation—Patients with LV failure and reduced EF are at somewhat increased risk for developing intracardiac thrombi and systemic arterial emboli. However, this risk appears to be primarily in patients who are in atrial fibrillation, who have had thromboemboli, or who have LV thrombus. DOACs appear to be as effective as warfarin for patients with LV thrombus.

12. Antiarrhythmic therapy—Patients with moderate to severe HF have a high incidence of both symptomatic and asymptomatic arrhythmias. Although less than 10% of patients have syncope or presyncope resulting from ventricular tachycardia, ambulatory monitoring reveals that up to 70% of patients have asymptomatic episodes of nonsustained ventricular tachycardia. These arrhythmias indicate a poor prognosis independent of the severity of LV dysfunction, but many of the deaths are probably not arrhythmia related. Beta-blockers, because of their marked favorable effect on prognosis in general and on the incidence of sudden death specifically, should be initiated in these as well as all other patients with HF (see Beta-Blockers above). Other evidence-based therapies for HF, including ACE inhibitors, ARBs, mineralocorticoid receptor antagonists, ARNIs, and SGLT-2 inhibitors all appear to reduce sudden cardiac death. Empiric antiarrhythmic therapy with amiodarone did not improve outcome in the SCD-HeFT trial, and most other agents are contraindicated

because of their proarrhythmic effects in this population and their adverse effect on cardiac function. For patients with systolic HF and atrial fibrillation, a rhythm control strategy has *not* been shown to improve outcome compared to a rate control strategy and thus should be reserved for patients with a reversible cause of atrial fibrillation or refractory symptoms. Then, amiodarone is the medication of choice.

13. Statin therapy—Even though vascular disease is present in many patients with chronic HF, the role of statins has not been well defined in patients with HF. The CORONA and the GISSI-HF trials show no benefits of statins in patients with chronic HF.

C. Nonpharmacologic Treatment

1. Implantable cardioverter defibrillators (ICDs)—Indications for ICDs include not only patients with symptomatic or asymptomatic arrhythmias but also patients with chronic HF and LV systolic dysfunction who are receiving contemporary HF treatments, including beta-blockers. In the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II), 1232 patients with prior MI and an EF less than 30% were randomized to an ICD or a control group. Mortality was 31% lower in the ICD group, which translated into 9 lives saved for each 100 patients who received a device and were monitored for 3 years. The Centers for Medicare and Medicaid Services provides reimbursement coverage to include patients with chronic HF and ischemic or nonischemic cardiomyopathy with an EF of 35% or less.

2. Biventricular pacing (resynchronization)—Many patients with HF due to systolic dysfunction have abnormal intraventricular conduction that results in dyssynchronous and hence inefficient contractions. Several studies have evaluated the efficacy of "multisite" pacing, using leads that stimulate the RV from the apex and the LV from the lateral wall via the coronary sinus. Patients with wide QRS complexes (generally 150 msec or more), reduced EFs, and moderate to severe symptoms have been evaluated. Results from trials with up to 2 years of follow-up have shown an increase in EF, improvement in symptoms and exercise tolerance, and reduction in death and hospitalization. The best responders to cardiac resynchronization therapy are patients with wider QRS, left bundle branch block, and nonischemic cardiomyopathy, and the lowest responders are those with narrow QRS and non–left bundle branch block pattern. Thus, as recommended in the 2022 AHA/ACC/HFSA guidelines, *resynchronization therapy is indicated for patients with class II to III HF, EF of 35% or less, sinus rhythm, and left bundle branch block pattern with QRS duration of 150 msec or more.*

3. Case management, diet, and exercise training—Thirty to 50 percent of HF patients who are hospitalized will be readmitted within 3–6 months. Strategies to prevent clinical deterioration, such as case management, home monitoring of weight and clinical status, and patient adjustment of diuretics, can prevent rehospitalizations and should be part of the treatment regimen of advanced HF. Involvement of a multidisciplinary team (rather than a single physician) and in-person (rather than just telephonic) communication appear to be important features of successful programs. Initiating life-saving medications during hospitalization for HF with rapid titration after discharge may improve outcomes.

Patients should routinely practice *moderate salt restriction* (2–2.5 g sodium or 5–6 g salt per day). More severe sodium restriction is usually difficult to achieve and unnecessary because of the availability of potent diuretic agents.

Exercise training improves activity tolerance in significant part by reversing the peripheral abnormalities associated with HF and deconditioning. In severe HF, restriction of activity may facilitate temporary recompensation. A large trial showed no significant benefit (nor harm) from a structured exercise training program on death or hospitalization, although functional status and symptoms were improved. *Thus, in stable patients, a prudent increase in activity or a regular exercise regimen can be encouraged.* Indeed, a gradual exercise program is associated with diminished symptoms and substantial increases in exercise capacity.

4. Coronary revascularization—Since underlying CAD is the cause of HF in the majority of patients, coronary revascularization has been thought to be able to both improve symptoms and prevent progression. While the STITCH trial failed to show an overall survival benefit from CABG among patients with multivessel coronary disease who were candidates for CABG, but who also had HF and an LVEF of 35% or less, at 5 years, there was benefit at 10 years of follow-up. Thus, revascularization does appear warranted for some patients with HF, including those with more severe angina or left main coronary disease (excluded from the STITCH trial).

5. Cardiac transplantation—Because of the poor prognosis of patients with advanced HF, cardiac transplantation is widely used. Many centers have 1-year survival rates exceeding 80–90%, and 5-year survival rates above 70%. Infections, hypertension and kidney dysfunction caused by cyclosporine, rapidly progressive coronary atherosclerosis, and immunosuppressant-related cancers have been the major complications. The high cost and limited number of donor organs require careful patient selection early in the course.

6. Other surgical treatment options—Externally powered and implantable **ventricular assist devices** can be used in patients who require ventricular support either to allow the heart to recover or as a bridge to transplantation. The latest generation devices are small enough to allow patients unrestricted mobility and even discharge from the hospital. *Continuous flow* devices appear to be more effective than *pulsatile flow* devices. However, complications are frequent, including bleeding, thromboembolism, and infection, and the cost is very high, exceeding $200,000 in the initial 1–3 months.

Although 1-year survival was improved in the REMATCH randomized trial, all 129 patients died by 26 months. Newer-generation continuous flow pump

ventricular assist devices have been shown to result in better survival than the first-generation pulsatile flow device used in REMATCH.

7. Palliative care—Despite the technologic advances of recent years, it should be remembered that many patients with chronic HF are older adults and have multiple comorbidities. Many of them will not experience meaningful improvements in survival with aggressive therapy. The goal of management for these patients and all those with serious illness should include symptomatic improvement and palliative care as they approach the end of life (see Chapter 5).

Treatment: Heart Failure With Preserved LVEF

Although half of all HF occurs among patients with normal LVEF, often with diastolic dysfunction, *the only therapy shown to reduce cardiovascular death or HF hospitalization in this population is SGLT-2 inhibitors, specifically dapagliflozin or empagliflozin.* The mainstays of treating HF with preserved EF are SGLT-2 inhibitors and diuretic therapy for fluid overload. Treating comorbidities like hypertension, diabetes, obesity, and arrhythmias (such as atrial fibrillation and high burden PVCs) is also important.

A. Correction of Reversible Causes

Hypertension, pericardial disease, and atrial tachycardias are potentially reversible factors that can contribute to HF with preserved LVEF. Since tachycardia is associated with shorter overall diastolic filling time, controlling accelerated heart rate may be important. With effective treatment available for familial and wild type transthyretin amyloid cardiomyopathy, this diagnosis should be considered for patients with unexplained HF with preserved EF. Treating obesity, in particular with **GLP-1 receptor agonists**, has shown promise to improve HF symptoms and exercise function.

B. Pharmacologic Treatment

1. Diuretic therapy—Diuretics are important to control symptoms of fluid overload in patients with HF with preserved LVEF, similar to symptoms from systolic HF.

2. SGLT-2 inhibitors—Both empagliflozin and dapagliflozin have been shown to decrease cardiovascular mortality and heart failure hospitalization or worsening of HF of patients with HFpEF. They cause mild diuresis and mild reduction in blood pressure, thus care is needed during initiation for patients who may be dehydrated or have low blood pressure.

3. Inhibitors of the renin–angiotensin–aldosterone system—ACE inhibitors and ARBs have *not* been shown to improve outcome in patients with HF and preserved LVEF, despite being good therapies for the comorbidity of hypertension. Sacubitril/valsartan does *not* substantially improve outcome in patients with HF and preserved LVEF, although does appear to improve outcome for patients with mildly reduced LVEF (41–50%). Spironolactone has *not* been shown to improve outcome in a large trial of patients with HF and preserved LVEF, but there may have been some benefit in patients enrolled in the Americas who had more clearly defined HF. Spironolactone should remain a therapeutic option, especially for patients who also have hypertension.

C. Nonpharmacologic Treatment

Unlike in patients with HF and reduced LVEF, ICD and resynchronization device treatments do *not* have a role in patients with preserved LVEF. Revascularization for patients with HF and preserved LVEF should be guided by the same considerations as for patients with HF with reduced LVEF.

Prognosis

Once manifested, HF with reduced LVEF carries a poor prognosis. Even with appropriate treatment, the 5-year mortality is approximately 50%. Mortality rates vary from less than 5% per year in those with no or few symptoms to greater than 30% per year in those with severe and refractory symptoms. These figures emphasize the critical importance of early detection and intervention. Higher mortality is related to older age, lower LVEF, more severe symptoms, CKD, and diabetes. The prognosis of HF has improved in the past two decades, probably at least in part because of the more widespread use of ACE inhibitors and beta-blockers, which markedly improve survival in those with HF with reduced LVEF.

When to Refer

Patients with new symptoms of HF not explained by an obvious cause should be referred to a cardiologist. Patients with continued symptoms of HF and reduced LVEF (35% or less) should be referred to a cardiologist for consideration of placement of an ICD or cardiac resynchronization therapy (if QRS duration is 120 msec or more, especially with left bundle branch block pattern).

When to Admit

- Patients with unexplained new or worsened symptoms or positive cardiac biomarkers concerning for acute myocardial necrosis.
- Patients with hypoxia, gross fluid overload, or pulmonary edema not readily resolved in an outpatient setting.

Anker SD et al; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385:1451. [PMID: 34449189]

Heidenreich PA et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022;79:1757. [PMID: 35379504]

Kosiborod MN et al; STEP-HFpEF Trial Committees and Investigators. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. N Engl J Med. 2023;389:1069. [PMID: 37622681]

McDonagh TA et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2022;24:4. [PMID: 35083827]
Packer M et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383:1413. [PMID: 32865377]
Solomon SD et al; DELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2022;387:1089. [PMID: 36027570]

ACUTE HEART FAILURE & PULMONARY EDEMA

ESSENTIALS OF DIAGNOSIS

- Acute onset or worsening of dyspnea at rest.
- Tachycardia, diaphoresis, cyanosis.
- Pulmonary rales, rhonchi; expiratory wheezing.
- Radiograph shows interstitial and alveolar edema with or without cardiomegaly.
- Arterial hypoxemia.

General Considerations

Typical causes of acute cardiogenic pulmonary edema include acute MI or severe ischemia, exacerbation of chronic HF, acute severe hypertension, AKI, acute volume overload of the LV (valvular regurgitation), and mitral stenosis. By far the most common presentation in developed countries is one of acute or subacute deterioration of chronic HF, precipitated by discontinuation of medications, excessive salt intake, myocardial ischemia, tachyarrhythmias (especially rapid atrial fibrillation), or intercurrent infection. Often in the latter group, there is preceding volume overload with worsening edema and progressive shortness of breath for which earlier intervention can usually avoid the need for hospital admission.

Clinical Findings

Acute pulmonary edema presents with a characteristic clinical picture of severe dyspnea, the production of pink, frothy sputum, and diaphoresis and cyanosis. Rales are present in all lung fields, as are generalized wheezing and rhonchi. Pulmonary edema may appear acutely or subacutely in the setting of chronic HF or may be the first manifestation of cardiac disease, usually acute MI, which may be painful or silent. Less severe decompensations usually present with dyspnea at rest, rales, and other evidence of fluid retention but without severe hypoxia.

Noncardiac causes of pulmonary edema include intravenous opioids, increased intracerebral pressure, high altitude, sepsis, medications, inhaled toxins, transfusion reactions, shock, and disseminated intravascular coagulation. These are distinguished from cardiogenic pulmonary edema by the clinical setting, history, and physical examination. Conversely, in most patients with cardiogenic pulmonary edema, an underlying cardiac abnormality can usually be detected clinically or by ECG, CXR, or echocardiogram.

The CXR reveals signs of pulmonary vascular redistribution, blurriness of vascular outlines, increased interstitial markings, and, characteristically, the butterfly pattern of distribution of alveolar edema. The heart may be enlarged or normal in size depending on whether HF was previously present. Assessment of cardiac function by echocardiography is important, since a substantial proportion of patients has normal EFs with elevated atrial pressures due to diastolic dysfunction. In cardiogenic pulmonary edema, BNP is elevated, and the PCWP is invariably elevated, usually over 25 mm Hg. In noncardiogenic pulmonary edema, the wedge pressure may be normal or even low.

Treatment

In full-blown pulmonary edema, the patient should be placed in a sitting position with legs dangling over the side of the bed; this facilitates respiration and reduces venous return. **Oxygen** is delivered by mask to obtain an arterial PO_2 greater than 60 mm Hg. Noninvasive pressure support ventilation may improve oxygenation and prevent severe CO_2 retention while pharmacologic interventions take effect. However, if respiratory distress remains severe, endotracheal intubation and mechanical ventilation may be necessary.

Morphine is highly effective in pulmonary edema and may be helpful in less severe decompensations when the patient is uncomfortable. The initial dosage is 2–8 mg intravenously (subcutaneous administration is effective in milder cases) and may be repeated after 2–4 hours. Morphine increases venous capacitance, lowering LA pressure, and relieves anxiety, which can reduce the efficiency of ventilation. However, morphine may lead to CO_2 retention by reducing the ventilatory drive. It should be avoided in patients with opioid-induced pulmonary edema, who may improve with opioid antagonists, and in those with neurogenic pulmonary edema.

Intravenous diuretic therapy (furosemide, 40 mg, or bumetanide, 1 mg—or higher doses if the patient has been receiving long-term diuretic therapy) *is usually indicated even if the patient has not exhibited prior fluid retention.* These agents produce venodilation prior to the onset of diuresis. The DOSE trial has shown that, for acute decompensated HF, bolus doses of furosemide are of similar efficacy as continuous intravenous infusion, and that higher-dose furosemide (2.5 times the prior daily dose) resulted in more rapid fluid removal without a substantially higher risk of kidney impairment.

Nitrate therapy accelerates clinical improvement by reducing both BP and LV filling pressures. Sublingual nitroglycerin or isosorbide dinitrate, topical nitroglycerin, or intravenous nitrates will ameliorate dyspnea rapidly prior to the onset of diuresis, and these agents are particularly valuable in patients with accompanying hypertension.

Intravenous nesiritide, a recombinant form of human BNP, is a potent vasodilator that reduces ventricular filling pressures and improves cardiac output. Its hemodynamic

effects resemble those of intravenous nitroglycerin with a more predictable dose–response curve and a longer duration of action. In clinical studies, nesiritide (administered as 2 mcg/kg by intravenous bolus injection followed by an infusion of 0.01 mcg/kg/min, which may be up-titrated if needed) produced a rapid improvement in both dyspnea and hemodynamics. The primary adverse effect is hypotension, which may be symptomatic and sustained. Because most patients with acute HF respond well to conventional therapy, the role of nesiritide may be primarily in patients who continue to be symptomatic after initial treatment with diuretics and nitrates.

A randomized placebo-controlled trial of 950 patients evaluating intravenous milrinone in patients admitted for decompensated HF who had no definite indications for inotropic therapy showed no benefit in increasing survival, decreasing length of admission, or preventing readmission. In addition, rates of sustained hypotension and atrial fibrillation were significantly increased. Thus, the role of positive inotropic agents appears to be limited to patients with refractory symptoms and signs of low cardiac output, particularly if life-threatening vital organ hypoperfusion (such as deteriorating kidney function) is present. In some cases, dobutamine or milrinone may help maintain patients who are awaiting cardiac transplantation.

Bronchospasm may occur in response to pulmonary edema and may itself exacerbate hypoxemia and dyspnea. Treatment with inhaled beta-adrenergic agonists or intravenous aminophylline may be helpful, but both may also provoke tachycardia and supraventricular arrhythmias.

In most cases, pulmonary edema responds rapidly to therapy. When the patient has improved, the cause or precipitating factor should be ascertained. In patients without prior HF, evaluation should include echocardiography and, in many cases, cardiac catheterization and coronary angiography. Patients with acute decompensation of chronic HF should be treated to achieve an euvolemic state and have their medical regimen optimized. Generally, an oral diuretic and an ACE inhibitor should be initiated, with efficacy and tolerability confirmed prior to discharge. In selected patients, early but careful initiation of beta-blockers in low doses should be considered.

MYOCARDITIS & THE CARDIOMYOPATHIES

INFECTIOUS MYOCARDITIS

ESSENTIALS OF DIAGNOSIS

- Often follows an upper respiratory infection.
- May present with chest pain (pleuritic or nonspecific) or signs of HF.
- Echocardiogram documents cardiomegaly and contractile dysfunction. Initial heart size is generally normal with thickened walls.
- Myocardial biopsy, though not sensitive, may reveal a characteristic inflammatory pattern. MRI has a role in diagnosis.
- COVID-19 myocarditis can occur in people with COVID-19 and rates of myocardial injury vary depending on severity of illness, underlying disease, and type of imaging.

General Considerations

Cardiac dysfunction due to primary myocarditis is generally caused by either an acute viral infection or a post viral immune response. Secondary myocarditis is the result of inflammation caused by nonviral pathogens, medications, chemicals, physical agents, hypersensitivity reactions, or inflammatory diseases (such as SLE).

Management of myopericarditis due to COVID-19 is similar to any cause of myocarditis. There is speculation that the SARS-CoV-2 spike protein may be able to bind to the ACE-2 membrane receptor on cardiomyocytes creating direct cellular injury and T-lymphocyte–mediated cytotoxicity augmented by a cytokine storm. This process activates more T cells and furthers a cycle of T-cell activation and further release of cytokines.

The accepted definition of myocarditis is biopsy dependent and includes the observation of 14 or more lymphocytes/mcL including up to 4 monocytes/mcL with the presence of 7 or more CD3-positive T lymphocytes/mcL. Injury can be fulminant, subclinical, or chronic. Both cellular and humoral inflammatory processes contribute to the progression to chronic injury, and there are subgroups that appear to benefit from immunosuppression.

Genetic predisposition is a likely factor in at least a few cases. Autoimmune myocarditis (eg, giant cell myocarditis) may occur with no identifiable viral infection. The heterogeneity of the clinical syndromes and the incomplete understanding of the immunopathology hinder a more complete understanding of the mechanisms involved.

Myocarditis can follow SARS-CoV-2 infection or rarely after vaccination. In both scenarios, younger male patients are at highest risk for this overall rare event. With vaccination, myocarditis is rare: the CDC reports rates of 5 to 97 cases per million people aged 18 to 39 years. With COVID-19, myocarditis affects under-resourced groups disproportionately with death rates highest among self-identified Black persons likely due to both an increase in comorbidities and health care disparities.

Clinical Findings

A. Symptoms and Signs

Patients may present several days to a few weeks after the onset of an acute febrile illness or a respiratory infection or they may present with HF without antecedent symptoms. The onset of HF may be gradual or may be abrupt and fulminant. In acute fulminant myocarditis, low output and shock may be present with severely depressed LV systolic function. The LV chamber size is typically not very enlarged. A pericardial friction rub may be present. In the

European Study of Epidemiology and Treatment of Inflammatory Heart Disease, 72% of participants had dyspnea, 32% had chest pain, and 18% had arrhythmias. Pulmonary and systemic emboli may occur. Pleural-pericardial chest pain is common. Examination reveals tachycardia, a gallop rhythm, and other evidence of HF or conduction defects. At times, the presentation may mimic an acute MI with ST changes, positive cardiac markers, and regional wall motion abnormalities despite normal coronaries. Microaneurysms may also occur and may be associated with serious ventricular arrhythmias. It has been estimated that approximately 10% of all dilated cardiomyopathy patients have viral myocarditis as the cause.

B. ECG and Chest Radiography

ECG may show sinus tachycardia, other arrhythmias, nonspecific repolarization changes, and intraventricular conduction abnormalities. The presence of Q waves or left bundle branch block portends a higher rate of death or cardiac transplantation. Ventricular ectopy may be the initial and only clinical finding. The CXR is nonspecific, but cardiomegaly is frequent, though not universal. Evidence for pulmonary venous hypertension is common and frank pulmonary edema may be present.

C. Diagnostic Studies

There is no specific laboratory finding that is consistently present, though the WBC count is usually elevated and the ESR and CRP usually are increased. Troponin I or T levels are elevated in about one-third of patients, but CK-MB is elevated in only 10%. Other biomarkers, such as BNP and NT-proBNP, are usually elevated. Echocardiography provides the most convenient way of evaluating cardiac function and can exclude many other processes. MRI with gadolinium enhancement reveals spotty areas of injury throughout the myocardium.

D. Endomyocardial Biopsy

Myocarditis can be confirmed with histologic evidence. The AHA/ACC/ESC class I recommendations for biopsy are (1) in patients with HF, a normal-sized or dilated LV less than 2 weeks after onset of symptoms, and hemodynamic compromise; or (2) in patients with a dilated LV 2 weeks to 3 months after onset of symptoms, new ventricular arrhythmias or AV nodal block (Mobitz II or complete heart block) or who do not respond to usual care after 1–2 weeks. However, these recommendations are not based on high level of evidence and thus should only be considered after imaging, such as MRI, and judgement that a treatable cause is likely to be found. In some cases, the identification of inflammation without viral genomes by PCR suggests that immunosuppression might be useful. Because the cardiac involvement is often patchy, the diagnosis even with biopsy can be missed in up to one-half of cases.

Treatment & Prognosis

Patients with fulminant myocarditis may present with acute cardiogenic shock. Acute myocarditis has been implicated as a cause of sudden death in 5–22% of such cases in athletes younger than 35 years. The ventricles are usually not dilated but thickened (possibly due to myxedema). There is a high death rate. Treatment is directed toward the clinical scenario with ACE inhibitors and beta-blockers if LVEF is less than 40%. NSAIDs should be used if myopericarditis-related chest pain occurs. Colchicine has been suggested if pericarditis predominates.

For COVID-19–related myocarditis, treatment is generally supportive. A 2022 ACC Consensus Statement suggests hospitalization for patients with mild or worse myocarditis, and consideration of corticosteroids for those with more severe myocarditis.

Specific antimicrobial therapy is indicated when an infecting agent is identified. Exercise should be limited during the recovery phase. Some experts believe digoxin should be avoided, and it likely has little value in this setting anyway. Controlled trials of immunosuppressive therapy with corticosteroids and IVIG have not suggested a benefit, though some recommend IVIG given at 2 g/kg over 24 hours in proven cases. Uncontrolled trials suggest that interferon might have a supportive role. Similarly, antiviral medication (such as pleconaril for enteroviruses) has been tried empirically. Studies are lacking as to when to discontinue the chosen therapy if the patient improves. Patients with fulminant myocarditis require aggressive short-term support, including an IABP or an LV assist device. If severe pulmonary infiltrates accompany the fulminant myocarditis, extracorporeal membrane oxygenation (ECMO) support may be temporarily required and has had notable success.

The question of what to do with the athlete in whom evidence of COVID-19 myocarditis has developed has led to a series of national discussions, some prompted by the cardiac MRI findings in young adults with minimal symptoms, although early reports of this being common have not been replicated. The higher troponin levels associated with poorer outcomes have generally occurred only in hospitalized patients. The findings of an abnormal cardiac MRI have not consistently proven to result in any long-term cardiac injury. Table 11–2 outlines the suggested guidelines by a Task Force from the American College of Cardiology Sports and Exercise Section.

When to Refer

Patients in whom myocarditis is suspected should be seen by a cardiologist at a tertiary care center where facilities are available for diagnosis and therapies available should a fulminant course ensue. The facility should have ventricular support devices and transplantation options available.

Boehmer TK et al. Association between COVID-19 and myocarditis using hospital-based administrative data—United States, March 2020–January 2021. MMWR Morb Mortal Wkly Rep. 2021;70:1228. [PMID: 34473684]

Gluckman TJ et al. 2022 ACC expert consensus decision pathway on cardiovascular sequelae of COVID-19 in adults: myocarditis and other myocardial involvement, post-acute sequelae of sars-cov-2 infection, and return to play: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2022;79:1717. [PMID: 35307156]

Table 11–2. American College of Cardiology Sports and Exercise Section Guidelines for athletes with COVID-19 myocarditis.

Myocarditis diagnosis if both of the following are present
• A clinical syndrome of < 3 months' duration
• Otherwise unexplained increase in serum troponin levels, ECG changes, arrhythmias, high-grade AV block, regional wall motion abnormalities, or pericardial effusion. MRI findings suggesting myocarditis including T1- or T2-weighted imaging or late gadolinium enhancement
Sports eligibility after myocarditis
• Must obtain a resting echocardiogram, 24-hour ambulatory ECG monitoring, and an exercise ECG no earlier than 3–6 months after the illness (class I, LOE C)
• Can resume exercise training if ALL of the following are met (class IIa, LOE C)
– Normal ventricular function
– Serum markers of myocardial injury, HF, and inflammation have returned to normal
– Clinically relevant arrhythmias on ambulatory ECG monitoring or exercise ECG are absent

AV, atrioventricular; LOE, level of evidence.

Shimabukuro TT. Update on myocarditis following mRNA COVID-19 vaccination. 2022 Jun 23. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-06-22-23/03-covid-shimabukuro-508.pdf

Siripanthong B et al. Recognizing COVID-19-related myocarditis: the possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm. 2020;17:1463. [PMID: 32387246]

NONINFECTIOUS MYOCARDITIS

A variety of medications, recreational drugs, and toxic substances can produce acute or chronic myocardial injury; the clinical presentation varies widely. The phenothiazines, lithium, chloroquine, disopyramide, antimony-containing compounds, and arsenicals can also cause ECG changes, arrhythmias, or HF. Hypersensitivity reactions to sulfonamides, penicillins, and aminosalicylic acid as well as other medications can result in cardiac dysfunction. Radiation can cause an acute inflammatory reaction as well as a chronic fibrosis of heart muscle, usually in conjunction with pericarditis.

Cardiotoxicity from cocaine may occur from coronary artery spasm, MI, arrhythmias, and myocarditis. A cocaine cardiomyopathy has also been described. Because many of these processes are believed to be mediated by cocaine's inhibitory effect on norepinephrine reuptake by sympathetic nerves, beta-blockers have been used in patients with fixed stenosis. In documented coronary spasm, calcium channel blockers and nitrates may be effective. Usual therapy for HF or conduction system disease is warranted when symptoms occur. Other recreational drug use has been associated with myocarditis in various case reports.

Systemic disorders are also associated with myocarditis. These include giant cell myocarditis, eosinophilic myocarditis, celiac disease, granulomatosis with polyangiitis, and sarcoidosis. A benefit from immunosuppressive therapy, especially in giant cell myocarditis has been suggested in a number of observational studies, including those directed primarily at T cells (ie, using muromonab-CD3). Treatment of eosinophilic myocarditis includes the use of high-dose corticosteroids and removal of the offending medication or underlying trigger, if known. Most studies suggest that HIV is only indirectly responsible for HIV cardiomyopathy, and other factors, gp 120 protein, adverse reaction to antiretroviral therapy, and opportunistic infections have been implicated more often. Epstein-Barr and herpes simplex viruses have been identified in some patients' myocardium.

The problem of cardiovascular side effects from cancer chemotherapy agents is an ever growing one and has spawned a new clinical area in cardiology called **cardio-oncology.** Anthracyclines (doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone) remain the cornerstone of treatment of many malignancies but may result in cardiomyopathy. HF can be expected in 5% of patients treated with a cumulative dose of 400–450 mg/m^2, and this rate is doubled if the patient is over age 65. While symptoms and evidence for myocardial dysfunction usually appear within 1 year of starting therapy, late-onset manifestation of HF may appear up to a decade later. The major mechanism of cardiotoxicity is thought to be due to oxidative stress inducing both apoptosis and necrosis of myocytes. There is also disruption of the sarcomere. This pathologic understanding is the rationale behind the superoxide dismutase mimetic and iron-chelating agent, dexrazoxane, to protect from the injury. The use of trastuzumab in combination with anthracyclines increases the risk of cardiac dysfunction up to 28%; this has been an issue since combined use of these agents is particularly effective in *HER2*-positive breast cancer. Other risk factors for patients receiving anthracyclines include the use of paclitaxel, concurrent radiation, and preexisting CVD (including hypertension, peripheral vascular disease, CAD, and diabetes). A summary of cardiotoxic cancer therapeutic agents and their role may be found in the 2019 AHA statement on cardio-oncology.

In patients receiving chemotherapy, it is important to look for subtle signs of cardiovascular compromise. Serial echocardiography, cardiac MR, or both can provide concrete data regarding LV function. Echo/Doppler myocardial global strain abnormalities may be the first abnormality observed (even prior to a drop in the LVEF) and assessment of the T2 signal from cardiac MRI may also provide early detection of cardiotoxicity. Biomarkers such as BNP or NT-proBNP may be of some value when serial measures are obtained. Other biomarkers may appear early in the course of myocardial injury (especially troponin and myeloperoxidase) and may allow for early detection of cardiotoxicity before other signs become evident. *There is some evidence that beta-blocker therapy may reduce the negative effects on myocardial function.* There are anecdotal data from animal models that NSAIDs may be harmful in patients with myocarditis. They should be avoided along with alcohol and strenuous physical exercise.

When to Refer

Many patients with myocardial injury from toxic agents can be monitored safely if ventricular function remains relatively preserved (EF greater than 40%) and no HF symptoms occur. Diastolic dysfunction may be subtle.

Once HF or a reduced LVEF becomes evident or significant conduction system disease becomes manifest, the patient should be evaluated and monitored by a cardiologist in case myocardial dysfunction worsens and further intervention becomes warranted.

Ye L et al. Myocardial strain imaging by echocardiography for the prediction of cardiotoxicity of chemotherapy treated patients: a meta-analysis. JACC Cardiovasc Imaging. 2020; 13:881. [PMID: 31734206]

DILATED CARDIOMYOPATHY

ESSENTIALS OF DIAGNOSIS

- Symptoms and signs of HF.
- Echocardiogram confirms LV dilation, thinning, and global dysfunction.
- Severity of RV dysfunction critical in long-term prognosis.

General Considerations

HF definitions have changed over the years and patients with a dilated cardiomyopathy are generally placed into the category of HF with reduced EF where the LVEF is defined as less than or equal to 40%. *In about half of the patients in this category, there is LV enlargement and it is this group that defines dilated cardiomyopathy*. This is a large group of heterogeneous myocardial disorders characterized by reduced myocardial contractility in the absence of abnormal loading conditions such as with hypertension or valvular disease. The prevalence averages 36 cases/100,000 in the United States and accounts for approximately 10,000 deaths annually. Black patients are afflicted three times as often as White patients. The prognosis is poor with 50% mortality at 5 years once symptoms emerge.

The causes are multiple and diverse. Up to 20–35% have a familial etiology. It is common for hereditary causes to first present with conduction system disease prior to a reduced LVEF. While a large proportion of dilated cardiomyopathy causes are listed as idiopathic, it is likely that genetic variants may be responsible for many of these. Endocrine, inflammatory, and metabolic causes include obesity, diabetes, thyroid disease, celiac disease, SLE, acromegaly, and growth hormone deficiency. Toxic, drug-induced, and inflammatory causes are listed in the prior section. Nutritional diseases such as deficiency of thiamine, selenium, and carnitine have also been documented. Dilated cardiomyopathy may also be caused by prolonged tachycardia either from supraventricular arrhythmias, from very frequent PVCs (more than 15% of heart beats), or from frequent RV pacing. Dilated cardiomyopathy is also associated with HIV, Chagas disease, rheumatologic disorders, iron overload, sleep apnea, amyloidosis, sarcoidosis, chronic alcohol usage, ESKD, or cobalt exposure ("Quebec beer-drinkers' cardiomyopathy"). Peripartum cardiomyopathy and stress-induced disease (takotsubo) are discussed separately.

Clinical Findings

A. Symptoms and Signs

In most patients, symptoms of HF develop gradually. It is important to seek out a history of familial dilated cardiomyopathy and to identify behaviors that might predispose patients to the disease. The physical examination reveals rales, an elevated JVP, cardiomegaly, S_3 gallop rhythm, often the murmurs of functional mitral or tricuspid regurgitation, peripheral edema, or ascites. In severe HF, Cheyne-Stokes breathing, pulsus alternans, pallor, and cyanosis may be present.

B. ECG and Chest Radiography

The major findings are listed in Table 11–3. Sinus tachycardia is common. Other common abnormalities include left bundle branch block and ventricular or atrial arrhythmias. The CXR reveals cardiomegaly, evidence for left and/or right HF, and pleural effusions (right more frequently than left).

