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258 Atrial Fibrillation

■ ■FURTHER READING Brugada J et al: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The task force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC) developed in collaboration with the Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J 41:655, 2020. Callans DJ: Josephson's Clinical Cardiac Electrophysiology: Techniques and Interpretations, 7th ed. Philadelphia, Wolters Kluwer, 2024. Jalife J, Stevenson W (eds): Zipes and Jalife's Cardiac Electrophysiol ogy: From Cell to Bedside, 8th ed. Philadelphia, Elsevier, 2022. Joglar JA et al: 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 83:109, 2024. William H. Sauer, Jorge E. Romero,

Paul C. Zei

Atrial Fibrillation PATHOPHYSIOLOGY AND EPIDEMIOLOGY Atrial fibrillation (AF) is a cardiac arrhythmia characterized by seemingly disorganized, rapid, and irregular atrial electrical activation, resulting in loss of organized atrial mechanical contraction. These rapid and irregular electrical signals input into the atrioventricular (AV) node, which deter mines ventricular activation and rate. The conducted ventricular rate is variable, resulting in an irregular, usually rapid ventricular rate, ranging typically between 110 and 160 beats/min in most. In some patients, the sustained ventricular rate can exceed 200 beats/min, whereas in others with either high vagal tone or AV nodal conduction disease, the ven tricular rate may be excessively slow (Fig. 258-1). The disorganized atrial activation is best appreciated in lead V1 for this patient. AF is the most common sustained arrhythmia; as a result, it is a major public health issue. Prevalence increases with age, with

> 95% of AF patients >60 years of age. The prevalence in humans over age 80 is ~20%. The lifetime risk of developing AF for men aged 40 years old is ~25%. AF is slightly more common in men than women and more common in whites than blacks. Risk factors for developing AF in addition to age and underlying cardiac disease include hypertension, diabetes mellitus, cardiac disease, family history of AF, obesity, thyroid disease, and sleep-disordered breathing. AF is not a benign condition, with a 1.5- to 1.9-fold increased risk of mortality after controlling for underlying cardiac disease. Perhaps the most important consequence of AF is a significantly increased risk of stroke compared to the

> general population, causing ~25% of all strokes. AF has been detected up to 8.9% of patients within 6 months following cryptogenic stroke using insertable cardiac monitors. The risk of dementia is increased in patients with AF, as is the risk of magnetic resonance imaging (MRI)-detected asymptomatic embolic infarct. AF, most often when ventricular rate remains uncontrolled for prolonged periods, increases the risk of developing congestive heart failure and cardiomyopathy. Moreover, as a corollary, patients with underlying heart disease, in particular cardiomyopathy and conges tive heart failure, are at higher risk for developing AF. AF is a marker for worsened morbidity and mortality in patients with existing heart disease, although the precise extent of the independent risk increase associated with AF in heart disease is unclear. AF may, on occasion, be associated with an identifiable precipitating factor, such as hyperthy roidism, acute alcohol intoxication, myocardial infarction, pulmonary

embolism, pericarditis, and cardiac surgery, where AF occurs in up to 50% of patients postoperatively.

AF is clinically most typically defined by the pattern of episodes. Paroxysmal AF is defined as a pattern of AF episodes that occur and terminate with a relatively short duration either spontaneously or by pharmacologic or electrical cardioversion, most commonly defined as 7 days or less. Persistent AF refers to AF that occurs continuously for

> 7 days but <1 year, whereas long-standing persistent AF refers to AF that has been persistent for >1 year. These descriptors for AF correlate somewhat with the underlying pathophysiology of AF. AF tends to be a progressive condition, with, at this point, no definitive “cure” that will completely eliminate AF durably in a predictable fashion. The patho physiology of AF, however, remains incompletely understood. Most data support a multifactorial process that leads to the development of manifest AF. Clinical and epidemiologic studies have demonstrated that, in addition to cardiovascular disease, age, alcohol use, obesity, hypertension, diabetes mellitus, and sleep-disordered breathing are associated with higher risk of developing AF. The proposed pathophys iology suggests a “final common pathway” of these risk factors leading to electrophysiologic changes in atrial tissues. Alterations in regulation of membrane channels and other proteins result in abnormal electrical excitability. Atrial tissues, in particular pulmonary vein musculature, exhibit enhanced automaticity, resulting in ectopic beats (premature atrial contractions), as shown in Fig. 258-2. Bouts of rapid atrial ectopy may then initiate either atrial tachycardia or frank AF. Additional cel lular and, eventually, tissue remodeling results in abnormal conduction properties throughout the atria, including, in particular, shortening of atrial tissue refractory periods. This enables sustained AF through a combination of rapid automaticity-based “drivers” and areas of

