Pharmacologic Management of Atrial Fibrillation and Flutter

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Introduction

Atrial fibrillation (AF) is the most commonly encountered sustained arrhythmia in clinical practice, affecting many millions of people in the USA, with the prevalence expected to triple by 2050 as the population ages [1]. Though inter-patient variability exists and AF may be asymptomatic, AF is generally associated with physical symptoms, a shortened life expectancy, and reduced quality of life (QoL).

The impact AF can have on a patient's health may take several forms. For example, AF can cause palpitations, angina, dyspnea, light-headedness, chronic fatigue, and/or impaired exercise tolerance. Even in the absence of such symptoms, AF may lead to several potentially significant associated conditions, including tachycardia-induced cardiomyopathy and thromboembolism.

Quality of life is adversely affected by the presence of AF in most populations, either due to the presence of symptoms, side effects of medications, or lifestyle disruptions associated with its therapy [2]. All-cause mortality in patients with AF is 1.5–1.9-fold higher than those without AF, regardless of the presence of symptoms [3]. This may be due to the effects of AF itself, toxicities associated with treatment, or commonly found comorbidities such as hypertension, heart failure, and/or valvular disease.

While antiarrhythmic drug (AAD) therapy can mitigate both symptoms and decreased QoL by maintaining sinus rhythm (SR) and/or reducing AF recurrences, clinical trials have thus far failed to conclusively demonstrate that the pursuit of SR with currently available AADs decreases mortality [4–7]. Further analysis of these trials has suggested the absence of AF may be associated with decreased mortality in those who can achieve it without significant proarrhythmia or toxicity [8]. While

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this may be feasible in some patients with some agents, as was demonstrated with dronedarone in the ATHENA trial where a reduction in a combined endpoint of cardiovascular hospitalization and death was attained in a high-risk AF population [9], given the currently available data, the main focus of drug treatment of AF at present remains improving symptoms and QoL in a way that minimizes the side effects and risks from therapy and minimizes the risk for thromboembolism. While ventricular rate control and anticoagulation remain vital components in achieving this goal, it must be emphasized that many patients will not have adequate relief of symptoms until a normal rhythm is established, even after controlling the ventricular rate. Rhythm control, therefore, remains an important and commonly employed [10, 11] part of the physician's armamentarium in treating AF in many patients.

Patterns of AF

Characterizing the pattern of AF is critical in selecting the appropriate rate or rhythm control treatment strategy for an individual patient (Table 16.1). Treatment algorithms in virtually all AF guidelines for therapy are based on this division. While several systems have been proposed to classify AF based on various characteristics, the system that is most practical for clinical use divides AF into groups based on duration of AF episodes and therapeutic history. Note, however, that the frequency of AF episodes is not characterized by this description, nor is the overall burden of AF (total time in AF as a percentage of total time monitored).

AF is termed *paroxysmal* when it terminates without drug or electrical cardioversion within 1 week, *persistent* when self-terminating episodes last longer than 1 week or when therapy is delivered to terminate the rhythm, and *permanent* when a strategy of rhythm control has been either abandoned or never tried and the patient remains in AF indefinitely. The paroxysmal and persistent categories are not mutually exclusive, as both may be seen in a particular individual at different times. The classification of a patient who presents with AF for the first time (new-onset AF) presents a special situation, since the history and clinical decision-making required

Table 16.1 Classification of patterns of AF [11]

Patterns of AF
Paroxysmal Episodes of AF last less than 1 week Terminates spontaneously, without electrical or pharmacologic cardioversion
Persistent Episodes of AF last longer than 1 week *or* Electrical or pharmacologic cardioversion is used to terminate AF
Permanent A strategy of rhythm control has been abandoned or never tried *and* AF is continually present Some also now use the additional term of long-standing persistent AF (generally lasting a year or more) to identify patients in whom drug therapy is no longer considered an option but ablation is

for classification under this system has not yet been established, and, in some cases, it may be due to an acute illness or precipitant with no recurrence after it has resolved. In this case, some time may be necessary to assess the patient's likelihood for spontaneous termination, recurrence, and response to any treatments delivered. Commonly, in all categories, it is assumed that the duration of any episode of AF is >30 sec and that AF is not due to reversible causes (hyperthyroidism, pneumonia, pericarditis, exogenous stimulants, etc.) [11].

Paroxysmal AF

By definition, paroxysmal AF is self-terminating and limited in duration. The choice of therapy is therefore dependent on the presence and severity of symptoms during episodes of AF and the frequency of events. Asymptomatic patients whose rates are controlled with or without medications may not require AAD therapy. Patients with rapid ventricular responses require rate control, which may be sufficient to control symptoms in certain cases. Ambulatory monitoring can be a valuable tool to ensure that rates are reasonable not only at rest but also during daily activities such that rates are comparable (or perhaps 10 bpm higher) during AF than during sinus rhythm at the same level of activity. Rhythm control strategies are most often reserved for those patients who have intolerable symptoms during AF not alleviated by rate-controlling medications and/or frequent annoying events. If episodes are infrequent and tolerable, rhythm control may take the form of intermittent cardioversion of each acute event (even though the episode might self-terminate as per PAF definition were they allowed to persist), most often pharmacologically (see below).

Persistent AF

Patients with persistent AF have either self-terminating episodes of AF that last longer than 1 week or, more commonly, episodes in which therapy is delivered for rhythm conversion. Electrical or pharmacologic cardioversion may be used to terminate events. Patients with persistent AF frequently have more significant degrees of abnormalities in left ventricular ejection fraction, left atrial enlargement, and left atrial contractile dysfunction than paroxysmal patients, abnormalities that may be reversible with the restoration of sinus rhythm [12]. For those patients who have disabling symptoms that are not alleviated by rate control or patients who require more than infrequent cardioversions, a chronic rhythm control strategy is indicated. For patients with infrequent and tolerable events (at least for hours or a day or so), as-needed cardioversion without further antiarrhythmic therapy may suffice. Pharmacologic cardioversion can be achieved with either a single dose of an AAD at the onset of episodes (the so-called "pill-in-the-pocket" approach) [13] or daily dosing of an AAD over a limited period of time. Alternatively, for patients (1) in whom intermittent therapy is inadequate or inconvenient, (2) whose episodes are

not infrequent, and/or (3) whose episodes are not adequately tolerated for even short periods of time, long-term daily maintenance antiarrhythmic drug (AAD) therapy may be used. For those patients who fail AAD therapy or for those who are intolerant of or unwilling to take them, catheter ablation therapy (a topic not covered in this chapter) is an alternative method of rhythm control in the paroxysmal and persistent AF populations [14]. As with PAF, anticoagulation of patients at "high risk" for thromboembolism is employed – and should be continued even if sinus rhythm is restored.

Permanent AF

By definition, a patient with permanent AF is one in whom a rhythm control strategy has been abandoned. Pharmacologic therapy in these patients therefore consists of rate control and, in "high-risk" patients, anticoagulation (see below). As recent advances in catheter ablation techniques expand the population of patients in whom maintenance of sinus rhythm can be achieved to include certain patients with long-term persistent AF [15] as well as left ventricular dysfunction [16], it has become feasible to reconsider the possibility of achieving sinus rhythm in the patient with otherwise presumed permanent AF. In many of these patients, adequate rhythm control may require adjunctive AAD therapy in addition to ablation.

Subclinical AF (SCAF)

Recently, several studies have brought to attention that patients with demographic and laboratory findings common in patients with AF but in whom AF has not presented clinically will be found to have "silent AF" on continuous monitoring, such as by pacemakers, defibrillators, or inserted cardiac monitors. The percentage of such findings of SCAF has varied with the population studied and the length of monitoring, but has been as high as 40% by 30 months. The significance of these findings and the need for treatment targeted at SCAF is under active investigation. Likely the significance relates to both the total AF burden and the specifics of the comorbidities present. Prophylactic therapies are likely to be proven appropriate in the highest risk patients.

Goals of Treatment

Rate Control Versus Rhythm Control

The goal of the pharmacologic treatment of AF, as in any other disease, is to improve the quality and, if possible, the quantity of life while minimizing any potential toxic effects of therapy. Other therapeutic goals specific to the treatment of AF include preventing or reversing cardiac structural changes caused by the persistence of AF and thromboembolism prevention.

In general, the approach to AF therapy has been divided into two possible strategies: (1) controlling the ventricular rate during AF episodes (rate control) and (2) preventing or reducing AF recurrences (rhythm control). Although this division is useful conceptually, it is somewhat artificial in clinical practice, since (a) a strategy of rhythm control does not assure that achievement and maintenance of SR occur and (b) most often, rate control agents are given to rhythm control patients in addition to their AADs to control rates during recurrences. In individual patients, treatment decisions are based on such factors as the severity, frequency, and type of symptoms, the presence of comorbidities, the functionality of the AV node, the toxicities of the treatments under consideration, and the preferences of the patient. In recent years, several trials have been done in order to establish an evidence basis to guide decision-making [4–7, 17, 18]. Below is a discussion of the relative efficacy of these two treatment strategies in achieving selected endpoints.

Mortality

As noted above, epidemiologically, AF has been associated with a significant increase in all-cause mortality compared to patients with SR [3]. It was reasonably expected, therefore, that if this association was causal, then maintenance of SR should lead to reduced mortality. Maintaining SR would then become an endpoint in its own right, without considering the presence or severity of symptoms. Several trials have been completed in recent years addressing this hypothesis [4–7, 17, 18].

The largest such trial completed is the AFFIRM trial, a study of 4060 patients aged 65 or older with AF and other risk factors for stroke or death randomized to either a rate control or rhythm control strategy. In the rate control arm, patients were treated with β (beta)-blockers, calcium channel blockers, and/or digoxin. Patients in the rhythm control arm were treated generally with Class III AADs (largely amiodarone) though some received Class I AADs. Overall mortality by intention-to-treat analysis (the primary endpoint) was not statistically different between the two groups. There was, in fact, a trend toward increased mortality in the rhythm control arm [7].

Other, smaller, trials have found similar results. The RACE trial compared rate and rhythm control strategies in 522 patients with persistent AF and mild-to-moderate heart failure. The rates of achievement of a combined endpoint that included mortality, heart failure hospitalization, pacemaker implantation, hemorrhage, thrombotic complications, and severe adverse events were no different between the two groups [6]. AF-CHF, the first trial to compare rhythm and rate control strategies in heart failure patients, found no difference in total mortality, with a higher rate of hospitalizations in the rhythm control group [17]. Other, yet smaller, randomized trials of treatment strategies in AF including STAF [4], HOT-CAFÉ [5], and PIAF [18] similarly found no differences in mortality between groups (although none were adequately powered to do so). These findings are also in keeping with the results obtained from sub-analyses of AAD therapy in other populations, including DIAMOND-AF [19] and CHF-STAT [20]. A meta-analysis

of available rate vs. rhythm control therapy trials came to the same conclusion and further found that a rhythm control strategy was associated with higher health-care utilization and costs [21].

Several features of these trials bear noting. First, they were designed to compare different *treatment strategies*, as opposed to different *rhythms or specific drugs*. This distinction is necessary because many patients with AF in whom rate control is pursued may continue to have periods of SR (as occurs in paroxysmal AF patients), while those seeking rhythm control may be in AF a significant proportion of time despite AAD or ablative therapy. Note, however, these trials were performed before the widespread availability of ablation, which may or may not adequately reduce AF. Second, there was a high overall degree of crossover between groups (14.9% from the rate control group and 37.5% in the rhythm control group at 5 years in the AFFIRM trial), such that by intention-to-treat analyses, a fair number of patients were analyzed as belonging to a treatment assignment that they did not remain in during the study [7].

Although an orthodox analysis of the randomized data described consistently fails to demonstrate a survival advantage for a strategy of rhythm control, there are data that suggest that when sinus rhythm can be maintained and the toxicities of AAD therapy avoided, patients do significantly better in SR than when left in AF. An on-treatment reanalysis of the AFFIRM data that classified patients into subgroups based on which treatment they actually received, as opposed to which treatment to which they were randomized, found that the presence of SR was associated with a lower risk of mortality, and AAD therapy was associated with increased mortality after adjustment for the presence of SR [8]. This suggests that beneficial effects of SR may have been cancelled out by a harmful effect of the drugs used to achieve it (again, largely amiodarone, which was associated with an increase in non-cardiovascular mortality). Other data from the DIAMOND-AF [19] and the CHF-STAT [20] found a similar positive survival benefit for the presence of SR, although similar analyses in some other drug trials have not duplicated these results [4–6, 18].