C. Diagnostic Studies

In the 2022 AHA/ACC/HFSA guideline, patients with dyspnea should have a BNP or NT-proBNP measured to help establish prognosis and disease severity (class I, level of evidence [LOE] A).

An echocardiogram is indicated to exclude unsuspected valvular or other lesions and confirm the presence of ventricular dilatation, reduced LV systolic function and associated RV systolic dysfunction, or pulmonary hypertension. Mitral Doppler inflow patterns also help in the diagnosis of concomitant diastolic dysfunction. Color flow Doppler can reveal tricuspid or mitral regurgitation, and continuous Doppler can estimate PA pressures. Intracavitary thrombosis is occasionally seen. Exercise or pharmacologic stress myocardial perfusion imaging may uncover underlying coronary disease. Radionuclide ventriculography provides a noninvasive measure of the EF and both RV and LV wall motion, though its use has been supplanted by cardiac MRI in most institutions. Cardiac MRI is particularly helpful in inflammatory or infiltrative processes, such as sarcoidosis or hemochromatosis, and is the diagnostic study of choice for RV dysplasia. MRI can also help define an ischemic etiology by noting gadolinium hyperenhancement consistent with myocardial scar from infarction or prior myocarditis. Cardiac catheterization is seldom of specific value unless myocardial ischemia is suspected, although right heart catheterization should be considered to help guide therapy when the clinical syndrome is not clear cut (class I indication, LOE C). Myocardial biopsy is rarely useful in establishing the diagnosis, although occasionally the

Table 11–3. Classification of the cardiomyopathies.

	Dilated	Hypertrophic	Restrictive
Frequent causes	Idiopathic, alcoholic, major catecholamine discharge, myocarditis, postpartum, chemotherapy, endocrinopathies, genetic diseases, burnt out HOCM, CAD, tachycardia-induced, cocaine	Hereditary syndrome, possibly chronic hypertension in older adults	Amyloidosis, post-radiation, post–open heart surgery, diabetes, endomyocardial fibrosis, Fabry disease, sarcoidosis
Symptoms	Left or biventricular HF	Dyspnea, chest pain, syncope	Dyspnea, fatigue, right HF > left HF
Physical examination	Cardiomegaly, S_3, elevated jugular venous pressure, rales	Sustained point of maximal impulse, S_4, variable systolic murmur, bisferiens carotid pulse	Elevated jugular venous pressure
ECG	ST–T changes, conduction abnormalities, ventricular ectopy	LVH, exaggerated septal Q waves	ST–T changes, conduction abnormalities, low voltage
CXR	Enlarged heart, pulmonary congestion	Mild cardiomegaly	Mild to moderate cardiomegaly
Echocardiogram, nuclear studies, MRI, PET, CT	LV dilation and dysfunction	LVH, asymmetric septal or other myocardial wall thickness > 15 mm, small LV size, normal or supranormal function, systolic anterior mitral motion, diastolic dysfunction. May be nonobstructive or apical	Small or normal LV size, normal or mildly reduced LV function. Gadolinium hyperenhancement on MRI
Cardiac catheterization	LV dilation and dysfunction, high diastolic pressures, low cardiac output. Coronary angiography important to exclude ischemic cause	Small, hypercontractile LV, dynamic outflow gradient, diastolic dysfunction	High diastolic pressure, "square root" sign, normal or mildly reduced LV function

HOCM, hypertrophic obstructive cardiomyopathy.

underlying cause (eg, sarcoidosis, hemochromatosis) can be discerned. Its use is considered a class IIa indication with LOE of C. It should not be used routinely. Biopsy is most useful in transplant rejection.

Treatment

The management of HF is outlined in the section on HF. Standard therapy includes control of BP and of contributing factors such as obesity, excessive alcohol, smoking, diabetes, or potentially cardiotoxic agents. All patients with reduced LVEF should be given ACE inhibitors, ARBs, or ideally sacubitril/valsartan, as well as selected beta-blockers, spironolactone, and SGLT-2 inhibitors. Calcium channel blockers should be avoided except as necessary to control ventricular response in atrial fibrillation or flutter or hypertension after being on all guideline-directed treatments for the HF. If congestive symptoms are present, diuretics should be added. Care in the use of mineralocorticoid receptor antagonists is warranted when the GFR is less than 30 mL/min/1.73 m^2 or when the potassium is elevated. *All patients with diabetes should be taking mineralocorticoid antagonists if the LVEF is less than or equal to 40%.* Systemic BP control is extremely important. If the resting heart rate is greater than 70 beats/min, the LVEF is less than 35%, and the patient has chronic stable HF, the use of ivabradine to slow the heart rate has also been approved. Ivabradine should not replace beta-blockers, however. Digoxin is a second-line medication but remains favored as an adjunct by some clinicians; digoxin may be beneficial to reduce recurrent hospitalizations and to control the ventricular response in atrial fibrillation in sedentary patients. Based on evidence from randomized, controlled trials in self-identified Black individuals, the use of hydralazine-nitrate combination therapy is recommended as another option.

When atrial fibrillation is present, rhythm control (especially with atrial fibrillation ablation) and heart rate control is important.

To help prevent sudden death, an ICD is reasonable (class IIa, LOE B) in asymptomatic ischemic cardiomyopathy patients with an LVEF of less than 30% on appropriate medical therapy (at least 3 months post-MI). Many patients may be candidates for cardiac synchronization therapy with biventricular pacing if there is significant mitral regurgitation and the QRS width is greater than 150 msec. Cardiac rehabilitation and exercise training have consistently been found to improve clinical status.

Few cases of cardiomyopathy are amenable to specific therapy for the underlying cause. Alcohol use should be discontinued, since there is often marked recovery of cardiac function following a period of abstinence in alcoholic cardiomyopathy. Endocrine causes (hyperthyroidism or hypothyroidism, acromegaly, and pheochromocytoma)

should be treated. Immunosuppressive therapy is not indicated in chronic dilated cardiomyopathy. There are some patients who may benefit from implantable LV assist devices either as a bridge to transplantation or as a temporary measure until cardiac function returns. LV assist devices can be considered as **destination therapy** in patients who are not candidates for cardiac transplantation. Arterial and pulmonary emboli are more common in dilated cardiomyopathy than in ischemic cardiomyopathy, and suitable candidates may benefit from long-term anticoagulation. All patients with atrial fibrillation should be so treated. *DOACs are preferred over warfarin unless there is associated moderate or severe mitral stenosis.* DOACs, which are safer than warfarin, should generally be preferred over warfarin when a mobile LV thrombus is observed on the echocardiogram.

Prognosis

The prognosis of dilated cardiomyopathy without clinical HF is variable, with some patients remaining stable, some deteriorating gradually, and others declining rapidly. Once HF is manifest, the natural history is similar to that of other causes of HF, with an annual mortality rate of around 11–13%. The underlying cause of HF has prognostic value in patients with unexplained cardiomyopathy. Patients with peripartum cardiomyopathy or stress-induced cardiomyopathy appear to have a better prognosis than those with other forms of cardiomyopathy. Patients with cardiomyopathy due to infiltrative myocardial diseases, HIV infection, or doxorubicin therapy have an especially poor prognosis.

When to Refer

Patients with new or worsening symptoms of HF with dilated cardiomyopathy should be referred to a cardiologist. Patients with continued symptoms of HF and reduced LVEF (35% or less) should be referred for consideration of placement of an ICD or cardiac resynchronization therapy (if QRS duration is 150 msec or more, especially with a left bundle branch block pattern). Patients with advanced refractory symptoms should be referred for consideration of heart transplant or LV assist device therapy.

When to Admit

Patients with hypoxia, fluid overload, or pulmonary edema not readily resolved in an outpatient setting should be admitted.

Heidenreich PA et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022;79:e263. Erratum in: J Am Coll Cardiol. 2023;81:1551. [PMID: 35379503]

Mazzarotto F et al. Reevaluating the genetic contribution of monogenetic dilated cardiomyopathy. Circulation. 2020;141:387. [PMID: 31983221]

Rosenbaum AN et al. Genetics of dilated cardiomyopathy: practical implications for heart failure management. Nat Rev Cardiol. 2020;17:286. [PMID: 31605094]

TAKOTSUBO CARDIOMYOPATHY

ESSENTIALS OF DIAGNOSIS

- Occurs after a major catecholamine discharge.
- Acute chest pain or shortness of breath.
- Predominately affects postmenopausal women.
- Presents as an acute anterior MI, but coronaries normal at cardiac catheterization.
- Imaging reveals apical LV ballooning due to anteroapical stunning of the myocardium.
- Most patients recover completely, although there are complications similar to MI.

General Considerations

Takotsubo syndrome often follows a high catecholamine surge. The resulting shape of the LV acutely suggests a rounded ampulla form similar to a Japanese octopus pot (takotsubo pot). Mid-ventricular ballooning has also been described. The key feature is that the myocardial stunning that occurs does *not* follow the pattern suggestive of coronary ischemia (even though about 15% of patients will have coexisting CAD, and some may have concomitant plaque rupture MI). *Over two-thirds of patients report a prior stressful event*, either emotional or physical, including hypoglycemia, lightning strikes, earthquakes, postventricular tachycardia, during alcohol withdrawal, following surgery, during hyperthyroidism, after stroke, and following emotional stress ("broken-heart syndrome"). Virtually any event that triggers excess catecholamines has been implicated in a wide number of case reports. Pericarditis and even tamponade have been described in isolated cases. Recurrences have also been described. In Western countries, it *predominantly affects women (up to 90%), primarily postmenopausal*. Among patients with stress cardiomyopathy, compared to patients with ACS, there are more neurologic and psychiatric disorders. Patients with COPD, migraines, or affective disorders who take beta-agonists may have an increased risk of a poor outcome. The prognosis was initially thought to be benign, but subsequent studies have demonstrated that *both short-term mortality and long-term mortality are higher than thought*. Indeed, mortality reported during the acute phase in hospitalized patients is approximately 4–5%, a figure comparable to that of STEMI in the era of primary percutaneous coronary interventions. Approximately 10% of patients will have cardiac and neurologic adverse outcomes over the next year.

The structures that mediate the stress response are in both the central and autonomic nervous systems. Acute stressors induce brain activation, increasing bioavailability of cortisol and catecholamine. Both circulating epinephrine and norepinephrine released from adrenal medullary chromaffin cells and norepinephrine released locally from sympathetic nerve terminals are

significantly increased. This catecholamine surge leads to myocardial damage through multiple mechanisms, including, direct catecholamine toxicity, adrenoceptor-mediated damage, epicardial and microvascular coronary vasoconstriction and/or spasm, and increased cardiac workload. The relative preponderance among postmenopausal women suggests that estrogen deprivation may be facilitating, possibly via endothelial dysfunction.

Clinical Findings

A. Symptoms and Signs

The symptoms are similar to any ACS. Typical angina and dyspnea are usually present. Syncope is rare, although arrhythmias are not uncommon.

B. ECG and Chest Radiography

The ECG reveals ST-segment elevation as well as deep anterior T-wave inversion. The dramatic T-wave inversions gradually resolve over time. The CXR is either normal or reveals pulmonary congestion.

C. Diagnostic Studies

The echocardiogram reveals LV apical dyskinesia usually not consistent with any particular coronary distribution. The urgent cardiac catheterization reveals the LV apical ballooning in association with normal coronaries. Initial cardiac biomarkers are positive but often taper quickly. In almost all cases, MRI hyperenhancement studies reveal no long-term scarring.

Treatment

Immediate therapy is similar to any acute MI. Initiation of long-term therapy depends on whether LV dysfunction persists. Most patients receive aspirin, beta-blockers, and ACE inhibitors until the LV fully recovers. Despite the presumed association with high catecholamines, the use of ACE inhibitors or ARBs, but not beta-blockers, has been associated with improved long-term survival. See Treatment of Heart Failure With Reduced LVEF.

Prognosis

The rate of severe in-hospital complications, including shock and death, appear to be similar between those with an ACS and takotsubo. Overall, prognosis is good unless there is a serious complication (such as mitral regurgitation, ventricular rupture, or ventricular tachycardia). Recovery of the LVEF is expected in most cases after a period of days to weeks.

When to Refer

All patients with an ACS should be urgently seen by a cardiologist for further evaluation and monitored until resolution of the ventricular dysfunction.

HYPERTROPHIC CARDIOMYOPATHY

ESSENTIALS OF DIAGNOSIS

- May present with dyspnea, chest pain, syncope.
- Though LV outflow gradient is classic, symptoms are primarily related to diastolic dysfunction.
- Echocardiogram is diagnostic. Any area of LV wall thickness > 1.5 cm defines the disease.
- Increased risk of sudden death.

General Considerations

In 2020, an ACC/AHA joint committee on clinical practice guidelines issued updated guidelines for the diagnosis and treatment of HCM. The guidelines address many clinical scenarios and provide a host of clinically relevant suggestions. *HCM is noted when there is LVH unrelated to any pressure or volume overload.* The definition has evolved over time; while it traditionally was defined by LV outflow obstruction due to septal hypertrophy, currently it is considered present any time that *any portion of LV wall is measured at more than 1.5 cm thick on an echocardiogram.* This allows for many forms to be considered that do not create LV outflow obstruction. The increased wall thickness reduces LV systolic stress, increases the EF, and can result in an "empty ventricle" at end systole. The interventricular septum may be disproportionately involved (**asymmetric septal hypertrophy**), but in some cases the hypertrophy is localized to the mid-ventricle or to the apex. In a normal heart, the LV apex may be paper thin; in HCM, the LV obstruction may trap blood just above the apex and the LV pressure may be very high there. This can result in the apex becoming aneurysmal. The LV outflow tract is usually narrowed during systole due to the hypertrophied septum and systolic anterior motion of the mitral valve occurs as the anterior mitral valve leaflet is pulled into the LV outflow. The obstruction is worsened by factors that increase myocardial contractility (sympathetic stimulation, digoxin, and postextrasystolic beat) or that decrease LV filling (Valsalva maneuver, peripheral vasodilators). The amount of obstruction is preload and afterload dependent and can vary from day to day. *The consequence of the hypertrophy is elevated LV diastolic pressures rather than systolic dysfunction.* Rarely, systolic dysfunction develops late in the course of the disease. The LV is usually more involved than the RV, and the atria are frequently significantly enlarged.

HCM is inherited as an autosomal-dominant trait with variable penetrance and is caused by pathogenic variants of one of a large number of genes, most of which code for myosin heavy chains or proteins regulating calcium handling. The prognosis is related to the specific gene pathogenic variant. Patients usually present in early adulthood. Elite athletes may demonstrate considerable hypertrophy that can be confused with HCM, but generally diastolic dysfunction is not present in the athlete and this finding

helps separate pathologic disease from **athletic hypertrophy**. The apical variety is particularly common in those of Asian descent. An **HCM in older adults** (usually in association with hypertension) has also been defined as a distinct entity (often a sigmoid interventricular septum is noted with a knob of cardiac muscle below the aortic valve). Mitral annular calcification is often present. Mitral regurgitation is variable and often dynamic, depending on the degree of outflow tract obstruction.

Clinical Findings

A. Symptoms and Signs

The most frequent symptoms are dyspnea and chest pain. Syncope is also common and is typically postexertional, when diastolic filling diminishes due to fluid loss and tachycardia increasing LV outflow tract obstruction. Residual circulating catecholamines accentuate the changes. Arrhythmias are an important problem. Atrial fibrillation is a long-term consequence of chronically elevated LA pressures and is a poor prognostic sign. Ventricular arrhythmias are also common, and sudden death may occur, often after extraordinary exertion.

Features on physical examination include a bisferiens carotid pulse, triple apical impulse (due to the prominent atrial filling wave and early and late systolic impulses), and a loud S_4. The JVP may reveal a prominent *a* wave due to reduced RV compliance. In cases with LV outflow obstruction, a loud systolic murmur is present along the left sternal border that increases with upright posture or Valsalva maneuver and decreases with squatting. These maneuvers help differentiate the murmur of HCM from that of aortic stenosis. In HCM, reducing the LV volume *increases* the outflow obstruction and the murmur intensity; whereas in valvular aortic stenosis, reducing the stroke volume across the valve *decreases* the murmur. Mitral regurgitation is frequently present as well.

B. ECG and Chest Radiography

LVH is nearly universal in symptomatic patients, though entirely normal ECGs are present in up to 25%, usually in those with localized hypertrophy. Exaggerated septal Q waves inferolaterally may mimic MI. The CXR is often unimpressive. Unlike with aortic stenosis, the ascending aorta is not dilated.

C. Diagnostic Studies

The echocardiogram is diagnostic, revealing LVH (involving the septum more commonly than the posterior walls), systolic anterior motion of the mitral valve, early closing followed by reopening of the aortic valve, a small and hypercontractile LV, and delayed relaxation and filling of the LV during diastole. The septum is usually 1.3–1.5 times the thickness of the posterior wall. Septal motion tends to be reduced. Doppler ultrasound reveals turbulent flow and a dynamic gradient in the LV outflow tract and, commonly, mitral regurgitation. Abnormalities in the diastolic filling pattern are present in 80% of patients.

Echocardiography can usually differentiate the disease from **ventricular noncompaction**, a congenital myocardial disease pattern with marked trabeculation that partially fills the LV cavity. Myocardial perfusion imaging may suggest septal ischemia in the presence of normal coronary arteries. Cardiac MRI confirms the hypertrophy and contrast enhancement frequently reveals evidence of scar at the junction of the RV attachment to the interventricular septum. Cardiac catheterization confirms the diagnosis and defines the presence or absence of CAD. Frequently, **coronary arterial bridging** (squeezing of the coronary in systole) occurs, especially in the septal arteries. Exercise studies are recommended to assess for ventricular arrhythmias and to document the BP response. Loop monitoring is recommended for determination of ventricular ectopy.

Treatment

Beta-blockers should be the initial medication in symptomatic individuals, especially when dynamic outflow obstruction is noted on the echocardiogram. The resulting slower heart rates assist with diastolic filling of the stiff LV. Dyspnea, angina, and arrhythmias respond in about 50% of patients. Calcium channel blockers, especially verapamil, have also been effective in symptomatic patients. Verapamil or nondihydropyridine calcium channel blockers, such as diltiazem, are class I recommendations. Their effect is due primarily to improved diastolic function; however, their vasodilating actions can also increase outflow obstruction and cause hypotension. Verapamil should not be used if there is hypotension or a resting gradient of over 100 mm Hg. Disopyramide is also effective because of its negative inotropic effects; it is usually used as an addition to the medical regimen rather than as primary therapy or to help control atrial arrhythmias. Oral diuretics are frequently necessary due to the high LV diastolic pressure and elevated LA pressures but should be used with caution to avoid dehydration that would increase obstruction. Digoxin is relatively contraindicated, except rarely for rate control in atrial fibrillation. For acute hypotension that does not respond to fluids, phenylephrine may be considered. In HCM patients without outflow obstruction, similar treatment should be used only if symptomatic and the use of oral diuretics is safer. In a very small number of these patients, apical myomectomy may be considered.

The FDA has approved mavacamten, an inhibitor of cardiac myosin ATPase, to treat adults with symptomatic NYHA class II-III obstructive hypertrophic cardiomyopathy to improve exercise capacity and symptoms.

Patients do best in sinus rhythm, and atrial fibrillation should be aggressively treated with antiarrhythmics or radiofrequency ablation. DOACs are preferred over warfarin if atrial fibrillation occurs. *Patients with HCM should be treated regardless of their CHA_2DS_2-VASc score.*

The 2020 AHA/ACC guidelines recommend a preventive ICD for HCM patients with documented cardiac arrest or sustained ventricular tachycardia (class I). It is a class IIa recommendation for an ICD if there are one or more of the

following risk factors: (1) sudden death in one or more first-degree or close relative 50 years of age or younger, (2) any LV wall greater than or equal to 30 mm, (3) any recent syncope likely to have been arrhythmogenic, (4) LV apical aneurysm, or (5) LV systolic dysfunction (EF less than 50%). It is a class IIb recommendation for an ICD if there is significant (greater than 15%) late gadolinium enhancement on cardiac MRI. In those who receive an ICD, antitachycardia pacing should be programmed to minimize shocks. The use of an ICD is contraindicated, though, if the purpose is simply to allow for the patient to play competitive sports.

Excision of part of the outflow myocardial septum (**myotomy–myomectomy**) by experienced surgeons is successful in patients with symptoms unresponsive to medical therapy. A few surgeons advocate mitral valve replacement, since this results in resolution of the gradient and prevents associated mitral regurgitation. In some cases, myomectomy has been combined with an Alfieri stitch on the mitral valve (a stitch that binds the midportion of the anterior and posterior mitral valve leaflets together). Rare cases of progression to LV dilation or patients with intractable symptoms can be considered for cardiac transplantation. Nonsurgical septal ablation can be performed by injection of alcohol into septal branches of the left coronary artery to create a controlled myocardial infarct in the regions of greatest wall thickness. It is considered first-line therapy, if feasible, for those with LV outflow tract obstruction greater than 50 mm Hg who do not respond to medical therapy or who are not deemed surgical candidates. In "burnt out" HCM, the medical therapy is similar to that of dilated cardiomyopathy. In those with refractory arrhythmias or HF, cardiac transplantation is an option.

Pregnancy results in an increased risk in patients with symptoms or outflow tract gradients of greater than 50 mm Hg. Genetic counseling is indicated before planned conception. In pregnant patients with HCM, continuation of beta-blocker therapy is recommended. For more details on the impact of HCM on sport, activity, and occupation (such as driving commercially or piloting an aircraft), the reader is referred to the discussions in the 2020 AHA/ACC guidelines.

When to Refer

Patients should be referred to a cardiologist to establish care, consider genetic testing, review the presence of any high-risk features, and discuss medications or the need for any intervention. This is particularly important if any symptoms are present.

Olivotto I et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020;396:759. [PMID: 32871100]

Ommen SR. 2020 AHA/ACC guidelines for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary. Circulation. 2020;142:e533. [PMID: 33215938]

RESTRICTIVE CARDIOMYOPATHY

ESSENTIALS OF DIAGNOSIS

- Right HF tends to dominate over left HF.
- Pulmonary hypertension is present.
- Amyloidosis is the most common cause.
- Echocardiography is key to diagnosis.
- Radionuclide imaging or myocardial biopsy can confirm amyloid.

General Considerations

Restrictive cardiomyopathy is characterized by *impaired diastolic filling with reasonably preserved LV chamber size*. The condition is relatively uncommon, with the most frequent cause being amyloidosis. The diagnosis of **cardiac amyloidosis** has dramatically increased in the last few years since diagnostic testing has improved and there is an awareness of its prevalence. The prevalence of AL amyloid is approximately 12 cases per million, the prevalence of variant or hereditary ATTR amyloid is about 0.3 cases per million, and the prevalence of wild type ATTR amyloid is 155–191 cases per million. Many experts believe the actual prevalence of wild type ATTR is much higher. While light-chain amyloid proteins can be toxic to cardiomyocytes, they may also internalize into many cell types and this may explain some of the cardiac dysfunction observed. ATTR refers to transthyretin, a protein normally found in the liver that helps transport thyroid hormones and vitamin A. Wild type (normal) occurs more commonly in older adults and in men, and previously was referred to as "senile systemic amyloidosis." Hereditary or variant ATTR is genetically transmitted, deposition occurs at an earlier age, and it has associated neurologic impact. TTR is a tetramer that can dissociate into four monomers and aggregate as amyloid fibrils. The differential diagnosis of a restrictive cardiomyopathy includes infiltrative disorders beside amyloidosis, such as sarcoidosis, Gaucher disease, and Hurler syndrome. Storage diseases such as hemochromatosis, Fabry disease, and glycogen storage diseases can also produce the picture. Noninfiltrative diseases, such as familial cardiomyopathy and pseudoxanthoma elasticum, can be implicated rarely, and other secondary causes include diabetes, systemic sclerosis (scleroderma), radiation, chemotherapy, CAD, and long-standing hypertension.

Clinical Findings

A. Symptoms and Signs

Restrictive cardiomyopathy must be distinguished from constrictive pericarditis (see Table 11–3). The key feature is that *ventricular interaction is accentuated with respiration in constrictive pericarditis and that interaction is absent in restrictive cardiomyopathy*. In addition, the pulmonary arterial pressure is invariably elevated in restrictive

cardiomyopathy due to the high PCWP and is normal in uncomplicated constrictive pericarditis. Symptoms may include angina, syncope, stroke, and peripheral neuropathy. Periorbital purpura, a thickened tongue, and hepatomegaly are all suggestive physical findings of amyloidosis.

B. Diagnostic Studies

To evaluate for suspected amyloidosis, first assess for monoclonal protein with serum light chain assay along with a serum and a urine immunofixation electrophoresis. If negative, primary or light chain amyloidosis can be ruled out. If positive, biopsy of affected tissue is the next step. Conduction disturbances are frequently present. Low voltage on the ECG combined with ventricular hypertrophy on the echocardiogram is suggestive of disease. **Technetium pyrophosphate imaging (bone scan imaging)** can also identify amyloid deposition in the myocardium, and it has become the noninvasive imaging modality of choice for diagnosing transthyretin (ATTR) amyloidosis. With typical scintigraphic findings in patients without a monoclonal gammopathy, biopsy is no longer necessary for diagnosis. Cardiac MRI presents a distinctive pattern of diffuse hyperenhancement of the gadolinium image in amyloidosis and is a useful screening test. Late gadolinium hyperenhancement of a high degree suggests more extensive cardiac involvement. The echocardiogram reveals a small, thickened LV with bright myocardium (speckled), rapid early diastolic filling revealed by the mitral inflow Doppler, and biatrial enlargement. Characteristic longitudinal strain patterns may help identify cardiac amyloidosis. The LV chamber size is usually normal with a reduced LVEF. Atrial septal thickening may be evident and an amyloid variant that primarily affects the atria has been described. Rectal, abdominal fat, or gingival biopsies can confirm systemic involvement, but myocardial involvement may still be present if these are negative and requires endomyocardial biopsy for the confirmation that cardiac amyloid is present. Demonstration of tissue infiltration on biopsy specimens using special stains followed by immunohistochemical studies and genetic testing are essential to define which specific protein is involved. TTR gene sequencing in patients in whom the TTR wild type or TTR variant is suspected and mass spectroscopy on all tissue in question are recommended highly. BNP and NT-proBNP are traditionally elevated and have been used to help distinguish constrictive pericarditis from a restrictive cardiomyopathy.

Treatment

Treatment for AL amyloidosis includes alkylator-based chemotherapy or high-dose melphalan followed by autologous stem cell transplantation. In immunoglobin light-chain amyloidosis, standard- or high-dose chemotherapy with stem cell rescue is often pursued. Treatment of ATTR amyloid is undergoing an evolution. Tafamidis helps prevent the misfolding of the TTR tetramer and is approved for treatment. Tafamidis is the only FDA-approved medication available for all ATTR cardiomyopathy. It reduced the composite of all-cause mortality and cardiovascular hospitalizations in trials. It is very expensive and thus not available to many patients.

In acute HF, diuretics can help, but excessive diuresis can produce worsening kidney dysfunction. As with most patients with severe right HF, loop diuretics, thiazides, and aldosterone antagonists are all useful. Atrial thrombi are not uncommon, although the role of anticoagulation in amyloidosis remains ill defined. Digoxin may precipitate arrhythmias and should *not* be used. Beta-blockers help slow heart rates and improve filling by increasing diastolic time. Verapamil presumably works by improving myocardial relaxation and increasing diastolic filling time. Slow heart rates are desired to allow for increased diastolic filling time. ACE inhibition or angiotensin II receptor blockade may improve diastolic relaxation and filling at times and can be tried with caution if the systemic BP is adequate. Corticosteroids may be helpful in sarcoidosis, but they are more effective for conduction abnormalities in this disease than in HF.

When to Refer

All patients with the diagnosis of a restrictive cardiomyopathy should be referred to a cardiologist to decide etiology and plan appropriate treatment. Unexplained LVH with relatively preserved LVEF and symptoms of HF should raise the question of cardiac amyloid, particularly now that there is effective treatment available.

Writing Committee; Kittleson MM et al. 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2023;81:1076. Erratum in: J Am Coll Cardiol. 2023;81:1135. [PMID: 36697326]

12 Disorders of Cardiac Rhythm

Kevin P. Jackson, MD

DISORDERS OF RATE & RHYTHM

Abnormalities of cardiac rhythm and conduction can be symptomatic (syncope, near syncope, dizziness, fatigue, or palpitations) or asymptomatic. In addition, they can be lethal (sudden cardiac death [SCD]) or dangerous to the extent that they reduce cardiac output, so that perfusion of the brain and myocardium is impaired. Stable supraventricular tachycardia (SVT) is generally well tolerated in patients without underlying heart disease but may lead to myocardial ischemia or HF in patients with coronary disease, valvular abnormalities, and systolic or diastolic myocardial dysfunction. Ventricular tachycardia, if prolonged, often results in hemodynamic compromise and may deteriorate into ventricular fibrillation if left untreated.

Whether slow heart rates produce symptoms at rest or with exertion depends on whether cerebral and peripheral perfusion can be maintained, which is generally a function of whether the patient is upright or supine and whether LV function is adequate to maintain stroke volume. If the heart rate abruptly slows, as with the onset of complete heart block or sinus arrest, syncope or convulsions (or both) may result. *Unless a clear, reversible cause is found, most symptomatic patients require implantation of a permanent pacemaker.*

The diagnosis of an abnormal tachyarrhythmia often can be made via cardiac monitoring, including in-hospital and ambulatory ECG monitoring, event recorders, continuous mobile cardiac telemetry, or implantable loop recorders. Additionally, optic sensors on wearable devices, such as smartwatches, utilize a passive irregular pulse notification algorithm to identify possible arrhythmia, with a positive predictive value for detection of atrial fibrillation of approximately 85%. Devices, such as Apple Watch, Fitbit and the AliveCor device, can record ECGs of the rhythm that can be transmitted to health care providers. More invasive testing, including catheter-based electrophysiologic studies (to assess sinus node function, atrioventricular [AV] conduction, and inducibility of arrhythmias), and tests of autonomic nervous system function (tilt-table testing) can also be performed.

Treatment of tachyarrhythmias varies and can include modalities such as antiarrhythmic medications and more invasive techniques such as catheter ablation.

Antiarrhythmic Medications

Antiarrhythmic medications are frequently used to treat arrhythmias but have variable efficacy and produce frequent side effects (Table 12–1). They are often divided into classes based on their electropharmacologic actions and many of these medications have multiple actions. The most frequently used classification scheme is the **Vaughan-Williams,** which consists of four classes.

Class I agents block membrane sodium channels. Three subclasses are further defined by the effect of the agents on the Purkinje fiber action potential. **Class Ia** medications (ie, quinidine, procainamide, disopyramide) slow the rate of rise of the action potential (V_{max}) and prolong its duration, thus slowing conduction and increasing refractoriness. **Class Ib** agents (ie, lidocaine, mexiletine) shorten action potential duration; they do not affect conduction or refractoriness. **Class Ic** agents (ie, flecainide, propafenone) prolong V_{max} and slow repolarization, thus slowing conduction and prolonging refractoriness, but more so than class Ia medications.

Class II agents are the beta-blockers, which decrease automaticity, prolong AV conduction, and prolong refractoriness.

Class III agents (ie, amiodarone, dronedarone, sotalol, dofetilide, ibutilide) block potassium channels and prolong repolarization, prolonging the QT interval. Drug-induced torsade de pointes occurs in up to 3% of patients on sotalol and dofetilide and these agents require careful monitoring.

Class IV agents are the calcium channel blockers, which decrease automaticity and AV conduction.

There are some antiarrhythmic agents that do not fall into one of these categories. The most frequently used are digoxin and adenosine. Digoxin inhibits the Na^+, K^+-ATPase pump. Digoxin prolongs AV nodal conduction and the AV nodal refractory period, but it shortens the action potential and decreases the refractoriness of the ventricular myocardium and Purkinje fibers. Adenosine can block AV nodal conduction and shortens atrial refractoriness.

Although the in vitro electrophysiologic effects of most of these agents have been defined, their use remains largely empiric. *All can exacerbate arrhythmias (**proarrhythmic effect**), and many depress LV function.*

Table 12–1. Antiarrhythmic medications. (Listed in alphabetical order within classes.)

