patients, because it does not have negative inotropic effects, particularly if use of AV nodal–blocking agents is limited by poor tolerance or is contraindicated. Its effect is modest but synergistic with the other AV nodal–blocking agents, but it is particularly limited when sympathetic tone is elevated. Typically, the goal of acute rate control is to reduce the ventricular rate to less than 100/min, but the goal must be guided by the clinical situation.

CHRONIC RATE CONTROL

For patients who remain in AF chronically, the goal of rate control is to alleviate and prevent symptoms and prevent deterioration of ventricular function from excessive rates. β-Adrenergic blockers, calcium channel blockers, and digoxin are used, sometimes in combination. Rate should be assessed with exertion and medications adjusted accordingly. Exertion-related symptoms are often an indication of inadequate rate control. The initial goal is a resting heart rate of less than 80 beats/min that increases to less than 100 beats/min with light exertion, such as walking. If it is difficult to slow the ventricular 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 remains normal. Periodic assessment of ventricular function is warranted because some patients develop tachycardia-induced cardiomyopathy.

If adequate rate control in AF is difficult to achieve, further consideration should be given to restoring sinus rhythm. Catheter ablation of the AV junction to create heart block and implantation of a permanent pacemaker reliably achieve rate control without the need for AV nodal agents, but implement life-long permanent pacing. Right ventricular apical pacing induces dyssynchronous ventricular activation that can be symptomatic or depress ventricular function in some patients. Biventricular pacing may be used to minimize the degree of ventricular dyssynchrony.

STROKE PREVENTION IN ATRIAL FIBRILLATION

The majority of patients warrant chronic anticoagulation, but selection of therapy should be individualized based on patient profile and risks and benefits of individual agents. Anticoagulation with a vitamin K antagonist is warranted for all patients with AF who have rheumatic mitral stenosis or mechanical heart valves for whom the newer anticoagulants have not been tested. Anticoagulation with a vitamin K antagonist (warfarin) or the newer oral anticoagulants is warranted for patients who have had more than 48 h of AF and are undergoing cardioversion, for patients who have a prior history of stroke, or for patients with a CHA_2DS_2-VASc score of ≥2, but it may be considered in patients with a risk score of 1. The approach to patients with paroxysmal AF is the same as for persistent AF. It is recognized that many patients who appear to have infrequent AF episodes 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 is not yet clear as a guide for anticoagulation in patients with a borderline risk profile. Bleeding is the major risk of anticoagulation. Major bleeding requiring transfusion or in a critical area (e.g., intracranial) occurs in approximately 1% of patients per year. Risk factors for bleeding include age >65–75 years, heart failure, history of anemia, and excessive alcohol or nonsteroidal anti-inflammatory drug use. Patients with coronary stents who require antiplatelet therapy with aspirin and a thienopyridine are at particularly high risk of bleeding.

Warfarin reduces the annual risk of stroke by 64% compared to placebo and by 37% compared to antiplatelet therapy. The newer anticoagulants, dabigatran, rivaroxaban, and apixaban, have been found to be noninferior to warfarin in individual trials, and analysis of pooled data suggests superiority to warfarin by small absolute margins of 0.4–0.7% in reduction of mortality, stroke, major bleeding, and intracranial hemorrhage. Warfarin is 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, thus limiting patient compliance. The newer agents are easier to use and achieve reliable anticoagulation promptly without requiring dosage adjustment based on blood tests. Dabigatran, rivaroxaban, and apixaban have renal excretion, cannot be used with severe renal insufficiency, and require dose adjustment for modest renal impairment, which is of particular concern in the elderly, who are at increased bleeding risk. Excretion can also be influenced by P-glycoprotein inducers and inhibitors. Warfarin anticoagulation can be reversed by administration of fresh frozen plasma and vitamin K. Reversing agents for the newer anticoagulants are lacking (but in development), and bleeding must be managed with supportive care, with the expectation that clotting will improve over 12 h as the anticoagulant is excreted.

The antiplatelet agents aspirin and clopidogrel are inferior to warfarin for stroke prevention in AF and do not reduce the risk of bleeding. Clopidogrel combined with aspirin is better than aspirin alone but inferior to warfarin and has greater bleeding risk than aspirin alone.

Chronic anticoagulation is contraindicated in some patients due to bleeding risks. Because most atrial thrombi are felt to 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. Percutaneous devices that occlude or ligate the left atrial appendage are being studied for safety and efficacy.

RHYTHM CONTROL

The decision to administer antiarrhythmic drugs or perform catheter 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 is likely because continued AF is a marker of disease severity. In 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 and patient selection bias may be factors that influenced the results of these trials. The impact of catheter ablation on mortality is not known. A rhythm control strategy is usually selected for patients with symptomatic paroxysmal AF, a first episode 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 usually easily achieved. Even if sinus rhythm is apparently maintained, anticoagulation is recommended according to the CHA_2DS_2-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 anticoagulation is reasonable, in addition to addressing possible aggravating factors, including hypertension, heart failure, and sleep apnea. If recurrences are infrequent, periodic cardioversion is reasonable.

Pharmacologic Therapy for Maintaining Sinus Rhythm The goal of pharmacologic therapy is to maintain sinus rhythm or reduce episodes of AF. Drug therapy can be instituted once sinus rhythm has been established or in anticipation of cardioversion. 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 AF episodes. Risks and side effects of antiarrhythmic drugs are a major consideration in selecting