func tional reentry. Further remodeling leads to the development of fibrosis and left atrial enlargement (Table 258-1). CHAPTER 258 Atrial Fibrillation These functional and anatomic changes in atrial tissues appear to correlate with the progression of clinical AF. AF tends to be a progres sive disease in most, although exceptions occur. Typically, for a period of time, patients experience sporadic ectopic beats and short runs of atrial tachycardia, likely originating from the pulmonary veins, preced ing the onset of frank AF. Other regions of the atria have been demonstrated to produce ecto pic depolarizations that may trigger AF; these include the posterior wall of the left atrium and muscular tissue sleeves within the superior vena cava, coronary sinus, or the remnant of the vein of Marshall. When enough frequent bursts of ectopic beats/tachycardia and/or changes in underlying substrate support the maintenance of AF for short periods, the patient develops episodes of paroxysmal AF. In the untreated patient, over time, as the electrical, contractile, and structural remodeling continues to progress, episodes of paroxysmal AF may be prolonged to the point of not terminating spontaneously, the hallmark of persistent AF. After further remodeling, not only do patients con tinue to long-standing persistent AF but also the efficacy of therapeutic interventions to restore sinus rhythm diminishes. CLINICAL PRESENTATION AND MANIFESTATIONS The clinical manifestations of AF result from (1) symptoms related to the irregular, often rapid but sometimes slow ventricular rates that result; (2) the hemodynamic consequences of altered cardiac function; (3) the consequences of cardioembolic phenomena; and/or (4) the impact of AF on cardiovascular function over time. AF is diagnosed by electrocardiogram (ECG), either by 12-lead standard ECG, limited lead ambulatory monitor ECG and implantable loop recorders, with findings of lack of organized atrial activity (no P wave), with an irregu lar ventricular response. The role of screening populations for AF is evolving with the use of wearable monitors and home ECG capabilities. With irregular, rapid ventricular rates, there is variable cardiac dis placement and contraction, resulting in the sensation of palpitations and awareness of the heartbeat, when of course, in a normal rhythm, most humans do not sense each heartbeat. Interestingly, many patients are, for the most part, unaware of the irregular ventricular beating for unknown reasons.

PART 6 Disorders of the Cardiovascular System I II III aVR aVL aVF V1 V2 V3 V4 V5 V6 I II III aVR aVL aVF V1 V2 V3 V4 V5 V6 FIGURE 258-1 Electrocardiogram of an irregularly irregular heart rhythm without discernable P waves. The disorganized atrial activation is best appreciated in lead V1 for this patient. Sinus P wave Blocked PAC PAC initiates AF Sinus P wave 25 mm/sec 10 mm/mV 0.5–40 Hz FIGURE 258-2 Surface electrocardiogram (ECG) of atrial ectopy initiating atrial fibrillation (AF). In this single-lead surface ECG recording, the tracing begins with two conducted sinus beats. A nonconducted premature atrial contraction (PAC) (labeled “blocked PAC”) is shown after the second QRS complex. After the next sinus P wave and QRS, an ectopic beat (PAC) initiates atrial fibrillation, as demonstrated by (somewhat organized) erratic atrial activity and an irregular ventricular response. TABLE 258-1 Categorization of Atrial Fibrillation (AF) by Clinical Temporal

Characteristics and Associated Features

PAROXYSMAL AF PERSISTENT AF LONG-STANDING PERSISTENT AF Definition Episodes self-terminate or via phar macologic or electrical CV in <7 days Episodes lasting >7 days and <1 year Persistent AF >1 year LA size Normal to mildly enlarged Mild to severely enlarged Typically, severely enlarged LA scar burden Low Moderate High Efficacy of AAD Often effective Not as effective Usually refractory When to offer ablation? First-line therapy reasonable First-line appropriate but usually offered after AAD failure After AAD failure, not always a good option Ablation technique PV isolation alone usually effective PV isolation and any identified non-PV AF source PV isolation; additional ablation for substrate modification likely needed Note: With paroxysmal, persistent, and long-standing persistent AF, definitions are based on duration of events and diagnosis overall. These categorizations correlate with LA size, LA scar burden, and resultant efficacy of medical and ablative therapies. Abbreviations: AAD, antiarrhythmic drugs; CV, cardioversion; LA, left atrium; PV, pulmonary vein.