Agent	Intravenous Dosage	Oral Dosage	Therapeutic Plasma Level	Route of Elimination	Side Effects
Class Ia: Action: Sodium channel blockers: Depress phase 0 depolarization; slow conduction; prolong repolarization.					
Indications: Supraventricular tachycardia, ventricular tachycardia, symptomatic ventricular premature beats.					
Disopyramide		Immediate release: 100–200 mg every 6 hours Sustained release: 200–400 mg every 12 hours	2–8 mg/mL	Renal	Urinary retention, dry mouth, markedly ↓ LVF, QT prolongation
Procainamide	Loading: 10–17 mg/kg at 20–50 mg/min Maintenance: 1–4 mg/min	50 mg/kg/day in divided doses every 4 hours (short-acting)	4–10 mg/mL; NAPA (active metabolite), 10–20 mcg/mL	Renal	
Quinidine	6–10 mg/kg (intramuscularly or intravenously) over 20 minutes (rarely used parenterally)	324–648 mg every 8 hours	2–5 mg/mL	Hepatic	GI, ↓ LVF, ↑ Dig
Class Ib: Action: Shorten repolarization.					
Indications: Ventricular tachycardia, prevention of ventricular fibrillation, symptomatic ventricular premature beats.					
Lidocaine	Loading: 1 mg/kg Maintenance: 1–4 mg/min		1–5 mg/mL	Hepatic	CNS, GI, ↓ LVF
Mexiletine		100–300 mg every 8–12 hours; maximum: 1200 mg/day	0.5–2 mg/mL	Hepatic	CNS, GI, leukopenia
Class Ic: Action: Depress phase 0 repolarization; slow conduction. (Propafenone is a weak calcium channel blocker and beta-blocker and prolongs action potential and refractoriness.)					
Indications: Ventricular tachycardia (in the absence of structural heart disease), refractory supraventricular tachycardia.					
Flecainide		50–150 mg twice daily	0.2–1 mg/mL	Hepatic	CNS, GI, AFL with 1:1 conduction, ventricular proarrhythmia
Propafenone		150–300 mg every 8–12 hours	Note: Active metabolites	Hepatic	CNS, GI, AFL with 1:1 conduction, ventricular proarrhythmia
Class II: Action: Beta-blockers, slow AV conduction.					
Indications: Supraventricular tachycardia, ventricular tachycardia, symptomatic ventricular premature beats, long QT syndrome.					
Esmolol	Loading: 500 mcg/kg over 1–2 minutes Maintenance: 50–300 mcg/kg/min	Other beta-blockers may be used concomitantly	Not established	Hepatic	↓ LVF, bradycardia, AV block
Metoprolol	5 mg every 5 minutes up to 3 doses	25–200 mg daily	Not established	Hepatic	↓ LVF, bradycardia, AV block, fatigue
Propranolol	1–3 mg every 5 minutes up to total of 5 mg	40–320 mg in 1–4 doses daily (depending on preparation)	Not established	Hepatic	↓ LVF, bradycardia, AV block, bronchospasm
Class III: Action: Prolong action potential.					
Indications: *Amiodarone:* refractory ventricular tachycardia, supraventricular tachycardia, prevention of ventricular tachycardia, atrial fibrillation, ventricular fibrillation; *Dofetilide:* atrial fibrillation and flutter; *Dronedarone:* atrial fibrillation (not persistent); *Ibutilide:* conversion of atrial fibrillation and flutter; *Sotalol:* ventricular tachycardia, atrial fibrillation.					
Amiodarone	150–300 mg infused rapidly, followed by 1 mg/min infusion for 6 hours and then 0.5 mg/min for 18 hours	800–1600 mg/day for 7–14 days; maintain at 100–400 mg/day	1–5 mg/mL	Hepatic	Pulmonary fibrosis, hypothyroidism, hyperthyroidism, photosensitivity, corneal and skin deposits, hepatitis, neurotoxicity, GI

(*continued*)

Table 12–1. Antiarrhythmic medications. (Listed in alphabetical order within classes.) (continued)

Agent	Intravenous Dosage	Oral Dosage	Therapeutic Plasma Level	Route of Elimination	Side Effects
Dofetilide		125–500 mcg every 12 hours		Renal (dose must be reduced with kidney dysfunction)	Torsades de pointes in 3%; interaction with cytochrome P-450 inhibitors
Dronedarone		400 mg twice daily		Hepatic (contra-indicated in severe impairment)	Contraindicated in HF (NYHA class IV or recent decompensation), persistent AF
Ibutilide	1 mg over 10 minutes, followed by a second infusion of 0.5–1 mg over 10 minutes			Hepatic and renal	Torsades de pointes in up to 3% of patients within 3 hours after administration; patients must be monitored with defibrillator nearby
Sotalol	75 mg every 12 hours	80–160 mg every 12 hours (maximum 320 mg daily)		Renal (dosing interval should be extended if creatinine clearance is < 60 mL/min)	Torsades de pointes in 1%; ↓ LVF, bradycardia, fatigue (and other side effects associated with beta-blockers)
Class IV: Action: Slow calcium channel blockers.					
Indications: Supraventricular tachycardia, ventricular tachycardia (outflow tract, idiopathic).					
Diltiazem	0.25 mg/kg over 2 minutes; second 0.35-mg/kg bolus after 15 minutes if response is inadequate; infusion rate, 5–15 mg/hour	120–360 mg daily in 1–3 doses depending on preparation		Hepatic metabolism, renal excretion	Hypotension, ↓ LVF, bradycardia
Verapamil	2.5 mg bolus followed by additional boluses of 2.5–5 mg every 1–3 minutes; total 20 mg over 20 minutes; maintain at 5 mg/kg/min	80–120 mg every 6–8 hours; 240–480 mg once daily with sustained-release preparation	0.1–0.15 mg/mL	Hepatic	Hypotension, ↓ LVF, constipation
Miscellaneous: Indications: Supraventricular tachycardia.					
Adenosine	6 mg bolus followed by rapid saline flush; may repeat with 12 mg bolus after 1–2 minutes if needed			Adenosine receptor stimulation, metabolized in blood	Transient flushing, dyspnea, chest pain, AV block, sinus bradycardia; effect ↓ by theophylline, ↑ by dipyridamole
Digoxin	0.5 mg over 20 minutes followed by increment of 0.25 or 0.125 mg to 1–1.5 mg over 24 hours	1–1.5 mg over 24–36 hours in 3 or 4 doses; maintenance, 0.125–0.5 mg/day	0.7–2 mg/mL	Renal	AV block, arrhythmias, GI, visual changes
Ivabradine		5–7.5 mg every 12 hours		Renal and fecal	Bradycardia, phosphenes (visual brightness)

AF, atrial fibrillation; AV, atrioventricular; Dig, elevation of serum digoxin level; ↓LVF, reduced LV function; NAPA, *N*-acetylprocainamide; NYHA, New York Heart Association.

The risk of antiarrhythmic agents has been highlighted by many studies, most notably the Coronary Arrhythmia Suppression Trial (CAST), in which two class Ic agents (flecainide, encainide) and a class Ia agent (moricizine) *increased* mortality rates in patients with asymptomatic ventricular ectopy after MI. Class Ic antiarrhythmic agents should therefore *not* be used in patients with prior MI or structural heart disease.

The use of antiarrhythmic agents for specific arrhythmias is discussed below.

Catheter Ablation for Cardiac Arrhythmias

Catheter ablation has become the primary modality of therapy for many symptomatic supraventricular arrhythmias, including AV nodal reentrant tachycardia, tachycardias involving accessory pathways, paroxysmal atrial tachycardia, and atrial flutter. Catheter ablation of atrial fibrillation is more complex and involves complete electrical isolation of the pulmonary veins (which are often the sites of initiation of atrial fibrillation) and at times placing linear lesions within the atria to prevent propagation throughout the atrial chamber. This technique is considered a reasonable therapy for symptomatic patients with medication-refractory atrial fibrillation or as an alternative to long-term antiarrhythmic medication treatment. In younger patients, catheter ablation of atrial fibrillation may be first-line therapy to improve symptoms and prevent progression to persistent atrial fibrillation. Catheter ablation of ventricular arrhythmias has proved more difficult, but experienced centers have demonstrated reasonable success with all types of ventricular tachycardias including bundle branch reentry, tachycardia originating in the ventricular outflow tract or papillary muscles, tachycardias originating in the specialized conduction system (fascicular ventricular tachycardia), and ventricular tachycardias occurring in patients with ischemic or dilated cardiomyopathy. Ablation of many of these arrhythmias can be performed from the endocardial surface via endovascular catheter placement or on the epicardial surface of the heart via a percutaneous subxiphoid approach.

Catheter ablation has also been successfully performed for the treatment of ventricular fibrillation when a uniform premature ventricular contraction (PVC) can be identified. In addition, patients with symptomatic PVCs or PVCs occurring at a high enough burden to result in a cardiomyopathy (usually more than 10,000/day) may be considered for catheter ablation as well.

Catheter ablation procedures are generally safe, with an overall major complication rate ranging from 1% to 5%. Major vascular damage during catheter insertion occurs in less than 2% of patients. There is a low incidence of perforation of the myocardial wall resulting in pericardial tamponade. Inadvertent damage to the AV node requiring permanent cardiac pacing occurs in less than 1% of patients. When transseptal access through the interatrial septum or retrograde LV catheterization is required, additional potential complications include damage to the heart valves, damage to a coronary artery, or systemic emboli. A rare but potentially fatal complication after catheter ablation of atrial fibrillation is the development of an atrioesophageal fistula resulting from ablation on the posterior wall of the left atrium just overlying the esophagus, estimated to occur in less than 0.1% of procedures.

SINUS ARRHYTHMIA, BRADYCARDIA, & TACHYCARDIA

ESSENTIALS OF DIAGNOSIS

- Wide variation in sinus rate is common in young, healthy individuals and generally not pathologic.
- Symptomatic bradycardia may require permanent pacemaker implantation, especially in older adults or patients with underlying heart disease.
- Sinus tachycardia is usually secondary to another underlying process (ie, fever, pain, anemia, alcohol withdrawal).
- Sick sinus syndrome manifests as sinus bradycardia, pauses, or inadequate heart rate response to physiologic demands (chronotropic incompetence).

General Considerations

Sinus arrhythmia is an irregularity of the normal heart rate defined as variation in the PP interval of more than 120 msec. This occurs commonly in young, healthy people due to changes in vagal influence on the sinus node during respiration (phasic) or independent of respiration (nonphasic). This is generally *not* a pathologic arrhythmia and requires no specific cardiac evaluation.

Sinus bradycardia is defined as a heart rate slower than 60 beats/min and may be due to increased vagal influence on the normal sinoatrial pacemaker or organic disease of the sinus node. In healthy individuals, and particularly in well-trained athletes, sinus bradycardia to rates of 50 beats/min or lower especially during sleep is a normal finding. However, in older adult patients and individuals with heart disease, sinus bradycardia may be an indication of true sinus node pathology. When the sinus rate slows severely, the atrial-nodal junction or the nodal-His bundle junction may assume pacemaker activity for the heart, usually at a rate of 35–60 beats/min.

Sinus tachycardia is defined as a heart rate faster than 100 beats/min that is caused by rapid impulse formation from the sinoatrial node. It is a normal physiologic response to exercise or other conditions in which catecholamine release is increased. The onset and termination are usually gradual, in contrast to paroxysmal supraventricular tachycardia (PSVT) due to reentry. In rare instances, otherwise healthy individuals may present with "inappropriate" sinus tachycardia where persistently elevated basal heart rates are not in-line with physiologic demands. Long-term consequences of this disorder are few.

Sick sinus syndrome is a broad diagnosis applied to patients with sinus arrest, sinoatrial exit block (recognized by a pause equal to a multiple of the underlying PP interval

or progressive shortening of the PP interval prior to a pause), or persistent sinus bradycardia. A common presentation in older adult patients is of recurrent SVT (often atrial fibrillation) accompanied by bradyarrhythmias (**"tachy-brady syndrome"**). The long pauses that often follow the termination of tachycardia cause the associated symptoms. Sick sinus syndrome may also manifest as **chronotropic incompetence,** defined as an inappropriate heart rate response to the physiologic demands of exercise or stress, and is an underrecognized cause of poor exercise tolerance.

Clinical Findings

In most patients, sinus arrhythmia (bradycardia or tachycardia) does not cause symptoms in the absence of underlying cardiac disease or other comorbidities. When severe sinus bradycardia results in low cardiac output, however, patients may report weakness, confusion, or syncope if cerebral perfusion is impaired. Sinus bradycardia is often exacerbated by medications (digitalis, calcium channel blockers, beta-blockers, sympatholytic agents, antiarrhythmics), and nonessential agents that may be responsible should be withdrawn prior to making the diagnosis.

Sinus tachycardia is most often *a normal response* to conditions that require an increase in cardiac output, including fever, pain, anxiety, anemia, HF, hypovolemia, or thyrotoxicosis. Alcohol and alcohol withdrawal are common causes of sinus tachycardia and other supraventricular arrhythmias. In patients with underlying cardiac disease, sinus tachycardia may cause dyspnea or chest pain due to increased myocardial oxygen demand or reduced coronary artery blood flow.

Symptoms from sinus node dysfunction are nonspecific and may be due to other causes. It is therefore essential that symptoms be demonstrated to coincide temporally with arrhythmias. This may require prolonged ambulatory monitoring or the use of an event recorder.

Treatment

Asymptomatic patients generally do not *require treatment. For symptomatic patients with bradycardia or sick sinus syndrome, implantation of a permanent pacemaker is usually indicated.* In patients without evidence of AV nodal or bundle branch conduction abnormality, a single chamber atrial pacemaker is reasonable. Based on the results of several RCTs, *atrial-based pacing (single or dual chamber) is superior to ventricular-only pacing for patients with sinus node dysfunction.* When a dual-chamber pacemaker is implanted for sinus node dysfunction with intact AV conduction, unnecessary ventricular pacing should be avoided because it may exacerbate HF, especially in patients with preexisting LV dysfunction. In most situations, sinus tachycardia will improve or resolve with treatment of the underlying cause. Inappropriate sinus tachycardia in the presence of symptoms (palpitations, dizziness, exertional intolerance) can be treated with a trial of beta-blockers or calcium channel blockers although treatment is often challenging. Ivabradine (5–7.5 mg twice daily), a selective inhibitor of the potassium funny channel (I_f) specific to the sinus node, may be an effective treatment option.

When to Refer

Patients with symptoms related to bradycardia or tachycardia when reversible etiologies have been excluded.

AV BLOCK

ESSENTIALS OF DIAGNOSIS

- Conduction disturbance between the atrium and ventricle that can be physiologic (due to enhanced vagal tone) or pathologic.
- Block occurs in the AV node (first-degree, second-degree Mobitz type I) or below the AV node (second-degree Mobitz type II, third-degree).
- Symptomatic AV block or block below the AV node in the absence of a reversible cause usually warrants permanent pacemaker implantation.

General Considerations

AV block can be physiologic (due to increased vagal tone) or pathologic (due to underlying heart disease such as ischemia, myocarditis, fibrosis of the conduction system, or after cardiac surgery). AV block is categorized as **first-degree** (PR interval greater than 200 msec with all atrial impulses conducted), **second-degree** (intermittent blocked beats), or **third-degree** (complete heart block, in which no atrial impulses are conducted to the ventricles). Second-degree AV block is further subclassified into **Mobitz type I (Wenckebach),** in which the AV conduction time (PR interval) progressively lengthens before the blocked beat, and **Mobitz type II,** in which there are intermittently nonconducted atrial beats not preceded by lengthening AV conduction. When only 2:1 AV block is present on the ECG, the differentiation between Mobitz type I or Mobitz type II is more difficult. If the baseline PR interval is prolonged (greater than 200 msec) or the width of the QRS complex is narrow (less than 120 msec), the block is usually nodal (Mobitz type I); if the QRS complex is wide (greater than or equal to 120 msec), the block is more likely infranodal (Mobitz type II).

AV dissociation occurs when an intrinsic ventricular pacemaker (accelerated idioventricular rhythm, ventricular premature beats, or ventricular tachycardia) is firing at a rate faster than or close to the sinus rate, such that atrial impulses arriving at the AV node when it is refractory may not be conducted. This phenomenon does not necessarily indicate AV block. No treatment is required aside from management of the causative arrhythmia.

Clinical Findings

The clinical presentation of first-degree and Mobitz type I block is typically benign and rarely produces symptoms. Normal, physiologic block of this type occurs in response to increases in parasympathetic output. This is commonly seen during sleep, with carotid sinus massage, or in

well-trained athletes. It may also occur as a medication effect (calcium channel blockers, beta-blockers, digitalis, or antiarrhythmics). Pathologic causes, including myocardial ischemia or infarction, inflammatory processes (ie, Lyme disease), fibrosis, calcification, or infiltration (ie, amyloidosis or sarcoidosis), should be considered.

Mobitz type II block and complete (third-degree) heart block are almost always due to pathologic disease involving the infranodal conduction system, and symptoms including fatigue, dyspnea, presyncope or syncope are common. With complete heart block, where no atrial impulses reach the ventricle, the ventricular escape rate is usually slow (less than 50 beats/min) and severity of symptoms may vary depending on the rate and stability of the escape rhythm. As for lesser degrees of AV block, pathologic causes should be explored.

Intraventricular conduction block is relatively common and may be transient (ie, related to increases in heart rate) or permanent. **Right bundle branch block** is often seen in patients with structurally normal hearts. The left bundle is composed of two components (anterior and posterior fascicles) and **left bundle branch block** is more often a marker of underlying cardiac disease, including ischemic heart disease, inflammatory or infiltrative disease, cardiomyopathy, and valvular heart disease. In asymptomatic patients with bifascicular block (block in two of three infranodal components—right bundle, left anterior, and left posterior fascicle), the incidence of occult complete heart block or progression to it is low (1% annually).

Treatment

Asymptomatic patients with first- or second-degree Mobitz type I AV block do *not* require any specific therapy. Patients should undergo treatment of any potentially reversible cause (ie, myocardial ischemia or medication effect). *Symptomatic patients with any degree of heart block should be treated* urgently *with atropine (initial dose 0.5 mg given intravenously) or temporary pacing (transcutaneous or transvenous).* The indications for permanent pacing are symptomatic bradyarrhythmias with any degree of AV block or asymptomatic high-degree AV block (second-degree Mobitz type II or third-degree heart block) not attributable to a reversible or physiologic cause. Patients with presumed cardiac syncope with normal heart rates and rhythm but bifascicular or trifascicular block on ECG should also be considered for permanent pacing.

A **standardized nomenclature for pacemaker generators** is used, usually consisting of four letters. The first letter refers to the chamber that is paced (A, atrium; V, ventricle; D, dual [for both]). The second letter refers to the chamber that is sensed (also A, V, or D). An additional option (O) indicates absence of sensing. The third letter refers to how the pacemaker responds to a sensed event (I, inhibition by a sensed impulse; T, triggering by a sensed impulse; D, dual modes of response; O, no response to sensed impulse). The fourth letter refers to the programmability or rate response capacity (R, rate modulation), a function that can increase the pacing rate in response to motion or respiratory rate when the intrinsic heart rate is inappropriately low.

A dual-chamber pacemaker that senses and paces in both chambers is the most physiologic approach to pacing patients who remain in sinus rhythm. **AV synchrony** is particularly important in patients in whom atrial contraction produces a substantial augmentation of stroke volume. For patients in permanent atrial fibrillation who require pacing for symptomatic bradycardia or pauses, catheter-based implantation of a leadless pacemaker directly to the RV endocardium may be considered. In patients with complete heart block with LV systolic dysfunction, implantation of a pacemaker capable of direct capture of the native specialized conduction system (His bundle or left bundle) or simultaneous LV and RV pacing (biventricular) may be indicated. Complications from pacemaker implantation include infection, hematoma, cardiac perforation, pneumothorax, and lead dislodgement.

When to Refer

Patients with symptomatic AV block (any degree) or asymptomatic high-degree (second-degree Mobitz type II or third-degree) AV block after reversible causes have been excluded.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

ESSENTIALS OF DIAGNOSIS

- Rapid, regular tachycardia most commonly seen in young adults and characterized by abrupt onset and offset.
- QRS duration narrow (less than 120 msec) except in the presence of bundle branch block or accessory pathway.
- Often responsive to vagal maneuvers, AV nodal blockers, or adenosine. Cardioversion rarely required.

General Considerations

PSVT is an intermittent arrhythmia that is characterized by a sudden onset and offset and a regular ventricular response. Episodes may last from a few seconds to several hours or longer. PSVT often occurs in patients without structural heart disease. The most common mechanism for PSVT is *reentry*, which may be initiated or terminated by a fortuitously timed atrial or ventricular premature beat. The reentrant circuit usually involves dual pathways (a slow and a fast pathway) within the AV node; this is referred to as **AV nodal reentrant tachycardia** and accounts for 60% of cases of PSVT. Less commonly (30% of cases), reentry is due to an *accessory pathway* between the atria and ventricles, referred to as **AV reciprocating tachycardia (AVRT)**. The pathophysiology and management of arrhythmias due to accessory pathways differ in important ways and are discussed separately below.

Clinical Findings

A. Symptoms and Signs

Symptoms of PSVT can be quite variable depending on the degree of heart rate elevation, resultant hypotension, or presence of other comorbidities. Symptoms may include palpitations, diaphoresis, dyspnea, dizziness, and mild chest pain (even in the absence of associated CHD). Syncope is rare.

B. ECG

Obtaining a 12-lead ECG when feasible is important to help determine the tachycardia mechanism. The QRS duration will be narrow (less than 120 ms) except in cases of PSVT with aberrant conduction (left bundle branch block, right bundle branch block, or antegrade conducting accessory pathway). The heart rate is regular and is usually 160–220 beats/min but may be greater than 250 beats/min. The P wave usually differs in contour from sinus beats and is often simultaneous with or just after the QRS complex.

Treatment

In the absence of structural heart disease, serious effects are rare, and most episodes resolve spontaneously. Particular effort should be made to terminate the episode quickly if cardiac failure, syncope, or anginal pain develops or if there is underlying cardiac or (particularly) coronary disease. Because reentry is the most common mechanism for PSVT, effective therapy requires that conduction be interrupted at some point in the reentry circuit and the vast majority of these circuits involve the AV node.

A. Mechanical Measures

A variety of maneuvers have been used to interrupt episodes, and *patients may learn to perform these themselves*. These maneuvers result in an acute increase in vagal tone and include the Valsalva maneuver, **lowering the head between the knees**, **coughing**, **splashing cold water on the face**, and **breath holding**. The **Valsalva maneuver** is performed with the patient semirecumbent (45 degrees), exerting around 40 mm Hg of intrathoracic pressure (by blowing through a 10 mL syringe) for at least 15 seconds. Moving the patient supine immediately following the strain maneuver and passively raising their legs for an additional 15 seconds may increase effectiveness of the maneuver. **Carotid sinus massage** is an additional technique often performed by clinicians but *should be avoided if the patient has a carotid bruit*. Firm but gentle pressure and massage are applied first over the right carotid sinus for 10–20 seconds and, if unsuccessful, then over the left carotid sinus. Pressure should not be exerted on both sides at the same time. **Facial contact with cold water** may cause transient bradycardia and termination of PSVT, a phenomenon known as the *diving reflex*. When performed properly, these maneuvers result in abrupt termination of the arrhythmia in 20–50% of cases.

B. Medication Therapy

If mechanical measures fail to terminate the arrhythmia, pharmacologic agents should be tried. **Intravenous adenosine** is recommended as the first-line agent due to its brief duration of action and minimal negative inotropic activity (Table 12–1). Because the half-life of adenosine is less than 10 seconds, the medication is given rapidly (in 1–2 seconds) as a 6 mg bolus followed by 20 mL of fluid. If this regimen is unsuccessful at terminating the arrhythmia, a second higher dose (12 mg) may be given. Adenosine causes block of electrical conduction through the AV node and results in termination of PSVT in approximately 90% of cases. Minor side effects are common and include transient flushing, chest discomfort, nausea, and headache. Adenosine may excite both atrial and ventricular tissue causing atrial fibrillation (in up to 12% of patients) or rarely ventricular arrhythmias, and therefore, administration should be performed with continuous cardiac monitoring and availability of an external defibrillator. Adenosine must also be used with caution in patients with reactive airways disease because it can promote bronchospasm.

When adenosine fails to terminate the arrhythmia or if a contraindication to its use is present, **intravenous calcium channel blockers**, including verapamil and diltiazem, may be used (Table 12–1). Verapamil in particular has been shown to be as effective at terminating PSVT in the acute setting (approximately 90%) as adenosine. Calcium channel blockers should be used with caution in patients with HF due to their negative inotropic effects. Their longer half-life compared to adenosine may result in prolonged hypotension despite restoration of normal rhythm. Etripamil, a short-acting calcium channel blocker that is self-administered intranasally, results in rapid conversion of PSVT in two-thirds of patients in preliminary studies and is under review by the FDA at the beginning of 2024.

Intravenous beta-blockers include esmolol (a very short-acting beta-blocker), propranolol, and metoprolol. While beta-blockers cause less myocardial depression than calcium channel blockers, the evidence of their effectiveness to terminate PSVT is limited. Although **intravenous amiodarone** is safe, it is usually not required and often ineffective for treatment of these arrhythmias.

C. Cardioversion

If the patient is hemodynamically unstable or if adenosine, beta-blockers, and calcium channel blockers are contraindicated or ineffective, synchronized electrical cardioversion (beginning at 100 J) should be performed.

Prevention

A. Catheter Ablation

Because of concerns about the safety and the intolerability of antiarrhythmic medications, *radiofrequency ablation is the preferred approach to patients with recurrent symptomatic reentrant PSVT,* whether it is due to dual pathways within the AV node or to accessory pathways.

B. Medications

AV nodal blocking agents are the medications of choice as first-line medical therapy (Table 12–1). Beta-blockers or

nondihydropyridine calcium channel blockers, such as diltiazem and verapamil, are typically used first. Patients who do not respond to agents that increase refractoriness of the AV node may be treated with antiarrhythmics. The class Ic agents (flecainide, propafenone) can be used in patients without underlying structural heart disease. In patients with evidence of structural heart disease, class III agents, such as sotalol or amiodarone, should be used because of the lower incidence of ventricular proarrhythmia during long-term therapy.

When to Refer

All patients with sustained or symptomatic PSVT should be referred to a cardiologist or cardiac electrophysiologist for long-term treatment options (including observation, pharmacotherapy, or ablation).

PSVT DUE TO ACCESSORY AV PATHWAYS (Preexcitation Syndromes)

ESSENTIALS OF DIAGNOSIS

- Two classic features of Wolff-Parkinson-White (WPW) pattern on ECG are short PR interval and wide, slurred QRS complex due to manifest preexcitation (delta wave).
- Most patients with WPW pattern do not have clinical history of arrhythmia but have a higher risk of SCD due to the possibility of rapidly conducted atrial fibrillation through the accessory pathway.
- Risk factors for SCD with WPW include age younger than 20, history of tachycardia, and rapid conduction properties at electrophysiologic testing.

General Considerations

Accessory pathways or bypass tracts between the atrium and the ventricle bypass the compact AV node and can predispose to reentrant arrhythmias, such as AVRT and atrial fibrillation. When direct AV connections conduct antegrade (manifest preexcitation) they produce a classic **WPW pattern** on the baseline ECG consisting of a short PR interval and a wide, slurred QRS complex **(delta wave)** owing to early ventricular depolarization of the region adjacent to the pathway. Although the morphology and polarity of the delta wave can suggest the location of the pathway, mapping by intracardiac recordings is required for precise anatomic localization.

Accessory pathways occur in 0.1–0.3% of the population and facilitate reentrant arrhythmias owing to the disparity in refractory periods of the AV node and accessory pathway. **WPW syndrome** refers to a patient with baseline WPW pattern on ECG with associated SVT. Whether the tachycardia is associated with a narrow or wide QRS complex is frequently determined by whether antegrade conduction is through the node (narrow) or the bypass tract (wide). Some bypass tracts only conduct in a retrograde direction. In these cases, the bypass tract is termed "concealed" because it is not readily apparent on a baseline (sinus) ECG. **Orthodromic reentrant tachycardia** accounts for approximately 90% of AVRT episodes and is characterized by conduction antegrade down the AV node and retrograde up the accessory pathway, resulting in a narrow QRS complex (unless an underlying bundle branch block or interventricular conduction delay is present). **Antidromic reentrant tachycardia** conducts antegrade down the accessory pathway and retrograde through the AV node, resulting in a wide and often bizarre-appearing QRS complex that may be mistaken for ventricular tachycardia. Accessory pathways often have shorter refractory periods than specialized conduction tissue and thus tachycardias involving accessory pathways have the potential to be more rapid.

Clinical Findings

Patients with WPW in whom arrhythmia develops often have palpitations, dizziness, or mild chest pain. Most patients that have a delta wave found incidentally on ECG (WPW pattern) do *not* have a clinical history of arrhythmia and are therefore asymptomatic. However, these patients are still at higher risk for SCD than the general population. Atrial fibrillation with antegrade conduction down the accessory pathway and a rapid ventricular response will develop in up to 30% of patients with WPW. If this conduction is very rapid, it can potentially degenerate to ventricular fibrillation. The 10-year risk of SCD in patients with WPW syndrome ranges from 0.15% to 0.24%. Risk factors include age younger than 20, a history of symptomatic tachycardia, and multiple accessory pathways.

Multiple risk stratification strategies have been proposed to identify asymptomatic patients with WPW pattern ECG who may be at higher risk for lethal cardiac arrhythmias. A sudden loss of preexcitation during ambulatory monitoring or exercise testing likely indicates an accessory pathway with poor conduction properties and therefore low risk for rapid anterograde conduction. In the absence of this finding, patients may be referred for invasive electrophysiology testing. During the study, patients found to have the shortest preexcited R-R interval during atrial fibrillation of 250 msec or less or inducible SVT are at increased risk for SCD and should undergo catheter ablation.

Treatment

A. Pharmacotherapy

Initial treatment of narrow-complex reentrant rhythms involving a bypass tract (orthodromic AVRT) is similar to other forms of PSVT and includes vagal maneuvers, intravenous adenosine, or verapamil. Treatment of wide-complex tachycardia in the presence of an accessory pathway, be it reentrant-type (antidromic AVRT) or atrial fibrillation with antegrade conduction down the bypass tract, must be managed differently. Agents such as calcium channel blockers and beta-blockers may increase the

refractoriness of the AV node with minimal or no effect on the accessory pathway, often leading to faster ventricular rates and increasing the risk of ventricular fibrillation. Therefore, these agents should be *avoided*. Intravenous class Ia (procainamide) and class III (ibutilide) antiarrhythmic agents will increase the refractoriness of the bypass tract and are the medications of choice for wide-complex tachycardias involving accessory pathways. If hemodynamic compromise is present, electrical cardioversion is warranted.

B. Catheter Ablation

For long-term management, catheter ablation is the procedure of choice in patients with accessory pathways and recurrent symptoms or asymptomatic patients with WPW pattern on ECG and high-risk features at baseline or during electrophysiology study. Success rates for ablation of accessory pathways with radiofrequency catheters exceed 95% in appropriate patients. Major complications from catheter ablation are rare but include AV block, cardiac tamponade, and thromboembolic events. Minor complications, including hematoma at the catheter access site, occur in 1–2% of procedures. For patients who are not candidates for catheter ablation, class Ic or class III antiarrhythmic medication may be considered.

When to Refer

- Asymptomatic patients with an incidental finding of WPW pattern on ECG with high-risk features.
- Patients with recurrent or prolonged tachycardia episodes despite treatment with AV nodal blocking agents.
- Patients with preexcitation and a history of atrial fibrillation or syncope.

ATRIAL FIBRILLATION

ESSENTIALS OF DIAGNOSIS

- Presents as an irregularly irregular heart rhythm on examination and ECG.
- Prevention of stroke should be considered in all patients with risk factors for stroke (those with HF, hypertension, age 65 or older, diabetes mellitus, prior history of stroke or transient ischemic attack [TIA], or vascular disease).
- Heart rate control with beta-blocker or calcium channel blockers generally required. Restoration of sinus rhythm with cardioversion, antiarrhythmic medications, or catheter ablation in symptomatic patients.

General Considerations

Atrial fibrillation is the most common chronic arrhythmia, with an estimated global prevalence of 50 million individuals. It occurs in rheumatic and other forms of valvular heart disease, dilated cardiomyopathy, hypertension, and CHD as well as in patients with no apparent cardiac disease; it may be the initial presenting sign in thyrotoxicosis, and this condition should be excluded with the initial episode. Atrial fibrillation often appears in a **paroxysmal** fashion before becoming the established rhythm. Pericarditis, chest trauma, thoracic or cardiac surgery, thyroid disorders, obstructive sleep apnea, or pulmonary disease as well as medications (beta-adrenergic agonists, inotropes, bisphosphonates, and certain chemotherapeutics) may cause attacks in patients with normal hearts. Acute alcohol excess and alcohol withdrawal (termed **holiday heart**) may precipitate atrial fibrillation. For regular, moderate drinkers, abstinence from alcohol reduces recurrences of atrial fibrillation by about 50%.

Atrial fibrillation is associated with a 2-fold risk of SCD, a 2.4-fold risk of stroke, and a 5-fold risk of HF. Atrial fibrillation increases the propensity for thrombus formation due to circulatory stasis in the left atrial appendage and consequent embolization, most devastatingly to the cerebral circulation. *Untreated, the rate of stroke is approximately 5% per year.* However, patients with significant obstructive valvular disease, chronic HF or LV dysfunction, diabetes mellitus, hypertension, or age over 75 years and those with a history of prior stroke or other embolic events are at substantially higher risk (up to nearly 20% per year in patients with multiple risk factors). In patients presenting with embolic stroke of unknown source (cryptogenic stroke), a substantial portion will have **asymptomatic** or **"subclinical"** atrial fibrillation detected with implantable loop recorders, allowing initiation of oral anticoagulation where appropriate.