An additional point to consider is that patients enrolled in the above mentioned rate vs. rhythm control trials had to be willing to be randomized to either strategy. Patients who were already rate controlled and still symptomatic were highly unlikely to enroll in such trials; hence, such trials should not be taken to indicate that rate control is a reasonable strategy for all AF patients. Similarly, these trials enrolled patients at increased risk for thromboembolism or death. Hence, their results should not be generalized to a lower risk population.

Taken together, the above data suggest that an a priori strategy of rhythm control with currently available AADs should not be undertaken with the expectation of a survival advantage. It is important to emphasize, however, that given the lack of clear increased mortality with rhythm control agents, these data do not suggest that a strategy of rhythm control be withheld from specific patients who have bothersome symptoms during AF in the presence of a controlled rate. It is possible that newer AADs with more favorable safety profiles will deliver the benefits of SR in some patient types without the toxicities of current therapies, as has been suggested by the ATHENA data [9].

Quality of Life and Exercise Tolerance

It is known that AF can adversely affect patients' QoL, exercise tolerance, and functional status in ways unrelated to objective measures of its severity [22], and treatment of AF can improve these endpoints compared to leaving AF untreated [7, 18].

In randomized trials, treatment with a strategy of rhythm control has not conclusively been found to deliver QoL improvements superior to those attained by a strategy of rate control [23–25]. Most studies have found, however, that those patients that are able to achieve SR do appear to have improvements in QoL that exceed those who remain in AF [24, 26]. An important exception is the AFFIRM trial, in which QoL was comparable whether patients were in sinus rhythm or in AF [25]. One explanation for this discrepancy may be the relatively low number of highly symptomatic patients enrolled in the older AFFIRM population.

Rhythm control may be superior to rate control in improving exercise tolerance. In several trials, exercise capacity improved more in patients treated with rhythm control strategies than with a rate control strategy [5, 18, 26, 27]. Finally, in those patients whose primary symptom in AF includes fatigue, as a general rule, rhythm control will be necessary for improvement.

Ventricular and Atrial Structure and Function

AF is associated with changes in the electrical, contractile, secretory, and structural functions of the heart and is synergistic to those associated with any underlying comorbidities. In the atria, structural changes are thought to play a role in the persistence of AF [28] and may explain why SR is more difficult to maintain after cardioversion in patients with a longer duration of preceding AF [29]. In AF, particularly when comorbidities also affect the left atrium, normal protective atrial endothelial secretory function is impaired, such that a prothrombotic state may occur.

Maintenance of SR has been associated with benefits in chamber remodeling in patients with and without clinical heart failure at baseline in some trials [12, 30, 31]. In the RACE, SR was associated with improvements in LV function and reduction in atrial sizes in patients with mild-to-moderate heart failure. Similar improvements were not seen in patients whom the ventricular rate was controlled, although it did prevent deterioration in LV function [30]. In a small study of patients with AF and heart failure that underwent catheter ablation, patients who achieved SR had reductions in LA and LV sizes and increases in ejection fraction, while those that remained in AF showed none of these changes [31]. Similar changes were noted in a larger study of patients undergoing catheter ablation who had relatively preserved baseline LV function [12]. Changes in electrophysiological parameters are also seen with the achievement of SR. Patients who maintain SR 1 week after cardioversion have increased atrial refractory periods and decreased sinus node recovery times and P-wave durations compared to immediately after cardioversion [32].

Prevention of Thromboembolism

AF can be associated with a substantially increased rate of thromboembolic events that is reducible with the use of oral anticoagulants [33, 34]. Anticoagulation, however, can be inconvenient [2], carries its own risks, and does not completely eliminate thromboembolic potential [35]. In years past, a strategy of rhythm control was often used with the anticipated goal of discontinuing oral anticoagulant therapy. Data from both the RACE and AFFIRM trials showed that the rates of thromboembolism were higher in rhythm control patients than in rate control patients, especially if anticoagulation was discontinued or of low dosage, illustrating that a strategy of maintaining SR by itself does not eliminate embolic risk in patients with high-risk markers associated with their prior AF [6, 7]. Important to note is that most of these patients were in SR at the time of their event.

Several observations may explain the above findings. First, restoring electrical normality to a fibrillating atrium does not immediately, if at all, restore mechanical normality [36], and the persistence of atrial dysfunction may result in a continued risk of stroke after SR is restored. Second, recurrences of AF can be asymptomatic and may go unnoticed unless rhythm monitoring is continuous [37]. Third, AF may either cause or be a marker of biochemical alterations at the endothelial and intra-atrial level that may increase stroke risk independent of mechanical considerations and that may persist after SR has been restored [38]. That is, AF and clot propensity may both be downstream effects of atrial dysfunction and that AF itself may not be the (sole) causative factor of increased thromboembolic risk. Certainly, the comorbidities that identify high-risk patients for thromboembolism associated with AF contribute on their own to atrial abnormalities, for example, hypertensives or diabetics have an increased risk for stroke independent of AF. Fourth, if a clot forms in the left atrium during AF, it need not embolize during AF; rather, it may even be more likely to do so after atrial contractility improves as SR persists.

The above suggests that stroke risk persists in "high-risk" patients with AF even after SR has been restored. As a general rule, patients in AF with indications for anticoagulation (see below) should be continued on it even after rhythm conversion. Pursuing rhythm control in an AF patient with stroke risk factors has not yet been shown to reduce their risk of stroke and should not be undertaken for this purpose alone.

Specific Drugs for Pharmacologic Cardioversion and for the Maintenance of Sinus Rhythm

Antiarrhythmic drugs are most commonly divided into classes based on the Vaughan-Williams classification system, which categorized them based on their major mechanism of action (Table 16.2). Recently, an updated classification system has been proposed so as to account for the newer drugs now available and additional information about specific AADs and their mechanisms that has become apparent since the original Vaughan-Williams classification was developed [39]. However, it is too soon to know if this more complex approach will become part of clinical care usage. This section will review the role of these AADs in the conversion to and maintenance of sinus rhythm in AF.

Table 16.2 The Vaughan-Williams antiarrhythmic drug classification

Vaughan-Williams classification					
	Na^+ channel		β-Receptor[a]	K^+ channel	Ca^+ channel
Ia	Ib	Ic	II	III	IV
Procainamide	Lidocaine	Propafenone	Metoprolol	Amiodarone[d]	Diltiazem
Quinidine	Mexiletine	Flecainide	Propranolol	Sotalol	Verapamil
Disopyramide	Phenytoin		Esmolol	Dofetilide	
			Carvedilol[b,c]	Dronedarone[d]	

[a]Among other β-receptor antagonists
[b]Carvedilol also exhibits α-receptor-blocking properties
[c]many other beta-blockers also exist
[d]Amiodarone and dronedarone possess additional properties beyond potassium channel blockade – see text. There are also additional agents with antiarrhythmic properties, such as digitalis, ranolazine, and others, that are not included in this drug classification system

Specific Drugs for Maintenance of Sinus Rhythm

Class Ia

Class Ia agents include quinidine, disopyramide, and procainamide. They are sodium channel-blocking agents that block the channel in a use-dependent fashion, thereby causing rate-dependent QRS widening. Drugs in this class also have other important ion channel and autonomic effects, such as I_{Kr} inhibition in the case of all three of these agents, I_{to} inhibition in the case of quinidine, and vagolytic effects in the case of disopyramide and, less so, quinidine. They have been used for the acute conversion of AF as well as maintenance of SR after conversion. The potassium channel inhibitory effects may be associated with torsades de pointes (TdP)-type proarrhythmia. This risk may be highest with quinidine.

Quinidine

Quinidine is among the first used and best studied of the AADs in AF. Oral quinidine has been shown to increase the odds of SR maintenance over placebo by about twofold in a systematic review of 44 antiarrhythmic trials [40]. It can also be used for the conversion of AF to SR. The PAFAC trial showed that the combination of quinidine plus verapamil achieved maintenance of sinus rhythm after electrical cardioversion in 65% of treated patients [41]. This efficacy was equal to sotalol and better than placebo. In this trial, verapamil appeared to substantially reduce the risk of TdP from quinidine. Overall, however, results have been more variable, success rates varying from 20% to 80% in different reports [42, 43]. Its use has always been limited by its bothersome side effect profile, which includes diarrhea and upper GI intolerance in up to a quarter of patients. More concerning, however, are several reports linking the use of quinidine with an increase in overall mortality [44, 45]. It lengthens the QT interval and carries a risk for torsades de pointes (TdP). If used for AF, quinidine must be initiated in-hospital. Dosing is dependent on the specific congener of the drug used. Serum levels are available and may help guide dosing. Quinidine is available for parenteral use. When used in this manner, which is rare, the daily dose is about 2/3 that of the oral dose.

Procainamide

Procainamide has an efficacy for the conversion of AF that is approximately equal to that of quinidine [46]. Negative inotropic effects, QT prolongation with a risk for TdP, and hypotension complicate intravenous administration for this purpose. It has an active metabolite, NAPA, with similar electrophysiologic characteristics. In one series, intravenous procainamide converted 52% of treated patients, although serious side effects occurred in 10%, including hypotension, bradycardia, and heart block [46]. While these concerns limit its use in most circumstances, it continues to be a drug option in the pharmacological conversion of AF in patients with WPW, where administration of conventional rate control agents is limited by concerns over AV nodal suppression and acceleration of ventricular response through enhanced accessory conduction. Procainamide IV is not FDA approved for AF; however, dosing has generally been the same as for ventricular tachyarrhythmias. Serum monitoring of levels is available and may help guide dosing.

Its long-term oral use for the maintenance of SR has been limited by a side effect profile that includes rash, GI intolerance, neutropenia, and the development of a lupus-like syndrome in up to 30% of long-term users and TdP risk. Oral procainamide is no longer obtainable in the USA as a result of significant market decline over the past few decades.

Disopyramide

There is limited amount of data regarding the use of disopyramide for the treatment of AF. One trial reported efficacy vs. placebo in the maintenance of SR after electrical cardioversion [47]. Substantial negative inotropic and vagolytic effects can limit its use in many patients. Its vagolytic actions may be of some benefit in patients with vagally mediated AF, such as those patients with lone AF that develops nocturnally. In such patients, in our experience, a single dose prior to bedtime may be adequate therapy. Pyridostigmine may reduce its vagolytic effects if substantial, as in men with prostate disorders.

Due to the side effects outlined above, concerns over mortality, and the availability of other classes of drugs, guidelines over the last 1–2 decades no longer consider Class Ia drugs as playing a role in the drug treatment of AF in the majority of patients [11]. However, quinidine may be particularly useful for AF in the setting of short QT syndrome.

Class Ib

Drugs of this class include lidocaine, mexiletine, and phenytoin. They have little effect on atrial myocardium due to their binding kinetics and the electrophysiology of atrial cells. Thus, they do not play a role in treating AF. The exception is mexiletine, which may be useful for AF suppression in patients with long QT type 3 (LQT3) [as may ranolazine].

Class Ic

Available Class Ic agents include flecainide and propafenone. These Class Ic agents potently block sodium channels in a use-dependent manner, have slow association/dissociation characteristics, and can prolong refractoriness. Propafenone has weak beta-blocking effects and even weaker calcium blocker effects in addition to its Class IC actions. Ninety percent of patients are rapid metabolizers of propafenone; the metabolites have Class Ic properties with a similar half-life to the parent, but do not have the beta-blocker actions. Rapid metabolizers need immediate-release propafenone dosed tid, whereas slower metabolizers can take it bid. To facilitate more uniform dosing and greater compliance, a sustained-release formulation of propafenone was developed, which is dosed bid in all patients. The total daily dose equivalent of the sustained-release formulation, however, is about 150% that of the immediate-release preparation. Flecainide has no active metabolites, has very weak $I\mathrm{k_r}$ inhibition, and is mainly cleared via the kidneys. Flecainide and propafenone have been used for the acute conversion of AF as well as maintenance of SR. Both drugs reduce conduction velocity in His-Purkinje tissue, and both can be suppressant to the sinus node. Thus, caution is required in sick sinus syndrome patients and in those with conduction system disease.