During AF, there is loss of the contribution of atrial systole to overall cardiac output and, with irregular ventricular rates, variable ventricular filling and, consequently, variable stroke volume. The resultant impact on overall cardiac output may result in exercise intolerance, fatigue, weakness, presyncope, or dyspnea. In patients with underlying cardiac disease, the additional hemodynamic compromise resulting from AF may result in exacerbation of the disease and/or heart failure symp toms. Patients with hypertrophic cardiomyopathy, coronary artery disease, valvular disease, heart failure with either depressed or pre served ejection fraction, or amyloidosis are particularly susceptible. In patients with concomitant AV nodal conduction disease, bradycardia during AF may result in presyncope or syncope. Pauses at the time of spontaneous conversion from AF to sinus rhythm, a manifestation of sinus node dysfunction that commonly occurs in patients with AF, may result in presyncope or syncope as well. With the loss of atrial mechanical contraction, blood stasis may pro mote in situ thrombosis, which, when embolized, may result in a range of clinical consequences, most importantly, ischemic stroke. Thrombus formation occurs primarily in the left atrial appendage. Over time, recurrent thromboembolism to the brain, even if asymptomatic, may result in debilitating neurologic sequelae, including cognitive impair ment. An increased risk of dementia in patients with AF may be the consequence of this phenomenon, although the contribution of chronic hypoperfusion in patients with long-standing persistent atrial fibrillation is unclear. In patients with prolonged periods of rapid ventricular rates resulting from AF, there is risk of developing a tachycardia-induced cardiomyopathy, with associated depressed left ventricular function. Tachycardia-induced myopathy appears generally to be reversible once ventricular rates are controlled. In patients with long-standing persis tent AF, the atria, especially the left atrium, tend to be more dilated and to contain a higher burden of fibrotic, noncontractile atrial tis sue. The hemodynamic consequences of a noncompliant, fibrotic left atrium, including elevated left atrial filling pressures, volume overload, and congestive heart failure, have been described as “stiff left atrial syndrome.” TREATMENT Atrial Fibrillation The treatment and management of the patient with AF centers on three aims: (1) control of patient symptoms through a strategy of rate control and/or rhythm control; (2) appropriate mitigation of thromboembolism risk; and (3) addressing modifiable risk factors for progression of AF. In the acute onset of AF, if significant hemo dynamic compromise, pulmonary edema, or evidence of coronary ischemia is present, emergent cardioversion is recommended. Elec trical cardioversion can be achieved with a QRS synchronous shock, preferably in a sedated patient, or via pharmacologic cardioversion, most

typically with the intravenous administration of the class III antiarrhythmic ibutilide. Ibutilide should be avoided in patients with baseline prolonged QT interval or severe left ventricular dys function, given the risk of torsades des pointes. In the hemodynam ically stable patient with new-onset AF, therapy should focus on control of ventricular rate to prevent hemodynamic sequelae, con sideration of anticoagulation to mitigate thromboembolic risk, and consideration of restoration and maintenance of sinus rhythm—a so-called rhythm control strategy. If restoration of sinus rhythm is being considered, a more immediate risk of thromboembolism must be factored into the management strategy. Although there is a lack of definitive data, it is presumed that if the presenting epi sode of AF is >48 h or if the episode duration is unknown, there is risk for precipitating a thromboembolic complication through cardioversion, whether electrically or pharmacologically achieved. Therefore, in this circumstance, the patient should be either initi ated on anticoagulation, with cardioversion deferred for at least 3 weeks after uninterrupted anticoagulation, or evaluated to exclude the presence of left atrial appendage thrombus. Most commonly,

transesophageal echocardiography (TEE) is used to evaluate for left atrial appendage thrombus, although cardiac computed tomogra phy (CT) angiography using delayed acquisition imaging has been demonstrated to have excellent sensitivity and specificity as well.

CHAPTER 258 CARDIOVERSION AND ANTICOAGULATION The major source of thromboembolism and stroke in nonvalvular AF is formation of thrombus in the left atrial appendage where flow is relatively stagnant, although thrombus occasionally forms in other locations as well, particularly in patients with mitral valvular disease and severely dilated left atrium. Following conversion from prolonged AF to sinus rhythm, atrial mechanical function can be delayed for weeks (i.e., atrial stunning), such that thrombi can form even during sinus rhythm. When AF has been present for >48 h and in patients at high risk for thromboembolism, such as those with mitral stenosis or hypertrophic cardiomyopathy, conversion to sinus rhythm is associated with an increased risk of thrombo embolism. Thromboembolism can occur soon or several days after restoration of sinus rhythm if appropriate anticoagulation measures are not taken. In patients with AF and left atrial appendage closure devices (e.g., Watchman device), electrical cardioversion is feasible without the need for oral anticoagulation if preprocedural trans esophageal echocardiography shows good device position, absence of device-related thrombus, and peri-device leak of ≤5 mm. Atrial Fibrillation Cardioversion within 48 h of the onset of AF without TEE or cardiac CT is common practice in patients who have not been anticoagulated, provided that they are not at high risk for stroke due to a prior history of embolic events, rheumatic mitral stenosis, or hypertrophic cardiomyopathy with marked left atrial enlarge ment. These low-risk patients with occasional episodes of AF can be instructed to notify their physician when AF occurs to arrange for cardioversion to be done within 48 h. If the duration of AF exceeds 48 h or is unknown, there is greater concern for thromboembolism after cardioversion, even in patients considered low risk (CHA2DS2-VASc of 0 or 1 [see below]) for stroke. There are two approaches to mitigate the risk related to car dioversion. One option is to anticoagulate continuously for 3 weeks before and a minimum of 4 weeks after cardioversion. A second more frequently used approach is to start anticoagulation and per form a TEE or high-resolution cardiac CT scan to detect the pres ence of thrombus in the left atrial appendage. If thrombus is absent, electrical or pharmacologic cardioversion can be performed and anticoagulation continued for a minimum of 4 weeks to allow time for recovery of atrial mechanical function. In either case, cardiover sion of AF is associated