Clinical Findings

A. Symptoms and Signs

Atrial fibrillation itself is rarely life-threatening; however, it can have serious consequences if the ventricular rate is sufficiently rapid to precipitate hypotension, myocardial ischemia, or tachycardia-induced myocardial dysfunction. Moreover, particularly in patients with risk factors, atrial fibrillation is a major preventable cause of stroke. Although some patients—particularly with advanced age or an inactive lifestyle—have relatively few symptoms if the rate is controlled, many patients are aware of the irregular rhythm. Most patients will report fatigue whether they experience other symptoms or not. The heart rate may range from quite slow to extremely rapid but is uniformly irregular unless underlying complete heart block with junctional escape rhythm or a permanent ventricular pacemaker is in place. *Atrial fibrillation is the only common arrhythmia in which the ventricular rate is rapid and the rhythm very irregular.*

B. ECG

The surface ECG typically demonstrates erratic, disorganized atrial activity between discrete QRS complexes occurring in an irregular pattern. The atrial activity may be very fine and difficult to detect on the ECG, or quite coarse and often mistaken for atrial flutter.

C. Echocardiography

Echocardiography provides assessment of chamber volumes, LV size and function, or the presence of concomitant valvular heart disease and should be performed in all patients with a new diagnosis of atrial fibrillation. TEE is the most sensitive imaging modality to identify thrombi in the left atrium or left atrial appendage prior to any attempt at chemical or electrical cardioversion.

Treatment

A. Newly Diagnosed Atrial Fibrillation

1. Initial management—

A. HEMODYNAMICALLY UNSTABLE PATIENT—If the patient is hemodynamically unstable, usually as a result of a rapid ventricular rate or associated cardiac or noncardiac conditions, hospitalization and immediate treatment of atrial fibrillation are required. Intravenous beta-blockers (esmolol, propranolol, and metoprolol) or calcium channel blockers (diltiazem and verapamil) are usually effective at rate control in the acute setting. Urgent electrical cardioversion is only indicated in patients with shock or severe hypotension, pulmonary edema, or ongoing MI or ischemia. *There is a potential risk of thromboembolism in patients undergoing cardioversion who have not received anticoagulation therapy if atrial fibrillation has been present for more than 48 hours or is of unknown duration*; however, in hemodynamically unstable patients the need for immediate rate control outweighs that risk. An initial biphasic shock with at least 200 J is administered in synchrony with the R wave. If sinus rhythm is not restored, an additional attempt with 360 J is indicated. If this fails, cardioversion may be successful after loading with intravenous ibutilide (1 mg over 10 minutes, repeated in 10 minutes if necessary).

B. HEMODYNAMICALLY STABLE PATIENT—If the patient has no symptoms, hemodynamic instability, or evidence of important precipitating conditions (such as silent MI or ischemia, decompensated HF, or hemodynamically significant valvular disease), hospitalization is usually *not* necessary. In most of these cases, atrial fibrillation is an unrecognized chronic or paroxysmal condition and should be managed accordingly (see Subsequent Management, below). For new-onset atrial fibrillation, basic blood tests (CBC, metabolic panel, and thyroid function) and echocardiography to assess for occult valvular or myocardial disease should be performed.

In stable patients with atrial fibrillation, an initial strategy of rate control and anticoagulation is often suitable. The choice of agent is guided by the hemodynamic status of the patient, associated conditions, and the urgency of achieving rate control. In the stable patient with atrial fibrillation, a nondihydropyridine calcium channel blocker or beta-blocker (orally or intravenously) is the first-line agent for ventricular rate control. In the setting of MI or ischemia, beta-blockers are the preferred agent. The most frequently used agents are either metoprolol (2.5–5 mg intravenous bolus, repeated up to three times at intervals of 5 minutes and then given orally at total daily doses of 25–200 mg) or, in unstable patients, esmolol (0.5 mg/kg intravenous bolus, followed by a titrated infusion of 0.05–0.3 mg/kg/min). If beta-blockers are contraindicated, calcium channel blockers are rapidly effective. Diltiazem (10–20 mg bolus, repeated after 15 minutes if necessary, followed by a maintenance infusion of 5–15 mg/hour) is the preferred calcium blocker if hypotension is present. Otherwise, verapamil (5–10 mg intravenously over 2–3 minutes, repeated after 30 minutes if necessary) may be used. Rate control using digoxin is relatively slow (onset of action more than 1 hour with peak effect at 6 hours); however, it may be useful as an adjunct when rate control with the previously cited agents is incomplete. Similarly, amiodarone, even when administered intravenously, has a relatively slow onset and is most useful when cardioversion is planned in the near future. Care should be taken in patients with hypotension or HF because the rapid intravenous administration of amiodarone may worsen hemodynamics.

Up to two-thirds of patients experiencing acute onset (shorter than 36 hours) of atrial fibrillation will spontaneously revert to sinus rhythm without the need for cardioversion. *If atrial fibrillation has been present for more than a week, spontaneous conversion is unlikely* and cardioversion may be considered for symptomatic patients. Importantly, *if the onset of atrial fibrillation was more than 48 hours prior to presentation (or unknown), a transesophageal echocardiogram should be performed prior to cardioversion to exclude left atrial thrombus.* If thrombus is present, the cardioversion is delayed until after a 3–6-week period of therapeutic anticoagulation and repeated imaging. Because atrial contractile activity may not recover for several weeks after restoration of sinus rhythm in patients who have been in atrial fibrillation for more than 48 hours, *therapeutic anticoagulation should be established pre-cardioversion and continued without interruption for at least 1 month afterwards*. Younger patients without HF, diabetes, hypertension, or other risk factors for stroke may not require long-term anticoagulation.

2. Subsequent management—If immediate cardioversion is not performed, adequate long-term rate control can usually be achieved with beta-blockers or nondihydropyridine calcium channel blockers. Choice of the initial rate control medication is best based on the presence of accompanying conditions: Patients with hypertension can be given beta-blockers or calcium blockers (see Tables 13–8, 13–10, and 13–11). Patients with CHD or HF should receive a beta-blocker (carvedilol, long-acting metoprolol or bisoprolol) preferentially, whereas beta-blockers should be avoided in patients with severe COPD or asthma. Digoxin may be used as a second agent when rate-control is inadequate with beta-blocker or calcium channel blocker alone (target serum concentration 0.5–1.2 ng/mL). In symptomatic patients, *a resting heart rate of less than 80 beats/min is targeted*. In asymptomatic patients without LV dysfunction, a more lenient resting heart rate of 85–110 beats/min is reasonable. Ambulatory monitoring to assess heart rate during exercise should be considered in all patients with a goal not to exceed maximum predicted heart rate (220 – age).

A. ANTICOAGULATION—*For patients with atrial fibrillation, even when it is paroxysmal or occurs rarely, the need for*

oral anticoagulation should be evaluated and treatment initiated for those without strong contraindication. Patients under the age of 65 years with atrial fibrillation in the absence of associated heart disease, hypertension, atherosclerotic vascular disease, diabetes mellitus, or history of stroke or TIA do not require antithrombotic treatment. Patients with **transient atrial fibrillation,** such as in the setting of acute MI or pneumonia, but no prior history of arrhythmia, are at high risk for future development of atrial fibrillation and appropriate anticoagulation should be initiated based on risk factors. If the cause is reversible, such as after coronary artery bypass surgery or associated with hyperthyroidism, then long-term anticoagulation may not be necessary.

Several risk scores based on clinical factors have been developed to guide anticoagulant use in patients with atrial fibrillation. The **CHA_2DS_2-VASc** score is considered the most validated and includes the traditional five risk factors that comprise the **$CHADS_2$** score (HF, hypertension, age 75 years or older, diabetes mellitus, and [2 points for] history of stroke or TIA) with three additional factors (age 65–74 years, female sex, and presence of vascular disease) (Table 12–2). If the CHA_2DS_2-VASc score is greater than or equal to 2 in men or 3 in women, oral anticoagulation is recommended. For patients at low-moderate risk (CHA_2DS_2-VASc score 1 in men, 2 in women), oral anticoagulation can be considered, taking into account risk, benefit, and patient preferences. In patients with atrial fibrillation and no clinical risk factors (CHA_2DS_2-VASc score 0), there is no indication for anticoagulant or antithrombotic therapy. In general, unless there is an indication for antiplatelet therapy (CHD, peripheral vascular disease), patients with atrial fibrillation should not be prescribed aspirin for stroke prevention.

Four DOACs—dabigatran, rivaroxaban, apixaban, and edoxaban—have been shown to be *at least as effective* as warfarin for stroke prevention in patients with atrial fibrillation and have been approved by the FDA for this indication (Table 12–3). These medications have *not* been studied in patients with moderate or severe mitral stenosis, and they should *not* be used for patients with mechanical prosthetic valves. The term "nonvalvular atrial fibrillation" is no longer used in the American or European guidelines since most patients with valvular heart disease (other than mitral stenosis) have been included in trials of DOACs and shown to be equally as effective in these patients.

Dabigatran (studied in the RE-LY trial) is superior to warfarin at preventing stroke at the 150 mg twice daily dose, and it is noninferior at the 110 mg twice daily dose, although this dose is not approved for treatment of atrial fibrillation in the United States. Both doses result in *less* intracranial hemorrhage than warfarin but also in *more* GI bleeding than warfarin. Neither dabigatran nor any of the DOACs should be used in patients with mechanical prosthetic heart valves where the medications are less effective and riskier.

Rivaroxaban is noninferior to warfarin for stroke prevention in atrial fibrillation (in the ROCKET-AF trial). Rivaroxaban is dosed at 20 mg once daily, with a reduced dose (15 mg/day) for patients with creatinine clearances between 15 and 50 mL/min. It should be *administered with food*, since that results in a 40% higher drug absorption. As with dabigatran, there is substantially less risk of intracranial hemorrhage with rivaroxaban than warfarin.

Apixaban is more effective than warfarin at stroke prevention while having a substantially lower risk of major bleeding (in the ARISTOTLE trial) and a lower risk of all-cause mortality. The apixaban dosage is 5 mg twice daily or 2.5 mg twice daily for patients with two of three high-risk criteria (age 80 years or older, body weight 60 kg or less, and serum creatinine of 1.5 mg/dL or more). Apixaban is

Table 12–2. CHA_2DS_2-VASc Risk Score for assessing risk of stroke and for selecting antithrombotic therapy for patients with atrial fibrillation.

CHA_2DS_2-VASc Risk Score	
HF or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke, transient ischemic attack, or thromboembolism	2
Vascular disease (previous MI, peripheral artery disease, or aortic plaque)	1
Age 65–74 years	1
Female sex (but not a risk factor if female sex is the only factor)	1

Adjusted stroke rate according to CHA_2DS_2-VASc score

CHA_2DS_2-VASc Score	Patients (n = 7329)	Adjusted stroke rate (%/year)
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7 %
9	14	15.2%

CHA_2DS_2-VASc score = 0: recommend no antithrombotic therapy

CHA_2DS_2-VASc score = 1 (men) or 2 (women): consider antithrombotic therapy with oral anticoagulation

CHA_2DS_2-VASc score > 1 (men) or > 2 (women): recommend antithrombotic therapy with oral anticoagulation

CHA_2DS_2-VASc, Cardiac failure, Hypertension, Age ≥ 75 years (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex category (female).

Data from Camm AJ et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation.

Table 12–3. DOACs for stroke prevention in patients with atrial fibrillation. (Listed in alphabetical order.)

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Class	Factor Xa inhibitor	Antithrombin	Factor Xa inhibitor	Factor Xa inhibitor
Bleeding risk compared to warfarin	Substantially lower risk of major bleeding Less intracranial bleeding	Less intracranial bleeding Higher incidence of GI bleeding	Lower risk of major bleeding Less intracranial bleeding	Less intracranial bleeding Higher incidence of GI bleeding
Dosage	5 mg twice daily	150 mg twice daily	60 mg once daily	20 mg once daily (give with food)
Dosage adjustments	2.5 mg twice daily for patients with at least two of three risk factors: 1. Age ≥ 80 years 2. Body weight ≤ 60 kg 3. Serum creatinine ≥ 1.5 mg/dL	75 mg twice daily for creatinine clearance[1] 15–30 mL/min	30 mg once daily for creatinine clearance[1] ≤ 50 mL/min FDA recommends not to use if creatinine clearance[1] > 95 mL/min	15 mg once daily for creatinine clearance[1] < 50 mL/min

[1]Creatinine clearance calculated by Cockcroft-Gault equation.
Data from Nishimura RA et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(23):e521–643.

associated with less intracranial hemorrhage and is well tolerated. Apixaban has been studied in a small trial of patients receiving hemodialysis, with pharmacokinetic studies suggesting a dose of 2.5 mg twice daily in these patients results in equivalent serum concentrations as 5 mg twice daily in patients with normal kidney function.

Edoxaban, 60 mg once a day, is noninferior to warfarin for stroke prevention with lower rates of major bleeding and lower rates of hemorrhagic stroke (studied in the ENGAGE-AF trial). Edoxaban carries a boxed warning in FDA labelleling that it should *not* be used in patients whose creatinine clearance is more than 95 mL/min because it is less effective in this population. The dose is decreased to 30 mg/day for patients whose creatinine clearance is less than or equal to 50 mL/min.

These four DOACs have important advantages over warfarin, and therefore, they are recommended preferentially over vitamin K antagonists (VKAs). In practice, these medications are often underdosed. They should be used at the doses shown to be effective in the clinical trials as shown in Table 12–3. *Even though labeled for "nonvalvular" atrial fibrillation, the DOACs are safe and effective for patients with moderate or severe valvular abnormalities, apart from moderate or severe mitral stenosis.* In part because of lower rates of intracerebral hemorrhage, *DOACs have particular advantage over warfarin in older adults and frail patients, including patients with history of falls.* For patients who fall, shared-decision making weighing risks and benefits should be incorporated. However, oral anticoagulation should generally be continued.

Warfarin remains first-line therapy in patients who have mechanical prosthetic valves, moderate or severe mitral stenosis, and those who cannot afford DOACs. Patients who have been stable while receiving warfarin for a long time, with a high time in target INR range, and who are at lower risk for intracranial hemorrhage will have relatively less benefit with a switch to a DOAC. One way to reduce bleeding for patients taking oral anticoagulants is to avoid concurrent aspirin, unless there is a clear indication, like recent MI or coronary stent. Even then, use of oral anticoagulant plus clopidogrel without aspirin, or with only a brief period of "triple" therapy and then discontinuation of aspirin, may be a reasonable approach.

There are some important practical issues with using the DOACs. It is important to *monitor blood counts and kidney function* at baseline and at least twice a year, or more often for those with impaired kidney function. Each of the DOACs interacts with other medications affecting the P-glycoprotein pathway, such as oral ketoconazole, verapamil, dronederone, and phenytoin. To transition patients from warfarin to a DOAC, wait until the INR decreases to about 2.0. Each of the medications has a half-life of about 10–12 hours for patients with normal kidney function. For elective procedures, stop the medications two to three half-lives (usually 24–48 hours) before procedures with low to moderate bleeding risk (ie, colonoscopy, dental extraction, cardiac catheterization), and five half-lives before major surgery. Discontinuation times should be extended in patients with impaired renal function, particularly with dabigatran. For patients discontinuing DOAC peri-procedurally, there is no need for bridging anticoagulation. While there are no practical tests to immediately measure the anticoagulant effect of the medications, a normal aPTT suggests little effect with dabigatran, and a normal prothrombin suggests little effect with rivaroxaban. Routine measurement of DOAC plasma concentrations is *not* recommended due to lack of established therapeutic ranges.

Approximately 2–4% of patients on oral anticoagulation have major bleeding which may require intervention. For bleeding, standard measures (ie, diagnosing and controlling the source, stopping antithrombotic agents, and replacing blood products) should be taken. If the DOAC was taken in the prior 6–8 hours, activated oral charcoal may be used to reduce absorption. If the patient is taking aspirin, consider platelet transfusion. Due to the short half-life of the DOACs (10–12 hours with normal kidney

function), supportive measures (local control, packed RBCs, platelets) may suffice until the medication has cleared. Antidotes should be considered for life-threatening bleeding or for patients with need for immediate surgery. A patient with severe bleeding while taking dabigatran may be treated with the reversal agent **idarucizumab** (given as 5 g IV infusion over 5 minutes), a humanized monoclonal antibody that binds the medication resulting in rapid reversal of its anticoagulation effect. **Andexanet alfa** (given as 400 mg bolus at a rate of 30 mg/min followed by 4 mg/min for up to 120 minutes), a factor Xa decoy, is FDA-approved for reversal of the factor Xa inhibitors rivaroxaban and apixaban. For life-threatening bleeding with warfarin or other VKAs, **four-factor prothrombin complex concentrate** in addition to intravenous vitamin K may partially reverse the anticoagulant effect and is preferred over fresh frozen plasma.

In patients who are unsuitable for long-term anticoagulation due to excessive bleeding risk, **left atrial appendage occluders** (including the Watchman and Amulet devices) have been shown to protect against stroke, although they may not be as effective as warfarin in preventing ischemic stroke. Occlusion of the left atrial appendage during cardiac surgery provides further protection against ischemic stroke over and above ongoing oral anticoagulant use.

b. Rate control or rhythm control—After assessing stroke risk and initiating anticoagulation where appropriate, two main treatment strategies for long-term management of atrial fibrillation exist: rate control or rhythm control, although they are not mutually exclusive. *Rate control should be considered background treatment in nearly all patients with atrial fibrillation, regardless of whether rhythm restoration is eventually pursued, and may be considered the primary treatment in patients with minimal to no symptoms related to long-standing atrial fibrillation.* In patients with recent-onset atrial fibrillation (less than 1 year), the EAST-AFNET 4 trial found that rhythm control with antiarrhythmic medication or catheter ablation is associated with a lower risk of death from cardiovascular causes, stroke, or hospitalization for HF.

The decision to pursue rhythm control is often individualized, based on symptoms, the type of atrial fibrillation (paroxysmal or persistent), comorbidities (such as HF), as well as general health status. As first treatment, elective cardioversion (200 J or more, biphasic energy) is recommended in patients in whom atrial fibrillation is thought to be of recent onset or when there is an identifiable precipitating factor. Similarly, cardioversion is appropriate in patients who remain symptomatic from the rhythm despite efforts to achieve rate control. In patients with atrial fibrillation duration of greater than 48 hours (or unknown), a minimum of 3 weeks of anticoagulation or exclusion of left atrial thrombus by TEE pre-cardioversion is required. Anticoagulation should be continued for at least 4 weeks following cardioversion to prevent thromboembolism. In patients with prior left atrial appendage occlusion, data on peri-cardioversion stroke risk and anticoagulation strategies are lacking. However, TEE is recommended to exclude device-related thrombus or peri-device leak which may prompt anticoagulant initiation.

In cases in which elective cardioversion is required, it may be accomplished pharmacologically or electrically. Pharmacologic cardioversion with intravenous ibutilide (1 mg over 10 minutes, repeated in 10 minutes if necessary) or procainamide (15 mg/kg over 30 minutes) may be used in a setting in which the patient can undergo continuous ECG monitoring for at least 4–6 hours following administration. Pretreatment with intravenous magnesium (1–2 g) may prevent rare episodes of torsades de pointes associated with ibutilide administration. The incidence of torsades de pointes with ibutilide is higher in patients with reduced cardiac function and therefore its use should be avoided in patients with LV EF 40% or less. In patients in whom a decision has been made to continue antiarrhythmic therapy to maintain sinus rhythm (see next paragraph), cardioversion can be attempted with an agent that is being considered for long-term use. For instance, after therapeutic anticoagulation has been established, amiodarone can be initiated on an outpatient basis (400 mg twice daily for 2 weeks, followed by 200 mg twice daily for at least 2–4 weeks and then a maintenance dose of 200 mg daily). Because amiodarone increases the prothrombin time in patients taking warfarin and increases digoxin levels, careful monitoring of anticoagulation and medication levels is required.

Other antiarrhythmic medications that can be used for long-term maintenance therapy include propafenone, flecainide, dronedarone, dofetilide, and sotalol. Dofetilide (125–500 mcg twice daily orally) must be initiated in hospital due to the potential risk of torsades de pointes and the downward dose adjustment that is required for patients with significant QT interval prolongation. Propafenone (150–300 mg orally every 8 hours) and flecainide (50–150 mg orally twice daily) should be avoided in patients with structural heart disease (CHD, systolic dysfunction, or significant LVH) and should be used in conjunction with an AV nodal blocking medication, especially if there is a history of atrial flutter. Sotalol (80–160 mg orally twice daily) should be initiated in the hospital in patients with structural heart disease due to a risk of torsades de pointes; it is not very effective for converting atrial fibrillation but can be used to maintain sinus rhythm following cardioversion. Dronedarone should not be used in patients with recent decompensated HF or when atrial fibrillation has become persistent.

In patients treated long-term with an antiarrhythmic agent, sinus rhythm will persist in 30–50%. Given this high rate of arrhythmia recurrence, the decision to maintain long-term anticoagulation should be based on risk factors (CHA_2DS_2-VASc score, Table 12–2) and not on the perceived presence or absence of atrial fibrillation, since future episodes may be asymptomatic.

B. Recurrent and Refractory Atrial Fibrillation

1. Recurrent paroxysmal atrial fibrillation—For select patients with symptomatic but rare (a few times a year) episodes of atrial fibrillation, an effective treatment strategy is on-demand pharmacologic cardioversion, termed **pill-in-the-pocket treatment**. Patients without coronary or structural heart disease may be given flecainide (200–300 mg) or propafenone (450–600 mg) in addition to a

beta-blocker or nondihydropyridine calcium channel blocker as a single dose at the onset of symptoms. It is recommended that the first such treatment take place in a monitored setting (eg, the emergency department or hospital) to evaluate safety and effectiveness. For more frequent, symptomatic arrhythmic episodes, daily antiarrhythmic agents are first-line therapy; however, they are not often successful in preventing all paroxysmal atrial fibrillation episodes and long-term tolerability is poor.

2. Refractory atrial fibrillation—Atrial fibrillation should be considered refractory if it causes persistent symptoms or limits activity despite attempts at rate or rhythm control. If antiarrhythmic or rate control medications fail to improve symptoms, **catheter ablation** around the pulmonary veins to isolate the triggers that initiate and maintain atrial fibrillation may be considered. It is a reasonable therapy for individuals with symptomatic paroxysmal or persistent atrial fibrillation that is refractory to pharmacologic therapy and for select patients (younger than 65 years or with concurrent HF) as first-line therapy. *The primary benefit of catheter ablation is an improvement in quality of life.* In the CABANA trial, there was no difference in the primary endpoint of death, disabling stroke, serious bleeding, or cardiac arrest in patients randomized to catheter ablation versus medical therapy as first treatment for symptomatic atrial fibrillation. Ablation is successful about 50–70% of the time but repeat ablation may be required in up to 20% of patients. The procedure is routinely performed in the electrophysiology laboratory using a catheter-based approach and adverse event rates are low when performed by experienced operators. **Surgical ablation** can also be performed via a subxiphoid approach, thoracoscopically via thoracotomy, or via median sternotomy in the operating room as a stand-alone or adjunct procedure. Finally, in symptomatic patients with poor rate control and deemed inappropriate for pulmonary vein isolation, **radiofrequency ablation** of the AV node and **permanent pacing** ensure rate control and may facilitate a more physiologic rate response to activity, but this is usually performed only after other therapies have failed.

When to Refer

- Symptomatic atrial fibrillation with or without adequate rate control.
- Asymptomatic atrial fibrillation with poor rate control despite AV nodal blockers.
- Patients at risk for stroke who have not tolerated oral anticoagulants.

Joglar J et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation. Circulation. 2024;149:e1. [PMID: 38033089]

Parkash R et al. Randomized ablation-based rhythm-control versus rate-control trial in patients with heart failure and atrial fibrillation: results from the RAFT-AF trial. Circulation. 2022;145:1693. [PMID: 35313733]

Whitlock RP et al. Left atrial appendage occlusion during cardiac surgery to prevent stroke. N Engl J Med. 2021;384:2081. [PMID: 33999547]

ATRIAL FLUTTER

ESSENTIALS OF DIAGNOSIS

- Rapid, regular tachycardia presenting classically with 2 to 1 block in the AV node and ventricular heart rate of 150 beats/min.
- ECG shows "sawtooth" pattern of atrial activity (rate 300 beats/min).
- Stroke risk should be considered equivalent to that with atrial fibrillation.
- Catheter ablation is highly successful and is considered the definitive treatment for typical atrial flutter.

General Considerations

Atrial flutter is less common than fibrillation. It may occur in patients with structurally normal hearts but is more commonly seen in patients with COPD, valvular or structural heart disease, ASD, or surgically repaired congenital heart disease.

Clinical Findings

Patients typically present with reports of palpitations, fatigue, or mild dizziness. In situations where the arrhythmia is unrecognized for a prolonged period of time, symptoms and signs of HF (dyspnea, exertional intolerance, edema) due to tachycardia-induced cardiomyopathy may develop. The ECG typically demonstrates a **"sawtooth" pattern** of atrial activity in the inferior leads (II, III, and AVF). The reentrant circuit generates atrial rates of 250–350 beats/min, usually with transmission of every second, third, or fourth impulse through the AV node to the ventricles.

Treatment

Ventricular rate control is accomplished using the same agents used in atrial fibrillation, but it is generally more difficult. Conversion of atrial flutter to sinus rhythm with class I antiarrhythmic agents is also difficult to achieve, and administration of these medications has been associated with slowing of the atrial flutter rate to the point at which 1:1 AV conduction can occur at rates in excess of 200 beats/min, with subsequent hemodynamic collapse. The intravenous class III antiarrhythmic agent ibutilide has been significantly more successful in converting atrial flutter (see Table 12–1). About 50–70% of patients return to sinus rhythm within 60–90 minutes following the infusion of this agent. Electrical cardioversion is also very effective for atrial flutter, with approximately 90% of patients converting following synchronized shocks of 100–200 J.

Although the organization of atrial contractile function in this arrhythmia may provide some protection against thrombus formation, *the risk of thromboembolism should be considered equivalent to that with atrial fibrillation* due to the common coexistence of these arrhythmias. As with

atrial fibrillation, anticoagulation should be established for at least 3 weeks or thrombus excluded with TEE pre-cardioversion for atrial flutter of greater than 48 hours or of unknown duration. Anticoagulation should be continued for at least 4 weeks after electrical or chemical cardioversion and chronically in patients with risk factors for thromboembolism.

Catheter ablation is the treatment of choice for long-term management of atrial flutter owing to the high success rate and safety of the procedure. The anatomy of the typical circuit is well defined and catheter ablation within the right atrium results in immediate and permanent elimination of atrial flutter in more than 90% of patients. Due to the frequent coexistence of atrial flutter with atrial fibrillation, however, some patients may require catheter ablation of both arrhythmias. If pharmacologic therapy is chosen, class III antiarrhythmics (amiodarone or dofetilide) are generally preferred (see Table 12–1).

When to Refer

All patients with atrial flutter should be referred to a cardiologist or cardiac electrophysiologist for consideration of definitive treatment with catheter ablation.

ATRIAL TACHYCARDIA

ESSENTIALS OF DIAGNOSIS

- Characterized by bursts of rapid, regular tachycardia.
- Multifocal atrial tachycardia commonly seen with severe COPD and presents with three or more distinct P wave morphologies on ECG, often confused for atrial fibrillation.
- Treatment of the underlying lung disease is most effective therapy.

General Considerations

Atrial tachycardia is an uncommon form of SVT characterized by paroxysms or bursts of rapid, regular arrhythmia due to focal atrial impulses originating outside of the normal sinus node. Common sites include the tricuspid annulus, the crista terminalis of the right atrium and the coronary sinus. **Multifocal atrial tachycardia** is a particular subtype seen in patients with severe COPD and characterized by varying P wave morphology (by definition, three or more foci) and markedly irregular PP intervals. The rate is usually between 100 beats/min and 140 beats/min, and it is often confused for atrial fibrillation. **Solitary atrial premature beats** are benign and generally not associated with underlying cardiac disease. They occur when an ectopic focus in the atria fires before the next sinus node impulse. The contour of the P wave usually differs from the patient's normal complex, unless the ectopic focus is near the sinus node. Acceleration of the heart rate by any means usually abolishes most premature beats.

Clinical Findings

Focal atrial tachycardias are usually intermittent and self-limiting although incessant forms do exist and may present with signs and symptoms of HF due to tachycardia-induced cardiomyopathy. Most patients report palpitations with an abrupt onset, similar to other forms of PSVT. Patients with underlying cardiac pathology (eg, CHD) can present with dyspnea or angina. Close inspection of the P wave on 12-lead ECG suggests a focus away from the sinus node, although certain locations (eg, high right atrial crista terminalis) may mimic sinus tachycardia. In this situation, the abrupt onset and offset of the arrhythmia are helpful in distinguishing atrial from sinus tachycardia, although electrophysiologic study is sometimes necessary.

Treatment

Initial management of atrial tachycardia is similar to other types of PSVT; however, vagal maneuvers and intravenous adenosine are generally less effective. Intravenous beta-blockers or calcium channel blockers can be given in the hemodynamically stable patient with a transition to oral formulations for long-term management. Antiarrhythmic medications or catheter ablation should be considered in patients who continue to have symptomatic episodes. Long-term anticoagulation is not indicated in the absence of coexistent atrial fibrillation or atrial flutter.

For patients with multifocal atrial tachycardia, treatment of the underlying condition (eg, COPD) is paramount; verapamil, 240–480 mg orally daily in divided doses, may be effective in some patients.

When to Refer

All patients with atrial tachycardia in whom initial medical management fails should be referred to a cardiologist or cardiac electrophysiologist.

VENTRICULAR PREMATURE BEATS (Ventricular Extrasystoles)

ESSENTIALS OF DIAGNOSIS

- Common but rarely symptomatic.
- Ambulatory ECG monitoring to quantify daily burden of PVCs.
- Asymptomatic patients with > 10% PVC burden should have periodic echocardiogram to exclude development of LV dysfunction.

General Considerations

Ventricular premature beats, or **PVCs,** are isolated beats typically originating from the outflow tract or His-Purkinje regions of ventricular tissue. In most patients, the presence of PVCs is a benign finding; however, they rarely may trigger ventricular tachycardia or ventricular fibrillation, especially in patients with underlying heart disease.

Clinical Findings

Patients may be asymptomatic or experience palpitations, dizziness, or vague chest pain. Some patients feel the irregular beat; however, symptoms can often be secondary to post-PVC augmentation of contractility or a post-PVC compensatory pause. Increase in the sinus rate with exercise generally abolishes premature beats in normal hearts. PVCs are characterized by wide QRS complexes that differ in morphology from the patient's normal beats. They are usually not preceded by a P wave, although retrograde ventriculoatrial conduction may occur. **Bigeminy** and **trigeminy** are arrhythmias in which every second or third beat is premature. Ambulatory ECG monitoring may reveal more frequent and complex PVCs than occur in a single routine ECG. An increased frequency of PVCs during exercise is associated with a higher risk of cardiovascular mortality and should be investigated further.

Treatment

If no associated cardiac disease is present and if the ectopic beats are asymptomatic, no therapy is indicated. Mild symptoms or anxiety from palpitations may be allayed with reassurance to the patient of the benign nature of this arrhythmia. If PVCs are frequent (bigeminal or trigeminal pattern) or multifocal, electrolyte abnormalities (ie, hypo- or hyperkalemia and hypomagnesemia) and occult cardiac disease (ie, ischemic heart disease or LV dysfunction) should be excluded. In addition, an echocardiogram should be performed in patients in whom a burden of PVCs of greater than 10,000 per day has been documented by ambulatory ECG monitoring. Pharmacologic treatment is indicated only for patients who are symptomatic or who develop cardiomyopathy thought to be due to a high burden of PVCs (generally greater than 10% of daily heart beats). Beta-blockers or nondihydropyridine calcium channel blockers are appropriate as first-line therapy. The class I and III antiarrhythmic agents (see Table 12–1) may be effective in reducing PVCs but are often poorly tolerated and can be proarrhythmic in up to 5% of patients. Catheter ablation is a well-established therapy for symptomatic individuals who do not respond to medication or for those patients whose burden of ectopic beats has resulted in a cardiomyopathy.

When to Refer

Patients with symptomatic PVCs who do not respond to initial medical management or asymptomatic patients with daily PVC burden greater than 10% on ambulatory ECG monitoring should be referred to a cardiologist or cardiac electrophysiologist.

VENTRICULAR TACHYCARDIA

ESSENTIALS OF DIAGNOSIS

- Fast, wide QRS complex on ECG.
- Associated with ischemic heart disease, particularly in older patients.
- In the absence of reversible cause, implantable cardioverter defibrillator (ICD) is recommended if meaningful life expectancy is > 1 year.

General Considerations

Ventricular tachycardia is defined as three or more consecutive ventricular premature beats. It is classified as either **nonsustained** (lasting less than 30 seconds and terminating spontaneously) or **sustained** with a heart rate greater than 100 beats/min. In individuals without heart disease, nonsustained ventricular tachycardia is generally associated with a benign prognosis. In patients with structural heart disease, nonsustained ventricular tachycardia is associated with an increased risk of subsequent symptomatic ventricular tachycardia and sudden death, especially when seen more than 48 hours after MI.