Propafenone and Flecainide

The largest studies of propafenone for maintenance of SR were the RAFT and ERAFT studies. RAFT (done in the USA and Canada) and ERAFT (done in Europe) were two trials with similar designs that studied the efficacy of twice-daily *sustained-release* propafenone in patients with PAF. Together, these trials studied over 1100 patients with PAF and randomized them to 325 mg twice a day, 425 mg twice a day, or placebo. In RAFT, a 225 mg twice-daily arm was studied as well. There was a dose-responsive increase in the time to recurrent symptomatic AF over placebo in all propafenone arms [48, 49]. This is consistent with other trials, which have reported similar efficacy [50]. The absolute efficacy rates for the same doses were greater in the RAFT than in the ERAFT trial, a result of a population in ERAFT that had a longer history of AF, a history of more frequent AF events, and more prior therapy resistance.

Flecainide has been found to prolong time to first AF relapse and time between symptomatic episodes in patients with PAF. In one placebo-controlled study, patients treated with flecainide had on average 27 days between symptomatic attacks and 6 days for placebo patients [51]. The efficacy of flecainide is probably similar to that of propafenone; one study comparing the drugs head to head in 200 patients found the chances of safe and effective treatment to be 77% for flecainide-treated and 75% for propafenone-treated patients [52].

Immediate-release propafenone, given as 600 mg orally, has been studied for the acute conversion of AF (initially in the observed setting), where it has been found to achieve SR in 62% of patients 8 hours after administration (about double that of placebo) [53]. Other trials have conversion rates at 8 hours of ~70–80% with both single doses of immediate-release propafenone (600 mg) or single doses of

flecainide (300 mg) with average times to conversion just under 4 hours. Intravenous administration is equally efficacious, but not commercially available in the USA [54]. Generally, unless a patient is already on a rate control drug, a single dose of a rate control agent, such as verapamil 80 mg of its immediate-release formulation, is given about 1 hour prior to the single dose pill-in-the-pocket propafenone or flecainide to protect against possible increased ventricular rates should Class Ic-induced atrial flutter develop (see below).

The safety and efficacy of single out-of-hospital doses of AADs for the conversion of AF have been reported. Alboni et al. studied this "pill-in-the-pocket" approach by giving either weight-based doses of flecainide (200 or 300 mg) or propafenone (450 or 600 mg) to patients with PAF and recurrent AF in whom pharmacological conversion was initially achieved in the hospital. Both drugs were effective in terminating palpitations within 6 hours in 94% of episodes and markedly reduced the number of hospitalizations vs. before the trial began [13]. When used, the first administration of these agents is usually given under observation, and in successful respondents, subsequent events may be treated at home. This is especially true of patients with unknown sinus and AV node function. In patients who are known not to have concomitant sinus node disease, conduction disease, or associated structural heart disease, however, initial administration as an outpatient may be employed. We have done so during the past 2 decades without difficulty. In patients with known sinus node dysfunction or other conduction system disease, caution should be used when administering Ic drugs in any setting.

Propafenone and flecainide are generally considered safe drugs for the chronic suppression of AF in patients with no or minimal heart disease. Perhaps the most serious cardiac side effect of these drugs is the risk of conversion to atrial flutter. Their sodium channel-blocking effects may prolong the flutter cycle length (slow the flutter rate), paradoxically increasing AV nodal impulse transmission, which can occasionally conduct 1:1 to the ventricles. While this is also true of Class Ia drugs, it may be more so with these two agents. To prevent this potentially dangerous situation, many physicians administer these drugs concomitantly with AV nodal blockers. Non-cardiac side effects of flecainide include dizziness and visual changes. The most common side effects of propafenone are a metallic taste disturbance and GI intolerance [55, 56]. In RAFT and ERAFT, discontinuation rates in excess of placebo were only seen with the highest dose, and serious adverse events did not exceed placebo event rates with any dose [48, 49].

The use of Class Ic agents is limited to patients without coronary disease and without structurally abnormal ventricles. This major limitation is in large part due to the results of the CAST trial. CAST studied the effects of flecainide, encainide, and moricizine on mortality in patients with premature ventricular depolarizations after myocardial infarction. The trial was stopped early after it was shown that patients in the encainide and flecainide arms had a higher rate of total mortality (3.0%) as well as fatal and nonfatal arrhythmic events (4.5%) than patients in the placebo arm (1.6% and 1.7%, respectively) [57]. Similar results were later reported in the moricizine arm [58].

As a result of the above findings, patients with risk factors for coronary disease must have documented normal coronary artery anatomy and/or normal results on

stress testing for inducible ischemia before the administration of a Class Ic agent, and these agents must be discontinued in those patients with clinical ischemic events or who develop evidence for coronary artery disease or ischemia from other causes as they age. Likewise, Class Ic agents should not be administered to patients with other ventricular pathophysiological states in which cell-to-cell conduction may be impaired, such as by fibrosis, infiltration, or inflammation, or in the presence of significant ventricular hypertrophy or clinical heart failure. If in doubt, propafenone may be preferable as several lines of evidence suggest a lower risk of proarrhythmic ventricular arrhythmias than with flecainide in ventricular arrhythmia studies.

Class II

Class II agents block β (beta)1- and β (beta)2-adrenergic receptors in the heart and vasculature with varying proportional affinity and are conventionally known as β (beta)-blockers. Some agents have effects on α (alpha)-adrenergic receptors as well (e.g., carvedilol). Some have mild-to-moderate beta agonist action (intrinsic sympathomimetic activity, ISA) as well (e.g., pindolol). Some agents have significant metabolism leading to highly variable serum levels and dose-related effects; these include propranolol and metoprolol which are more reliable if taken with food or if taken as their sustained action preparations. As with sustained action propafenone, the daily dose equivalent with the sustained acting preparations is greater than with the immediate-release congeners. Other beta-blockers, such as nadolol or betaxolol, are not metabolized, but rather are renally excreted. They do not have significant CNS penetration, making them better tolerated (re: side effects of nightmares and fatigue that plague some patients given beta-blockers), and they have more reliable dose-effect relationships. Thus, when using a beta-blocker, familiarity with its pharmacologic properties is essential for their optimal use.

While β (beta)-blockade is generally prescribed for control of the ventricular rate in AF, some basic and clinical data suggest that it may have direct effects in preventing AF occurrence. Data from experiments using isolated human right atrial cardiomyocytes show that chronic treatment with β (beta)-blockers decreases I_{to} current density and phase 1 of the action potential, which prolongs action potential duration and the atrial refractory period [59]. Clinical data support this association. Observational data have suggested a link between β (beta)-blocker use and a decreased incidence of AF [60], and randomized data studying the role of β (beta)-blockers after cardioversion suggest an effect in maintaining sinus rhythm. One placebo-controlled trial of extended release metoprolol showed a decrease in the rate of relapse after cardioversion for persistent AF from 59.9% in the placebo arm to 48.7% [61]. Atenolol and bisoprolol have also been studied in similar circumstances and have been found to be equally effective as sotalol in decreasing AF recurrence after cardioversion without the risk of life-threatening TdP [62, 63], although this similarity in efficacy may only be true when comparing to sotalol in lower doses (see more on sotalol below).

Randomized and meta-analysis data [64] suggest that β (beta)-blockade appears to have particular efficacy in preventing AF after cardiac surgery. The administration of metoprolol after cardiac surgery decreases the incidence of AF occurrence modestly (39% vs. 31% in the placebo arm in one trial) [65]. This efficacy of metoprolol is increased substantially by the use of a strategy 48-h titrated-dose intravenous metoprolol infusion [66]. Carvedilol may be particularly effective in post-cardiac surgery AF prevention, having been shown to be superior to both placebo [67] and metoprolol for this purpose. In one randomized active treatment comparison, the incidence of post-cardiac surgery AF was reduced from 36% in the metoprolol arm to 16% in the carvedilol arm [68]. There is similar data in heart failure patients that suggests greater efficacy for carvedilol than metoprolol.

Less evidence is available regarding the ability of β (beta)-blockers to achieve conversion to SR without electrical cardioversion. Although in one small trial, 50% of the patients given intravenous esmolol converted to SR compared with 12% of patients given verapamil [69], no placebo-controlled data are available, and the administration of β (beta)-blockers for this purpose alone is not recommended [11].

Finally, beta-blockers may also enhance AF rhythm control beyond just rate control by inhibiting catecholamine-induced reversal of the electrophysiologic actions of AADs, something other rate control agents (aside from perhaps verapamil) do not do. Additionally, due to its ISA, pindolol should be the beta-blocker of choice in patients with sinus node dysfunction as it is the least likely to adversely affect sinus rates and has in some series increased the baseline sinus rate about 5 bpm, rather than decreasing it.

Class III

The available Class III agents for AF rhythm control are amiodarone, dofetilide, dronedarone, and sotalol. They all have in common their ability to block K^+ current during repolarization, which has the effect of prolonging the APD and the surface QT interval, although they differ in their pharmacology and full spectrum of antiarrhythmic effects. Amiodarone, dronedarone, and sotalol affect the AV node as well as atrial tissue and will result in some degree of ventricular rate slowing during AF. Amiodarone is available orally and for intravenous administration, as is sotalol. Dofetilide and dronedarone are only available orally.

The major limitation to the use of Class III antiarrhythmics, as a class, is the risk of TdP, a specific type of polymorphic ventricular tachycardia characterized by a rotating axis and QRS amplitude. The basis of the increased risk of TdP with Class III agents is potassium channel inhibition, which prolongs repolarization and can induce early afterdepolarizations. Although TdP most commonly terminates spontaneously, sustained episodes yielding syncope as well as degeneration to ventricular fibrillation can occur. Although all Class III agents have this effect on the QT, some Class III agents (dofetilide, sotalol) appear to have a greater propensity to cause TdP than others (amiodarone, dronedarone) [70]. Moreover, there is some data to suggest that TdP is less likely to stop spontaneously with dofetilide than with

sotalol. The inter-drug differences in TdP risk may be a result of degree of ion channel specificity, differences in the degree of use dependence, and/or actions on non-potassium channels [71]. Patient factors appear to be important as well. For example, women have a longer QT interval than men at baseline and are twice as likely to develop TdP with all QT interval-prolonging drugs. Risk increases in the setting of hypokalemia, hypomagnesemia, and bradycardia [72]. It also increases in the presence of ventricular hypertrophy and impaired metabolism/elimination of the causative drugs. Vigilance in monitoring the QT interval, electrolyte status, and renal function is required to mitigate proarrhythmic risk. The time of greatest risk in AF patients given these drugs is at the time of conversion when post-conversion pauses or bradycardia may occur.

An important issue in the assessment of proarrhythmic risk is the difficulty in accurately measuring the QT interval in AF. Commonly used corrections do not account for variability in the RR interval and are inaccurate at the extremes of heart rate often seen in AF. Recently, a QT correction formula has been derived for use in AF that appears to be more accurate than conventional corrections [73].

Sotalol

Sotalol is a medication with both Class II (β (beta)-blocking) and Class III (K^+-channel-blocking) effects. It is administered as a racemic mixture of l- and d-sotalol and has efficacy for both ventricular and atrial arrhythmias. Although both isomers contribute to sotalol's Class III properties by blocking the rapid component of the delayed rectifier current (Ik_r) and thereby prolonging repolarization, the l-isomer is responsible for virtually all of sotalol's β (beta)-blocking properties. As opposed to amiodarone, sotalol (as well as dofetilide) may decrease defibrillation thresholds in patients with implantable defibrillators [74].

Sotalol is renally excreted. Beta-blocking effects of sotalol are present in doses as low as 40 mg bid and generally plateau at doses between 240 and 320 mg/d. In contrast, in patients with normal creatinine clearance, Class III effects only begin at 80 mg bid and increase progressively thereafter as the dose increases.

Oral sotalol has generally been found to be ineffective for the conversion of AF to SR [75–77] and is not recommended for this purpose [11]. However, it has been found to be effective for the maintenance of SR [78, 79]. In a double-blind placebo-controlled multicenter trial comparing 80, 120, and 160 mg twice-daily sotalol regimens with placebo in 253 patients with AF who were in SR at the time of enrollment, time to recurrence of AF was significantly longer in the groups taking the higher two dosages of sotalol (229 and 175 days) than placebo (27 days) [78]. Similar results were found in another trial that included patients with paroxysmal supraventricular tachycardias in addition to AF [79]. No deaths or episodes of TdP were reported in either trial, which followed strict exclusion and dosing protocols.

Direct comparisons of sotalol with amiodarone have generally found sotalol to be the inferior agent for the maintenance of SR [80–82]. As mentioned above, both the CTAF and SAFE-T trials found greater efficacy for amiodarone than sotalol in freedom from recurrence of AF [80, 81] although some selection biases were present in these trials. Analysis of the AFFIRM data as well as systematic meta-analysis

reached the same conclusion [40, 82]. A possible exception may be in patients with ischemic disease. In the SAFE-T trial, the median time to AF recurrence among ischemic patients was equal between the amiodarone and sotalol groups [81].