with a substantial risk of recurrence, which may not be symptomatic. It should be noted that these recommen dations for short-term anticoagulation and thrombus exclusion at the time of cardioversion lack contemporary robust data to support these strategies. Longer-term maintenance of anticoagulation is considered based on the patient's individual risk for stroke, com monly assessed using the CHA2DS2-VASc score. ACUTE RATE CONTROL The goal of rate control in AF is to allow more diastolic filling time, improving cardiac output and reducing patient symptoms. In the longer term, adequate rate control will minimize the risk of congestive heart failure and tachycardia-induced cardiomyopathy. Acute rate control can be achieved with beta blockers and/or the calcium channel blockers verapamil and diltiazem administered either intravenously or orally, as warranted by the urgency of the clinical situation. Digoxin has been used for several years for rate control, particularly in patients with labile blood pressure and in patients with cardiomyopathy susceptible to congestive heart fail ure, because it lacks the negative inotropic effect seen in calcium channel blockers and beta blockers. It acts synergistically with beta blockers and calcium channel blockers and, therefore, may be useful as an added agent when rate control is inadequate. However, recent evidence suggests increased mortality with its chronic use, and so its utilization has declined.

CHRONIC RATE CONTROL For patients who remain in AF chronically, the goal of rate control is to both alleviate symptoms and prevent deterioration of ventricular function from excessive rates. β-Adrenergic blockers and calcium channel blockers are often used either alone or in combination. Exertion-related symptoms are often an indication of inadequate rate control. Rate should be assessed with exertion and medications adjusted accordingly. Adequate rate control is defined as a resting heart rate of <80 beats/min that increases to <100 beats/min with light exertion, such as walking. If it is difficult to slow the ventricu lar rate to that degree, allowing a resting rate of up to 110 beats/min is acceptable provided it does not cause symptoms and ventricular function is normal; however, periodic assessment of ventricular function is warranted because some patients develop tachycardiainduced cardiomyopathy. In patients with permanent atrial fibrilla tion, a lenient rate-control strategy (resting heart rate <110 beats/ min) is as effective as strict rate-control strategy (resting heart rate <80 beats/min and heart rate during moderate exercise <110 beats/ min) in terms of death from cardiovascular causes, hospitalization for heart failure and stroke, systemic embolism, bleeding, and lifethreatening arrhythmic events, and this strategy is easier to achieve.

PART 6 Disorders of the Cardiovascular System If adequate rate control in AF is difficult to achieve, further con sideration should be given to restoring sinus rhythm (see below). Catheter ablation of the AV junction to create permanent AV block and implantation of a permanent pacemaker reliably achieve rate control without the need for AV nodal–blocking agents, a so-called "ablate and pace" strategy. These patients not only remain in AF but also become dependent on the pacemaker to support ventricular rate. The typical pacing configuration with placement of a ventricu lar lead in the right ventricular apex may induce dyssynchronous ventricular activation that can depress ventricular function in some patients. Biventricular pacing or direct pacing of the left bundle branch area may be used to minimize the degree of ventricular dyssynchrony. AV nodal ablation and cardiac resynchronization therapy have been demonstrated to be superior to pharmacologic therapy in improving quality of life and in reducing the develop ment of heart failure, heart failure hospitalizations, and all-cause mortality in patients with permanent AF and a narrow QRS, irre spective of their baseline left ventricular ejection fraction. STROKE PREVENTION IN ATRIAL

FIBRILLATION Thromboembolic complications, in particular, stroke, are the most significant and potentially life-threatening sequelae of AF. There fore, appropriate stroke prevention strategies are a key aspect of AF management. The mainstay of stroke prevention is continuous anticoagulation therapy, most commonly using an oral medication. Specific patient populations have a high risk of stroke, includ ing patients with hypertrophic cardiomyopathy, mitral stenosis, and prior stroke history, and therefore, anticoagulation is recom mended, barring contraindications. AF in patients without mitral stenosis is commonly referred to as nonvalvular AF. In most patients with AF, the decision about whether a stroke prevention regimen is indicated is largely based on an assessment of stroke risk, balanced by the risk of the preventative therapy. The risk of stroke appears to be most accurately predicted by the presence of underly ing risk factors known to increase stroke risk. The CHA2DS2-VASc scoring system (Fig. 258-3) is a widely used tool to estimate stroke risk. Anticoagulation is currently recommended in the United States and Europe for patients with a score of ≥1 unless the lone risk factor is female gender. Stroke risk increases with increasing CHA2DS2-VASc score, such that annual stroke risk may be as high as nearly 20% without anticoagulation. On the other hand, antico agulation carries a risk of serious and potentially life-threatening bleeding complications, in particular, intracranial hemorrhage and gastrointestinal bleed. Bleeding risk is often assessed using the HAS-BLED scoring system (Fig. 258-3). If bleeding risk is deemed to be outweighed by stroke risk, anticoagulation is recommended. It is important to note the conventional wisdom that the perceived burden of AF has not been shown to predict stroke risk. The