Ventricular tachycardia is a frequent complication of acute MI and dilated cardiomyopathy but may occur in chronic coronary disease, HCM, myocarditis, and in most other forms of myocardial disease. It can also be a consequence of atypical forms of cardiomyopathies, such as arrhythmogenic RV cardiomyopathy. However, idiopathic ventricular tachycardia can also occur in patients with structurally normal hearts. **Accelerated idioventricular rhythm** is a regular wide-complex rhythm with a rate of 60–120 beats/min, usually with a gradual onset. It occurs commonly in acute infarction and following reperfusion with thrombolytic medications. Treatment is not indicated unless there is hemodynamic compromise or more serious arrhythmias. **Torsades de pointes,** a form of ventricular tachycardia in which the QRS morphology twists around the baseline, may occur in the setting of severe hypokalemia, hypomagnesemia, or in the setting of a prolonged QT interval (inherited or medication-induced).

Clinical Findings

A. Symptoms and Signs

Patients commonly experience palpitations, dyspnea, or lightheadedness, but on rare occasion may be asymptomatic. Syncope or cardiac arrest can be presenting symptoms in patients with underlying cardiac disease or other severe comorbidities. Episodes may be triggered by exercise or emotional stress.

B. Diagnostic Studies

Comprehensive blood laboratory work should be performed because ventricular tachycardia *can occur in the setting of hypokalemia and hypomagnesemia*. Cardiac markers may be elevated when ventricular tachycardia presents in the setting of acute MI or as a consequence of underlying CAD and demand ischemia. In patients with sustained, hemodynamically tolerated ventricular tachycardia, a 12-lead ECG during tachycardia should be obtained. Cardiac evaluation with echocardiography or cardiac MRI, ambulatory ECG monitoring, and exercise testing may be warranted depending on the clinical situation. Survivors of cardiac arrest or life-threatening

ventricular arrhythmia should be evaluated for ischemic heart disease (CT or invasive coronary angiography) and undergo revascularization when appropriate.

There is generally no role for invasive electrophysiologic study in patients with sustained ventricular tachycardia who otherwise meet criteria for ICD. In patients with structural heart disease and syncope of unknown cause, or in situations in which the mechanism of wide-complex tachycardia is uncertain, electrophysiologic study may provide important information.

C. Differentiation of Aberrantly Conducted Supraventricular Beats from Ventricular Beats

The distinction on 12-lead ECG of ventricular tachycardia from SVT with aberrant conduction may be difficult in patients with a wide-complex tachycardia; it is important because of the differing prognostic and therapeutic implications of each type. Findings favoring a **ventricular origin** include: (1) AV dissociation; (2) a QRS duration exceeding 0.14 second; (3) sinus capture or fusion beats; (4) left axis deviation with right bundle branch block morphology; (5) monophasic (R) or biphasic (qR, QR, or RS) complexes in V_1; and (6) a qR or QS complex in V_6. **Supraventricular origin** is favored by: (1) a typical right or left bundle branch block morphology; (2) QRS duration less than 0.14 second; and (3) the presence of preexcitation syndrome by history or on prior ECG. *Patients with a wide-complex tachycardia, especially those with known cardiac disease, should be presumed to have ventricular tachycardia if the diagnosis is unclear.*

Treatment

A. Initial Management

The treatment of acute ventricular tachycardia is determined by the degree of hemodynamic compromise and the duration of the arrhythmia. In patients with structurally normal hearts, the prognosis is generally benign and syncope is uncommon. The etiology is often triggered activity from the RV or LV outflow tract, and immediate treatment with a short-acting intravenous beta-blocker or verapamil may terminate the episode.

In the presence of known or suspected structural heart disease, assessment of hemodynamic stability determines the need for urgent direct current cardioversion. When ventricular tachycardia causes hypotension, HF, or myocardial ischemia, immediate synchronized direct current cardioversion with 100–200 J should be performed. If ventricular tachycardia recurs, intravenous amiodarone (150-mg bolus followed by 1 mg/min infusion for 6 hours and then 0.5 mg/min for 18 hours) should be administered to achieve a stable rhythm with further attempts at cardioversion as necessary. Significant hypotension can occur with rapid infusions of amiodarone.

In patients with sustained ventricular tachycardia who are hemodynamically stable, medical treatment with intravenous amiodarone, lidocaine, or procainamide can be used; however, direct current cardioversion should be performed if the ventricular tachycardia fails to terminate or symptoms worsen. Empiric magnesium replacement (1–2 g intravenously) may help, especially for polymorphic ventricular tachycardia. If polymorphic ventricular tachycardia recurs, increasing the heart rate with isoproterenol infusion (up to 20 mcg/min) or atrial pacing with a temporary pacemaker (at 90–120 beats/min) will effectively shorten the QT interval to prevent further episodes. In patients with polymorphic ventricular tachycardia in the setting of a normal QT interval, myocardial ischemia should be considered with prompt evaluation and coronary revascularization performed as indicated.

B. Long-Term Management

Patients with symptomatic or sustained ventricular tachycardia in the absence of a reversible precipitating cause (acute MI or ischemia, electrolyte imbalance, medication toxicity, etc) are at high risk for recurrence. In patients with structurally normal hearts and ventricular tachycardia with typical outflow tract (left bundle branch block with inferior axis) or left posterior fascicle (right bundle branch block with superior axis) appearance on ECG, suppressive treatment with beta-blocker or a nondihydropyridine calcium channel blocker may be tried. Catheter ablation has a high success rate in these patients who fail initial medical treatment. In patients with significant LV dysfunction, subsequent sudden death is common and ICD implantation is recommended if meaningful survival is expected to be longer than 1 year. Beta-blockers are the mainstay for medical treatment of ventricular tachycardia in patients with structural heart disease. Antiarrhythmic medications (eg, amiodarone or sotalol) have *not* been shown to lower mortality in these patients but may decrease subsequent episodes and reduce the number of ICD shocks. Catheter ablation is an important treatment option for those patients with recurrent tachycardia who do not respond to or are intolerant of medical therapy. Owing to the potential side effects from long-term antiarrhythmic use, catheter ablation may be considered as a first-line treatment especially for patients with ischemic cardiomyopathy.

When to Refer

Any patient with sustained ventricular tachycardia or syncope of unknown cause in the presence of underlying structural cardiac disease.

Arenal Á et al. 2022 Substrate ablation vs antiarrhythmic drug therapy for symptomatic ventricular tachycardia. J Am Coll Cardiol. 2022;79:1441. [PMID: 35422240]

VENTRICULAR FIBRILLATION & SUDDEN DEATH

ESSENTIALS OF DIAGNOSIS

- Most patients with SCD have underlying CHD.
- In the absence of reversible cause, ICD is recommended.

General Considerations

SCD is defined as unexpected nontraumatic death in clinically well or stable patients who die within 1 hour after onset of symptoms. *The causative rhythm in most cases is ventricular fibrillation.* **Sudden cardiac arrest** is a term reserved for the successful resuscitation of patients with ventricular fibrillation, either spontaneously or via intervention (defibrillation).

Clinical Findings

Approximately 70% of cases of SCD are attributable to underlying CHD; in up to 40% of patients, SCD may be the initial manifestation of CHD. In patients younger than 35, most cases of SCD are caused by inherited heart disease (long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, HCM, arrhythmogenic RV cardiomyopathy, dilated cardiomyopathy). Over the age of 35, CHD is the most common cause of SCD, although inherited causes are common up until the age of 50. Noninherited forms of heart disease can also lead to SCD, including valvular heart disease (aortic stenosis, pulmonic stenosis), congenital heart disease, and myocarditis. Prompt evaluation to exclude reversible causes of sudden cardiac arrest should begin immediately following resuscitation. Laboratory testing should be performed to exclude severe electrolyte abnormalities (particularly hypokalemia and hypomagnesemia) and acidosis and to evaluate cardiac biomarkers. Caution should be taken in attributing cardiac arrest solely to an electrolyte disturbance, however, because laboratory abnormalities may be secondary to resuscitation and not causative of the event. A 12-lead ECG should be performed to evaluate for ongoing ischemia or conduction system disease. Ventricular function should be evaluated with echocardiography. Evaluation for ischemic heart disease (CT or coronary angiography) should be performed to exclude coronary disease as the underlying cause, since revascularization may prevent recurrence. In the absence of coronary disease, contrast-enhanced cardiac MRI may be used to evaluate for the presence of myocardial scar, which is a strong predictor of recurrent ventricular tachycardia/ventricular fibrillation in patients with nonischemic cardiomyopathy.

Treatment

Unless ventricular fibrillation occurs shortly after MI, is associated with ischemia, or is seen with a correctable process (such as an electrolyte abnormality or medication toxicity), surviving patients require intervention since recurrences are frequent. Survivors of cardiac arrest have improved long-term outcomes if a **targeted temperature management protocol** is rapidly initiated and continued for 24–36 hours after cardiac arrest.

Patients who survive sudden cardiac arrest have a high incidence of recurrence, so an **ICD** is generally indicated. Sudden cardiac arrest in the setting of acute ischemia or infarct should be managed with prompt coronary revascularization. However, implantation of a prophylactic ICD in patients immediately after MI is associated with a trend toward *worse* outcomes. These patients may be managed with a **wearable cardioverter defibrillator** until recovery of ventricular function can be assessed by echocardiogram at a later date (6–12 weeks following MI or coronary intervention). In patients in whom ventricular function remains low (EF less than or equal to 35%), a permanent subcutaneous ICD (when pacing is not required) or transvenous ICD should be implanted.

When to Refer

All survivors of sudden cardiac arrest should be referred to a cardiologist or cardiac electrophysiologist.

INHERITED ARRHYTHMIA SYNDROMES

ESSENTIALS OF DIAGNOSIS

- Includes long QT syndrome, Brugada syndrome, arrhythmogenic RV cardiomyopathy, and catecholaminergic polymorphic ventricular tachycardia.
- Genetic testing for patients with suspected congenital long QT syndrome based on family history, ECG or exercise testing, or severely prolonged QT interval (greater than 500 msec) on serial ECGs.
- Patients with long QT syndrome or catecholaminergic polymorphic ventricular tachycardia should be treated long term with an oral beta-blocker (nadolol or propranolol).
- ICD is indicated for patients with ventricular arrhythmia or syncope despite medical treatment.

General Considerations

Inherited arrhythmia syndromes may result in life-threatening ventricular arrhythmias due to gene mutations in cardiac channels resulting in abnormal electrolyte regulation across the cardiac cell membrane. **Congenital long QT syndrome** is an uncommon disease (1 in 2500 live births) that is characterized by a long QT interval (usually greater than 470 msec) and ventricular arrhythmia, typically polymorphic ventricular tachycardia. **Acquired long QT syndrome** is usually secondary to use of antiarrhythmic agents (sotalol, dofetilide), methadone, antidepressant medications, or certain antibiotics; electrolyte abnormalities; myocardial ischemia; or significant bradycardia. **Brugada syndrome** accounts for up to 20% of SCD in the absence of structural heart disease and is most often due to a defect in a sodium channel gene. **Arrhythmogenic RV cardiomyopathy** is an inherited cardiomyopathy that predominantly affects the RV and is characterized by areas of myocardial replacement with fibrosis and adipose tissue that frequently causes ventricular arrhythmia. **Catecholaminergic polymorphic ventricular tachycardia** is a rare but important cause of SCD associated with exercise.

Clinical Findings

Patients with an inherited arrhythmia syndrome have a variable clinical presentation; they may be asymptomatic or have palpitations, sustained tachyarrhythmia, syncope, or sudden cardiac arrest. In young patients, syncopal episodes may be misdiagnosed as a primary seizure disorder. Personal and family history should be thoroughly reviewed in all patients. A 12-lead ECG should be performed with careful attention to any abnormality in the ST segment, T wave, and QT interval. A corrected QT interval longer than 500 msec on serial ECGs in the absence of a secondary cause (medication or electrolyte abnormality) identifies a high-risk subset of patients with long QT syndrome. Ambulatory ECG monitoring may be used to evaluate for ventricular arrhythmias as well as dynamic changes to the QT interval or T wave. Exercise ECG testing may be performed in patients with suspected long QT syndrome to assess for lack of appropriate QT interval shortening with higher heart rates. In cases where the cause of sudden cardiac arrest is suspected to be heritable, genetic testing under the guidance of a multidisciplinary genetics team is recommended to both determine the diagnosis and to facilitate the identification of first-degree family members at risk for developing the same disease.

Treatment

Management of polymorphic ventricular tachycardia (torsades de pointes) that occurs in the setting of a long QT interval differs from that of other forms of ventricular tachycardia. Class Ia or III antiarrhythmics, which prolong the QT interval, should be avoided—or withdrawn immediately if being used in patients with long QT syndrome. Intravenous beta-blockers may be effective in treating electrical storm due to long QT syndrome or catecholaminergic polymorphic ventricular tachycardia. Increasing the heart rate, whether by infusion of beta-agonist (dopamine or isoproterenol) or temporary atrial or ventricular pacing, is an effective approach that can both break and prevent the rhythm.

Long-term treatment of patients with inherited arrhythmia syndromes depends on the presence of high-risk features. Use of beta-blockers (particularly propranolol or nadolol) is the mainstay of treatment for patients with long QT syndrome or catecholaminergic polymorphic ventricular tachycardia. Surgical cervicothoracic sympathectomy should be considered for patients who do not respond to or are intolerant of beta-blockers. There is no reliable medication therapy for Brugada syndrome and prevention of arrhythmias focuses on prompt treatment of exacerbating triggers, particularly fever. Antiarrhythmic medications should be avoided in patients with inherited arrhythmia syndromes except for specific identified genetic abnormalities under the direction of a specialist. ICD implantation is generally recommended for patients with an inherited arrhythmia syndrome in whom sudden cardiac arrest is the initial presentation. An ICD should be considered in patients with recurrent sustained ventricular arrhythmias or syncope despite medical therapy.

When to Refer

Any patient with known or suspected inherited arrhythmia syndrome or with severe corrected QT interval prolongation (greater than 500 msec on serial ECGs) should be referred to a cardiologist or cardiac electrophysiologist.

Stiles MK et al. 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. Heart Rhythm. 2021;18:e1. [PMID: 33091602]

SYNCOPE

ESSENTIALS OF DIAGNOSIS

- Transient loss of consciousness and postural tone from vasodepressor or cardiogenic causes with prompt recovery without resuscitative measures.
- High-risk features include history of structural heart disease, abnormal ECG, and age greater than 60 years.

General Considerations

Syncope is a symptom defined as a transient, self-limited loss of consciousness, usually leading to a fall. Thirty percent of the adult population will experience at least one episode of syncope. It accounts for approximately 3% of emergency department visits. A specific cause of syncope is identified in about half of cases during the initial evaluation. The prognosis is relatively favorable except when accompanying cardiac disease is present. In many patients with recurrent syncope or near syncope, arrhythmias are not the cause. This is particularly true when the patient has no evidence of associated heart disease by history, examination, standard ECG, or noninvasive testing. The history is the most important component of the evaluation to identify the cause of syncope.

Reflex (neurally mediated) syncope may be due to excessive vagal tone or impaired reflex control of the peripheral circulation. The most frequent type is **vasovagal syncope** or the "common faint," which is often initiated by a stressful, painful, or claustrophobic experience. Enhanced vagal tone with resulting hypotension is the cause of syncope in **carotid sinus hypersensitivity** and **postmicturition syncope;** vagal-induced sinus bradycardia, sinus arrest, and AV block are common accompaniments and may themselves be the cause of syncope.

Orthostatic (postural) hypotension is another common cause of vasodepressor syncope, especially in older adult patients; in patients with diabetes or others with autonomic neuropathy; in patients with blood loss or hypovolemia; and in patients taking vasodilators, diuretics, and adrenergic-blocking medications. In addition, a syndrome of **chronic idiopathic orthostatic hypotension** exists primarily in older men. In most of these conditions,

the normal vasoconstrictive response to assuming upright posture, which compensates for the abrupt decrease in venous return, is impaired.

Cardiogenic syncope can occur on a mechanical or arrhythmic basis. There is usually no prodrome; thus, injury secondary to falling is common. Mechanical problems that can cause syncope include aortic stenosis (where syncope may occur due to the inability of the heart to adequately increase stroke volume in circumstances of increased peripheral demand), pulmonary stenosis, HCM, congenital lesions associated with pulmonary hypertension or right-to-left shunting, and left atrial myxoma obstructing the mitral valve. Episodes are commonly exertional or postexertional. More commonly, cardiac syncope is due to disorders of automaticity (sick sinus syndrome), conduction disorders (AV block), or tachyarrhythmias (especially ventricular tachycardia and SVT with rapid ventricular rate).

Clinical Findings

A. Symptoms and Signs

Vasovagal syncope often has a prodrome of **vasodepressor premonitory symptoms**, such as nausea, diaphoresis, tachycardia, and pallor. Episodes can be aborted by lying down or removing the inciting stimulus. Cardiogenic syncope by contrast is characteristically abrupt in onset, often resulting in injury, transient (lasting for seconds to a few minutes), and followed by prompt recovery of full consciousness. In orthostatic (postural) hypotension, a greater than normal decline (20 mm Hg) in BP immediately upon arising from the supine to the standing position is observed, with or without tachycardia depending on the status of autonomic (baroreceptor) function.

B. Diagnostic Tests

The evaluation for syncope depends on findings from the history and physical examination (especially orthostatic BP evaluation, auscultation of carotid arteries, and cardiac examination).

1. ECG—A resting ECG is recommended for all patients undergoing evaluation for syncope. High-risk findings on ECG include non-sinus rhythm, complete or partial left bundle branch block, and voltage criteria indicating LVH. Patients with a normal initial evaluation, including unremarkable history and physical, absence of cardiac disease or significant comorbidities and normal baseline ECG may not need further testing. When initial evaluation suggests a possible cardiac arrhythmia, continuous ambulatory ECG monitoring, event recorder (for infrequent episodes), or a wearable or implantable cardiac monitor can be considered. *Caution is required before attributing a patient's syncopal event to rhythm or conduction abnormalities observed during monitoring without concomitant symptoms.* For instance, dizziness or syncope in older patients may be unrelated to incidentally observed bradycardia, sinus node abnormalities, or ventricular ectopy.

2. Autonomic testing—Tilt-table testing may be useful in patients with suspected vasovagal syncope where the diagnosis is unclear after initial evaluation, especially when syncope is recurrent. The hemodynamic response to tilting determines whether there is a *cardioinhibitory*, *vasodepressor*, or *mixed* response. The overall utility of the test is improved when there is a high pretest probability of neurally mediated syncope, since the sensitivity and specificity of the test in the general population are only moderate.

3. Electrophysiologic studies—Electrophysiologic study has limited role in the evaluation of syncope, particularly in patients without structural heart disease or when there is a low suspicion for arrhythmic etiology. In patients with ischemic heart disease, LV dysfunction, known conduction disease, or arrhythmia, electrophysiologic study may help elucidate the mechanism of syncope and guide treatment decisions. The diagnostic yield in patients with structural heart disease is approximately 50%.

Treatment

In patients with vasovagal syncope, treatment consists largely of education on the benign nature of the condition and counseling to avoid predisposing situations. **Counterpressure maneuvers** (squatting, leg-crossing, abdominal contraction) can be helpful in limiting or terminating episodes. Medical therapy is reserved for patients with symptoms despite these measures. Midodrine is an alpha-agonist that can increase peripheral vasoconstriction and decrease venous pooling during vasovagal episodes and has been shown to reduce the frequency of syncopal episodes in small randomized trials. Fludrocortisone and beta-blockers have also been used but generally provide minimal benefit. SSRIs have shown some benefit in select patients. There is generally no role for permanent pacemaker implantation in patients with vasovagal syncope, with the possible exception of patients older than age 40 years with prolonged (longer than 3 seconds), symptomatic episodes of asystole documented on ambulatory monitoring. Pacemaker implantation based solely upon tilt-table–induced asystolic (cardioinhibitory) response is rarely indicated. Catheter ablation of ganglionated plexi (cardioneuroablation) in patients with vasovagal syncope with significant cardioinhibitory response significantly decreased recurrent syncope compared to medical therapy in a small RCT. Future trials will help understand the role of cardioneuroablation in the broader management of vasovagal syncope.

If symptomatic bradyarrhythmias or supraventricular tachyarrhythmias are detected and felt to be the cause of syncope, therapy can usually be initiated without additional diagnostic studies. **Permanent pacing** is indicated in patients with cardiogenic syncope and documented severe pauses (greater than 3 seconds), bradycardia, or high-degree AV block (second-degree Mobitz type II or complete heart block) when symptoms are correlated to the arrhythmia.

An important consideration in patients who have experienced syncope, symptomatic ventricular tachycardia, or aborted sudden death is to provide recommendations concerning **automobile driving restrictions**. Patients with syncope thought to be due to temporary factors (acute MI,

bradyarrhythmias subsequently treated with permanent pacing, medication effect, electrolyte imbalance) should be advised after recovery not to drive for at least 1 week. Patients with symptomatic ventricular tachycardia or aborted sudden death, whether treated pharmacologically, with an ICD, or with ablation therapy, warrant longer driving restriction (3–6 months). Significant variability in legal restrictions exists depending on region, and providers should be familiar with their local driving laws and restrictions and advise patients accordingly.

When to Refer

- Patients with syncope and underlying structural heart disease, documented arrhythmia, or conduction disturbance.
- Unclear etiology of syncope with high-risk features (HF, abnormal ECG findings, advanced age, multiple unexplained episodes).

Systemic Hypertension

Michael Sutters, MD, MRCP (UK)

13

INTRODUCTION

Based on the National Health and Nutrition Examination Survey period 2017–2020, 32.9% of adults in the United States meet the traditional criteria of having hypertension (blood pressure greater than 140/90 mm Hg or being treated for hypertension). An estimated 79% of people with hypertension defined in this way are aware of the diagnosis. Ninety-one percent of those aware of the diagnosis are receiving antihypertensive treatment. Blood pressure is controlled below 140/90 mmHg in only 48% of those receiving antihypertensive therapy. Cardiovascular morbidity and mortality increase as both systolic and diastolic blood pressures rise, but in individuals over age 50 years, the systolic pressure and pulse pressure are better predictors of complications than diastolic pressure. The prevalence of hypertension increases with age. Adequate blood pressure control reduces the incidence of ACS by 20–25%, stroke by 30–35%, and HF by 50%.

HOW IS BLOOD PRESSURE MEASURED & HYPERTENSION DIAGNOSED?

Blood pressure should be measured with a well-calibrated sphygmomanometer. The bladder width within the cuff should encircle at least 80% of the arm circumference. Readings should be taken after the patient has been resting comfortably, back supported in the sitting or supine position, for at least 5 minutes and at least 30 minutes after smoking cigarettes or coffee ingestion. Blood pressure readings made in the office with devices that permit multiple automated measurements after a pre-programmed rest period produce data that are independent of digit preference bias (tendency to favor numbers that end with zero or five) and avoid the "white coat" phenomenon (where blood pressure is elevated in the clinic but normal at home). Blood pressure measurements taken outside the office environment, either by intermittent self-monitoring (home blood pressure) or with an automated device programmed to take measurements at regular intervals (ambulatory blood pressure), are more powerful predictors of outcomes and are advocated in clinical guidelines.

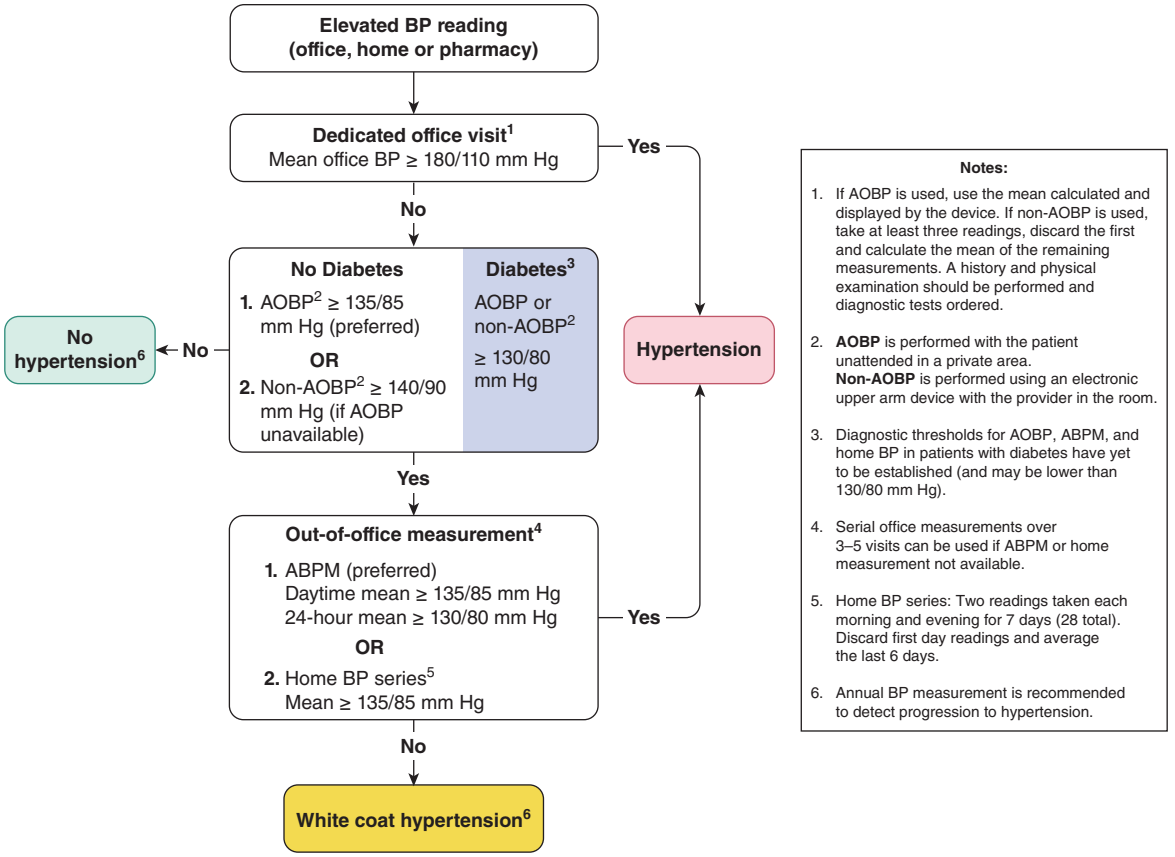
A single elevated blood pressure reading is not sufficient to establish the diagnosis of hypertension. The major exceptions to this rule are hypertension presenting with unequivocal evidence of life-threatening end-organ damage, as seen in hypertensive emergency, or, in the absence of life-threatening end organ injury, when blood pressure is greater than 220/125 mm Hg. In less severe cases, the diagnosis of hypertension depends on a series of measurements of blood pressure since readings can vary and tend to regress toward the mean with time. Patients whose initial blood pressure is in the hypertensive range exhibit the greatest fall toward the normal range between the first and second encounters. However, the concern for diagnostic precision needs to be balanced by an appreciation of the importance of establishing the diagnosis of hypertension as quickly as possible since a 3-month delay in treatment of hypertension in high-risk patients is associated with a two-fold increase in cardiovascular morbidity and mortality. The 2017 guidelines from the American College of Cardiology and American Heart Association (ACC/AHA) (based on conventional office-based measurements) contain the following definitions:

Normal blood pressure < 120/80 mm Hg
Elevated blood pressure 120–129/< 80 mm Hg
Stage 1 hypertension 130–139/80–89 mm Hg
Stage 2 hypertension ≥ 140/90 mm Hg.

As exemplified by Hypertension Canada's guidelines (Figure 13–1), automated and home blood pressure measurements have assumed greater prominence in the diagnostic algorithms published by many national hypertension workgroups. Equivalent blood pressures for these different modes of measurement are described in Table 13–1. Home blood pressure measurements can provide reliable data; the measurements should be done twice daily (morning and evening) over 3 successive days. Obtain blood pressure after a 5-minute rest; two readings separated by 1 minute should be averaged.

Blood pressure is normally lowest at night and the loss of this nocturnal dip is a dominant predictor of cardiovascular risk, particularly risk of thrombotic stroke. An accentuation of the normal morning increase in blood pressure is associated with increased likelihood of cerebral hemorrhage.

It is important to recognize that patients in whom hypertension is diagnosed do not automatically require drug treatment; this decision depends on the clinical setting and evaluation of cardiovascular risk.



▲ **Figure 13–1.** According to these recommendations, if AOBP measurements are not available, blood pressures recorded manually in the office may be substituted if taken as the mean of the last two readings of three consecutive readings. Note that the blood pressure threshold for diagnosing hypertension is higher if recorded manually in these guidelines. If home blood pressure monitoring is unavailable, office measurements recorded over three to five separate visits can be substituted. ABPM, ambulatory blood pressure measurement; AOBP, automated office blood pressure; BP, blood pressure. (Reproduced with permission from Leung AA, Daskalopoulou SS, Dasgupta K, et al. Hypertension Canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. Can J Cardiol. 2017;33(5):557–576.)

White Coat, Masked, & Labile Hypertension

The term "white coat" hypertension applies to patients whose blood pressure is elevated in the office but normal at home. Cardiovascular risk in white coat hypertension is elevated but less so than in established hypertension. Masked hypertension describes the opposite situation, where blood pressure is normal in the office setting but elevated at home. "Masked" hypertension is associated with a cardiovascular risk at least as high as in established hypertension. Variability of systolic blood pressure, often described as labile hypertension, predicts cardiovascular events independently of mean systolic blood pressure.

Table 13–1. Corresponding blood pressure values across a range of blood pressure measurement methods.

Manual Measurement in Clinic[1]	Home Blood Pressure Measurement	Ambulatory Blood Pressure Measurement (Daytime)	Ambulatory Blood Pressure Measurement (Nighttime)	Ambulatory Blood Pressure Measurement (24-Hour)
120/80 mm Hg	120/80 mm Hg	120/80 mm Hg	100/65 mm Hg	115/75 mm Hg
130/80 mm Hg	130/80 mm Hg	130/80 mm Hg	110/65 mm Hg	125/75 mm Hg
140/90 mm Hg	135/85 mm Hg	135/85 mm Hg	120/70 mm Hg	130/80 mm Hg
160/100 mm Hg	145/90 mm Hg	145/90 mm Hg	140/85 mm Hg	145/90 mm Hg

[1]Clinic manual blood pressures are critically dependent on technique. The use of automated devices in an unattended setting typically result in systolic blood pressures 9–13 mm Hg lower than clinic manual pressures. Data abstracted from Greenland P et al. The New 2017 ACC/AHA Guidelines "up the pressure" on diagnosis and treatment of hypertension. JAMA. 2017;318:2083.

Filippone EJ et al. Controversies in Hypertension I: the optimal assessment of blood pressure load and implications for treatment. Am J Med. 2022;135:1043. [PMID: 35636476]

APPROACH TO HYPERTENSION

Etiology & Classification

A. Primary Essential Hypertension

Primary essential hypertension describes the hypertension in 95% of patients with hypertension. This elevated blood pressure results from complex interactions between multiple genetic and environmental factors. The onset is usually between ages 25 and 50 years; it is uncommon before age 20 years. The best understood pathways underlying hypertension include overactivation of the sympathetic nervous and renin-angiotensin-aldosterone systems (RAAS), blunting of the pressure-natriuresis relationship, variation in cardiovascular and renal development, and elevated intracellular sodium and calcium levels.

Exacerbating factors include obesity, sleep apnea, increased salt intake, excessive alcohol use, polycythemia, NSAID therapy, and low potassium intake. Coffee and cigarette smoking may cause a transient increase in blood pressure but do not seem to be associated with sustained elevations. Obesity is associated with an increase in intravascular volume; elevated cardiac output; activation of the renin-angiotensin system; and, probably, increased sympathetic outflow. Lifestyle-driven weight reduction lowers blood pressure modestly, but the dramatic weight reduction following bariatric surgery results in improved blood pressure in most patients, and actual remission of hypertension in 20–40% of cases. In patients with sleep apnea, treatment with continuous positive airway pressure (CPAP) has been associated with improvements in blood pressure. Increased salt intake probably elevates blood pressure in some individuals so dietary salt restriction is recommended in patients with hypertension. Excessive use of alcohol also raises blood pressure, perhaps by increasing plasma catecholamines. Hypertension can be difficult to control in patients who consume more than 40 g of ethanol (two drinks) daily or drink in "binges." Cigarette smoking raises blood pressure by increasing plasma norepinephrine. Although the long-term effect of smoking on blood pressure is less clear, the synergistic effects of smoking and high blood pressure on cardiovascular risk are well documented. The relationship of exercise to hypertension is variable. Aerobic exercise lowers blood pressure in previously sedentary individuals, but increasingly strenuous exercise in already active subjects has less effect. The relationship between stress and hypertension is not established. Polycythemia, whether primary, drug-induced, or due to diminished plasma volume, increases blood viscosity and may raise blood pressure. NSAIDs produce increases in blood pressure averaging 5 mm Hg and are best avoided in patients with borderline or elevated blood pressures. Low potassium intake is associated with higher blood pressure in some patients; an intake of 90 mmol/day is recommended.

The complex of abnormalities termed the **"metabolic syndrome"** (upper body obesity, insulin resistance, and hypertriglyceridemia) is associated with both the development of hypertension and an increased risk of adverse cardiovascular outcomes. Affected patients usually also have low HDL cholesterol levels and elevated catecholamines and inflammatory markers such as CRP.