Although less efficacious than amiodarone, sotalol has generally been found to have an efficacy for AF reduction/prevention equal to Class Ic agents. A 100-patient randomized trial of propafenone and sotalol in patients who failed previous treatment with Ia agents found no difference between the drugs, with ~40% of patients in each group maintaining SR [83]. This is consistent with data from the CTAF trial, where an equal percentage of patients (37%) in the propafenone and sotalol arms were free of AF at 1 year [80]. One of sotalol's biggest advantages over Class Ic agents is that its β (beta)-blocking properties may make it effective in controlling the ventricular rate during periods of AF breakthrough. In fact, β (beta)-blockers are often administered with Ic agents to mitigate the risk of rapid conduction after conversion of AF to atrial flutter. Because of the risk of TdP, sotalol should not be used only as a rate control agent.

The most important concerns regarding sotalol, which is not organ toxic, are bradycardia, which is dose dependent, and proarrhythmic TdP. The risk of TdP is 2–4% for all indications, although it is highest in those treated for sustained VT and VF and lower in those treated for AF [74, 84]. TdP is more common at higher doses of sotalol (> 320 mg/day), in the presence of decreased renal function (the drug is renally excreted), and female gender [72, 85]. Sotalol may be given to patients with heart failure, but caution should be used in patients with congestive symptoms. In the heart failure population, sotalol is associated with an increased risk of TdP [84] but a decrease in the incidence of shocks in those with an implantable defibrillator [86]. Due to concerns about increased risk of TdP in hypertrophic hearts, the guidelines have not recommended the use of sotalol in patients with more than minimal hypertrophy [11].

Dofetilide

Dofetilide is a highly specific blocker of the rapid component of the delayed rectifier potassium current (I_{Kr}). At least one report suggests that it may also inhibit the late sodium channel. Its effects on the action potential are similar to that of other Class III agents, namely, prolongation of phases 2 and 3 and therefore the surface QT interval. Its main drawback is the potential for proarrhythmic TdP (see below), which is influenced by dose, QT interval, and renal function. Dofetilide is renally excreted and has a renal and QT interval dosing algorithm. Dofetilide also has numerous drug interactions, including some with verapamil and diltiazem that must be noted. For these reasons, it should only be used by physicians who are well familiarized with its complex pharmacology. In its clinical AF trials, TdP was often not self-terminating.

Dofetilide can be used for the conversion of AF to SR. Intravenous dofetilide, which is not commercially available, converted 31% of patients with either AF or atrial flutter into SR compared to 0% with placebo, although efficacy was significantly greater in patients with atrial flutter (54%) than those with AF (15%) [87]. Other trials using oral dofetilide have found comparable conversion rates from AF

as well as atrial flutter [19, 88, 89], but the availability of ibutilide, an available and established intravenous Ik_r blocker, coupled with the need for in-hospital initiation of dofetilide makes its use for this purpose unusual.

Oral dofetilide has been studied in several randomized trials and shown to be efficacious in the maintenance of SR. The SAFIRE-D trial evaluated three doses of dofetilide in patients with AF and atrial flutter. Among 250 patients who converted to SR, all doses of dofetilide achieved higher rates of SR maintenance at 1 year (up to 58% for 500 mcg bid dofetilide) than placebo. Adverse events included TdP in 0.8% (two patients) and one sudden cardiac death, thought to be arrhythmic [89]. The SAFIRE data are consistent with the findings of the EMERALD trial, in which 671 patients with AF were randomized to dofetilide (in one of three dosages), sotalol (but only at 80 mg bid), or placebo. Dofetilide was more effective than either sotalol or placebo. The sotalol comparative findings of the EMERALD trial may be limited, however, in that the one dose level of sotalol used was low and that the trial was only presented in abstract form.

The DIAMOND trial was a study of the effect of dofetilide compared to placebo on mortality in patients with heart failure with or without ischemic heart disease. Overall survival was not different between the two groups. Among those patients with AF or atrial flutter, cardioversion occurred in 59% compared with 34% with placebo and was maintained at 1 year in 79% and 42% of patients, respectively. Restoration of SR was associated with decreased mortality, and dofetilide treatment overall was associated with a decreased rate of hospitalizations. Torsades occurred in four patients (1.6%) with no fatalities [19].

Overall, dofetilide is an effective drug for the conversion of AF or maintenance of SR. Although dofetilide probably has a neutral effect on mortality in patients with heart failure [90], it does have a measurable, if low, risk of TdP, which may not be self-terminating. It must therefore be initiated in a monitored setting, with careful dose adjustments for changes in creatinine clearance (it is renally excreted) and QTc. Since direct comparisons to other AADs with more established efficacy and safety profiles are lacking, it is often not used first line except in heart failure patients [11].

Dronedarone

Dronedarone is a non-iodinated benzofuran derivative of amiodarone without thyroid toxicity and only a minimal risk of pulmonary effects or hepatic effects. Its most common side effects are nausea and diarrhea. These may be less if taken with food. Like amiodarone, serum levels are higher with dronedarone when taken with food versus fasting, so like amiodarone, dronedarone should consistently be taken with food. Unlike amiodarone, dronedarone dosing is bid and only 400 mg doses are available. Among its many ion channel- and receptor-blocking effects, it has AV nodal suppression such that the ventricular rate during AF typically decreases 10–15 bpm. In similarly designed phase III trials (ADONIS and EURIDIS) of dronedarone in patients with paroxysmal or persistent AF that had been cardioverted, dronedarone was associated with a significant increase in time to recurrence compared with placebo (158 vs. 59 days in ADONIS and 96 vs. 41 days in EURIDIS)

and a decrease in the ventricular rate during recurrent episodes [91]. Enthusiasm for dronedarone waned after the results of the ANDROMEDA trial, which evaluated the effect of dronedarone on mortality on patients with recent or active Class IV heart failure in which increased mortality with dronedarone therapy was noted [92]. However, in a retrospective analysis, mortality was increased only in those patients in whom angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) had been discontinued. Insufficiently appreciated at the time, dronedarone decreases renal tubular secretion of creatinine, increasing serum creatinine levels without actually effecting filtration rate, creating the false impression of renal dysfunction. Inappropriate withdrawal of the ACE inhibitors and ARBs, stalwarts of heart failure therapy, rather than just direct effects of dronedarone, which has some calcium-blocking properties, may have been an important contributor to the ANDROMEDA results. Subsequent to ANDROMEDA, the results of the ATHENA trial that evaluated the safety of dronedarone on mortality and rhythm control in 2628 high-risk patients with AF were reported. Without any excessive discontinuation of ACE inhibitors in this trial, which studied patients with similar characteristics to those in AFFIRM, there was a 24% decrease in the combination of all-cause mortality and cardiovascular hospitalization (the trial's primary endpoint) [9]. Reductions in arrhythmic death, acute coronary syndrome, and other clinically important endpoints, including AF, also occurred. In the USA, dronedarone was approved to decrease cardiovascular hospitalization in nonpermanent AF patients with characteristics similar to ATHENA trial enrollees, who do not have Class IV heart failure or recent decompensation. Subsequent to ATHENA, the PALLAS trial was performed [93]. In PALLAS, which enrolled only patients with permanent AF, most of whom had a history of prior unstable heart failure and many of whom were concomitantly taking digitalis, an increased risk of mortality, stroke, and other adverse outcomes was seen on dronedarone vs. placebo. Accordingly, again, dronedarone should not be used in patients with significant heart failure and should not be used in permanent AF for ventricular rate control.

Amiodarone

Amiodarone is a complicated antiarrhythmic that, while classified as Class III, displays characteristics of all antiarrhythmic drug classes. It has a very large volume of distribution due to extensive accumulation in various locations. The half-life of amiodarone is uncertain, but is considered weeks to months. Accordingly, it takes a considerable amount of time to reach steady state and to wash out if it is discontinued. Therefore, amiodarone is often "loaded" before steady-state dosages can be prescribed. The "load" commonly considered suitable in patients with AF is 5 grams (half the 10-gram load typically used for ventricular tachyarrhythmias). Serum levels of amiodarone and its active metabolite are available and may be helpful in determining if loading has been adequate and if washout has been accomplished. Amiodarone has an extensive side effect profile, including optic nerve, pulmonary, neurologic, skin, thyroid, and hepatic toxicity that necessitates long-term follow-up and screening of liver function, thyroid, eye, and pulmonary status on a scheduled basis, regardless of the absence of symptoms for those chronically exposed.

Additionally, amiodarone may increase defibrillation thresholds in patients with implantable defibrillators. Amiodarone is burdened with innumerable drug interactions. No drug should be co-administered with amiodarone without first checking on the interaction potential and required dosing adjustment. If a patient is to be switched from amiodarone to another AAD, the alternative drug should start with a low dose that is later increased as amiodarone washes out and its drug interaction effects dissipate. Despite this formidable description, data from several randomized trials indicate that amiodarone is the most effective antiarrhythmic currently available for rhythm control in treatment of AF [80–82, 94, 95], for which it does not have FDA approval.

The CTAF trial studied 403 patients with persistent and paroxysmal AF with least one episode in the preceding 6 months given open-label amiodarone or another AAD. The other AAD was either propafenone or sotalol (in randomized modest doses), given sequentially in an order that was determined in a second randomization. After initial cardioversion, 65% of amiodarone-treated patients were free from recurrent AF (defined as symptomatic AF lasting at least 10 min) compared with 37% of the propafenone- or sotalol-treated patients. Among those with AF relapse, amiodarone was associated with a longer time to first recurrence than propafenone and sotalol (> 498 compared with 98 days). There was a trend toward increased discontinuation of study medication due to side effects in the amiodarone arm (18% vs. 11%) [80]. Some, but not all, additional comparisons of amiodarone to propafenone and sotalol [95, 96] in patients with paroxysmal AF are consistent with the above findings.

Amiodarone has also been studied in patients with persistent AF. In the SAFE-T trial, 665 patients were randomized to amiodarone, sotalol, or placebo in a blinded fashion. At 1 year, SR was maintained in 52% of amiodarone, 32% of sotalol, and 13% of placebo-treated patients. The median time of recurrence of AF was 487, 74, and 6 days, respectively. In subgroup analysis, the median time to recurrence in patients with ischemic disease was not significantly different between amiodarone and sotalol. Restoration and maintenance of SR were associated with improvements in QoL and exercise capacity [81].

The results described above are supported by data obtained from the AFFIRM trial, where amiodarone was associated with a greater frequency of cardioversion-free SR maintenance than either sotalol or Class I agents [82], as well as by results of a systematic meta-analysis of 44 trials, which found that amiodarone was the most effective drug for the treatment of AF (odds ratios of 0.19, 0.31, and 0.43 for the maintenance of SR compared to placebo, Class I drugs, and sotalol, respectively) [40]. Amiodarone's efficacy may be lowered somewhat by a side effect profile that is greater than with other AADs. One trial found that when taking both tolerability and efficacy into account, propafenone was favored over amiodarone in maintaining SR [94].

Intravenous amiodarone is also effective in converting AF to SR, although its particular pharmacokinetics requires a substantial dosing period (usually >24 hours) and total dose (usually 1–2 gm) before adequate tissue levels accumulate, reducing its immediate-term efficacy. Slowing of ventricular rate, however, may occur with

as little as 300–400 mg of IV amiodarone. For the acute conversion of recent-onset AF, one meta-analysis concluded that oral amiodarone was minimally more effective than placebo for conversion at 6–8 but significantly so at 24 hours [96], while another found an odds ratio of 4.33 for conversion to SR after 48 hours but 1.4 before [97]. In AF of more chronic duration, amiodarone was found to be equally as efficacious as sotalol in the SAFE-T trial after 28 days of treatment (27% vs. 24%, respectively) [80] and equal to propafenone in another study (47% vs. 41%, respectively) [98]. Although efficacy was equal in this latter study, all conversions on amiodarone occurred after 7 days of therapy.

Amiodarone is also effective at increasing the efficacy of electrical cardioversion of patients with chronic AF who do not achieve spontaneous cardioversion on drug. Amiodarone pretreatment renders electrical cardioversion in chronic AF more effective than placebo or diltiazem pretreatment (68–88% efficacy) [99, 100]. It also decreases the frequency of (37% amiodarone vs. 80% placebo) and increased the duration (8.8 months amiodarone vs. 2.7 months placebo) between relapses after cardioversion [99].