CHA2DS2-VASc HAS-BLED Risk Criteria Congestive heart failure

Hypertension

Age >75

Abnormal renal or liver function 1 each Hypertension

Bleeding diasthesis Stroke history

Diabetes mellitus

Labile INR (on warfarin)

Prior stroke or TIA

Elderly (Age >65)

Vascular disease

Drugs that predispose to bleeding or alcohol 1 each Age >65

Sex category (F)

Annual Stroke or Major Bleeding Rate (%) as a Function of Score

CHA2DS2-VASc HAS-BLED

FIGURE 258-3 CHA2DS2-VASc and HAS-BLED systems. The CHA2DS2-VASc scoring system gives a point for each outlined stroke risk factor, whereas the HAS-BLED scoring system gives a point for each bleeding risk factor, as outlined in the table. In the chart below the table, the corresponding risk of stroke (CHA2DS2-VASC) or major bleed event (HAS-BLED) is plotted as a percent risk per annum as a function of score. F, female; INR, international normalized ratio; TIA, transient ischemic attack. approach to patients with paroxysmal AF is therefore the same as for persistent AF. It is recognized that many patients who appear to have infrequent AF episodes based on office visits often have asymptomatic episodes that put them at risk. Absence of AF during periodic monitoring is not sufficient to indicate low risk. The role of continuous monitoring with implanted recorders or pacemakers as a guide for anticoagulation in patients with a borderline risk profile is not clear. Subclinical AF is short-lasting and asymptomatic and can usually be detected only by long-term continuous monitoring with implantable loop recorders, pacemakers, or defibrillators. Subclinical AF is associated with an increased risk of stroke by a factor of 2.5. In patients with subclinical AF lasting 6 min to 24 h, apixaban has been shown to decrease the risk of stroke or systemic embolism but increases the risk of major bleeding. Therefore, a more accurate accounting for the impact of AF burden on stroke risk remains to be clarified. Antiplatelet agents alone are generally not sufficient. In non valvular AF, warfarin reduces the annual risk of stroke by 64% compared to placebo and by 37% compared to antiplatelet therapy. Patients with AF with an increased risk of stroke also have an increased risk of venous thromboembolism, which appears to be lower with oral anticoagulation. The direct-acting anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban were noninferior to warfarin in individual trials of nonvalvular AF patients, and intent-to-treat analysis of pooled data suggests superiority to warfa rin by small absolute margins of 0.4–0.7% in reduction of mortality, stroke, major bleeding, and intracranial hemorrhage. Warfarin is required for patients with rheumatic mitral stenosis or mechanical heart valves. Among patients with rheumatic heart disease–associ ated AF, warfarin therapy has led to a lower rate of a composite of cardiovascular events or death than rivaroxaban therapy, without

a higher rate of bleeding. Similarly, apixaban and dabigatran have failed to demonstrate noninferiority to warfarin and are less effec tive than warfarin for the prevention of valve thrombosis or throm boembolism in patients with mechanical heart valves. Warfarin can be an inconvenient agent that requires several days to achieve a therapeutic effect (prothrombin time [PT]/international normalized ratio [INR] >2), requires monitoring of PT/INR to adjust dose, and has many drug and food interactions that can hin der patient compliance and render maintaining a therapeutic effect challenging. The direct-acting agents are easier to use and achieve reliable anticoagulation promptly without requiring dosage adjust ment based on blood tests. Dabigatran, rivaroxaban, and apixaban have renal excretion and require dose adjustment for modest renal impairment, which is of particular concern in the elderly, who are at increased bleeding risk. Limited experience with apixaban and rivaroxaban demonstrates safety and efficacy in patients undergo ing chronic hemodialysis for end-stage kidney disease. Excretion can also be influenced by P-glycoprotein inducers and inhibitors. Warfarin anticoagulation can be reversed by administration of fresh frozen plasma, prothrombin complex concentrate, and vitamin K. Reversal agents are available for dabigatran (idarucizumab), and Xa inhibitors are available (andexanet alfa), and both are admin istered intravenously. These agents may be prothrombotic, and administration must be judicious. The antiplatelet agents aspirin and clopidogrel are inferior to warfarin for stroke