B. Secondary Hypertension

Approximately 5% of patients have hypertension secondary to identifiable specific causes (Table 13–2). Secondary hypertension should be suspected in patients in whom hypertension develops at an early age or after the age of 50 years, and in those previously well controlled who become refractory to treatment. Hypertension resistant to maximum doses of three medications is another clue, although multiple medications are usually required to control hypertension in persons with diabetes.

1. Genetic causes—Hypertension can be caused by pathogenic variants in single genes, inherited on a Mendelian basis. Although rare, these conditions provide important insight into blood pressure regulation and possibly the

Table 13–2. Causes of secondary hypertension.

Renal
Parenchymal kidney disease
Polycystic kidney disease
Systemic sclerosis (scleroderma)
Page kidney (subcapsular compression of the kidney)
Variants in genes encoding ion transport proteins
Vascular
Renal artery stenosis
Coarctation
Endocrine
Conn syndrome (hyperaldosteronism)
Licorice
Cushing syndrome (hypercortisolism)
Thyroid disease
Pheochromocytoma
Acromegaly
Variants in steroid gene regulatory domains
Hypercalcemia
Autonomic
Neurogenic
Medications
NSAIDs
Corticosteroids
Calcineurin inhibitors
Stimulants
Decongestants
Angiogenesis inhibitors
Tyrosine kinase inhibitors
Estrogen
Erythropoietin
Alcohol, cocaine
Gemcitabine
Atypical antipsychotics
MAO inhibitors
Other
Obstructive sleep apnea
Pregnancy

genetic basis of primary essential hypertension. Glucocorticoid remediable aldosteronism is an autosomal dominant cause of early-onset hypertension with normal or high aldosterone and low renin levels. The syndrome of hypertension exacerbated in pregnancy is inherited as an autosomal dominant trait. In these patients, a variant of the mineralocorticoid receptor makes it abnormally responsive to progesterone and, paradoxically, to spironolactone. Liddle syndrome is an autosomal dominant condition characterized by early-onset hypertension, hypokalemic alkalosis, low renin, and low aldosterone levels. Gordon syndrome, or pseudohypoaldosteronism type II, is most often transmitted in an autosomal dominant pattern and presents with early-onset hypertension associated with hyperkalemia, metabolic acidosis, and relative suppression of aldosterone.

2. Kidney disease—Renal parenchymal disease is the most common cause of secondary hypertension. Blood pressure is elevated in CKD due to increased intravascular volume, increased activity of the RAAS, and activation of the sympathetic nervous system.

3. Renal vascular hypertension—Renal artery stenosis is present in 1–2% of patients with hypertension. The most common cause is atherosclerosis, but fibromuscular dysplasia should be suspected in women younger than 50 years. Excessive renin release occurs due to reduction in renal perfusion pressure, while attenuation of pressure natriuresis contributes to hypertension in patients with a single kidney or bilateral lesions.

Renal vascular hypertension should be suspected in the following circumstances: (1) documented onset is before age 20 or after age 50 years, (2) hypertension is resistant to three or more drugs, (3) there are epigastric or renal artery bruits, (4) there is atherosclerotic disease of the aorta or peripheral arteries (15–25% of patients with symptomatic lower limb atherosclerotic vascular disease have renal artery stenosis), (5) there is an abrupt increase (more than 25%) in the serum creatinine after administration of ACE inhibitors, or (6) episodes of pulmonary edema are associated with abrupt surges in blood pressure. (See Renal Artery Stenosis, Chapter 24.)

4. Primary hyperaldosteronism—Increased aldosterone secretion from an adrenal adenoma or bilateral adrenal hyperplasia is the most common remediable cause of secondary hypertension.

Hyperaldosteronism should be considered in patients with resistant hypertension, blood pressures consistently greater than 150/100 mm Hg, hypokalemia (although this is often absent), or adrenal incidentaloma, and in those with a family history of hyperaldosteronism. Mild hypernatremia and metabolic alkalosis also may occur. Aldosterone plays an important but underrecognized role in hypertension. Estimates of the prevalence of hyperaldosteronism far exceed the rate at which cases are identified. Excess aldosterone results in significant damage to multiple organ systems, not just by the increased blood pressure but by direct effects that induce myocardial and renal fibrosis and stiffen the arterial wall. A secretory adrenal adenoma is potentially cured by adrenalectomy. When unregulated aldosterone secretion occurs from both adrenals or when adrenalectomy is not feasible, the actions of aldosterone can be blocked, at least partially, by aldosterone-receptor blockers (eg, spironolactone, eplerenone) and amiloride. Novel nonsteroidal mineralocorticoid receptor antagonists and aldosterone synthase inhibitors hold promise for even more comprehensive reversal of the effects of aldosterone.

Most cases of primary hyperaldosteronism lack the classic clinical features. Conventional screening tests relying on spot plasma aldosterone measurements often fail to detect excessive aldosterone secretion because of the episodic releaser of aldosterone from the adrenal gland. Some experts suggest measuring 24-hour urinary aldosterone excretion in patients who newly present with hypertension and have plasma renin levels below 1 ng/mL (8 mU/L); according to this approach the presence of primary hyperaldosteronism is suggested when total urinary aldosterone excretion exceeds 12 mcg/24 h. In patients with established hypertension on treatment, a decline in systolic blood pressure of more than 10 mm Hg after a 4-week trial of spironolactone is indicative of aldosterone-dependent hypertension.

5. Cushing syndrome—Hypertension occurs in about 80% of patients with spontaneous Cushing syndrome. Excess glucocorticoid may act through salt and water retention (via mineralocorticoid effects), increased angiotensinogen levels, or permissive effects in the regulation of vascular tone. Diagnosis and treatment of Cushing syndrome are discussed in Chapter 28.

6. Pheochromocytoma—Pheochromocytomas are discussed in Chapter 28. They are found in less than 0.1% of all patients with hypertension and in approximately two individuals per million population. Chronic vasoconstriction of the arterial and venous beds leads to a reduction in plasma volume and predisposes to postural hypotension. Glucose intolerance develops in some patients. Hypertensive crisis in pheochromocytoma may be precipitated by a variety of drugs, including tricyclic antidepressants, antidopaminergic agents, metoclopramide, and naloxone.

7. Coarctation of the aorta—This uncommon cause of hypertension is discussed in Chapter 10. Evidence of radial-femoral delay should be sought in all younger patients with hypertension.

8. Hypertension associated with pregnancy—Hypertension occurring de novo or worsening during pregnancy, including preeclampsia and eclampsia, is one of the most common causes of maternal and fetal morbidity and mortality (see Chapter 21). Autoantibodies with the potential to activate the angiotensin II type 1 receptor have been causally implicated in preeclampsia, in resistant hypertension, and in progressive systemic sclerosis.

9. Estrogen use—A small increase in blood pressure occurs in most women taking oral contraceptives. A more significant increase of 8/6 mm Hg systolic/diastolic is noted in about 5% of women, mostly in obese individuals older than age 35 who have been treated for more than 5 years. This is caused by increased hepatic

synthesis of angiotensinogen. The lower dose of postmenopausal estrogen does not generally cause hypertension but rather maintains endothelium-mediated vasodilation.

10. Other causes of secondary hypertension—Hypertension has been associated with hypercalcemia, acromegaly, hyperthyroidism, hypothyroidism, baroreceptor dysfunction (sometimes seen after treatment of head and neck cancer), compression of the ventrolateral medulla, and increased intracranial pressure. Certain medications may cause or exacerbate hypertension—most importantly cyclosporine, tacrolimus, angiogenesis inhibitors, and erythrocyte-stimulating agents (such as erythropoietin). Decongestants, NSAIDs, cocaine, and alcohol should also be considered. Over-the-counter products should not be overlooked.

When to Refer

Referral to a hypertension specialist should be considered in cases of severe, resistant, or early-/late-onset hypertension or when secondary hypertension is suggested by screening.

Bhalla V et al; American Heart Association Council on the Kidney in Cardiovascular Disease; Council on Hypertension; Council on Peripheral Vascular Disease; and Council on Cardiovascular Radiology and Intervention. Revascularization for renovascular disease: a scientific statement from the American Heart Association. Hypertension. 2022;79:e128. [PMID: 35708012]

Funder JW. Primary aldosteronism: three strikes and out. Hypertension. 2021;77:900. [PMID: 33566688]

Singh V et al. Monogenic etiology of hypertension. Med Clin North Am. 2024;108:157. [PMID: 37951648]

Complications of Untreated Hypertension

Elevated blood pressure results in structural and functional changes in the vasculature and heart. Many adverse outcomes in hypertension are associated with thrombosis rather than bleeding, possibly because increased vascular shear stress converts the normally anticoagulant endothelium to a prothrombotic state. The excess morbidity and mortality related to hypertension approximately doubles for each 6 mm Hg increase in diastolic blood pressure. Target-organ damage varies markedly between individuals with similar levels of office hypertension; home and ambulatory pressures are superior to office readings in the prediction of end-organ damage.

A. Hypertensive Cardiovascular Disease

Cardiac complications are the major causes of morbidity and mortality in primary (essential) hypertension. For any level of blood pressure, LVH is associated with incremental cardiovascular risk in association with HF (through systolic or diastolic dysfunction), ventricular arrhythmias, myocardial ischemia, and sudden death.

The occurrence of HF is reduced by 50% with antihypertensive therapy. Hypertensive LVH regresses with therapy and is most closely related to the degree of systolic blood pressure reduction. Diuretics have produced equal or greater reductions of LV mass when compared with other drug classes. Conventional beta-blockers are less effective in reducing LVH but play a specific role in patients with established CAD or impaired LV function.

B. Hypertensive Cerebrovascular Disease and Dementia

Hypertension is the major predisposing cause of hemorrhagic and ischemic stroke. Cerebrovascular complications are more closely correlated with the degree of elevation of systolic rather than diastolic blood pressure. The incidence of these complications is markedly reduced by antihypertensive therapy. Preceding hypertension is associated with a higher incidence of subsequent dementia of both vascular and Alzheimer types. Home and ambulatory blood pressure may be a better predictor of cognitive decline than office readings in older people. Effective blood pressure control reduces the risk of cognitive dysfunction developing later in life.

C. Hypertensive Kidney Disease

Chronic hypertension is associated with injury to vascular, glomerular, and tubulointerstitial compartments within the kidney. Nephrosclerosis is particularly prevalent in persons of sub-Saharan African ancestry, in whom susceptibility is linked to *APOL1* variants in which case hypertension results from kidney disease rather than causing it.

D. Aortic Dissection

Hypertension is a contributing factor in many patients with dissection of the aorta. Its diagnosis and treatment are discussed in Chapter 14.

E. Atherosclerotic Complications

Most Americans with hypertension die of complications of atherosclerosis, but the impact of antihypertensive therapy on atherosclerotic complications is less clear than that seen in the prevention of HF, stroke, and kidney disease. Prevention of cardiovascular outcomes related to atherosclerosis probably requires control of multiple risk factors, of which hypertension is only one.

Supiano MA et al. New guidelines and SPRINT results: implications for geriatric hypertension. Circulation. 2019;140:976. [PMID: 31525101]

Clinical Findings

The clinical and laboratory findings of hypertension arise from involvement of the target organs: heart, brain, kidneys, eyes, and peripheral arteries.

A. Symptoms

Mild to moderate primary essential hypertension is largely asymptomatic for many years. The most frequent symptom, headache, is nonspecific. A patient's belief that they can feel when their blood pressure is elevated is a barrier to effective home blood pressure monitoring.

The classification of the more urgent presentations of hypertension has been reduced to two categories, uncontrolled hypertension and hypertensive emergency.

Uncontrolled hypertension is usually asymptomatic and typically presents as an incidental finding.

Hypertensive emergencies are defined as events where uncontrolled hypertension results in end-organ damage. Presenting symptoms will depend on the pattern of organ injury. Hypertensive encephalopathy is characterized by headache, somnolence, and vomiting that usually improve with prompt control of hypertension. The symptom complex associated with posterior reversible encephalopathy syndrome includes headache, seizures, altered consciousness, and disturbance of vision. Focal neurologic deficits indicate cerebral infarction or hemorrhage. Intracranial hemorrhage may be intraparenchymal, ventricular, or subarachnoid and is often felt as an abrupt onset of the worst headache ever experienced. Subarachnoid hemorrhage may cause loss of consciousness and neck stiffness.

Symptoms associated with acute elevation of LV afterload include angina and dyspnea. Aortic dissection or rupture causes chest or abdominal pain that is usually severe.

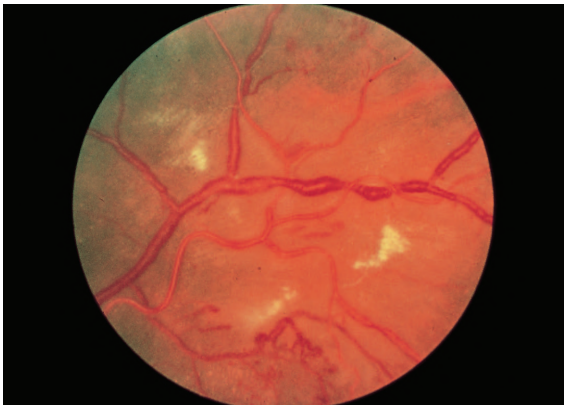
Hypertension in patients with pheochromocytomas that secrete predominantly norepinephrine is usually sustained but may be episodic. The typical attack lasts from minutes to hours and is associated with headache, anxiety, palpitation, profuse perspiration, pallor, tremor, and nausea and vomiting. Blood pressure is markedly elevated, and angina or acute pulmonary edema may occur. In primary aldosteronism, patients may have muscular weakness, polyuria, and nocturia due to hypokalemia; hypertensive emergency is rare. Chronic hypertension often leads to LVH and diastolic dysfunction, which can present with exertional and paroxysmal nocturnal dyspnea. Cerebral involvement in chronic hypertension manifests as stroke due to thrombosis or hemorrhage from microaneurysms of small penetrating intracranial arteries.

B. Signs

Like symptoms, physical findings depend on the cause of hypertension, its duration and severity, and the degree of effect on target organs.

1. Blood pressure—Blood pressure is taken in both arms and, if lower extremity pulses are diminished or delayed, in the legs to exclude coarctation of the aorta. If blood pressure differs between right and left arms, the higher reading should be recorded as the actual blood pressure and subclavian stenosis suspected in the other arm. An orthostatic drop of at least 20/10 mm Hg is often present in pheochromocytoma. Older patients may have falsely elevated readings by sphygmomanometry because of noncompressible vessels. This may be suspected in the presence of Osler sign—a palpable brachial or radial artery when the cuff is inflated above systolic pressure. Occasionally, it may be necessary to make direct measurements of intra-arterial pressure, especially in patients with apparent severe hypertension who do not tolerate therapy.

2. Retinas—Narrowing of arterial diameter to less than 50% of venous diameter, copper or silver wire appearance, exudates, hemorrhages, and hypertensive retinopathy are associated with a worse prognosis. The typical changes of severe hypertensive retinopathy are shown in Figure 13–2 (see Chapter 7).



▲ **Figure 13–2. Severe, chronic hypertensive retinopathy with hard exudates, increased vessel light reflexes, and sausage-shaped veins.** (Used, with permission, from Richard E. Wyszynski, MD, in Knoop KJ, Stack LB, Storrow AB, Thurman RJ. *The Atlas of Emergency Medicine,* 4th ed. McGraw-Hill, 2016.)

3. Heart—An LV heave indicates severe hypertrophy. Aortic regurgitation may be auscultated in up to 5% of patients, and hemodynamically insignificant aortic regurgitation can be detected by Doppler echocardiography in 10–20%. A presystolic (S_4) gallop due to decreased compliance of the LV is quite common in patients in sinus rhythm.

4. Pulses—Radial-femoral delay suggests coarctation of the aorta; loss of peripheral pulses occurs due to atherosclerosis, less commonly aortic dissection, and rarely Takayasu arteritis, all of which can involve the renal arteries.

C. Laboratory Findings

Recommended testing includes hemoglobin; serum electrolytes and serum creatinine; fasting blood sugar level (hypertension is a risk factor for the development of diabetes, and hyperglycemia can be a presenting feature of pheochromocytoma); plasma lipids (necessary to calculate cardiovascular risk and as a modifiable risk factor); serum uric acid (hyperuricemia is a relative contraindication to diuretic therapy); and UA.

D. ECG and CXR

Electrocardiographic criteria are highly specific but not very sensitive for LVH. The "strain" pattern of ST–T wave changes is a sign of more advanced disease and is associated with a poor prognosis. A CXR is not necessary in the workup of uncomplicated hypertension.

E. Echocardiography

The primary role of echocardiography should be to evaluate clinical symptoms or signs of cardiac disease.

F. Diagnostic Studies

Additional diagnostic studies are indicated only if the clinical presentation or routine tests suggest secondary or complicated hypertension. These may include 24-hour urine free cortisol, urine or plasma metanephrines, and plasma aldosterone and renin concentrations to screen for endocrine causes of hypertension. Renal ultrasound will detect structural changes (such as polycystic kidneys, asymmetry, and hydronephrosis); increased echogenicity and reduced cortical volume are reliable indicators of advanced CKD. Evaluation for renal artery stenosis should be undertaken in concert with subspecialist consultation.

G. Summary

Since most hypertension is essential or primary, few studies are necessary beyond those listed above. If conventional therapy is unsuccessful or if secondary hypertension is suspected, further studies and perhaps referral to a hypertension specialist are indicated.

Nonpharmacologic Therapy

Lifestyle modification is recommended for all patients with elevated blood pressure. In a study from China of persons older than 60 years or who had a history of stroke and hypertension, study participants were randomized to intake of ordinary salt or a salt substitute containing 75% sodium chloride and 25% potassium chloride (by mass). Those using the salt substitute had a 14% decline in the rate of the primary endpoint of stroke, and a roughly 12% decline in the secondary endpoints of cardiovascular events and all-cause mortality. A diet rich in fruits, vegetables, and low-fat dairy foods and low in saturated and total fats (DASH diet) has been shown to lower blood pressure. Increased dietary fiber lowers blood pressure. For every 7 g of dietary fiber ingested, cardiovascular risk could be lowered by 9%. The effect of diet on blood pressure may be mediated by shifts in the microbial species in the gut, the intestinal microbiota. Hand squeezing exercises three times a week can lower systolic blood pressure by 6 mm Hg. The protocol comprises four repeats of 2 minutes at 30% of maximum force (using a handheld dynamometer) with 1- to 3-minute rest intervals between squeezes. The acute increase in systolic blood pressure above resting systolic blood pressure during vigorous exercise, known as the exercise pressor response, is around 50 mm Hg in normal individuals. In persons with hypertension, the exercise pressor response is elevated to about 75 mm Hg. This exaggerated response is not reduced by antihypertensive medications, even in those with otherwise controlled hypertension, and is exacerbated by increased dietary sodium intake. The use of cell phone applications to support behavioral changes to lower blood pressure has shown efficacy in randomized studies. There is limited evidence on the long-term benefit of stress reduction strategies such as biofeedback, yoga, and mindfulness. The impact of a variety of dietary supplements (such as garlic extract and fish oil) upon long-term blood pressure control also is uncertain. The effects of a range of lifestyle changes upon blood pressure is listed in Table 13–3.

Table 13–3. The impact of lifestyle modifications.

Modification	Intervention	Resulting Decrease in Blood Pressure
Weight loss	Target BMI 18.5–24.9	5–20 mm Hg/ 10-kg loss
DASH diet	Fruit, vegetables, low-fat dairy	8–14 mm Hg
Sodium intake	< 100 mmol/day (< 6 g salt)	2–8 mm Hg
Alcohol intake	Male ≤ 2 drinks/day Female ≤ 1 drink/day	4 mm Hg
Exercise	Aerobic 30 minutes/day Dynamic 90–150 minutes/ week Isometric (hand grip 4 repetitions 3 times/ week)	5–10 mm Hg
Mindfulness	Meditation and breathing control	5 mm Hg

DASH, Dietary Approaches to Stop Hypertension.

Kario K et al. Digital therapeutics in hypertension: evidence and perspectives. Hypertension. 2022;79:2148. [PMID: 35726619]
Maniero C et al. Non-pharmacological factors for hypertension management: a systematic review of international guidelines. Eur J Prev Cardiol. 2023;30:17. [PMID: 35947982]
Neal B et al. Effect of salt substitution on cardiovascular events and death. N Engl J Med. 2021;385:1067. [PMID: 34459569]
Rodrigues GD et al. Are home-based exercises effective to reduce blood pressure in hypertensive adults? A systematic review. Clin Hypertens. 2022;28:28. [PMID: 36104807]

Who Should Be Treated with Medications?

Treatment should be offered to all persons in whom blood pressure reduction, irrespective of initial blood pressure levels, will reduce cardiovascular risk with an acceptably low rate of medication-associated adverse effects. The ACC/AHA, Hypertension Canada, and the European Society of Hypertension and European Society of Cardiology (ESH/ESC) have developed independent guidelines for the evaluation and management of hypertension. There is broad agreement that drug treatment is necessary in those with office-based blood pressures exceeding 160/100 mm Hg, irrespective of cardiac risk. Similarly, the American, Canadian, and European guidelines agree that treatment thresholds should be lower in the presence of elevated cardiovascular risk. American guidelines stand apart in recommending initiation of antihypertensive pharmacotherapy in those with blood pressure of 140–159/90–99 mm Hg, even if the 10-year risk for

Table 13–4. Comparison of blood pressure treatment thresholds from the 2017 ACC/AHA guidelines, the 2020 Hypertension Canada guidelines, and the 2018 ESH/ESC guidelines.

Guidelines[1]	Cardiovascular Risk	Threshold for Pharmacotherapy (mm Hg)	Target (mm Hg)
ACC/AHA	Not increased	> 140/90	< 130/80 (reasonable)
Hypertension Canada	Not increased	> 160/100	< 140/90 (< 130/80 for diabetes)
ESH/ESC	Not increased	> 140/90[2]	All < 140/90, most < 130/80, not < 120
ACC/AHA	Increased	< 130/80	< 130/80 (recommended)
Hypertension Canada	Increased	> 130 systolic[3]	< 120 systolic
ESH/ESC	Increased	> 130/80	120–130/< 80
ACC/AHA > 65 yr	Risk due to advanced age	> 130/80	< 130 systolic
Hypertension Canada age >75 yr)[4]	Not Increased[4]	< 130 systolic[4]	< 120 systolic
ESH/ESC > 65 yr	Not increased	> 140/90[5]	130–140/> 80[6]

[1]In the Hypertension Canada guidelines, blood pressure values are based on automated office blood pressure readings. ACC/AHA and ESH/ESC guidelines employ non-automated office blood pressure measurements.
[2]Consider drug treatment if lifestyle changes fail to control blood pressure.
[3]Consider drug treatment at systolic blood pressure > 130 mm Hg if very high risk, eg, established CVD, especially coronary disease.
[4]Recommendations for persons > 75 years are not explicitly stated in the Hypertension Canada guidelines. They removed separate goals for older adults but consider age > 75 years to be a risk signifier triggering an approach that many would view as overly aggressive in the extremely old.
[5]The European guidelines indicate a slightly more conservative treatment threshold of > 160/90 mm Hg for those > 80 years.
[6]This target range is also suggested in the European guidelines for patients > 80 years.
ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; ESH, European Society of Hypertension.

atherosclerotic CVD is less than 10% (https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/). By contrast, the Canadian guidelines suggest lifestyle modifications in this low-cardiovascular-risk group, while the European guidelines recommend initiation of pharmacotherapy only if elevated pressure in this low-risk population persists after lifestyle modification. The AHA has extended the European guidelines for the stepped management of patients at low cardiovascular risk to individuals with stage 1 hypertension (130–139/80–89 mm Hg), while acknowledging that there are no RCT data demonstrating that mortality or risk of cardiovascular events can be reduced by treating mild hypertension in low-risk individuals. Table 13–4 compares the US, Canadian, and European guidelines for the treatment of hypertension. Since evaluation of total cardiovascular risk (Table 13–5) is important in deciding who to treat with antihypertensive medications, risk calculators are essential clinical tools. The ACC has an online toolkit relevant to primary prevention (https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/), and an associated app called ASCVD Risk Estimator Plus (downloadable at https://www.acc.org/ASCVDApp). The interaction between risk and age deserves careful attention. At any given level of calculated risk, treatment is likely to have a greater impact in the young than in older adults. Consequently, setting absolute risk thresholds for treatment might lead to undertreatment of the young and overtreatment of older adults.

Table 13–5. Cardiovascular risk factors.

Major risk factors
Hypertension[1]
Cigarette smoking
Obesity (BMI ≥ 30)[1]
Physical inactivity
Dyslipidemia[1]
Diabetes mellitus[1]
Microalbuminuria or estimated GFR < 60 mL/min/1.73 m^2
Age (> 55 years for men, > 65 years for women)
Family history of premature CVD (< 55 years for men, < 65 years for women)
Target-organ damage
Heart
LVH
Angina or prior MI
Prior coronary revascularization
HF
Brain
Stroke or transient ischemic attack
CKD
Peripheral arterial disease
Retinopathy

[1]Components of the metabolic syndrome.
Data from Chobanian AV et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289:2560.

Goals of Treatment

Traditionally, the most widely accepted goal for blood pressure management has been less than 140/90 mm Hg. However, observational studies of untreated individuals suggest that there does not seem to be a blood pressure level below which decrements in cardiovascular risk taper off, and a number of RCTs have suggested that treatment to blood pressure targets considerably below 140 mm Hg may benefit certain patient groups.

The SPRINT study suggests that outcomes improve in nondiabetic patients with considerably elevated cardiovascular risk when treatment lowers systolic pressure to less than 120 mm Hg compared to less than 140 mm Hg. On the other hand, in the HOPE3 study of largely nondiabetic patients at somewhat lower risk than those in SPRINT, reducing blood pressure by an average of 6/3 mm Hg systolic/diastolic from a baseline of 138/82 mm Hg provided no significant outcomes benefits. Therefore, it appears that blood pressure targets should be lower in people at greater estimated cardiovascular risk. In response to the SPRINT study, the 2020 Hypertension Canada guidelines urge prescribers to consider a blood pressure goal of less than 120/80 mm Hg in patients considered at elevated risk for cardiovascular events. The 2017 ACC/AHA guidelines take a different approach by defining a 130/80–mm Hg goal as "reasonable" in patients without elevated risk hypertension, strengthening this to "recommended" in patients with elevated risk hypertension. The 2018 ESH/ESC guidelines specify a target of less than 140 mm Hg systolic for all, and less than 130 mm Hg for most if tolerated. Treatment targets in older adults are discussed below. Some experts note that manual office measurements of around 130/80 mm Hg are likely to approximate the lower blood pressure targets specified in the SPRINT study, which used automated office blood pressure measuring devices that have been demonstrated to read as much as 16/7 mm Hg lower than manual office readings. The Canadian guidelines acknowledge this disparity in measurement methods by specifying that automated office devices should be used in the monitoring of patients selected for the aggressive blood pressure goal of less than 120/80 mm Hg. Table 13–4 compares the treatment threshold and target recommendations laid out in the American, Canadian, and European guidelines.

Lowering systolic blood pressure to less than 130 mm Hg seems especially important in stroke prevention. The ACCORD study examined the effect of treatment of systolic pressures to below 130–135 mm Hg in patients with diabetes. In the original analysis, the lower blood pressure treatment goal significantly *increased* the risk of serious adverse effects (with no additional gain in terms of heart, kidney, or retinal disease). There was, however, significant additional *reduction* in the risk of stroke, indicating that lower blood pressure targets might be justified in patients with diabetes at high risk for cerebrovascular events. Results from the SPS3 trial of patients with a history of lacunar stroke were consistent with the ACCORD study, showing that treatment to a mean systolic blood pressure of 127 mm Hg vs 138 mm Hg reduced the risk of recurrent stroke. Blood pressure management in acute stroke is discussed below.

How Low to Go?

Although observational studies indicate that the blood pressure–risk relationship holds up at levels considerably below 120 mm Hg, there has been uncertainty about whether this is true for treated blood pressure. This question was addressed in a secondary analysis of data from the ONTARGET and TRANSCEND studies in which participants with elevated cardiovascular risk but no history of stroke were treated with telmisartan (plus or minus ramipril) or placebo. The risk of the composite cardiovascular endpoint was lowest at a treated systolic blood pressure range between 120 mm Hg and 140 mm Hg. Increased risk was observed at blood pressures below and above this range. The risk of stroke was the only exception, with incremental benefit observed below a treated systolic of 120 mm Hg. With respect to diastolic blood pressure on treatment, composite risk began to increase at levels below 70 mm Hg. This suggests that the blood pressure–cardiovascular risk relationship evident in observational studies of untreated hypertension may not hold in the case of treated blood pressure and that there are grounds for a degree of caution in treating below a systolic pressure of 120 mm Hg.

In seeking to simplify decision making in the treatment of hypertension, some authors have suggested that a systolic blood pressure goal in the 120–130 mm Hg range would be safe and effective in high-risk patients, and a systolic blood pressure of around 130 mm Hg would be reasonable in lower-risk patients, irrespective of diastolic pressures. Diastolic blood pressure will track with systolic blood pressure; the main concern about diastolic blood pressure is that treatment will lower it too much in patients who have wider pulse pressures. However, it seems that a lower diastolic blood pressure as a consequence of treatment does not negate the benefits of systolic blood pressure control, even though wider pulse pressures at baseline are associated with cardiovascular mortality. Notably, the risk attributable to lower diastolic blood pressure is likely related to myocardial ischemia, since it is mitigated by coronary reperfusion.

Treatment of Other Cardiovascular Risk Factors

Data from multiple studies indicate that statins should be part of the strategy to reduce overall cardiovascular risk. The HOPE3 study of persons at intermediate cardiovascular risk showed that 10 mg of rosuvastatin reduced average LDL cholesterol from 130 mg/dL to 90 mg/dL (3.36–2.33 mmol/L), and significantly reduced the risk of multiple cardiovascular events, including MI and coronary revascularization. Low-dose aspirin (81 mg/day) is no longer recommended in the primary prevention of MI or stroke. Low-dose aspirin is effective in prevention of recurrent cardiovascular events, but blood pressure should first be controlled to minimize the risk of cerebral hemorrhage. Despite modest effects on blood pressure, SGLT-2 blockers, nonsteroidal mineralocorticoid receptor antagonists, and GLP-1 agonists reduce cardiovascular risk through modulation of multiple pathways of injury.

Jones DW et al; American Heart Association Council on Hypertension; Council on the Kidney in Cardiovascular Disease; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Lifelong Congenital Heart Disease and Heart Health in the Young; and Stroke Council. Management of stage 1 hypertension in adults with a low 10-year risk for cardiovascular disease: filling a guidance gap: a scientific statement from the American Heart Association. Hypertension. 2021;77:e58. [PMID: 33910363]

Visseren FLJ et al; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur J Prev Cardiol. 2022;29:5. [PMID: 34558602]

DRUG THERAPY: CURRENT ANTIHYPERTENSIVE AGENTS

The specific classes of antihypertensive medications are discussed below.

A. Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors are commonly used as the initial medication in mild to moderate hypertension (Table 13–6). Their primary mode of action is inhibition of the RAAS, but they also inhibit bradykinin degradation, stimulate the synthesis of vasodilating prostaglandins, and can reduce sympathetic nervous system activity. ACE inhibitors appear to be more effective in younger White patients. They are relatively less effective in Black and older persons and in predominantly systolic hypertension. Although as single therapy they achieve adequate antihypertensive control in only about 40–50% of patients, the combination of an ACE inhibitor and a diuretic or calcium channel blocker is potent.

ACE inhibitors are the agents of choice in persons with type 1 diabetes with frank proteinuria or evidence of kidney dysfunction because they delay the progression to ESKD. Many authorities have expanded this indication to include persons with type 1 and type 2 diabetes mellitus with microalbuminuria who do not meet the usual criteria for antihypertensive therapy. ACE inhibitors may also delay the progression of nondiabetic kidney disease. The Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated that the ACE inhibitor ramipril reduced the number of cardiovascular deaths, nonfatal MIs, and nonfatal strokes and also reduced the incidence of new-onset HF, kidney dysfunction, and new-onset diabetes in a population of patients at high risk for vascular events. Although this was not specifically a hypertensive population, the benefits were associated with a modest reduction in blood pressure, and the results inferentially support the use of ACE inhibitors in similar hypertensive patients. ACE inhibitors are a drug of choice (usually in conjunction with a diuretic and a beta-blocker) in patients with HF with reduced EF and are indicated also in asymptomatic patients with reduced EF.

How to initiate therapy—Baseline serum potassium and creatinine levels should be measured prior to starting medications that interfere with the RAAS and repeated 1–2 weeks after initiation of therapy to detect hyperkalemia or disproportionate elevation of creatinine. Minor dose adjustments of these medications rarely trigger significant shifts in these values.