Class IV

Non-dihydropyridine calcium channel antagonists, verapamil and diltiazem, block L-type calcium current in cardiomyocytes and AV nodal tissue. Like β (beta)-blockers, they are generally used for the control of ventricular rate in AF. Several studies have investigated potential inherent antiarrhythmic effects of calcium channel blockade. Verapamil, unlike diltiazem, has some antiadrenergic properties via impaired transmission at sympathetic ganglionic nerve terminals. Some studies have suggested that treatment with verapamil can abrogate atrial electrical remodeling seen in acute AF [101–103], suggesting it may have particular benefits when used for rate control in these patients. Some studies, however, have suggested possible proarrhythmic effects of acute calcium blocker administration [104]. Although some data have suggested a modest effect in preventing atrial arrhythmias after thoracic surgery compared to placebo [105], data for its use in maintaining SR after cardioversion have been disappointing [106].

Overall, the data supporting a role for calcium channel blockers in AF outside of rate control are weak, and they are not recommended for this purpose [11].

Specific Drugs for Conversion to Sinus Rhythm

Although AF may convert when any AAD is used, most do not have pharmacological conversion as part of their approved indications; and, other than the pill-in-the-pocket use of propafenone and flecainide, in general, the agents listed above are not specifically given to achieve cardioversion. In contrast, ibutilide (available in limited countries, including the USA) and vernakalant (available in Europe but not in the USA) are.

Ibutilide

Ibutilide, like dofetilide, is a blocker of Ik_r, although it also delays inactivation of the slow inward sodium currents that occur during early repolarization to some degree (likely more so in ventricular than in atrial tissue). In addition to prolonging the QT interval, ibutilide may infrequently cause some mild slowing of the sinus rate [107, 108]. Ibutilide is only available as intravenous infusion and is therefore only used for acute arrhythmia termination.

Two separate trials of ibutilide in patients with AF or atrial flutter of relatively recent onset using two 10-min 1 mg infusions separated by 10 min showed acute conversion rates of 35–47% [109, 110]. Conversion was more common in patients with atrial flutter (63%) than in those with AF (31%), in those with a shorter duration of arrhythmia, and in those with a normal left atrial size [110]. Conversion rates of acute AF and atrial flutter after cardiac surgery have been even higher. Concomitant administration of 4 g of intravenous magnesium with ibutilide enhanced the efficacy of conversion and attenuated increases in QT interval in one trial [111]. Alternatively, $MgSO_4$ may be administered upon conversion to SR or upon the development of ventricular ectopy to reduce the subsequent risk of TdP. Off-label, ibutilide has been given as 2 mg over 30 minutes (the same total dose as above) with the infusion stopped if conversion to sinus rhythm occurs prior to its completion, in hopes that the lower total dose received will have a lower risk of TdP.

The rate of TdP with ibutilide has been 1.7% (sustained) to 8.3% (overall) in large trials [109, 110, 112] and is more common in women [113] and in the other conditions that enhance TdP risk as noted above. Like sotalol, ibutilide exhibits reverse use dependence. Prolongation of the QT is therefore exaggerated at slower heart rates, which may explain an increased propensity toward TdP during bradycardia. Patients treated with ibutilide should have ECG (QT interval) monitoring after the infusion until the QT returns to its baseline level (usually 4 hours or less).

Vernakalant

Vernakalant is an atrial-specific AAD that blocks the ultrarapid K^+ current (Ik_{ur}) and the transient outward current (I_{to}) and has a mild effect on Na^+ channels. Trials of intravenous vernakalant in medical patients have found it to have an efficacy for the acute conversion of relatively recent-onset AF (3–7 days) of 52% compared with 3% of placebo-treated patients, with an average conversion time of 8–11 minutes. Vernakalant was not efficacious in converting atrial flutter, and there were no reported instances of TdP [114]. Intravenous vernakalant was submitted to the FDA for an indication of AF conversion, but an additional trial to increase the size of the overall population studied was requested prior to approval but never completed. However, it was approved and is available in Europe, where another additional trial showed it to be more effective than amiodarone for rapid conversion.

Drugs Used for Rhythm Control that Have Not Been Classically Considered as Antiarrhythmics

Many drugs that do not directly affect the action potential and are not conventionally classified as antiarrhythmics have been studied for their ability to treat AF. These agents are beyond the scope of this chapter, but the interested reader is referred to detailed reviews [115, 116].

Ranolazine

Ranolazine is an inhibitor of the late sodium current that is approved for the management of angina. While it is not approved for AF, ranolazine has been shown to be effective for both converting AF to sinus rhythm and for reducing AF recurrences [117–123]. It is only available orally. When used for AF, ranolazine is dosed the same as for angina: 500 or 1000 mg bid. Its side effects are mainly constipation and occasionally dizziness. It does not cause bradycardia or hypotension, it has not been shown to be proarrhythmic (although it does increase the QT interval by <10 seconds), and it has not been organ toxic. When given in association with QT-prolonging AADs, such as dofetilide, ranolazine has blocked the development of TdP. Ranolazine can be used in patients with and without structural heart disease/ischemia. It also reduces HgB A1C and improves diastolic dysfunction. For AF, ranolazine has been shown effective following cardiac surgery as well as in some patients who have failed both other AADs and ablation or with contraindications to other AADs due to heart failure [124–131]. Additionally, ranolazine has worked as pill-in-the-pocket for converting AF to sinus rhythm (with an average time to conversion <6–8 hours following a dose of 2 gm) [132]. Ranolazine has also been shown to enhance the efficacy of both amiodarone and dronedarone for the termination and the prevention of recurrent AF when given in combination [133–137]. In the HARMONY trial, medium dose ranolazine (750 mg bid) combined with either of two reduced doses of dronedarone (200 mg and 250 mg bid) decreased PAF events to a greater degree than ranolazine alone, dronedarone alone, or placebo. Unfortunately, this combination of lower doses is not yet commercially available.

Specific Drugs for the Control of Ventricular Rate in AF

The main determinant of the ventricular response to AF in patients without an accessory AV nodal connection is the functional refractory period of the AV node, which is in turn determined by intrinsic factors and the balance of sympathetic and parasympathetic tone. Drugs used to slow the ventricular response in AF act either by directly increasing AV nodal conduction/refractoriness properties or by changing autonomic characteristics. Multiple drugs are available for this function, including β (beta)-blockers, non-dihydropyridine calcium channel antagonists, digoxin, and, much less commonly, clonidine. Other medications usually reserved for control of the atrial rhythm, including amiodarone, sotalol, dronedarone, and, to a lesser

extent, propafenone, also have rate-slowing effects in AF. Sotalol, dronedarone, and propafenone should not be used for this purpose. They are mentioned here only to alert the reader that the doses of other rate control agents may need to be adjusted when given in combination with these drugs.

Beta-blockers, calcium channel blockers, and/or digitalis can be combined to achieve rate control if they are not effective alone, especially in patients with normal ventricular function. Negative inotropy is a concern in patients with systolic failure, while combination therapy may increase the risk of bradycardia, especially in those patients with AF and sinus node dysfunction. Permanent pacing may be indicated for paroxysmal AF patients in whom the ventricular rate in AF cannot be controlled without periods of symptomatic bradycardia in SR or for permanent AF patients who have large rate swings in the arrhythmia with rapid rates requiring AV nodal suppression but slow rates necessitating pacer implantation. Alternatively, pindolol should be considered as its ISA properties have reduced the need for pacemaker implantation in this circumstance. Digitalis should not be used in vagal-mediated AF as it may increase the AF burden.

The determination of adequate rate control should be done during ambulation, not just at rest, as a slow resting rate may not equate with control during sympathetic stimulation or other stimulants. Accordingly, for most patients, ambulatory monitoring or exercise testing should be performed when assessing rate control in AF.

Class I

Class I agents are not used for the control of ventricular rate in AF. Although propafenone has weak β (beta)-blocking properties (~1/40th the potency of propranolol on a milligram for milligram basis) and very weak calcium channel-blocking actions, they are too small to provide any clinically meaningful ventricular rate control. Other Class I agents, such as quinidine and disopyramide, have vagolytic effects and have the potential to increase AV nodal conduction.

Class II

By inhibiting adrenergic input into the AV node, β (beta)-blockers act to increase AV nodal refractoriness, thereby prolonging the functional refractory period of the AV node. They are especially effective postoperatively and under circumstances of increased sympathetic tone. Although used mainly for this purpose, they may also have antiarrhythmic effects in certain circumstances, as noted above.

For the acute control of rapid AF, intravenous formulations of β (beta)-blockers such as metoprolol, atenolol, and propranolol can effectively control ventricular rate. Esmolol, a short-acting selective β (beta)1-antagonist, can be particularly useful as a continuous infusion in difficult-to-control cases.

For long-term management, oral β (beta)-blockers such as metoprolol, atenolol, nadolol, bisoprolol, carvedilol, or propranolol (among others) may be given. A

systematic review of the use of β (beta)-blockers for rate control found that compared to placebo, β (beta)-blockers are effective for the control of ventricular rate in AF both at rest and during exercise, usually without deleterious effects on exercise tolerance. Among those β (beta)-blockers studied, nadolol and atenolol were the most efficacious [138]. Notably, they are renally cleared rather than hepatically metabolized and have more prolonged and stable serum concentrations (as does betaxolol). In the AFFIRM trial, β (beta)-blockers were the most effective class of drugs for rate control, achieving target heart rates in 70% of patients vs. 54% for calcium channel blockers [139].

Newer agents such as carvedilol, a nonselective agent with β (beta)- and α (alpha)-adrenergic-blocking activity, are also effective in controlling ventricular rate in AF. In the heart failure population, in whom β (beta)-blocker administration is indicated for its beneficial effects on overall survival [140], carvedilol has been shown to decrease the ventricular rate both at rest and during exercise [141]. Notably, as compared to metoprolol in several studies, carvedilol also has some antiarrhythmic actions and lower mortality risk in heart failure. The efficacy of β (beta)-blockade in this population is of substantial clinical utility, as the administration of diltiazem has been associated with increased mortality events in patients with baseline reductions in ejection fraction [142]. In patients with the brady-tachy syndrome, pindolol is the beta-blocker of choice as its intrinsic sympathomimetic actions prevent worsening of sinus bradyarrhythmias in about 85% of such patients, while its beta-blocking effects are useful in control of the ventricular rate in AF [143].

Class III

Amiodarone, dronedarone, and sotalol can each slow the ventricular rate in AF, although their toxicities and availability of alternative rate control agents limit their use for this purpose alone (see above). Sotalol has effective β (beta)-blocking properties at higher doses and has an advantage over other antiarrhythmics in that breakthrough AF occurs at a slower rate. In one study, sotalol was more effective in controlling ventricular rate during exercise than metoprolol [74].

Amiodarone also has rate-slowing effects in patients that do not achieve conversion. It may have a limited role in rate control in critically ill patients with rapid AF in whom intravenous administration of conventional agents may precipitate or exacerbate heart failure and in whom electrical cardioversion is contraindicated or not desirable. In one study, intravenous amiodarone decreased the mean heart rate in critically ill patients with rapid AF by 37 beats per minute and increased mean blood pressure, while intravenous esmolol, diltiazem, and digoxin had no effect on the heart rate and reduced mean blood pressure overall [144]. Intravenous amiodarone, however, can cause hypotension. Dronedarone, in addition to its effects on preventing AF, is useful for slowing the ventricular rate, as was shown in the ADONIS/EURIDIS and ERATO trials [145]. Rates at rest on Holter monitoring and rates during exercise testing were both improved with this agent (averaging about 10–15 bpm). However, after PALLAS (see above), dronedarone is contraindicated simply for rate control.

Class IV

Calcium channel blockers slow the ventricular response in AF by decreasing L-type calcium current in the AV node, which reduces the height of the action potential, prolongs its duration, and increases the AV nodal functional refractory period.

Both of the most common non-dihydropyridine calcium channel blockers currently in use, diltiazem and verapamil, are effective medications for rate control in AF. They are subject to the same cautions noted above as β (beta)-blockers with regard to bradycardia and decreased inotropy in specific populations [142]. Like beta-blockers, both can slow sinus rates as well as prolong AV conduction. Chronic treatment of patients with systolic dysfunction may be a particular issue with verapamil and diltiazem, as noted above, although calcium channel blockers may be particularly helpful in patients with bronchospastic disease which β (beta)-blockers may aggravate. Particular caution must be exercised when administering combination beta-blockers and calcium channel blockers to patients with symptomatic systolic dysfunction as these patients may be particularly prone to hemodynamic compromise.