prevention in AF and do not have less risk of bleeding. Clopidogrel combined with aspirin is better than aspirin alone for stroke prevention, but this combination is inferior to warfarin and has a greater bleeding risk than aspirin alone. Bleeding is the major risk of anticoagulation. Major bleeding requiring transfusion and intracranial bleeding occur in ~1% of patients per year with warfarin. Direct-acting anticoagulants appear to have a lower risk of intracranial bleeding compared with warfarin without sacrificing protective effects against thromboembolism. Risk factors for bleeding include age >65–75 years, heart failure, renal insufficiency, prior bleeding, and excessive alcohol or non steroidal anti-inflammatory drug use. In patients who require dual antiplatelet therapy (e.g., aspirin and clopidogrel) after coronary or peripheral arterial stenting, there is a substantially increased bleeding risk when standard oral anticoagulation with warfarin or a direct-acting anticoagulant is added. In AF patients undergo ing percutaneous coronary intervention, the combination of oral platelet inhibition with a P2Y12 inhibitor (preferably clopidogrel) is recommended. Triple antithrombotic therapy, preferably including a direct-acting anticoagulant, should be considered in patients with high ischemic risk (e.g., acute coronary syndrome) and for up to 30 days. Chronic anticoagulation is contraindicated in some patients due to bleeding risks. Because most atrial thrombi likely originate in the left atrial appendage, surgical removal of the appendage, combined with atrial maze surgery, may be considered for patients undergoing surgery, although removal of the appendage has not been unequivocally shown to reduce the risk of thromboembolism. Percutaneously deployed devices that occlude or ligate the left atrial appendage are also available, appear to be noninferior to warfarin in reducing stroke risk, and are considered in patients who have a high risk of thromboembolism but serious bleeding risk from TABLE 258-2 Novel Oral Anticoagulant Dosing DABIGATRAN RIVAROXABAN APIXABAN EDOXABAN Standard dose 150 mg bid 20 mg qd 5 mg bid 60 mg qd Reduced dose 110 mg bid 15 mg qd 2.5 mg bid 30 mg qd Dose reduction criteria Dabigatran 110 mg bid in patients with: age ≥80 years, concomitant use of verapamil, or increased bleeding risk Creatine clearance 15–49 mL/min Note: As of publication, four novel or direct oral anticoagulants are available and indicated for stroke prevention for atrial fibrillation. The standard dosing, reduced dosing, and criteria for reduced dosing are shown for each agent.

chronic oral anticoagulation (Table 258-2). Importantly, left atrial appendage closure devices (i.e., Watchman) provide stroke preven tion comparable to warfarin, with additional significant reductions in major bleeding, particularly hemorrhagic stroke, and all-cause mortality. Furthermore, left atrial appendage closure devices appear to be noninferior to direct-acting anticoagulants in preventing major AF-related cardiovascular, neurologic, and bleeding events.

CHAPTER 258 RHYTHM CONTROL The decision to administer antiarrhythmic drugs or perform cath eter ablation to attempt maintenance of sinus rhythm (commonly referred to as the rhythm control strategy) is mainly guided by patient symptoms and preferences regarding the benefits and risks of therapies. In general, patients who maintain sinus rhythm have better survival than those who continue to have AF. This may be because continued AF is a marker of disease severity or that AF promotes deterioration in cardiac function. In older randomized trials, administration of antiarrhythmic medications to maintain sinus rhythm did not improve survival or symptoms compared to a rate control strategy, and the drug therapy group had more hospitalizations. Disappointing efficacy and toxicities of available antiarrhythmic drugs, in retrospect inappropriate discontinuation of anticoagulation in the rhythm control arms, and patient selec tion bias may be factors that influenced the results of these trials. Recently, a randomized trial evaluating an early

rhythm control strategy (within 1 year of initial presentation) compared to standard rate control demonstrated a reduction in cardiovascular events, including death from cardiovascular causes and stroke. Differences between this study and earlier randomized trials that failed to show a significant difference in outcomes in rate versus rhythm control included the use of catheter ablation and a high adherence rate to anticoagulation despite apparent rhythm control. In patients with heart failure due to depressed left ventricular function, a catheter ablation–based strategy to maintain sinus rhythm appears to pro vide all-cause mortality benefit compared with a medical rhythm control strategy. Furthermore, the combination of catheter ablation and guideline-directed medical therapy in patients with symp tomatic AF and end-stage heart failure who are referred for heart transplantation evaluation is associated with a lower likelihood of a composite of death from any cause, implantation of a left ven tricular assist device, or urgent heart transplantation than medical therapy alone. Atrial Fibrillation A rhythm control strategy is usually selected for patients with symptomatic paroxysmal AF, recurrent episodes of symptomatic persistent AF, AF with difficult rate control, and AF that has resulted in depressed ventricular function or that aggravates heart failure. A rhythm control strategy is more likely to be favored in younger patients than in sedentary or elderly patients in whom rate control is more easily achieved. Even if sinus rhythm is apparently maintained, anticoagulation is recommended according to the CHA2DS2-VASc stroke risk profile because asymptomatic episodes of AF are common. Following a first episode of persistent AF, a strategy using AV nodal–blocking agents, cardioversion, and anti coagulation is reasonable, in addition to addressing possible aggra vating factors. If recurrences are infrequent, periodic cardioversion is reasonable. However, if a patient has frequent symptomatic AF despite rate control, then a rhythm control strategy incorporating At least 2 of 3 criteria: age

≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL

(133 mol/L) If any of the following: creatinine clearance 30–50 mL/min, body weight ≤60 kg, or concomitant use of dronedarone, cyclosporine, erythromycin, or ketoconazole

catheter ablation and/or antiarrhythmic medications is indicated. Based on recent randomized trial data demonstrating superiority of ablation over medications for maintenance of sinus rhythm and benefits of an early rhythm control strategy, catheter ablation is considered first-line therapy, especially for individuals with parox ysmal AF.