Side effects—An advantage of the ACE inhibitors is their relative freedom from troublesome side effects (Table 13–6). Severe hypotension can occur in patients with bilateral renal artery stenosis. An increase in serum creatinine of greater than 25% from baseline suggests volume contraction or renovascular disease and is usually reversible with discontinuation of the ACE inhibitor. Hyperkalemia may develop in patients with kidney disease and type IV renal tubular acidosis (commonly seen in patients with diabetes) and in older adults. A chronic dry cough is common, seen in 10% of patients or more, and may require stopping the drug. Skin rashes are observed with any ACE inhibitor. Angioedema is an uncommon but potentially dangerous side effect of all agents of this class because of their inhibition of kininase. Exposure of the fetus to ACE inhibitors during the second and third trimesters of pregnancy has been associated with a variety of defects due to hypotension and reduced renal blood flow.

B. Angiotensin II Receptor Blockers

ARBs can improve cardiovascular outcomes in patients with hypertension as well as in patients with HF and type 2 diabetes with nephropathy. ARBs have not been compared with ACE inhibitors in RCTs in patients with hypertension, but two trials comparing losartan with captopril in HF and post–MI LV dysfunction showed trends toward worse outcomes in the losartan group. By contrast, valsartan seems as effective as ACE inhibitors in these settings. Within group heterogeneity of antihypertensive potency and duration of action might explain such observations. The Losartan Intervention for Endpoints (LIFE) trial in nearly 9000 patients with hypertension and electrocardiographic evidence of LVH—comparing losartan with the beta-blocker atenolol as initial therapy—demonstrated a significant reduction in stroke with losartan. Of note is that in patients with diabetes, death and MI were also reduced. Treatment with losartan was also associated with a lower occurrence of new-onset diabetes.

In a subgroup analysis from the LIFE trial, atenolol appeared to be superior to losartan in African-American persons, while the opposite was the case in non–African-American persons. A similar reduced efficacy of lisinopril compared to diuretics and calcium channel blockers was observed in Black persons in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attach Trial (ALLHAT), suggesting that ACE inhibitors and ARBs may not be the preferred agents in Black patients (see Table 13–14). In the treatment of hypertension, combination therapy with an ACE inhibitor and an ARB is not advised because it increases the risk of CKD and hyperkalemia and offers no advantage over monotherapy at maximum dose with addition of a complementary class where necessary.

Side effects—Unlike ACE inhibitors, the ARBs rarely cause cough and are less likely to be associated with skin rashes or angioedema (Table 13–6). However, as seen with

Table 13–6. Antihypertensive drugs: renin and ACE inhibitors and ARBs.

Medication (Proprietary Name)	Oral Dosage	Adverse Effects	Comments
Renin Inhibitors			
Aliskiren (Tekturna)	*Initial:* 150 mg once daily *Range:* 150–300 mg once daily	Angioedema, hypotension, hyperkalemia. Contraindicated in pregnancy.	Probably metabolized by CYP3A4. Absorption is inhibited by high-fat meal.
Aliskiren and HCTZ (Tekturna HCT)	*Initial:* 150 mg/12.5 mg once daily *Range:* 150 mg/12.5 mg–300 mg/25 mg once daily		
ACE Inhibitors			
Benazepril (Lotensin)	*Initial:* 10 mg once daily *Range:* 5–40 mg in 1 or 2 doses	Cough, hypotension, dizziness, hyperkalemia, kidney dysfunction, angioedema; taste alteration and rash (may be more frequent with captopril); rarely, proteinuria, blood dyscrasia. Contraindicated in pregnancy.	More fosinopril is excreted by the liver in patients with kidney dysfunction (dose reduction may or may not be necessary). Captopril and lisinopril are active without metabolism. Captopril, enalapril, lisinopril, and quinapril are approved for HF.
Benazepril and HCTZ (Lotensin HCT)	*Initial:* 5 mg/6.25 mg once daily *Range:* 5 mg/6.25 mg–20 mg/25 mg		
Benazepril and amlodipine (Lotrel)	*Initial:* 10 mg/2.5 mg once daily *Range:* 10 mg/2.5 mg–40 mg/10 mg		
Captopril (Capoten)	*Initial:* 6.25–25 mg two to three times daily *Range:* 50–150 mg in 2 or 3 doses		
Captopril and HCTZ (Capozide)	*Initial:* 25 mg/15 mg twice daily *Range:* 25 mg/15 mg–50 mg/25 mg		
Enalapril (Vasotec)	*Initial:* 5 mg once daily *Range:* 5–40 mg in 1 or 2 doses		
Enalapril and HCTZ (Vaseretic)	*Initial:* 5 mg/12.5 mg once daily *Range:* 5 mg/12.5 mg–20 mg/50 mg		
Fosinopril (Monopril)	*Initial:* 10 mg once daily *Range:* 10–80 mg once daily		
Fosinopril and HCTZ (Monopril-HCT)	*Initial:* 10 mg/12.5 mg once daily *Range:* 10 mg/12.5 mg–80 mg/50 mg		
Lisinopril (Prinivil, Zestril)	*Initial:* 5–10 mg once daily *Range:* 5–40 mg once daily		
Lisinopril and HCTZ (Prinzide or Zestoretic)	*Initial:* 10 mg/12.5 mg once daily *Range:* 10 mg/12.5 mg–80 mg/50 mg		
Moexipril (Univasc)	*Initial:* 3.75–7.5 mg once daily *Range:* 7.5–30 mg in 1 or 2 doses		
Perindopril (Aceon)	*Initial:* 4 mg once daily *Range:* 4–16 mg once daily		
Perindopril and amlodipine (Prestalia)	*Initial:* 3.5 mg/2.5 mg once daily *Range:* 3.5 mg/2.5–14 mg/10 mg once daily		
Quinapril (Accupril)	*Initial:* 10–20 mg once daily *Range:* 10–80 mg in 1 or 2 doses		
Quinapril and HCTZ (Accuretic)	*Initial:* 10 mg/12.5 mg once daily *Range:* 10 mg/12.5 mg–20 mg/25 mg		
Ramipril (Altace)	*Initial:* 2.5 mg once daily *Range:* 2.5–20 mg in 1 or 2 doses		
Trandolapril (Mavik)	*Initial:* 1 mg once daily *Range:* 1–4 mg once daily		
Trandolapril and verapamil (Tarka)	*Initial:* 2 mg/180 mg SR once daily *Range:* 2 mg/180 mg SR–4 mg/240 mg SR		

(*continued*)

Table 13–6. Antihypertensive drugs: renin and ACE inhibitors and ARBs. (continued)

Medication (Proprietary Name)	Oral Dosage	Adverse Effects	Comments
ARBs			
Azilsartan (Edarbi)	*Initial:* 40 mg once daily *Range:* 40–80 mg once daily	Hyperkalemia, kidney dysfunction, rare angioedema. Combinations have additional side effects. Contraindicated in pregnancy.	Losartan has a flat dose-response curve. Valsartan and irbesartan have wider dose-response ranges and longer durations of action. Addition of low-dose diuretic (separately or as combination pills) increases the response.
Azilsartan and chlorthalidone (Edarbychlor)	*Initial:* 40 mg/12.5 mg once daily *Range:* 40 mg/12.5–40 mg/25 mg once daily		
Candesartan cilexetil (Atacand)	*Initial:* 8 mg once daily *Range:* 8–32 mg once daily		
Candesartan cilexetil and HCTZ (Atacand HCT)	*Initial:* 16 mg/12.5 mg once daily *Range:* 32 mg/12.5 mg once daily		
Eprosartan (Teveten)	*Initial:* 600 mg once daily *Range:* 400–800 mg in 1–2 doses		
Irbesartan (Avapro)	*Initial:* 150 mg once daily *Range:* 150–300 mg once daily		
Irbesartan and HCTZ (Avalide)	*Initial:* 150 mg/12.5 mg once daily *Range:* 150 mg/12.5 mg–300 mg/25 mg once daily		
Losartan and HCTZ (Hyzaar)	*Initial:* 50 mg/12.5 mg once daily *Range:* 50 mg/12.5 mg–100 mg/25 mg once daily		
Olmesartan (Benicar)	*Initial:* 20 mg once daily *Range:* 20–40 mg once daily		
Olmesartan and HCTZ (Benicar HCT)	*Initial:* 20 mg/12.5 mg once daily *Range:* 20 mg/12.5 mg–40 mg/25 mg once daily		
Olmesartan and amlodipine (Azor)	*Initial:* 20 mg/5 mg once daily *Range:* 20 mg/5 mg–40 mg/10 mg		
Olmesartan and amlodipine and HCTZ (Tribenzor)	*Initial:* 20 mg/5 mg/12.5 mg once daily *Range:* 20 mg/5 mg/12.5 mg–40 mg/10 mg/25 mg once daily		
Telmisartan (Micardis)	*Initial:* 20–40 mg once daily *Range:* 20–80 mg once daily		
Telmisartan and HCTZ (Micardis HCT)	*Initial:* 40 mg/12.5 mg once daily *Range:* 40 mg/12.5 mg–80 mg/25 mg once daily		
Telmisartan and amlodipine (Twynsta)	*Initial:* 40 mg/5 mg once daily *Range:* 40 mg/5 mg–80 mg/10 mg once daily		
Valsartan (Diovan)	*Initial:* 80 mg once daily *Range:* 80–320 mg once daily		
Valsartan and HCTZ (Diovan HCT)	*Initial:* 80 mg/12.5 mg once daily *Range:* 80 mg/12.5 mg–320 mg/25 mg once daily		
Valsartan and amlodipine (Exforge)	*Initial:* 160 mg/5 mg once daily *Range:* 160 mg/5 mg–320 mg/10 mg once daily		
Other Combination Products			
Amlodipine and valsartan and HCTZ (Exforge HCT)	*Initial:* 5 mg/160 mg/12.5 mg once daily *Range:* 5 mg/160 mg/12.5 mg–10 mg/320 mg/25 mg once daily		

HCTZ, hydrochlorothiazide; SR, sustained release.

ACE inhibitors, problematic hyperkalemia can occur, and patients with bilateral renal artery stenosis may exhibit hypotension and worsened kidney function. Olmesartan has been linked to a sprue-like syndrome, presenting with abdominal pain, weight loss, and nausea, which subsides upon drug discontinuation. There is evidence from an observational study suggesting that ARBs and ACE inhibitors are less likely to be associated with depression than calcium channel blockers and beta-blockers.

C. Renin Inhibitors

Since renin cleavage of angiotensinogen is the rate-limiting step in the renin-angiotensin cascade, the most efficient inactivation of this system would be expected with renin inhibition. Conventional ACE inhibitors and ARBs probably offer incomplete blockade, even in combination. Aliskiren, a renin inhibitor, binds the proteolytic site of renin, thereby preventing cleavage of angiotensinogen. Aliskiren effectively lowers blood pressure, reduces albuminuria, and limits LVH, but it has yet to be established as a first-line drug since large-scale prospective trial data are lacking. The combination of aliskiren with ACE inhibitors or ARBs in persons with type 2 diabetes mellitus offers no advantage and might even increase the risk of adverse cardiac or renal consequences.

D. Calcium Channel Blocking Agents

These agents act by causing peripheral vasodilation but with less reflex tachycardia and fluid retention than other vasodilators (Table 13–7). They are effective as single-drug therapy in approximately 60% of patients in all demographic groups and all grades of hypertension (Table 13–8). For these reasons, they may be preferable to beta-blockers and ACE inhibitors in Black and older persons. Verapamil and diltiazem should be combined cautiously with beta-blockers because of their potential for depressing atrioventricular (AV) conduction and sinus node automaticity as well as contractility.

Calcium channel blockers are equivalent to ACE inhibitors and thiazide diuretics in prevention of CHD, major cardiovascular events, cardiovascular death, and total mortality. A protective effect against stroke with calcium channel blockers is well established, and in two trials (ALLHAT and the Systolic Hypertension in Europe trial), these agents appeared to be more effective than diuretic-based therapy.

Side effects—The most common side effects of calcium channel blockers are headache, peripheral edema, bradycardia, and constipation (especially with verapamil in older adults) (Table 13–8). The dihydropyridine agents—nifedipine, nicardipine, isradipine, felodipine, nisoldipine, and amlodipine—are more likely to produce symptoms of vasodilation, such as headache, flushing, palpitations, and peripheral edema. Edema is minimized by coadministration of an ACE inhibitor or ARB. Calcium channel blockers have negative inotropic effects and should be used cautiously in patients with cardiac dysfunction. Amlodipine is the only calcium channel blocker with established safety in patients with severe HF.

E. Diuretics

Thiazide diuretics (Table 13–9) are the antihypertensives that have been most extensively studied and most consistently effective in clinical trials. They lower blood pressure initially by decreasing plasma volume, but during long-term therapy, their major hemodynamic effect is reduction of peripheral vascular resistance. Most of the antihypertensive effect of these agents is achieved at lower dosages (typically, 12.5 mg of hydrochlorothiazide or equivalent), but their biochemical and metabolic effects are dose related. Chlorthalidone has the advantage of better 24-hour blood pressure control than hydrochlorothiazide in clinical trials. Thiazides may be used at higher doses if plasma potassium is above 4.5 mmol/L. The loop diuretics (such as furosemide) may lead to electrolyte and volume depletion more readily than the thiazides and have short durations of action. Because of these adverse effects, loop diuretics should be reserved for use in patients with kidney dysfunction (serum creatinine greater than 2.5 mg/dL [208.3 mcmol/L]; estimated eGFR less than 30 mL/min/1.73 m^2) in which case they are more effective than thiazides at controlling excess volume. However, results from the CLICK study demonstrated that the

Table 13–7. Special properties of calcium channel blockers.

Medication	Peripheral Vasodilation	Cardiac Automaticity and Conduction	Contractility
Amlodipine	+++	↓/0	↓/0
Amlodipine and atorvastatin	+++	↓/0	↓/0
Diltiazem	++	↓↓	↓↓
Felodipine	+++	↓/0	↓/0
Isradipine	+++	↓/0	↓
Nicardipine	+++	↓/0	↓
Nifedipine			
Nisoldipine	+++	↓/0	↓
Verapamil	++	↓↓↓	↓↓↓

Table 13–8. Antihypertensive drugs: calcium channel blocking agents.

Medication (Proprietary Name)	Oral Dosages	Adverse Effects	Comments
Nondihydropyridine Agents			
Diltiazem		Edema, headache, bradycardia, bloating and constipation, dizziness, AV block, HF, urinary frequency.	Also approved for angina
(Cardizem SR)	*Initial:* 90 mg SR twice daily *Range:* 180–360 mg SR in 2 doses		
(Cardizem CD)	*Initial:* 180 mg ER once daily *Range:* 180–360 mg ER once daily		
(Cartia XT)	*Initial:* 180 or 240 mg ER once daily *Range:* 180–480 mg ER once daily		
(Dilt-XR)	*Initial:* 180 or 240 mg ER once daily *Range:* 180–540 mg ER once daily		
(Taztia XT)	*Initial:* 120 or 180 mg ER once daily *Range:* 120–540 mg ER once daily		
(Tiazac)	*Initial:* 120 or 240 mg ER once daily *Range:* 120–540 mg ER once daily		
Verapamil		Same as diltiazem but more likely to cause constipation and HF.	Also approved for angina and arrhythmias
(Calan)	*Initial:* 40 mg three times daily *Range:* 120–480 mg in 3 divided doses		
(Calan SR)	*Initial:* 120 mg ER once daily *Range:* 120–480 mg ER in 1 or 2 doses		
(Verelan)	*Initial:* 120 or 240 mg ER once daily *Range:* 240–480 mg ER once daily		
(Verelan PM)	*Initial:* 100 or 200 mg ER once daily at bedtime *Range:* 100–400 mg ER once daily at bedtime		
Dihydropyridines			
Amlodipine (Norvasc)	*Initial:* 2.5 mg once daily *Range:* 2.5–10 mg once daily	Edema, dizziness, palpitations, flushing, headache, hypotension, tachycardia, bloating and constipation, urinary frequency.	Also approved for angina
Amlodipine and atorvastatin (Caduet)	*Initial:* 2.5 mg/10 mg once daily *Range:* 10 mg/80 mg once daily	Edema (amlodipine), myopathy and hepatotoxicity (atorvastatin).	Amlodipine approved for angina
Felodipine (Plendil)	*Initial:* 5 mg ER once daily *Range:* 5–10 mg ER once daily		
Isradipine (DynaCirc)	*Initial:* 2.5 mg twice daily *Range:* 2.5–5 mg twice daily		
Nicardipine (Cardene)	*Initial:* 20 mg three times daily *Range:* 20–40 mg three times daily		Also approved for angina
Nifedipine (Procardia XL)	*Initial:* 30 or 60 mg ER once daily *Range:* 30–120 mg ER once daily		Also approved for angina
Nisoldipine (Sular)	*Initial:* 17 mg daily *Range:* 17–34 mg daily		

SR, sustained release; ER, extended release.

antihypertensive effect of chlorthalidone was fully maintained in patients with eGFR 15–29 mL/min/1.73 m^2. Relative to beta-blockers and ACE inhibitors, diuretics are more potent in Black persons, older individuals, obese persons, and other subgroups with increased plasma volume or low plasma renin activity (or both). They are relatively more effective in persons who smoke cigarettes than in those who do not smoke. Long-term thiazide administration also mitigates the loss of bone mineral content in older women at risk for osteoporosis.

Overall, diuretics administered alone control blood pressure in 50% of patients with mild to moderate hypertension and can be used effectively in combination with all other agents, including SGLT-2 blockers. They are also useful for lowering isolated or predominantly systolic hypertension.

Table 13–9. Antihypertensive drugs: diuretics (in descending order of preference).

Medications (Proprietary Names)	Oral Doses	Adverse Effects	Comments
Thiazides and Related Diuretics			
Chlorthalidone (Thalitone)	*Initial:* 12.5 or 25 mg once daily *Range:* 12.5–50 mg once daily	↓K^+, ↓Mg^{2+}, ↑Ca^{2+}, ↓Na+, ↑uric acid, ↑glucose, ↑LDL cholesterol, ↑triglycerides; rash, erectile dysfunction.	Better 24-hour blood pressure control than HCTZ because of longer half-life.
Hydrochlorothiazide (HCTZ) (Esidrix, Microzide)	*Initial:* 12.5 or 25 mg once daily *Range:* 12.5–50 mg once daily		Low dosages effective in many patients without associated metabolic abnormalities.
Metolazone (Zaroxolyn)	*Initial:* 2.5–5 mg once daily *Range:* 1.25–20 mg in 1 or 2 divided doses		More effective with concurrent kidney disease.
Indapamide (Lozol)4	*Initial:* 2.5 mg once daily *Range:* 2.5–5 mg once daily		Does not alter serum lipid levels.
Bendroflumethiazide (Aprinox Neo-Naclex)	*Initial:* 2.5 mg once daily		Not available in United States.
Loop Diuretics			
Furosemide (Lasix)	*Initial:* 20 mg twice daily *Range:* 40–320 mg in 2 or 3 doses	Same as thiazides, but with higher risk of excessive diuresis and electrolyte imbalance. Increases calcium excretion.	Short duration of action a disadvantage; should be reserved for patients with kidney disease or fluid retention. Poor antihypertensive.
Ethacrynic acid (Edecrin)	*Initial:* 25–50 mg once daily *Range:* 50–400 mg once or twice daily		
Bumetanide (Bumex)	*Initial:* 0.25 mg twice daily *Range:* 0.5–10 mg in 2 or 3 doses		
Torsemide (Demadex)	*Initial:* 10–20 mg once daily *Range:* 10–100 mg once or twice daily		Effective blood pressure medication at low dosage.
Aldosterone Receptor Blockers			
Spironolactone (Aldactone)	*Initial:* 12.5 or 25 mg once daily *Range:* 12.5–100 mg once daily	Hyperkalemia, metabolic acidosis, gynecomastia.	Can be useful add-on therapy in patients with refractory hypertension.
Amiloride	*Initial:* 5 mg once daily *Range:* 5–10 mg in 1 or 2 divided doses		
Eplerenone (Inspra)	*Initial:* 25 mg once daily *Range:* 25–100 mg once daily		
Combination Products			
HCTZ and triamterene (Dyazide, Maxzide-25 [25/37.5 mg])	*Initial:* 25 mg/37.5 mg once daily *Range:* 25 mg/37.5 mg–50 mg/75 mg once daily	Same as thiazides plus GI disturbances, hyperkalemia rather than hypokalemia, headache; triamterene can cause kidney stones and kidney dysfunction; spironolactone causes gynecomastia. Hyperkalemia can occur if this combination is used in patients with advanced kidney disease or those taking ACE inhibitors.	Use should be limited to patients with demonstrable need for a potassium-sparing agent.
HCTZ and amiloride	*Initial:* 25 mg/2.5 mg once daily *Range:* 50 mg/5 mg–100 mg/10 mg once daily		
HCTZ and spironolactone (Aldactazide [25/25 mg; 50/50 mg])	*Initial:* 25 mg/25 mg once daily *Range:* 25 mg/25 mg–100 mg/100 mg once daily		

Side effects—The adverse effects of diuretics relate primarily to the metabolic changes listed in Table 13–9. Erectile dysfunction, skin rashes, and photosensitivity are less frequent. Hypokalemia has been a concern but is uncommon at the recommended dosages. The risk can be minimized by limiting dietary salt or increasing dietary potassium; potassium replacement is not usually required to maintain serum K^+ at greater than 3.5 mmol/L. Higher serum K^+ levels are prudent in patients at special risk from intracellular potassium depletion, such as those taking digoxin or with a history of ventricular arrhythmias, in which case a potassium-sparing agent could be used. Compared with ACE inhibitors and ARBs, diuretic therapy is associated with a slightly higher incidence of mild new-onset diabetes. Diuretics of all types can cause hyponatremia, but this side effect occurs most commonly with thiazides; the pathophysiology is complex and incompletely understood. Diuretics also increase serum uric acid and may precipitate gout. Increases in blood glucose, triglycerides, and LDL cholesterol may occur but are relatively minor during long-term low-dose therapy. The potential for worsening of diabetes is outweighed by the advantages of blood pressure control, and diuretics should not be withheld from patients with diabetes.

F. Mineralocorticoid Receptor Blockers

The steroidal mineralocorticoid receptor blockers spironolactone and eplerenone have reemerged in the treatment of hypertension, particularly in resistant hypertension, and are helpful additions to most other antihypertensive medications. Consistent with the importance of aldosterone in primary essential hypertension, the steroidal mineralocorticoid receptor blockers are effective at lowering blood pressure in Black persons and all other patients with hypertension regardless of renin level. Aldosterone plays a central role in target-organ damage, including the development of ventricular and vascular hypertrophy and renal and myocardial fibrosis. Mineralocorticoid receptor antagonists ameliorate these consequences of hypertension, to some extent independently of effects on blood pressure. This is especially true for the nonsteroidal mineralocorticoid receptor blocker finerenone, which significantly reduces the risk of cardiovascular and renal injury in persons with diabetes with only modest blood pressure lowering activity. Amiloride blocks aldosterone-mediated activation of the epithelial sodium channel, is useful in preventing diuretic-associated hypokalemia, and lowers blood pressure in hyperaldosteronism and resistant hypertension. Mineralocorticoid receptor blockers, and to a lesser extent amiloride, offer an alternative to adrenalectomy in primary hyperaldosteronism.

Side effects—Spironolactone can cause breast pain and gynecomastia in men through activity at the progesterone receptor, an effect not seen with the more specific eplerenone. Spironolactone is a weak androgen receptor agonist and should be avoided in patients with prostate cancer treated with androgen synthase inhibitors. Hyperkalemia is more likely if the pretreatment plasma potassium exceeds 4.5 mmol/L or eGFR is below 45 mL/min/1.73 m^2. Hyperkalemia is less pronounced with finerenone.

G. Beta-Blocking Agents

These drugs lower blood pressure by decreasing heart rate and cardiac output. The beta-blockers also decrease renin release and are more efficacious in populations with elevated plasma renin activity, such as younger White patients. Beta-blockers neutralize the reflex tachycardia caused by vasodilators and are useful in patients with associated conditions that benefit from the cardioprotective effects of these agents. These include individuals with angina pectoris, previous MI, persistent sinus tachycardia, and stable HF as well as those with migraine headaches and somatic manifestations of anxiety.

Although all beta-blockers appear to be similar in antihypertensive potency, they differ in pharmacologic properties (these differences are summarized in Tables 13–10 and 13–11), including specificity to the cardiac beta-1-receptors (cardioselectivity) and whether they block the beta-2-receptors in the bronchi and vasculature*; at higher dosages, however, all agents are nonselective.* The beta-blockers also differ in their pharmacokinetics, lipid solubility—which determines whether they cross the blood-brain barrier predisposing to CNS side effects—and route of metabolism. Metoprolol succinate reduces mortality and morbidity in patients with chronic stable HF with reduced EF (see Chapter 11). Carvedilol and nebivolol maintain cardiac output and are also beneficial in these patients. Carvedilol and nebivolol may reduce peripheral vascular resistance by concomitant alpha-blockade (carvedilol) and increased nitric oxide release (nebivolol). Because of the lack of efficacy in primary prevention of MI and inferiority compared with other drugs in prevention of stroke and LVH, traditional beta-blockers should not be used as first-line agents in the treatment of hypertension without specific compelling indications (such as active CAD).

Side effects—The side effects of beta-blockers include inducing or exacerbating bronchospasm in predisposed patients; sinus node dysfunction and AV conduction depression (resulting in bradycardia or AV block); nasal congestion; Raynaud phenomenon; and CNS symptoms with nightmares, excitement, depression, and confusion. Fatigue, lethargy, and erectile dysfunction may occur. The traditional beta-blockers (but not the vasodilator beta-blockers carvedilol and nebivolol) have an adverse effect on lipids and glucose metabolism. Beta-blockers are used cautiously in patients with type 1 diabetes since they can mask the symptoms of hypoglycemia and prolong these episodes by inhibiting gluconeogenesis. These drugs should also be used with caution in patients with advanced peripheral vascular disease associated with rest pain or nonhealing ulcers, but they are generally well tolerated in patients with mild claudication. Nebivolol can be safely used in patients with stage II claudication (claudication at 200 m).

In treatment of pheochromocytoma, beta-blockers should not be administered until alpha-blockade (eg, phentolamine) has been established. Otherwise, blockade of vasodilatory beta-2-adrenergic receptors will allow unopposed vasoconstrictor alpha-adrenergic–receptor activation with worsening of hypertension. *For the same reason, beta-blockers should not be used to treat hypertension arising from cocaine use.*

Table 13–10. Antihypertensive drugs: beta-blocking agents.

Medication (Proprietary Name)	Oral Dosage	Comments[1]
Acebutolol (Sectral)	*Initial:* 200–400 mg once daily *Range:* 200–1200 mg in 2 doses	Positive ANA; rare lupus-like syndrome; also indicated for arrhythmias. Doses > 800 mg have beta-1 and beta-2 effects.
Atenolol (Tenormin)	*Initial:* 25 mg once daily *Range:* 25–100 mg in 1 or 2 doses	Also indicated for angina and post-MI. Doses > 100 mg have beta-1 and beta-2 effects.
Atenolol/chlorthalidone (Tenoretic)	*Initial:* 50 mg/25 mg once daily *Range:* 50 mg/25 mg–100 mg/25 mg once daily	
Betaxolol (Kerlone)	*Initial:* 5–10 mg once daily *Range:* 10–20 mg once daily	
Bisoprolol (Zebeta)	*Initial:* 2.5–5 mg once daily *Range:* 5–20 mg once daily	Also effective for HF.
Bisoprolol and HCTZ (Ziac)	*Initial:* 2.5 mg/6.25 mg once daily *Range:* 2.5 mg/6.25 mg–10 mg/6.25 mg once daily	Low-dose combination approved for initial therapy.
Carvedilol (Coreg)	*Initial:* 6.25 mg twice daily *Range:* 12.5–25 mg twice daily	Alpha:beta blocking activity 1:9; may cause orthostatic symptoms; effective for HF. Nitric oxide potentiating vasodilatory activity.[2]
Carvedilol (Coreg CR)	*Initial:* 20 mg ER once daily *Range:* 20–80 mg ER once daily	
Labetalol (Trandate)	*Initial:* 100 mg twice daily *Range:* 200–2400 mg in 2 doses	Alpha:beta blocking activity 1:3; more orthostatic hypotension, fever, hepatotoxicity.
Metoprolol succinate (Toprol-XL [SR preparation])	*Initial:* 25 mg once daily *Range:* 25–400 mg once daily	Also indicated for angina. Approved for HF. Doses > 100 mg have beta-1 and beta-2 effects.
Metoprolol tartrate (Lopressor)	*Initial:* 50 mg twice daily *Range:* 50–200 mg twice daily	Also indicated for angina and post MI. Doses > 100 mg have beta-1 and beta-2 effects.
Metoprolol and HCTZ (Lopressor HCT)	*Initial:* 50 mg/12.5 mg twice daily *Range:* 50 mg/25 mg–200 mg/50 mg in single or divided doses	
Nadolol (Corgard)	*Initial:* 20 mg once daily *Range:* 20–320 mg once daily	
Nebivolol (Bystolic)	*Initial:* 5 mg once daily *Range:* 40 mg once daily	Nitric oxide potentiating vasodilatory activity.[2]
Pindolol (Visken)	*Initial:* 5 mg twice daily *Range:* 10–60 mg in 2 doses	In adults, 35% renal clearance.
Propranolol		
(Inderal)	*Initial:* 20 mg twice daily *Range:* 40–320 mg in 2 doses	Also indicated for angina and post-MI.
(Inderal LA)	*Initial:* 80 mg ER once daily *Range:* 120–320 mg ER once daily	
(InnoPran XL)	*Initial:* 80 mg ER once nightly *Range:* 80–120 mg ER once nightly	
Propranolol and HCTZ (generic)	*Initial:* 40 mg/25 mg twice daily *Range:* 40 mg/25 mg–80 mg/25 mg twice daily	
Timolol (generic)	*Initial:* 10 mg twice daily *Range:* 10–60 mg in 2 doses	Also indicated for post-MI; 80% hepatic clearance.

[1]Adverse effects of all beta-blockers: bronchospasm, fatigue, sleep disturbance and nightmares, bradycardia and atrioventricular block, worsening of HF, cold extremities, GI disturbances, erectile dysfunction, ↑ triglycerides, ↓ HDL cholesterol, rare blood dyscrasias.
[2]Carvedilol and nebivolol stimulate release of nitric oxide by vascular endothelium, which may augment the vasodilatory effects of drugs such as hydralazine and prazosin.
ER, extended release; HCTZ, hydrochlorothiazide; SR, sustained release.

Table 13–11. Special properties of beta-blocking agents.

Medication	Beta-1 Selectivity[1]	ISA[2]	MSA[3]	Lipid Solubility	Renal vs Hepatic Elimination
Acebutolol	+	+	+	+	H > R
Atenolol	+	0	0	0	R
Atenolol/chlorthalidone	+	0	0	0	R
Betaxolol	+	0	0	+	H > R
Bisoprolol	+	0	0	0	R = H
Bisoprolol and HCTZ	+	0	0	0	R = H
Carvedilol	0	0	0	+++	H > R
Labetalol	0	0/+	0	++	H
Metoprolol succinate	+	0	+	+++	H
Metoprolol tartrate	+	0	+	+++	H
Metoprolol and HCTZ	+	0	+	+++	H
Nadolol	0	0	0	0	R
Nebivolol	+	0	0	++	H
Pindolol	0	++	+	+	H > R
Propranolol	0	0	++	+++	H
Propranolol and HCTZ	0	0	++	+++	H
Timolol	0	0	0	++	H > R

[1]Agents with beta-1 selectivity are less likely to precipitate bronchospasm and decrease peripheral blood flow in low doses, but selectivity is only relative.
[2]Agents with ISA cause less resting bradycardia and lipid changes.
[3]MSA generally occurs at concentrations greater than those necessary for beta-blockade. The clinical importance of MSA by beta-blockers has not been defined.
HCTZ, hydrochlorothiazide; ISA, intrinsic sympathomimetic activity; MSA, membrane-stabilizing activity; SR, sustained release; 0, no effect; +, some effect; ++, moderate effect; +++, most effect.

Great care should be exercised if the decision is made, in the absence of compelling indications, to remove beta-blockers from the treatment regimen because abrupt withdrawal can precipitate acute coronary events and severe increases in blood pressure.

Messerli FH et al. β blockers switched to first-line therapy in hypertension. Lancet. 2023;402:1802. [PMID: 37844590]

H. Alpha-Antagonists

Prazosin, terazosin, and doxazosin (Table 13–12) block postsynaptic alpha-receptors, relax smooth muscle, and reduce blood pressure by lowering peripheral vascular resistance. These agents are effective as single-drug therapy in some individuals, but tachyphylaxis may appear during long-term therapy. Unlike some beta-blockers and diuretics, alpha-blockers have no adverse effect on serum lipid levels. In fact, alpha-blockers increase HDL cholesterol while reducing total cholesterol; whether this is beneficial in the long term has not been established.

Side effects—Side effects are relatively common (Table 13–12). These include marked hypotension after the first dose which, therefore, should be small and given at bedtime. Post-dosing palpitations, headache, and nervousness may continue to occur during long-term therapy; these symptoms may be less frequent or severe with doxazosin because of its more gradual onset of action. In ALLHAT, however, persons receiving doxazosin as initial therapy had a significant increase in HF hospitalizations and a higher incidence of stroke relative to those receiving diuretics, prompting discontinuation of this arm of the study. Cataractectomy in patients exposed to alpha-blockers can be complicated by the floppy iris syndrome, even after discontinuation of the drug, so the ophthalmologist should be alerted that the patient has been taking the drug prior to surgery.