Diltiazem and verapamil appear to be equally effective in decreasing ventricular response in AF both at rest and with exercise and may provide more benefits in QoL and exercise tolerance than β (beta)-blockers [146, 147]. A systematic review of calcium channel blockers for control of ventricular rate in AF found similar results [138]. Intravenous formulations may be useful for the acute control of ventricular rate, although infusions are generally required, and hypotension may be a limiting side effect [148].

Digoxin

Digoxin is a cardiac glycoside derived from the foxglove plant. Its main effects are to increase parasympathetic tone, thereby prolonging the functional refractory period of the AV node. It also increases inotropy by inhibiting the Na^+/K^+ ATPase pump, which indirectly increases myocyte Ca^{2+} availability. It is renally cleared, and doses must therefore be adjusted in renal failure.

Digoxin has no role in the conversion of AF, having been shown in randomized trials against placebo to be ineffective for this purpose [149, 150]. Digoxin is, however, extensively used for the control of the ventricular rate in AF. However, because of its mechanism of action, it is most efficacious under conditions in which modulation of parasympathetic tone is most relevant. For example, in a systematic review, the majority of trials of rate control agents in AF that involved digoxin found that while it was effective in slowing resting heart rate, it did not control the ventricular response under exercise conditions [138]. Although some data have suggested that digoxin can be as effective as other agents at rate control in AF [139], most active patients will not achieve adequate control with digoxin monotherapy and must be managed with at least one additional agent. It is therefore most appropriate to use for rate control in sedentary patients and in those with systolic heart failure. Digitalis may increase vagal-induced AF.

Drug Selection in Specific Populations

In all cases, a thorough history and physical exam including basic laboratory tests and evaluation of cardiac function should be performed in every AF patient in order to identify possible reversible causes and precipitants of AF, such as valvular disease, metabolic abnormalities, and thyroid function. The effects of lesser recognized factors, such as caffeine, stress, alcohol, and obesity on the initiation of AF, should not be underestimated. One study demonstrated acute stress, high coffee consumption, and body mass index over 30 as independent risk factors for the development of AF, and acute ingestion of excessive amounts of alcohol is known to precipitate AF in otherwise healthy individuals. Not all types of alcoholic drinks may be equally arrhythmogenic, as specific components (such as tannins contained in wine) may play a role in particular patients. Precipitant issues should be addressed in all patients with AF.

When the decision to initiate antiarrhythmic therapy has been made, drug selection in a particular patient is based on the balance of efficacy and safety of the various available agents in particular patient populations as well as potential pharmacokinetic/pharmacodynamic interactions with any AAD being used. The relevant patient characteristics include left ventricular systolic function, ventricular mass, presence of coronary disease, previous infarction, and renal function (Table 16.3). Recommendations are summarized in Table 16.4 [11].

Table 16.3 Important clinical characteristics in choosing AADs for AF

Important clinical characteristics in choosing AADs
LV dysfunction
Congestive symptoms preclude sotalol use, but reduced LVEF alone does not
Proarrhythmic risk precludes Class Ic use if LV dysfunction or ventricular scar is present
Amiodarone considered first line
Dofetilide may be considered as first or second line
Dronedarone should be contraindicated in severe heart failure, current or recent
Ranolazine is an option
LV mass
Significant LVH precludes Class I, sotalol, or dofetilide use, though disopyramide has been used in hypertrophic cardiomyopathy
Amiodarone considered first line
Ranolazine is an option
Coronary artery disease
Class Ic agents contraindicated
Sotalol, dronedarone, or dofetilide considered first line
Amiodarone considered second line due to toxicities
Ranolazine is an option
Impaired renal function
Toxic metabolites may accumulate with procainamide use
Dofetilide and sotalol contraindicated with severe renal dysfunction, dosing adjustment needed for lesser dysfunction
Caution advised with Class Ic use
Prolonged baseline QT interval
Increased proarrhythmic risk with Class Ia and III AADs

Table 16.4 The selection of AADs in specific populations

Approach to AAD selection for AF rhythm control		
Characteristic	First line	Second line
No or minimal disease	Flecainide Propafenone Sotalol Dronedarone Ranolazine (literature supported but not in the current guidelines)	Amiodarone Dofetilide
Hypertension with LVH	Amiodarone	–
Coronary disease	Sotalol Dofetilide	Amiodarone Ranolazine
Heart failure	Amiodarone Dofetilide	Ranolazine

Minimal Disease

For patients with structurally normal ventricles and normal renal function, first-line drugs include propafenone and flecainide as well as sotalol and dronedarone. These agents are safe and efficacious in this population and can spare patients the toxicities of long-term amiodarone use. All four are essentially devoid of organ toxicity except for very rare reports of liver and lung toxicity with dronedarone – especially if previously present with amiodarone. The Class Ic AADs are also essentially devoid of ventricular proarrhythmic risk in this population, and the TdP risk of sotalol in this circumstance should be less than 1–2% if administered properly. Ranolazine is also reasonable in this patient group.

Although the use of Ia agents for AF rhythm control is discouraged, and they no longer appear in the latest practice guidelines, the vagolytic properties of disopyramide may be of benefit for those cases in which vagal tone is known to be a substantial AF precipitant.

Coronary Disease

For patients with coronary disease who require drug therapy beyond β (beta)-blockade, amiodarone [151, 152], sotalol [153], and ranolazine [120] have neutral effects on mortality in the general post-infarct population. Sotalol is considered first-line therapy given its β (beta)-blocking capacity, although dofetilide plus a rate control agent may also be used. Amiodarone, although effective, is reserved for second-line therapy given its toxicities. Dronedarone is another alternative so long as severe heart failure is absent, as is ranolazine.

For patients with coronary disease and previous infarction, Class Ic agents are contraindicated given an increased mortality when used in this population [57]. These agents are also generally withheld in patients with coronary disease who have not yet had infarction given concern over the potential for proarrhythmia in even

reversible ischemia. Their use in patients without coronary disease but with substantial risk factors is up to the discretion of the physician but requires vigilance in screening for the development of coronary lesions.

Heart Failure

Patients with left ventricular systolic dysfunction and congestive failure are generally treated with ACE inhibitors/ARB and β (beta)-blocker for their beneficial effects on overall survival. These medications, by improving overall hemodynamics and possibly independently, may lower the AF burden in this population. In two large trials of carvedilol in patients with congestive failure [154, 155], patients treated with carvedilol had lower rates of AF and atrial flutter than those treated with placebo.

For patients who require additional drug therapy, the risk of proarrhythmia precludes the use of Ic agents, and congestive symptoms (though not a reduced LVEF alone) would preclude sotalol. Amiodarone is a preferred agent in this population, given its established safety and efficacy [156]. Dofetilide may also be considered as it has been shown to have efficacy in the heart failure population with a neutral effect on overall mortality. If heart failure is severe, dronedarone is contraindicated. Ranolazine is not contraindicated by impaired LV function.

LVH

Substantial left ventricular hypertrophy is a risk factor for thromboembolism in AF [33], is a risk factor for coronary disease and demand ischemia, and is thought to increase the risk of TdP [157, 158]. What constitutes "substantial" is not well established, and some consider a cutoff wall thickness of 14 mm. Because of these concerns, current guidelines advise against the routine use of Class Ic agents, sotalol, or dofetilide in the presence of substantial LVH. Class Ia agents should also be avoided when LVH is present for the same reason. Amiodarone, which carries a lower risk of TdP, is the first and only medication recommended by the guidelines when substantial LVH is present. Those patients with conditions that have a predisposition toward LVH, such as hypertension, but who have minimal or no hypertrophy on imaging, are treated in guideline algorithms as if they have no cardiac disease. Dronedarone has not been studied for AF in this specific circumstance. Additionally, ongoing management of patient's underlying condition is essential.

Anticoagulation

Stroke is one of the most feared complications of AF, occurring in 5% of AF patients per year overall and 14% of those who have already had a stroke [159]. Clinical characteristics including female gender, diabetes, hypertension, clinical heart

failure, prior stroke, and vascular disease [160–162] have been found to increase the risk of stroke. In a pooled analysis of the early AF stroke prevention trials, the relative risk of stroke was 1.4 for patients with congestive failure, 1.6 for hypertension, 1.7 for diabetes, and 2.5 for prior stroke. Age is also an important risk factor, with a continuous relative risk of 1.4 per decade of life [163]. In patients over 75, AF has been found to account for half of all strokes, and AF is the most common cause of disabling strokes among elderly women [164, 165]. Patients under age 60 with none of the above risk factors ("lone AF") have an extremely low incidence of stroke over the long term (1.3% in 15 years) [166].

While early studies suggested that thromboembolic risk was independent of the amount of AF present [167, 168], more recent studies, including some in patients with implanted cardiac devices that have the ability to directly measure atrial activity, have suggested a link between AF burden and increasing risk of stroke [169–171].

The TRENDS study found that patients with a burden of atrial high-rate events (AHREs) greater than 5.5 hours were roughly twice as likely to have stroke or thromboembolism compared with those with lesser burden of AHRE [172]. A lower threshold for increased risk for subclinical AF was seen in the ASSERT study, which found that patients with subclinical AHREs as brief as 6 minutes had a higher incidence of ischemic stroke or thromboembolism. In this study, stroke risk increased with increasing quartile of longest AHRE episode, with a duration of greater than about 18 hours conferring a statistically significant higher risk [173].

While there may be an interaction between AF burden and stroke risk, most patients with AF do not have implanted cardiac devices that can report AF burden, and a substantial number of AF episodes are asymptomatic, even in patients with occasional symptomatic events [174]. Thus, current risk stratification schemes do not yet consider AF burden or classification (paroxysmal, persistent, or chronic) in calculating stroke risk (see below) and rather consider its presence or absence as a dichotomous variable. Current practice, therefore, is to continue preventative stroke therapy in indicated AF patients regardless of classification, even with apparently effective rhythm with antiarrhythmic therapy or ablation.

Several stratification tools have been created to identify patients at high risk based on clinical characteristics. In prior years, the most well-established tool was the $CHADS_2$ score (Table 16.5), which was studied in a population of 1733 patients aged 65–95 with nonrheumatic AF. For each one-point increase in the $CHADS_2$ score, the risk of stroke without treatment increases by 1.5-fold [33].

Although the $CHADS_2$ has useful predictive value, the recognition that additional clinical characteristics could enhance the diagnostic resolution of the $CHADS_2$ scale led in 2010 to the introduction of the CHA_2DS_2-VASC scoring system, which modifies the original by adding categories for gender and vascular disease and emphasizes the effect of age on stroke risk by assigning one point for age 65–74 and two points for age $\geq$ 75 (Table 16.6) [175]. In a cohort of 1084 patients, a study of the CHA_2DS_2-VASC showed improvement in predictive value over the original $CHADS_2$ system. It fares particularly well in predicting low-risk patients; no thromboembolic events were seen in the cohort of patients predicted to be low risk. Its utility in this regard was confirmed in a Danish study of 47,576 non-anticoagulated

Table 16.5 The $CHADS_2$ risk score and associated stroke risk [33]

$CHADS_2$ score	
Clinical risk	Score
Congestive heart failure	1
Hypertension	1
Age ≥ 75	1
Diabetes mellitus	1
Stroke or TIA history	2

		$CHADS_2$ score		
Score	No. patients	No. strokes	Adjusted stroke rate per 100 patient-years	95% CI
0	120	2	1.9	1.2–3.0
1	462	17	2.8	2.0–3.8
2	523	23	4.0	3.1–5.1
3	337	25	5.9	4.6–7.3
4	220	29	8.5	6.3–11.1
5	65	6	12.5	8.2–17.5
6	5	2	18.2	10.5–27.4

Table 16.6 The CHA_2DS_2-VASc risk score and associated stroke risk [33]

CHA_2DS_2-VASc score	
Clinical risk	Score
Congestive heart failure	1
Hypertension	1
Age 65–74	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke or TIA history	2
Female gender	1
Arterial vascular disease	1

		CHA_2DS_2-VASc score		
Score	No. patients	No. strokes	Thromboembolism rate at 1 year	95% CI
0	103	0	0	0–0
1	162	1	0.6	0.0–3.4
2	184	3	1.6	0.3–4.7
3	203	8	3.9	1.7–7.6
4	208	4	1.9	0.5–4.9
5	95	3	3.2	0.7–9.0
6	57	2	3.6	0.4–12.3
7	25	2	8.0	1.0–26.0
8	9	1	11.1	0.3–48.3
9	1	1	100	2.5–100

registry patients with AF and $CHADS_2$ scores of 0–1 who were reclassified by CHA_2DS_2-VASC. In this population, all of whom were considered to be low risk by $CHADS_2$ criteria, risk of stroke or thromboembolism increased from 0.84% per 100 person-years in patients with a CHA_2DS_2-VASC score of 0 to 8.18% in those with a CHA_2DS_2-VASC score of 4 [176].