PART 6 Disorders of the Cardiovascular System Pharmacologic Therapy for Maintaining Sinus Rhythm The goal of pharmacologic therapy is to maintain sinus rhythm or reduce episodes of AF. Risks and side effects of antiarrhythmic drugs are a major consideration in selecting therapy. Drug therapy can be instituted once sinus rhythm has been established or in anticipa tion of cardioversion. However, antiarrhythmic medications may in some instances pharmacologically cardiovert the patient into sinus rhythm. Therefore, an appropriate anticoagulation strategy approach similar to electrical cardioversion is recommended, par ticularly at the time of initiation of therapy. β-Adrenergic blockers and calcium channel blockers help control ventricular rate, improve symptoms, and possess a low-risk profile, but have low efficacy for preventing or terminating AF episodes. Class I sodium channel– blocking agents (e.g., flecainide, propafenone, disopyramide) are options for patients without significant structural heart disease, but negative inotropic and proarrhythmic effects warrant avoidance in patients with coronary artery disease or heart failure. The class III agents sotalol and dofetilide can be administered to patients with coronary artery

disease or structural heart disease but have ~3% risk of inducing excessive QT prolongation and torsades des pointes. Dofetilide should be initiated only in a hospital with ECG monitoring, and many physicians take this approach with sotalol as well. Dronedarone increases mortality in patients with heart failure or long-standing persistent AF. All these agents have modest efficacy in patients with paroxysmal AF, of whom ~30–50% will benefit. Amiodarone is more effective, maintaining sinus rhythm in approximately two-thirds of patients. It can be administered to patients with heart failure and coronary artery disease. However,

> 40% of patients experience amiodarone-related toxicities during long-term therapy, and thus, careful monitoring of potential toxici ties, including skin, liver, lung, and thyroid abnormalities, must be accompanied with this therapy. Catheter and Surgical Ablation for Maintaining Sinus Rhythm Suc cessful catheter ablation avoids antiarrhythmic drug toxicities, but procedural risks and efficacy depend on operator experience. For patients with previously untreated but recurrent paroxysmal AF, catheter ablation has superior efficacy compared to antiarrhythmic drug therapy, and ablation is even more clearly superior to antiar rhythmic drugs for patients who have recurrent AF despite drug treatment. Long-term control of AF is more difficult to achieve in patients with persistent and long-standing persistent AF, likely because of more extensive atrial abnormalities and associated greater comorbidities in these patients that may promote ongo ing progression of atrial abnormalities that in turn promote AF recurrence. FIGURE 258-4 A. (Left) Electroanatomic map superimposed on a cardiac computed tomography reconstruction of a left atrium with mapping catheter in the posterior wall of this chamber. (Middle) Final radiofrequency lesion set around the pulmonary veins. (Right) Multipolar catheter in the right inferior pulmonary vein B. Spontaneous pulmonary vein (PV) ectopy initiating fibrillatory conduction contained within the isolated vein while 12-lead electrocardiogram shows normal sinus rhythm.

Catheter ablation involves percutaneous venous access (typically via the femoral veins), trans (atrial) septal puncture, and radiofre quency ablation or cryoablation to electrically isolate the left atrial regions around the pulmonary vein antra, abolishing the ability of triggering foci in these regions to initiate AF and also likely impact ing the substrate for reentry in the left atrium (Fig. 258-4). Gaps in healed ablation areas or emergence of new trigger sites outside the pulmonary veins necessitate a repeat procedure in 10–30% of patients. Several alternative energy sources to create ablative lesions are being evaluated for ablation of AF and other arrhythmias, includ ing laser, external beam radiation, and pulsed field electroporation. Pulsed-field ablation uses electric fields generated by short pulses of high energy and has shown promise by specifically targeting myocardium without generating heat or damaging adjacent tissue (Fig. 258-5). Myocardial cells are uniquely sensitive to high-voltage, short-duration electric fields with electroporation thresholds of 268–375 V/cm compared to other tissue types including nerves, endothelium, vascular smooth muscle, and blood cells, all of which have electroporation thresholds >1600 V/cm. The pulse waveforms used to generate an electric field can have many different character istics including voltage amplitude, pulse width, cycle period, voltage polarity (monophasic vs. biphasic), electrode