To summarize, alpha-blockers should generally not be used as initial agents to treat hypertension—except perhaps in men with symptomatic prostatism or nightmares linked to PTSD.

I. Drugs with Central Sympatholytic Action

Methyldopa, clonidine, guanabenz, and guanfacine (Table 13–12) lower blood pressure by stimulating alpha-adrenergic receptors in the CNS, thus reducing efferent peripheral sympathetic outflow. There is considerable experience with methyldopa in pregnant women, and it is still used in this population. Clonidine is available as patches, which may have particular value in noncompliant patients. All of these central sympatholytic agents are effective as single therapy in some patients, but they are usually used as second- or third-line agents because of the high frequency of drug intolerance.

Table 13–12. Alpha-blocking agents, sympatholytics, and vasodilators.

Medication (Proprietary Names)	Dosage	Adverse Effects	Comments
Alpha-Blockers			
Doxazosin (Cardura)	*Initial:* 1 mg at bedtime *Range:* 1–16 mg once daily	Syncope with first dose; postural hypotension, dizziness, palpitations, headache, weakness, drowsiness, sexual dysfunction, anticholinergic effects, urinary incontinence; first-dose effects may be less with doxazosin.	May ↑ HDL and ↓ LDL cholesterol. May provide short-term relief of obstructive prostatic symptoms. Less effective in preventing cardiovascular events than diuretics.
Doxazosin (Cardura XL)	*Initial:* 4 mg ER once daily *Range:* 4–8 mg ER once daily		
Prazosin (Minipress)	*Initial:* 1 mg two or three times daily; take first dose at bedtime *Range:* 2–20 mg in 2 or 3 doses		
Terazosin (Hytrin)	*Initial:* 1 mg at bedtime *Range:* 1–20 mg in 1 or 2 doses		
Central Sympatholytics			
Clonidine (Catapres)	*Initial:* 0.1 mg twice daily *Range:* 0.2–0.6 mg in 2 doses	Sedation, dry mouth, sexual dysfunction, headache, bradyarrhythmias; side effects may be less with guanfacine. Contact dermatitis with clonidine patch.	"Rebound" hypertension may occur even after gradual withdrawal.
Clonidine (Catapres TTS [transdermal patch])	*Initial:* 0.1 mg/day patch weekly *Range:* 0.1–0.3 mg/day patch weekly		
Clonidine and chlorthalidone (Clorpres)	*Initial:* 0.1 mg/15 mg one to three times daily *Range:* 0.1 mg/15 mg–0.6 mg/30 mg in single or divided doses		
Guanfacine (Tenex)	*Initial:* 0.5–1 mg once daily at bedtime *Range:* 1–3 mg once daily		
Methyldopa (Aldochlor)	*Initial:* 250 mg two or three times daily *Range:* 500–3000 mg in 2 doses	Hepatitis, hemolytic anemia, fever.	Avoid in favor of safer agents.
Peripheral Neuronal Antagonists			
Reserpine (not available in the United States)	*Initial:* 0.1 mg once daily *Range:* 0.05–0.25 mg once daily	Depression (less likely at dosages < 0.25 mg), night terrors, nasal stuffiness, drowsiness, peptic disease, GI disturbances, bradycardia.	
Direct Vasodilators			
Hydralazine (Apresoline)	*Initial:* 10 mg four times daily *Range:* 50–300 mg in 2–4 doses	GI disturbances, tachycardia, headache, nasal congestion, rash, lupus-like syndrome.	May worsen or precipitate angina.
Minoxidil (generic)	*Initial:* 5 mg once daily *Range:* 10–40 mg in 1–3 divided doses	Tachycardia, fluid retention, headache, hirsutism, pericardial effusion, thrombocytopenia.	Should be used in combination with beta-blocker and diuretic.

ER, extended release.

Side effects—Side effects include sedation, fatigue, dry mouth, postural hypotension, and erectile dysfunction. An important concern is rebound hypertension following withdrawal. Methyldopa also causes hepatitis and hemolytic anemia and should be restricted to individuals who have already tolerated long-term therapy.

J. Peripheral Sympathetic Inhibitors

These agents are usually used only in refractory hypertension. Reserpine remains a cost-effective antihypertensive agent (Table 13–12). Its reputation for inducing mental depression and its other side effects—sedation, nasal stuffiness, sleep disturbances, and peptic ulcers—has made it unpopular, though these problems are uncommon at low dosages. Guanethidine and guanadrel inhibit catecholamine release from peripheral neurons but frequently cause orthostatic hypotension (especially in the morning or after exercise), diarrhea, and fluid retention.

K. Arteriolar Dilators

Hydralazine and minoxidil (Table 13–12) relax vascular smooth muscle and produce peripheral vasodilation. When given alone, they stimulate reflex tachycardia; increase myocardial contractility; and cause headache, palpitations, and fluid retention. To counteract these effects, the agents are usually given in combination with

diuretics and beta-blockers in resistant patients. Hydralazine produces frequent GI disturbances and may induce a lupus-like syndrome. Minoxidil causes hirsutism and marked fluid retention; this very potent agent is reserved for the most refractory of cases.

Antihypertensive Medications & the Risk of Cancer

A number of observational studies have examined the association between long-term exposure to antihypertensive medications and cancer. Weak associations have been suggested by some of these studies, but results have been mixed. In the absence of large-scale prospective studies with cancer as a prespecified outcome measure, the effect of antihypertensive drugs on the risk of cancer remains uncertain. By contrast, the beneficial effect of these drugs on cardiovascular outcomes has been clearly established. Concern about increased risk of cancer should not be minimized, but at present there are no compelling data to prompt a change in prescribing patterns.

Kidoguchi S et al. Antihypertensive drugs and cancer risk. Am J Hypertens. 2022;35:767. [PMID: 35595533]

Procedures That Modulate the Activity of the Autonomic Nervous System

Before the advent of antihypertensive medications, lumbar sympathectomy was used to lower blood pressure. In a more specific and less invasive approach, the renal sympathetic nerves can be ablated via the luminal surface of the renal arteries. The SPYRAL HTN-OFF MED study, using an intensive and closely controlled ablation strategy, demonstrated a modest but clinically meaningful blood pressure reduction compared to a control group who received a sham intervention. This effect on blood pressure has been confirmed by several subsequent studies and is equivalent to the effect of one hypertensive medication. Studies of sympathetic nerve ablation have demonstrated a 20–30% nonresponse rate. It seems probable that renal sympathetic nerve ablation will emerge as an alternative or adjunctive modality in the treatment of hypertension and may have particular value in the management of resistant hypertension and drug intolerance. However, there are no cardiovascular outcomes data to support the procedure, and the cost is substantial. Resistant hypertension is also very often pseudoresistant, arising as a consequence of unrecognized nonadherence, which can be addressed once identified. Potential candidates for renal sympathetic denervation should be referred to centers with expertise in identifying suitable candidates and skill in the denervation procedure.

Developing an Antihypertensive Regimen

Historically, data from large placebo-controlled trials supported the overall conclusion that antihypertensive therapy with diuretics and beta-blockers had a major beneficial effect on a broad spectrum of cardiovascular outcomes, reducing the incidence of stroke by 30–50% and of HF by 40–50%, and halting progression to accelerated hypertension syndromes. The decreases in fatal and nonfatal CHD and cardiovascular and total mortality were less dramatic, ranging from 10% to 15%. Similar placebo-controlled data pertaining to the newer agents are generally lacking, except for stroke reduction with the calcium channel blocker nitrendipine in the Systolic Hypertension in Europe trial. However, there is substantial evidence that ACE inhibitors, and to a lesser extent ARBs, reduce adverse cardiovascular outcomes in other related populations (eg, patients with diabetic nephropathy, HF, or post-MI and individuals at high risk for cardiovascular events). Most large clinical trials that have compared outcomes in relatively unselected patients have failed to show a difference between newer agents—such as ACE inhibitors, calcium channel blockers, and ARBs—and the older diuretic-based regimens with regard to survival, MI, and stroke. Where differences have been observed, they have mostly been attributable to subtle asymmetries in blood pressure control rather than to any inherent advantages of one agent over another. Recommendations for initial treatment identify ACE inhibitors, ARBs, and calcium channel blockers as valid choices. Because of their adverse metabolic profile, initial therapy with thiazides might best be restricted to older patients. Thiazides are acceptable as first-line therapy in Black persons because of specific efficacy in this group.

As discussed above, beta-blockers are not ideal first-line drugs in the treatment of hypertension without compelling indications for their use (such as active CAD or HF). Vasodilator beta-blockers (such as carvedilol and nebivolol) may produce better outcomes than traditional beta-blockers; however, this possibility remains untested.

In principle, restoration of nocturnal dipping by dosing some antihypertensive medications at the end of the day seems desirable. However, the impact of nocturnal dosing of antihypertensive medications on hypertension control and clinical outcomes remains unresolved. The HYGIA study reported significant benefits of evening compared to morning dosing. However, many experts have criticized this study. Because of the risk of ischemic events from profound nocturnal hypotension and because clinical benefits remain uncertain, nocturnal dosing is not generally recommended.

Medications that interrupt the renin-angiotensin cascade are more effective in young White persons, in whom renin tends to be higher. Calcium channel blockers and diuretics are more effective in Black or older persons, in whom renin levels are generally lower. Many patients require two or more medications and even then a substantial proportion fail to achieve the goal blood pressure. A stepped care approach to the drug treatment of hypertension is outlined in Table 13–13. In patients with diabetes, three or four drugs are usually required to reduce systolic blood pressure to goal. In many patients, blood pressure cannot be adequately controlled with any combination. As a result, debating the appropriate first-line agent is less relevant than determining the most appropriate combinations of agents.

The mnemonic ABCD can be used to remember four classes of antihypertensive medications. These four classes can be divided into two categories: AB and CD. AB refers

Table 13–13. A stepped care approach to the initiation and titration of antihypertension medications.[1,2]

Step 1	ACE inhibitor/ARB **or**[3] Calcium channel blocker **or** Thiazide diuretic[4]
Step 2	ACE inhibitor/ARB **plus** Calcium channel blocker **or** thiazide diuretic[5]
Step 3	ACE inhibitor/ARB **plus** calcium channel blocker **plus** thiazide diuretic
Step 4	ACE inhibitor/ARB **plus** calcium channel blocker **plus** thiazide diuretic **plus** spironolactone[6]

[1]Allow 2 weeks to reach full effect of each drug. Proceed through steps until target blood pressure is attained.
[2]Beta-blockers can be used at any stage if specifically indicated, eg, HF or angina.
[3]Initiation with combination therapy should be considered in patients with higher levels of blood pressure and higher cardiovascular risk.
[4]Thiazide or calcium channel blocker is more effective initial therapy in Blacks and older people.
[5]If required, add a calcium channel blocker rather than diuretic in younger patients to avoid long-term exposure to metabolic side effects of diuretics.
[6]Alternatives to spironolactone include eplerenone, amiloride, or triamterene. Watch for hyperkalemia, especially if also receiving ACE inhibitor/ARB. Avoid potassium-sparing diuretics in advanced CKD. If more than three drugs are required at maximum dose, consider specialist referral.

to drugs that block the RAAS (**A**CE/ARB and **b**eta-blockers). CD refers to those that work in other pathways (**c**alcium channel blockers and **d**iuretics). Combinations of drugs between the two categories are more potent than combinations from within a category. Many experts recommend the use of a fixed-dose combination (between two categories) of antihypertensive agents as first-line therapy in patients with substantially elevated systolic pressures (greater than 160/100 mm Hg) or difficult-to-control hypertension (which is often associated with diabetes or kidney dysfunction). Because of the unwanted metabolic effects of thiazides, calcium channel blockers may be the preferred second agent in the younger patient who is already taking an ACE inhibitor or ARB. However, studies have repeatedly confirmed the effectiveness of thiazide diuretics as first-line agents in prevention of multiple clinical endpoints. Based on the results from the ACCOMPLISH trial, a combination of ACE inhibitor and calcium channel blocker may prove optimal for patients at high risk for cardiovascular events. The initial use of low-dose combinations allows faster blood pressure reduction and is likely to be better accepted by patients. Data from the ALTITUDE study (in patients with type 2 diabetes and CKD or CVD or both) indicate that the addition of aliskiren to either ARB or ACE inhibitor was associated with worse outcomes and cannot be recommended, at least in this population. A suggested approach to treatment, tailored to patient demographics, is outlined in Table 13–14.

Table 13–14. Choice of antihypertensive agent based on demographic considerations.[1,2]

	Black Persons, All Ages[3]	All Others, Age < 55 Years	All Others, Age > 55 Years
First-line	CCB or diuretic[4,5]	ACE inhibitor or ARB[6] or CCB or diuretic[4,5]	CCB or diuretic[4,5]
Second-line	ARB[6] or ACE inhibitor[6,7] or vasodilating beta-blocker[8]	Vasodilating beta-blocker[8]	ACE inhibitor[6] or ARB[6] or vasodilating beta-blocker[8]
Resistant hypertension	Aldosterone receptor blocker	Aldosterone receptor blocker	Aldosterone receptor blocker
Additional options	Centrally acting alpha-agonist or peripheral alpha-antagonist[9]	Centrally acting alpha-agonist or peripheral alpha-antagonist[9]	Centrally acting alpha-agonist or peripheral alpha-antagonist[9]

[1]Compelling indications may alter the selection of an antihypertensive drug.
[2]Start with full dose of one agent, or lower doses of combination therapy. In more severe hypertension (≥ 140/90 mm Hg), consider initiating therapy with a fixed-dose combination.
[3]The reasons why the responses to some medications tend to differ in Black patients are complex and poorly understood. Observations such as these should not be taken as evidence of biological differences based on racial categories.
[4]For patients with significant kidney dysfunction, use loop diuretic instead of thiazide.
[5]The adverse metabolic effects of thiazide diuretics and beta-blockers should be considered in younger patients but may be less important in the older patient.
[6]Women of childbearing age should avoid ACE inhibitors and ARBs or discontinue as soon as pregnancy is diagnosed.
[7]Despite the elevated risk of angioedema and cough in Black patients, ACE inhibitors are generally well tolerated and are a useful adjunct.
[8]There are theoretical advantages in the use of vasodilating beta-blockers such as carvedilol and nebivolol.
[9]Alpha-antagonists may precipitate or exacerbate orthostatic hypotension in older adults.
CCB, calcium channel blocker.

In sum, as a prelude to treatment, the patient should be informed of common side effects and the need for diligent compliance. In patients with blood pressure less than 160/90 mm Hg in whom pharmacotherapy is indicated, treatment should start with a single agent or two-drug combination at a low dose. Follow-up visits usually should be at 4- to 6-week intervals to allow for full medication effects to be established (especially with diuretics) before further titration or adjustment. If, after titration to usual doses, the patient has shown a discernible but incomplete response and a good tolerance of the initial drug, another medication should be added. See Goals of Treatment, above. As a rule of thumb, a blood pressure reduction of 10 mm Hg can be expected for each antihypertensive agent added to the regimen and titrated to the optimum dose. In those with more severe hypertension, or with comorbidities (such as diabetes) that are likely to render them resistant to treatment, initiation with combination therapy is advised and more frequent follow-up is indicated. "Polypills" combining multiple drugs in a single pill are effective and well tolerated in initial treatment of hypertension. Most guidelines recommend the use of home blood pressure monitors in the diagnosis of hypertension. Digital technology makes it possible to monitor the patient's self-measured response to therapy with direct transmission of blood pressure readings to the clinic. The availability of blood pressure profiles generated from multiple home-gathered data points over continuous intervals allows more precise control of the cumulative hypertensive burden.

Evaluation for secondary hypertension should be considered in patients who adhere to their medications and do not respond to conventional combination regimens.

Medication Nonadherence

Adherence to antihypertensive treatment is alarmingly poor. In one European study of antihypertensive medication adherence, only 39% of patients were found to be taking their medications continuously over a 10-year period. Collaborative care, using clinicians, pharmacists, social workers, and nurses to encourage adherence, has had a variable and often rather modest effect on blood pressure control. Adherence is enhanced by patient education and by use of home blood pressure measurement. The choice of antihypertensive medication is important. Better adherence has been reported for patients whose medications could be taken once daily or as combination pills. Adherence is best with ACE inhibitors and ARBs and worse with beta-blockers and diuretics.

Sex-Specific Considerations in Hypertension

Because of the preponderance of male recruitment into large-scale clinical trials, the impact of a patient's sex on the evaluation and management of hypertension remains uncertain. The limited data that exist suggest a steeper relationship in women between 24-hour ambulatory and nighttime systolic blood pressure and the risk of cardiovascular events. There are many sex-specific effects on the mechanisms and end-organ impact of hypertension. In younger adults, men are more likely to be hypertensive than women, a relationship that reverses in later life. Regression of LVH in response to ACE inhibitors is less pronounced in women. Women are more likely to have isolated systolic hypertension, probably because they develop more dynamic LV systolic function and greater vascular stiffness than men. Fibromuscular dysplasia of the renal artery is much more common in women than men. The side effects of many antihypertensive drugs are more pronounced in women than men, including ACE inhibitor–associated cough and hyponatremia and hypokalemia in response to diuretics. Conversely, thiazides can help preserve bone density. Dependent edema due to amlodipine is more likely in women, and women are more sensitive to beta-blockers. There are no data to support a different blood pressure target in women, but this question has not been examined in dedicated clinical trials.

Treatment of Hypertension in Diabetes

Patients with hypertension and diabetes are at particularly high risk for cardiovascular events. Data from the ACCORD study of patients with diabetes demonstrated that most of the benefits of blood pressure lowering were seen with a systolic target of less than 140 mm Hg. Although there was a reduction in stroke risk at a systolic target below 120/70 mm Hg, treatment to this lower target was associated with an *increased* risk of serious adverse effects. US and Canadian guidelines recommend a blood pressure goal of less than 130/80 mm Hg in patients with diabetes. Because of the beneficial effects of ACE inhibitors in diabetic nephropathy, they should be part of the initial treatment regimen. ARBs or perhaps renin inhibitors may be substituted in those intolerant of ACE inhibitors. While the ONTARGET study showed that combinations of ACE inhibitors and ARBs in persons with atherosclerosis or type 2 diabetes with end-organ damage appeared to minimize proteinuria, this strategy slightly increased the risks of progression to dialysis and of death; thus, it is not recommended. Most patients with diabetes require combinations of three to five agents to achieve target blood pressure, usually including a diuretic and a calcium channel blocker or beta-blocker. Patients with type 2 diabetes can be treated with agents that are not considered traditional antihypertensive drugs yet probably improve cardiovascular outcomes independent of their rather modest effects to lower blood pressure. Inhibitors of sodium-glucose transport protein 2 (SGLT-2) are widely employed in clinical practice. In the CREDENCE trial of patients with diabetic nephropathy, canagliflozin, an SGLT-2 inhibitor, improved glycemic control, generally modestly lowered blood pressure by 3–4 mm Hg, improved renal outcomes, and reduced cardiovascular risk. In the FIGARO-DKD study of patients with diabetes and CKD stage 2–4, finerenone lowered blood pressure by a modest 3 mm Hg but showed significant benefits in prevention of cardiovascular outcomes and possible benefit in slowing the progression of kidney disease. Cardiovascular and renal outcomes in type 2 diabetes are also improved with GLP-1 agonists despite modest reductions in blood pressure. There is a lack of outcomes data in type 1 diabetes, but it seems likely that

similar benefits would be observed with these three drug classes. SGLT-2 inhibitors, however, increase the risk of diabetic ketoacidosis in type 1 diabetes. In addition to rigorous blood pressure control, treatment of persons with diabetes should include aggressive treatment of other risk factors.

Neuen BL et al. Estimated lifetime cardiovascular, kidney and mortality benefits of combination treatment with SGLT2 inhibitors, GLP-1 receptor agonists, and non-steroidal MRA compared with conventional care in patients with type 2 diabetes and albuminuria. Circulation. 2024;149:450. [PMID: 37952217]

Tonelli M et al. Increasing societal benefit from cardiovascular drugs. Circulation. 2022;146:1627. [PMID: 36409780]

Treatment of Hypertension in Chronic Kidney Disease

Hypertension is present in 40% of patients with a GFR of 60–90 mL/min/1.73 m^2 and 75% of patients with a GFR less than 30 mL/min/1.73 m^2. The rate of progression of CKD is markedly slowed by treatment of hypertension. In the SPRINT trial, the reduction in cardiovascular risk associated with lower blood pressure targets was also observed in the subgroup with a GFR of less than 60 mL/min/1.73 m^2. However, an effect of *lower* blood pressure targets on the slowing of CKD progression appears to be restricted to those with pronounced proteinuria. In the SPRINT trial, the lower blood pressure goal was associated with increased risk of AKI, but this was generally reversible and not associated with elevated biomarkers for ischemic injury. Most experts recommend a blood pressure target of less than 130/80 mm Hg in patients with CKD, with consideration of more intensive lowering if proteinuria greater than 1 g per 24 hours is present. Medications that interrupt the renin-angiotensin cascade can slow the progression of kidney disease and are preferred for initial therapy, especially in those with albuminuria of greater than 300 mg/g creatinine. Transition from thiazide to loop diuretic is often necessary to control volume expansion as the eGFR falls below 30 mL/min/1.73 m^2, but thiazide diuretics maintain antihypertensive efficacy in advanced CKD. ACE inhibitors remain protective and safe in kidney disease associated with significant proteinuria and serum creatinine as high as 5 mg/dL (380 mcmol/L). However, the use of drugs blocking the RAAS cascade in patients with advanced CKD should be supervised by a nephrologist. Kidney function and electrolytes should be measured 1 week after initiating treatment and subsequently monitored carefully in patients with kidney disease. An increase in creatinine of 20–30% is acceptable and expected; more exaggerated responses suggest the possibility of renal artery stenosis or volume contraction. Although lower blood pressure levels are associated with acute decreases in GFR, this appears not to translate into an increased risk of developing ESKD in the long term. Persistence with ACE inhibitor or ARB therapy as the serum potassium level exceeds 5.5 mEq/L is probably not warranted, since other antihypertensive medications are renoprotective as long as goal blood pressures are maintained. However, diuretics and SGLT-2 inhibitors can help control mild hyperkalemia, and there are novel cation exchange polymers (such as patiromer) that sequester potassium in the gut and are more effective and better tolerated than sodium polystyrene sulfonate. The renoprotective effects of SGLT-2 inhibitors observed in diabetes has also been demonstrated in patients with CKD and proteinuria who do not have diabetes.

Treatment of Hypertension in Black Patients

Substantial evidence indicates that Black Americans are not only more likely to become hypertensive and more susceptible to the cardiovascular and renal complications of hypertension but also respond differently to many antihypertensive medications. The REGARDS study illustrates these differences. At systolic blood pressures less than 120 mm Hg, Black and White Americans between 45 and 64 years of age had equal risk of stroke. For a 10 mm Hg increase in systolic blood pressure, the risk of stroke was threefold higher in Black participants. At levels above 140–159/90–99 mm Hg, the hazard ratio for stroke in Black compared to White participants between 45 and 64 years of age was 2.35. This increased susceptibility may reflect environmental factors, such as structural racism, diet, activity, stress, or access to health care services; differences in occurrence of comorbid conditions such as diabetes or obesity; or genetic ancestry and epigenetics. More studies are needed to determine the source of these differences, and it should be noted that racial disparities are not synonymous with inherent biologic differences based on race. In all persons with hypertension, a multifaceted program of education and lifestyle modification is warranted. Community-based interventions and self-monitoring of blood pressure are promising approaches. Early introduction of combination therapy has been advocated, but there are no clinical trial data to support a lower than usual blood pressure goal in Black patients. Because it appears that ACE inhibitors and ARBs—in the absence of concomitant diuretics—are less effective in Black than in White patients, initial therapy should generally be a diuretic or a diuretic in combination with a calcium channel blocker. However, inhibitors of the RAAS do lower blood pressure in Black patients, are useful adjuncts to the recommended diuretic and calcium channel blockers, and should be used in patients with hypertension and compelling indications such as HF and kidney disease (especially in the presence of proteinuria) (Table 13–15). *Black patients have an elevated risk of ACE inhibitor–associated angioedema and cough, so ARBs would be the preferred choice.*

Treatment of Hypertension in Older Adults

Several studies in persons over 60 years of age have confirmed that antihypertensive therapy prevents fatal and nonfatal MI and reduces overall cardiovascular mortality. Updated guidelines suggest that blood pressure goals should not generally be influenced by age alone. A subgroup analysis of the SPRINT study found that people older than age 75 years showed benefit at the 120 mm Hg systolic treatment target. Importantly, these benefits were

Table 13–15. Recommended antihypertensive medications for coexisting indications.

Indication	Antihypertensive Medication					
	Diuretic	Beta-Blocker	ACE Inhibitor	ARB	Calcium Channel Blocker	Aldosterone Antagonist
HF	√	√	√	√		√
Following MI		√	√			√
High coronary disease risk	√	√	√		√	
Diabetes	√	√	√	√	√	
Chronic kidney disease			√	√		
Recurrent stroke prevention	√		√			

also evident in patients classified as frail. This more aggressive approach was, however, associated with greater risk of falls and worsening kidney function, indicating that close monitoring is required in older patients being treated to lower blood pressure. It is also important to note that the SPRINT study did not include patients with diabetes mellitus, stroke, or orthostatic hypotension.

Blood pressure treatment goals should be individualized in older adults. In the SPRINT MIND study, the lower systolic blood pressure target of 120 mm Hg was associated with a 15% reduction in the incidence of mild cognitive impairment and probable all cause dementia compared to the 140 mm Hg in the target group. Based upon this data, aggressive control of hypertension in high-risk individuals would have a significant impact on the prevalence of dementia. As discussed above, it is important to note that blood pressure measurements in the SPRINT study were made by automated devices, which are known to read lower than conventional office measurements.

How to initiate antihypertensive therapy in older patients—The same medications are used in older patients but at 50% lower doses. Pressure should be reduced more gradually with a safe intermediate systolic blood pressure goal of 160 mm Hg. As treatment is initiated, older patients should be carefully monitored for orthostasis, altered cognition, and electrolyte disturbances. Older adults are especially susceptible to problems associated with polypharmacy, including drug interactions and dosing errors.

Management of Supine Hypertension in Patients with Orthostatic Hypotension

Supine hypertension is common in patients with orthostatic hypotension and is associated with increased cardiovascular risk. Treatment of orthostasis can exacerbate supine hypertension and vice versa. Life expectancy is often reduced in patients with profound autonomic nervous system dysfunction. Treatment of nocturnal hypertension might be considered with the use of shorter acting agents (eg, captopril, hydralazine, losartan, or quick-release nifedipine). In patients with supine hypertension, medications used to *increase* blood pressure during the day should not be given within 5 hours of bedtime.

Follow-Up of Patients Receiving Hypertension Therapy

Once blood pressure is controlled on a well-tolerated regimen, follow-up visits can be infrequent and laboratory testing limited to those appropriate for the patient and the medications used. Yearly monitoring of blood lipids is recommended, and an ECG could be repeated at 2- to 4-year intervals depending on whether initial abnormalities are present and on the presence of coronary risk factors. Patients who have had excellent blood pressure control for several years, especially if they have lost weight and initiated favorable lifestyle modifications, might be considered for a trial of reduced antihypertensive medications.

Chapman N et al. Arterial hypertension in women: state of the art and knowledge gaps. Hypertension. 2023;80:1140. [PMID: 36919603]
Ferdinand KC et al. Eliminating hypertension disparities in U.S. non-Hispanic black adults: current and emerging interventions. Curr Opin Cardiol. 2023;38:304. [PMID: 37115906]
Milani RV et al. New aspects in the management of hypertension in the digital era. Curr Opin Cardiol. 2021;36:398. [PMID: 33871402]
O'Hagan ET et al. Hypertension therapy using fixed-dose polypills that contain at least three medications. Heart. 2023;109:1273. [PMID: 36810213]
Suchard MA et al. Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis. Lancet. 2019;394:1816. [PMID: 31668726]
Supiano MA et al. New guidelines and SPRINT results: implications for geriatric hypertension. Circulation. 2019;140:976. [PMID: 31525101]

RESISTANT HYPERTENSION

Resistant hypertension is defined as the failure to reach blood pressure control in patients who are adherent to full doses of an appropriate three-drug regimen (including a diuretic). Adherence is a major issue: the rate of partial or complete noncompliance probably approaches 50% in this group of patients. In the approach to resistant hypertension, the clinician should first confirm compliance and rule out

Table 13–16. Causes of resistant hypertension.

Improper blood pressure measurement
Nonadherence
Volume overload and pseudotolerance[1]
Excess sodium intake
Volume retention from kidney disease
Inadequate diuretic therapy
Drug-induced or other causes
Inadequate doses
Inappropriate combinations
NSAIDs; cyclooxygenase-2 inhibitors
Cocaine, amphetamines, other illicit drugs
Sympathomimetics (decongestants, anorectics)
Oral contraceptives
Adrenal steroids
Cyclosporine and tacrolimus
Erythropoietin
Licorice (including some chewing tobacco)
Selected over-the-counter dietary supplements and medicines (eg, ephedra, ma huang, bitter orange)
Associated conditions
Obesity
Excess alcohol intake
Identifiable causes of hypertension (see Table 13–2)

[1]Pseudotolerance is blunting of the antihypertensive action of vasodilators because they promote salt retention.
Data from Chobanian AV et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289:2560.

"white coat hypertension," ideally using ambulatory or home-based measurement of blood pressure. Exacerbating factors should be considered (as outlined above). Finally, identifiable causes of resistant hypertension should be sought (Table 13–16). Aldosterone may play an important role in resistant hypertension and aldosterone receptor blockers and amiloride can be very useful. If goal blood pressure cannot be achieved following completion of these steps, consultation with a hypertension specialist should be considered. Renal sympathetic nerve ablation is a consideration for these patients in the absence of other options, but trials examining clinically relevant long-term outcomes are lacking.

Azzam O et al. Taming resistant hypertension: the promise of novel pharmacologic approaches and renal denervation. Br J Pharmacol. 2024;181:319. [PMID: 37715452]

UNCONTROLLED HYPERTENSION & HYPERTENSIVE EMERGENCY

Historically there has been a profusion of terms describing various forms of acute hypertensive presentations including hypertensive crisis, accelerated hypertension, hypertensive emergency, malignant hypertension, hypertensive encephalopathy, posterior reversible encephalopathy syndrome, hypertensive urgency, and uncontrolled hypertension. Some expert guidelines have condensed this profusion of terms into two categories, uncontrolled hypertension and hypertensive emergency, which are based on the absence (uncontrolled hypertension) or presence (hypertensive emergency) of acute hypertension-mediated end-organ injury.

The diagnosis of hypertensive emergency is made when significant hypertension (usually but not always exceeding 180/120 mm Hg) is the cause of injury to the heart, retina, brain, kidneys, large arteries, or microcirculation. Preeclampsia is a special case discussed in Chapter 21. Acute elevation of blood pressure in the absence of evidence of end-organ injury is described as uncontrolled hypertension. This scheme distinguishes patients whose blood pressure must be controlled immediately from those whose blood pressure control may safely be secured over hours to days. In hypertensive emergency, hospital admission is required to manage the consequences of organ injury and to closely monitor the blood pressure response to intravenous blood pressure–lowering therapy. By contrast, uncontrolled hypertension can be managed with conventional oral hypotensive therapy with a limited period of observation and ambulatory follow-up; hospital admission is unnecessary. In a hypertensive emergency, the profile of organ injury will determine the choice of antihypertensive agent, the rate at which blood pressure should be reduced, and the interval and final blood pressure goals in response to therapy.

A. How to Detect End-Organ Injury in Hypertensive Emergency

Often, the presence of end-organ injury is apparent from the history and physical examination with an obvious focal or global neurologic deficit, abnormal retinal examination, absent pulses, asymmetric blood pressure readings, severe chest pain, back pain, or frank pulmonary edema. Blood tests should be selected to screen for thrombotic microangiopathy, AKI, and myocardial damage. Urine is examined for blood and protein, and for screening for substances of abuse (typically cocaine or ecstasy). Where clinically indicated, various imaging modalities may confirm pulmonary edema, myocardial dysfunction, aortic dissection, or acute intracranial bleed, thrombosis, or cerebral microvascular injury (eg, posterior reversible encephalopathy syndrome).

Acute hypertensive microangiopathy—The complex of elevated blood pressure associated with retinopathy (retinal hemorrhages, cotton wool spots, or papilledema), AKI, and thrombotic microangiopathy has been termed **malignant hypertension.** Approximately 10% of patients will also have evidence of hypertensive encephalopathy (seizures, lethargy, cortical blindness, or coma) that is not always accompanied by classic hypertensive retinopathy. The susceptibility of the posterior cerebrum to hypertensive injury arises from the sparsity of sympathetic innervation in this region and consequently limited autoregulatory capacity. The microangiopathic changes of thrombocytopenia, schistocytes, and elevated LDH also occur in hemolytic uremic syndrome (HUS) and