Table 16.7 Trials of the prevention of thromboembolism in AF

Stroke prevention trials in AF		
Trial	Summary	References
EAFT	Warfarin vs. placebo (secondary prevention)	[139]
BAATAF	Low-intensity warfarin vs. placebo (or ASA)	[148]
SPAF I	Warfarin vs. ASA vs. placebo	[149]
AFASAK	Warfarin vs. ASA	[150]
CAFA	Warfarin vs. placebo	[151]
VA Study	Low-intensity warfarin vs. placebo	[152]
RE-LY	Dabigatran 110 mg vs. 150 mg vs. warfarin	#
ARISTOTLE	Apixaban 5 mg vs. warfarin	#
ROCKET-AF	Rivaroxaban 20 mg vs. warfarin	#

Current guidelines recommend the use of CHA_2DS_2-VASc score in stratifying thromboembolic risk in patients with nonvalvular AF. In general, oral anticoagulation is started in patients with a score of ≥ 2 who have paroxysmal or persistent AF and do not have contraindications to anticoagulation therapy. For patients with a CHA_2DS_2-VASc score of 0, current guidelines state that it is reasonable to omit antithrombotic therapy, and for those with a CHA_2DS_2-VASc score of 1, ASA alone, oral anticoagulation, and no antithrombotic treatment are options [177, 178] (Table 16.7).

Drugs for Anticoagulation of AF Patients

Warfarin and ASA

The utility of warfarin in stroke prevention in AF was largely established in six large clinical trials published between 1989 and 1999 (Table 16.6) [161, 179–183]. Together, these trials showed a 62% decrease in stroke for adjusted-dose warfarin monotherapy, significantly better than aspirin (ASA) or placebo. The benefit of warfarin is present in all age groups, in risk profiles, and in those both with and without prior stroke [161, 163, 184]. The generally recommended INR range is 2–3. Stroke rates rise steeply at values below 2, while higher levels of anticoagulation increase rates of major bleeding without equal benefit in stroke prevention [185, 186]. The rate of increase in bleeding with INRs above 3.0 is more gradual than the steep increase in risk for embolism at INRs below 2.0.

The effect of ASA on stroke risk is more modest than that of warfarin and has not been seen in every trial. In one meta-analysis, ASA therapy was associated with a 20% reduction in stroke events overall, although it seems to be less effective in those at highest risk [159]. Part of the utility of ASA may be in its superior prevention of non-cardioembolic stroke in patients with atherosclerotic risk factors [187]. ASA appears to be most useful in patients judged to be at lower risk of stroke. One pooled analysis found that in patients aged 65–75 without other stroke risk factors, the baseline stroke rate (4.3%/year) was decreased to nearly the same degree by ASA therapy (1.4%/year) as with warfarin (1.1%/year) and concluded that ASA treatment seemed adequate in low-risk populations [184]. There are no data

regarding the effects of different ASA dosing regimens, although only 325 mg daily showed efficacy in the ASA-warfarin trials. Adding low-dose warfarin therapy to ASA is inferior to adjusted-dose warfarin monotherapy in stroke prevention, as shown in the SPAF III trail, and is not recommended [188]. ASA therapy in combination with clopidogrel is inferior to warfarin [189] but superior to ASA therapy alone, although with a small increase in bleeding endpoints [190].

The greatest hazard of anticoagulant or antiplatelet therapy is the risk of bleeding, particularly intracranial hemorrhage. Hemorrhage risk is higher with warfarin therapy than with ASA [191] and is highest in those given combined therapy [192]. Particular care must be taken in elderly patients, in whom stroke prevention therapy is effective, although it has been associated with a higher risk of bleeding than in younger patients in some [179, 193], though not all, trials [194].

NOACs

Initial trials in the pharmacological prevention of thromboembolism focused on the role of warfarin, which was the only systemic oral anticoagulant available at the time. Although warfarin's utility in stroke prevention in AF is now well established, its narrow therapeutic window requires frequent monitoring, a regulation of dietary vitamin K intake, and close consideration of its over 800 reported drug-drug interactions. As a result, the time patients spend with therapeutic levels of warfarin ranges from about 55–65% in clinical trials [195–197] and is likely lower in the community setting [198].

More recently, newer anticoagulants that do not require routine monitoring of drug levels have been introduced. Since 2010, the direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban, rivaroxaban, and edoxaban have been approved for the reduction of thromboembolic risk in AF. A fourth factor Xa inhibitor, betrixaban, has been studied for the prevention of venous thromboembolism in hospitalized patients, but has not been approved for the treatment of AF [199]. Together, the newer anticoagulants are referred to as either *novel* or *direct* oral anticoagulants (NOACs or DOACs). Overall, DOACs have been found to be equivalent and in some cases superior to warfarin both in thromboembolic risk reduction and bleeding risk. The most recent practice guidelines recommend the use of DOACs that are first-line therapy over warfarin in eligible patients [200].

It should be noted that the DOACs currently used for stroke prevention in AF were evaluated in AF of nonvalvular origin, defined as AF in the absence of a mechanical prosthetic valve or mitral stenosis greater than moderate severity. In AF patients with valvular AF or mechanical prosthetic valves, warfarin remains the treatment of choice. A summary of DOACs is presented in Table 16.8.

Dabigatran

Dabigatran is a direct inhibitor of thrombin. It is administered as a prodrug (dabigatran etexilate), which is converted by a serum esterase into the active drug. It has a half-life of 12–17 hours and is excreted primarily by the kidney [201].

Its utility in thromboembolic risk reduction in AF was studied in the RE-LY trial, a prospective, open-label, randomized, non-inferiority study (with blinding of event

Table 16.8 DOACs approved for use in AF

		DOACs	
Drug	Inhibitor of	oral half-life	Manufacturer-recommended creatinine clearance (mL/min) adjusted dosing
Dabigatran	Thrombin	12–17 hours	> 30: 150 mg bid 15–30: 75 mg bid < 15: no dosing recommendation[a]
Rivaroxaban	Factor Xa	5–9 hours	≥ 50: 20 mg daily < 50: 15 mg daily[a]
Apixaban	Factor Xa	12 hours	*Non-ESRD patients* Usual dose 5 mg bid ≥ 2 of age > 80, weight < 60 kg, serum Cr > 1.5: 2.5 mg bid *Stable dialysis patients* Usual dose: 5 mg bid ≥ 1 of age > 80, weight < 60 kg: 2.5 mg bid
Edoxaban	Factor Xa	10–14 hours	> 95: not recommended 50–95: 60 mg daily 30–50: 30 mg daily < 30: not recommended[a]

[a]Current practice guidelines recommend against the use of dabigatran, rivaroxaban, and edoxaban in patients on dialysis and/or with end-stage renal disease [2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation]

analyses) of dabigatran compared with warfarin. RE-LY enrolled AF 18113 patients with EF < 40, age ≥ 75, or age 65–75 with either diabetes, hypertension, or coronary artery disease. Key exclusions included patients with severe valvular disease, recent CVA, or a creatinine clearance of <30 ml/min. The mean age of participants was 71 years, and the mean $CHADS_2$ score was 2.1. Patients were randomized to one of three groups: dabigatran in either twice-daily 110 mg or 150 mg doses and warfarin. Dabigatran 150 mg was superior to warfarin in the primary outcome of stroke or thromboembolism (1.69%/year vs. 1.11%/year), while the 110 mg dose was non-inferior to warfarin (1.53%/year). Both dabigatran doses were superior to warfarin in the rates of hemorrhagic CVA (0.38%/year for warfarin, 0.12%/year for dabigatran 110 mg, and 0.10%/year for dabigatran 150 mg). For the endpoint of major bleeding, dabigatran 110 mg (2.71%/year) was superior, and the 150 mg dose (3.11%/year) was non-inferior to warfarin (3.36%/year). Mortality reduction was borderline significant for dabigatran 150 mg bid. In subgroup analysis, both gastrointestinal bleeding and myocardial infarction were both seen more frequently in the 150 mg dabigatran group. A subsequent FDA study of 134,000 Medicare patients found that dabigatran use was associated with lower mortality and higher gastrointestinal bleeding than warfarin and failed to find a higher rate of infarction [202].

Dabigatran is the only DOAC that has been assessed in a randomized trial for use in mechanical prosthetic valves. The RE-ALIGN trial randomized patients with either new or prior aortic or mitral mechanical valves to warfarin or dabigatran. The dose of dabigatran was adjusted to achieve a minimum plasma level and was higher

in most patients than is typically used for AF. The study was terminated prematurely due to an excess thromboembolic and bleeding risk in the dabigatran group [203].

Uninterrupted dabigatran has also been evaluated in comparison to uninterrupted warfarin in patients undergoing ablation for AF. The RE-CIRCUIT trial showed a decreased incidence of major bleeding and pericardial tamponade in 704 patients during and for 8 weeks after ablation with only one thrombotic event occurring in the warfarin group [204].

Commercially, in the USA, for AF, dabigatran is available in 150 mg and 75 mg dosages. The 75 mg dose is recommended for patients with a creatinine clearance of 15–30 mL/min, although it was not studied in the RE-LY trial. It is not recommended for patients with a creatinine clearance <15 mL/min.

The most common side effect of dabigatran is dyspepsia. Proton pump inhibitors can be effective at decreasing dyspepsia but, in one study, decreased the rate of absorption of the drug [205]. Taking the drug with food may also decrease the GI symptoms. In RE-LY, the discontinuation rate because of GI symptoms was about 5% higher than on placebo.

Apixaban

Apixaban is a direct inhibitor of factor Xa. It has a half-life of 12 hours when given orally due to prolonged absorption. When given parenterally (a route not commercially available), the half-life is 5 hours. About 27% of the administered dose (and about half of the absorbed dose) is excreted renally [196].

Apixaban is the only DOAC that has been compared directly to ASA for AF. The AVERROES trial was a double-blind trial of twice-daily apixaban compared to ASA in AF patients deemed unsuitable for warfarin. The trial was stopped prematurely due to the superiority of apixaban in reducing stroke or systemic embolism. The rates of bleeding were similar in the two groups [206].

Apixaban was compared to warfarin in the ARISTOTLE trial, a double-blind study that randomized 18,201 patients with AF or atrial flutter and at least one $CHADS_2$ risk factor to either apixaban or warfarin [207]. Key exclusions included moderate or severe mitral stenosis, reversible AF, recent CVA, a requirement for concurrent ASA and clopidogrel or ASA alone ≥165 mg, and a creatinine clearance of <25 mL/min or a serum creatinine of >2.5 mg/dL. The mean $CHADS_2$ score was 2.1, and the mean age was 70 years. Apixaban was given twice daily at 5 mg and was reduced to 2.5 mg twice daily for patients who had ≥2 of the following: age > 80 years, weight < 60 kg, or a serum creatinine of >1.5 mg/dL.

Apixaban was superior to warfarin for the primary outcome of ischemic and hemorrhagic CVA (1.27% vs. 1.60%/year), as well as for the outcomes of death from any cause (3.52% vs. 3.94%/year), and major bleeding (2.13% vs. 3.09%/year). Hemorrhagic CVAs were reduced from 0.47%/year with warfarin to 0.24%/year with apixaban.

Although patients with creatinine clearance <25 mL/min and serum creatinine >2.5 mg/dL were excluded from both AVERROES and ARISTOTLE, data in a limited number of stable hemodialysis determined that apixaban levels in these patients were only modestly increased, and dialysis had a limited impact on apixaban

clearance compared with patients with normal renal function [208]. On the basis of these data, prescription guidelines have been adjusted to include a 5 mg twice-daily dosing for patients on stable hemodialysis, with an adjustment to 2.5 mg in patients with weight < 60 kg or age > 80 years.

Rivaroxaban

Rivaroxaban is an inhibitor of factor Xa. Although its half-life is 5–9 hours, based on efficacy and safety data obtained in phase II trials, it is administered daily for thromboembolism prevention in AF [209]. It is approximately 33% renally excreted. To maximize absorption, it should be given with a meal; in the ROCKET-AF trial, this was in the evening.