polarity (unipolar vs. bipolar), and the number of pulses delivered in a train. There are limited data evaluating the impact of how each of these variables affect lesion safety and efficacy (Fig. 258-5). Therefore, unlike radiofrequency ablation, pulsed-field ablation in its current clinical iteration lacks the ability to titrate and tailor energy delivery during ablation. In patients with paroxysmal AF, sinus rhythm is maintained for >1 year after a single ablation procedure in ~80% of patients and is achieved in >90% of patients after multiple procedures in some studies. Among patients with paroxysmal AF receiving a catheter-based therapy, pulsed-field ablation has demonstrated to be noninferior to conventional thermal ablation (i.e., radiofre quency ablation and cryoablation) with respect to freedom from a composite of initial procedural failure, documented atrial tachyar rhythmia after a 3-month blanking period, antiarrhythmic drug use, cardioversion, or repeat ablation and with respect to device- and procedure-related serious adverse events at 1 year. Many patients become more responsive to antiarrhythmic drugs or become less symptomatic with a reduced AF burden after a pulmonary vein isolation procedure, and thus, repeat ablation may not be required for symptom control in some. Ablation is less effective in patients with persistent AF, particularly long-standing persistent AF, especially when associated with more extensive car diac disease, comorbidities, and evidence of moderate and severe left atrial enlargement. More extensive ablation is often required, targeting areas that likely support reentry and/or AF maintenance and regions outside but adjacent to the pulmonary venous antra. Most ablation targets and strategies beyond pulmonary vein isolation have failed to show systematic outcome improvement in randomized controlled clinical trials. However, individualized

Smooth Muscle Cells 1600 V/cm Nerve 3800 V/cm Red Blood Cells 1600 V/cm Pulse Train Voltage Voltage Pulse Width Cycle Waveform Variables • Pulse amplitude (voltage) • Pulse polarity (monophasic-biphasic) • Number of pulses in a train • Pulse width • Cycle period FIGURE 258-5 Pulsed-field electroporation. (Top) Pulsed-field ablation has the potential to target specifically myocardial tissue without negatively affecting adjacent structures or cells such as red blood cells, nerves, the esophagus, or arteries. (Bottom) Numerous factors are involved in creating long-lasting transmural lesions with pulse-field ablation; a combination of most of these parameters will eventually help in delivering electroporation effectively and safely into the myocardial tissue. Catheters currently undergoing clinical evaluation for pulsed-field ablation (PFA). (Reproduced from CD Matos et al: Pulsed Field Ablation of Atrial Fibrillation: A Comprehensive Review. Rev Cardiovasc Med 24:337, 2023 and Reproduced with permission from NA Steiger, JE Romero. Pulsed-field ablation: What are the unknowns and when will they cease to concern us. J Cardiovasc Electrophysiol 33:1489, 2022.) (A) Farawave, reproduced with permission from Boston Scientific; (B) PVAC, reproduced with permission from Medtronic; (C) Sphere-9, reproduced with permission from Medtronic; (D) Varipulse. ablation of atrial low-voltage myocardium in addition to pulmonary vein isolation significantly improved outcomes in patients with persistent AF in one study. Similarly, in patients with persistent AF, treatment with combined catheter ablation and vein of Marshall ethanol infusion had better outcomes compared with catheter abla tion alone. Ablation of areas of rapid activity during AF and cre ation of empiric ablation lines to block conduction across regions of the atria have not been proven to improve outcomes in unselected patients. Other ablation targets include non–pulmonary vein foci that fire in response to high-dose isoproterenol and regions with repetitive rotational or focal activation during AF. More than one ablation procedure is often required to maintain sinus rhythm in patients with persistent and long-standing persistent AF because of lack of lesion durability and complex atrial substrate with non–pul monary vein sources that may be incompletely treated at the initial ablation session (Table 258-3).

Endothelium 1750 V/cm CHAPTER 258 Nerve 3800 V/cm Atrial Fibrillation Myocardium 375 V/cm A D C Time B Catheter Variables • Contact force • Electrode surface area • Electrode polarity (uni vs bipolar) • Electrode shape (torus vs ring) • Electrode and tissue orientation Catheter ablation has a 2–7% risk of major procedure-related complications, with the long-term trend suggesting steady improve ment in complication rates. Complication rates are clearly lowest with high-volume operators and centers. Complications include stroke (0.5–1%), cardiac tamponade (1%), phrenic nerve paraly sis, bleeding from femoral access sites, and fluid overload with heart failure, which can emerge 1–3 days after the procedure. It is important to recognize the potential for delayed presentation of some complications. Ablation within the pulmonary vein can lead to pulmonary vein stenosis, presenting weeks to months after the procedure with dyspnea or hemoptysis. The esophagus abuts the posterior wall of the left atrium where it is subject to injury, and esophageal ulcers can form immediately after the procedure and may rarely lead to a fistula between the left atrium and esophagus (estimated incidence of <0.1%) that presents as endocarditis and stroke 10 days to 3 weeks after the procedure. Early diagnosis

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