ROCKET-AF was a randomized, double-blind, double-dummy trial comparing rivaroxaban to warfarin for the prevention of stroke or thromboembolism in 14,264 patients with nonvalvular AF and prior stroke or ≥ 2 of ejection fraction ≤35%, hypertension, age > 75 years, or diabetes. Rivaroxaban was given at a 20 mg daily dose in those with normal renal function and 15 mg daily in patents with creatinine clearance 30–49 mL/min. Key exclusions included hemodynamically significant mitral stenosis, prosthetic heart valve, recent stroke, treatment with ASA > 100 mg, and a creatinine clearance of <30 mL/min. The mean $CHADS_2$ score was about 3.5, and the median age was 73 years.

In an intention-to-treat analysis [as was used for the primary analyses of the above DOAC AF vs. warfarin trials], for the primary endpoint of ischemic and hemorrhagic stroke or thromboembolism, rivaroxaban was non-inferior (though not superior) to warfarin (2.1% vs. 2.4%/year). Rates of major and nonmajor clinically relevant bleeding were similar between the two groups (14.9% vs. 14.9%/year), as were rates of major bleeding (3.6% vs. 3.4%/year). There was a significant decrease in hemorrhagic strokes in the rivaroxaban group (0.5% vs. 0.7%/year).

The manufacturer recommends a dose of 20 mg daily rivaroxaban to patients with a creatinine clearance of ≥50 mL/min and 15 mg daily in those with a creatinine clearance of <50 mL/min. Although patients with a creatinine clearance of <30 mL/min were not studied in ROCKET-AF, pharmacologic studies suggest that a dose of 15 mg daily in patients with a creatinine clearance of ≤15 mL/min (including those on stable dialysis) should achieve serum levels similar to those in patients with moderate renal dysfunction [210]. Current practice guidelines, such as the 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation, however, recommend against the use of rivaroxaban (as well as edoxaban and dabigatran) in patients on dialysis and/or with end-stage renal disease due to the lack of clinical data in such patients.

Edoxaban

Like rivaroxaban and apixaban, edoxaban is an inhibitor of factor Xa. Its half-life is 10–14 hours, but, similar to rivaroxaban, edoxaban is given as a daily dose due to safety and efficacy data obtained in phase II trials [211]. It has 50% renal excretion, and the dose is adjusted for renal dysfunction.

Edoxaban was studied in the ENGAGE AF-TIMI 48 trial, which was a randomized, double-blind, double-dummy trial of 21,105 AF patients ≥ age 21 with $CHADS_2$ score ≥ 2 randomized to either 60 mg edoxaban, 30 mg edoxaban, or warfarin. In both edoxaban groups, the dose was cut in half (to either 30 mg or 15 mg) if the creatinine clearance was between 30 and 50 mL/min or the weight was <60 kg. Key exclusions were reversible AF, the need for concomitant dual antiplatelet therapy, increased bleeding risk, or moderate or severe mitral stenosis. About 75% of the population had a $CHADS_2$ score of ≤3, and about 40% were ≥ 75 years of age.

For the primary endpoint of time to first ischemic or hemorrhagic stroke or thromboembolism, a pre-specified modified intention-to-treat analysis showed that the 60 mg edoxaban dose (1.18%/year) was superior to warfarin (1.8%/year), while 30 mg edoxaban (1.61%/year) was non-inferior to warfarin. In an intention-to-treat analysis, neither edoxaban dose proved superiority to warfarin. Major bleeding was significantly decreased in both edoxaban doses (1.61% and 2.75%/year for 30 mg and 60 mg, respectively) compared with warfarin (3.43%/year). There were significantly fewer hemorrhagic strokes in both edoxaban doses (0.26% and 0.47%/year for 30 mg and 60 mg, respectively) compared with warfarin (0.47%/year). There was a statistically significant decreased risk of death from any cause in the 30 mg edoxaban group (and a trend toward decreased death in the 60 mg edoxaban group) compared to warfarin.

Based on these data, edoxaban is available as a daily 60 mg dose for patients with a creatinine clearance of 50–95 mL/min and 30 mg daily in those with a creatinine clearance of 30–50 mL/min. In ENGAGE AF-TIMI 48, an increased risk of thromboembolic events was seen in patients with a creatinine clearance of >95 mL/min due to increased clearance of the drug. The drug should therefore not be used in such patients.

Interactions

Dabigatran, apixaban, rivaroxaban, and edoxaban are all substrates for the efflux transport P-glycoprotein. Theoretically, therefore, inhibitors of P-glycoprotein (such as ketoconazole, rifampin, amiodarone, quinidine, dronedarone, and clarithromycin) would be expected to increase bleeding risk, and inducers (such as carbamazepine, rifampin, phenytoin, and St. John's wort) reduce efficacy. Care should be exercised with the co-administration of any of these medications. However, since the factor Xa inhibitors are also hepatically metabolized, whereas dabigatran is not, use of a P-glycoprotein inhibitor in the absence of a hepatic enzyme inhibitor is not contraindicated with these agents in contrast to dabigatran. Both apixaban and rivaroxaban are contraindicated with drugs that are strong combined P-glycoprotein and P 450 CYP-3A inhibitors (such as ketoconazole and ritonavir). No dose reduction is recommended for edoxaban with the concomitant use of P-glycoprotein inhibitors, as dose reduction in these patients in ENGAGE AF-TIMI 48 led to reduced serum levels.

Transitioning to and from Warfarin and DOACs

When transitioning from warfarin to DOACS, the general recommendation is to start the DOAC when the INR falls below a certain level (< 3 for rivaroxaban, < 2.5 for edoxaban, and < 2 for dabigatran and apixaban).

When transitioning between DOACs, it is generally recommended to start the new DOAC at the usual next dosing interval for the prior medication. When transitioning from parenteral intravenous anticoagulants to DOACs, the DOAC should be started at the usual next dosing interval (edoxaban, apixaban) or between 0 and 2 hours prior (rivaroxaban, dabigatran). When transitioning from unfractionated heparin to edoxaban, an interval of 4 hours is recommended.

In trials evaluating apixaban, rivaroxaban, and edoxaban, an increase risk of thromboembolic events was seen with the discontinuation of the DOAC, leading to these medications receiving a black-box warning advising the use of an alternative anticoagulant whenever possible when these medications are prematurely discontinued. This is not due to rebound, but, rather, to the short half-life of these drugs as compared to the time of effect when warfarin was started upon their discontinuation in the absence of heparin bridging. The transition from DOAC to warfarin is particularly difficult, as warfarin may take several days to achieve a therapeutic INR, the value of which may itself be affected by the concomitant administration of a DOAC. One approach to minimize this difficulty is to stop the DOAC, start a parenteral anticoagulant and warfarin at the time of the next scheduled dose, and stop the parenteral anticoagulant when the INR is therapeutic.

Specific manufacturer recommendations include to start warfarin 3 days prior to starting dabigatran (2 days if the creatinine clearance is 30–50 mL/min and 1 day if it is 15–30 mL/min) and to start half-dose edoxaban at the time of warfarin initiation, stopping edoxaban when the INR ≥ 2.

Reversal

At the time of their approval, one of the disadvantages of the DOACs was the inability to easily reverse the anticoagulation. While dabigatran is partially dialyzable, the remaining DOACs are sufficiently protein-bound that dialysis does not significantly alter their concentration.

In 2015, the monoclonal antibody idarucizumab was approved by the FDA for the acute reversal of the effects of dabigatran. In the RE-VERSE AD trial, it was found that 5 mg idarucizumab durably and rapidly reversed the anticoagulant effects of dabigatran in a population of 503 patients presenting with serious clinical bleeding or the need for urgent surgery [212].

More recently, andexanet alfa, a recombinant factor Xa, has been assessed for the reversal of inhibitors of factor Xa. In studies with both apixaban and rivaroxaban, an intravenous bolus followed by infusion of recombinant factor Xa significantly diminished anti-Xa activity in healthy subjects, which led to FDA approval of the medication in 2018 [213]. As the medication has yet been not studied with edoxaban, it is not approved for use with this medication. A prospective trial in patients

with clinical bleeding is underway. Importantly, however, the dosing is not the same when used to reverse apixaban vs. rivaroxaban.

The synthetic cation ciraparantag is an agent capable of reversing the anticoagulant effects of unfractionated and low-molecular-weight heparin, fondaparinux, and DOACs via noncovalent hydrogen bonding and charge-charge interactions and is currently under investigation [214].

Triple Therapy

AF patients who undergo percutaneous coronary intervention (PCI) for coronary artery disease are commonly placed on dual antiplatelet with ASA and a $P2Y_{12}$ inhibitor in addition to anticoagulant therapy and are at higher risk of bleeding than patients on anticoagulants and aspirin alone. Several studies have assessed alternative drug regimens in such patients. The WOEST trial showed that in AF patients on warfarin who underwent PCI, treatment with ASA and clopidogrel (in addition to warfarin) resulted in increased bleeding compared to therapy with clopidogrel and warfarin alone [215]. Similarly, decreased risk of bleeding has been seen when using either dabigatran [216] or low-dose rivaroxaban [217] in combination with a $P2Y_{12}$ inhibitor alone after PCI. It should be noted, however, that these trials were not powered specifically to detect differences in rates of thrombosis. Some evidence indicates that for patients that require triple therapy with an anticoagulant, $P2Y_{12}$ inhibitor, and aspirin, clopidogrel may have less bleeding risk than prasugrel [218]. In patients on oral anticoagulation after drug-eluting stent placement, the randomized ISAR-TRIPLE trial determined that after 9 months of follow-up, there was no difference in bleeding or thrombotic events among patients receiving aspirin, oral anticoagulation, and either 6 months or 6 weeks of clopidogrel [219].

Atrial Flutter

Atrial flutter can be defined generally by surface EKG as a non-sinus atrial arrhythmia with an atrial rate between 200 and 400 bpm [220]. Defined mechanistically, "atrial flutter" as will be discussed here refers to a reentrant circuit rotating around the tricuspid valve. Also known as "typical" flutter, this rhythm most commonly travels in a counterclockwise manner and produces characteristic negative sawtooth flutter waves in the inferior leads on EKG.

Both atrial flutter and AF may occur in the same patient. Most often, periods of AF initiate flutter by forming functional components of the flutter circuit [221], although atrial flutter may exist in the absence of AF. A large population cohort study showed that among patients hospitalized with an episode of atrial flutter, nearly 50% were hospitalized with AF in the ensuing 5 years [222].

Atrial flutter can cause a similar spectrum of symptoms as AF, including thromboembolism. In some patients, because of the rapid organized manner of impulses reaching the AV node, the ventricular response to atrial flutter is more rapid and more difficult to control in AF than during AF. Conduction that occurs in a 1:1 manner may be poorly tolerated and result in syncope. The goals of treatment in atrial

flutter are therefore similar to those in AF, that is, the alleviation of symptoms, prevention of thromboembolism, and the minimization of treatment toxicities.

One of the main differences in treatment of AF and atrial flutter is that since atrial flutter is caused by a defined circuit that can be easily accessed through the venous system, catheter ablation can be accomplished with little morbidity and with an approximately 90% cure rate [224]. As a result, ablation is considered much earlier in the course of treatment than in AF. When ablation is not pursued or desired, AAD treatment may be used for the pharmacological conversion, as an adjunct to electrical cardioversion, and for the long-term maintenance of SR. Although Class Ia agents [46, 55] have been shown to be effective for cardioverting atrial flutter, the best evidence is for Class III drugs, particularly dofetilide and ibutilide. Intravenous administration of ibutilide has a 63% efficacy rate for the conversion of atrial flutter to SR compared to 31% for AF [109], while oral treatment with dofetilide is significantly more likely to maintain SR when given for atrial flutter than for AF [89]. Studies of AADs in atrial flutter have generally included AF patients, so efficacy in this population alone has not been well established for most drugs. As with AF, clinical characteristics must be taken into account to choose an AAD that maximizes safety.

Anticoagulation for the prevention of systemic embolization is an important component of atrial flutter therapy, as it is with AF. The risk of stroke may be slightly lower for patients solely with atrial flutter than with AF, but it remains elevated compared to normal controls, and the frequent coexistence of the two rhythms makes this distinction irrelevant in most patients [223, 225]. Patients with atrial flutter are therefore treated with the same anticoagulation strategy as those with AF described above.

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