# Management of Atrial Fibrillation: Focus on Rate Versus Rhythm Control

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*Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults and accounts for approximately one-third of all arrhythmias requiring admission to the hospital. Treatment strategies are determined by the classification of AF, whether paroxysmal or persistent, as well as numerous patient-specific cardiac and medical considerations (eg, pre-existing congestive heart failure or previous myocardial infarction). Thromboembolic risk also influences whether patients are treated with antiplatelet or anticoagulant medications. Several large clinical trials have deemed both rate and rhythm control acceptable treatment strategies for AF. Additionally, nonpharmacologic approaches such as surgical and electroablative options also exist. The clinician must exercise sound clinical judgment when deciding which treatment approach is best suited for a particular patient.*

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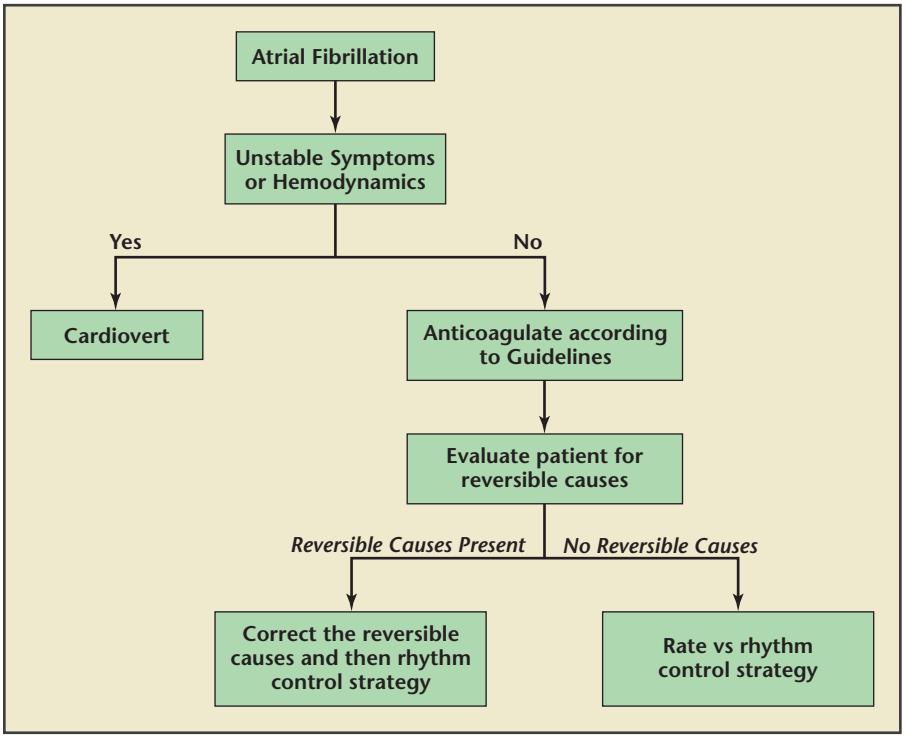
**Key words:** Anticoagulation • Atrial fibrillation • Rate control • Rhythm control

Atrial fibrillation (AF) is frequently encountered by clinicians because it is the most common cardiac arrhythmia in adults and accounts for approximately one-third of all arrhythmias requiring admission to the hospital.[1] Patients with AF are at increased risk for mortality with a relative increase in risk of death of 1.5 for men and 1.9 for women after adjusting for other risk factors. AF has increased morbidity from symptoms related to rapid ventricular rates, changes in hemodynamics, and thromboembolic phenomena.[2,3] AF is a significant independent risk factor for stroke (as found in the Framingham Heart Study) and increases with age; approximately 36% of all strokes in individuals aged 80 to 89 years are attributable to AF.[4] AF is also a predisposing factor in developing and exacerbating congestive heart failure (CHF), due in part

to the absence of coordinated synchronized atrial contraction and loss of the atrial kick. Tachycardia-mediated cardiomyopathy can also occur with AF, indicating the need for management of the arrhythmia when treating the underlying CHF.[5] Many patients are followed by both general clinical cardiologists and by electrophysiologists for treatment of underlying heart disease and the often-associated AF. Identification and treatment of underlying heart disease, pulmonary disease (eg, chronic obstructive pulmonary disease and obstructive sleep apnea), obesity, and other comorbidities are critical steps in the treatment and control of AF. Appreciation of these factors and treatment of these underlying issues is critical before the clinician can ponder the decision of not only rate versus rhythm control, but also anticoagulation.[6,7]

Whether AF is classified as paroxysmal or persistent impacts the treatment options (of rate vs rhythm control) and anticoagulation strategies, as well as outcomes for each of these therapies. A general initial protocol for AF management can be found in Figure 1. Paroxysmal AF is defined as recurrent episodes that are self-sustained, lasting less than 7 days with spontaneous reversion to sinus rhythm (Figure 1). Episodes of persistent AF last more than 7 days or require either pharmacologic or electrical cardioversion to sinus rhythm. Within this definition is also long-standing persistent AF, which is AF of greater than 1 year's duration. Permanent AF is AF for which cardioversion has failed or has not been attempted. The term *permanent AF* is not usually used when referring to patients who are being considered for the rhythm control strategy because in these patients there has been a failure to convert and maintain sinus rhythm, or a decision has been made not to intervene (Figure 2).[8,9] According to the American College of Cardiology/American Heart Association/European Society of Cardiology guidelines, patients should be characterized by their most frequent pattern of AF and managed accordingly (Figures 1 and 2).

**Figure 1.** *General initial protocol for patients presenting with atrial fibrillation.*




## Anticoagulation

There are multiple schemes to determine thromboembolic risk and how it should influence the decision to treat patients with antiplatelet agents or anticoagulants. Currently, the most commonly followed recommendations regarding anticoagulation follow the $CHADS_2$ (Congestive heart failure, Hypertension, Age > 75, Diabetes mellitus, and prior Stroke or transient ischemic attack) criteria, which were established based on a retrospective study looking at the stroke risk in patients with nonrheumatic AF who had a crude average rate of stroke of 4.5%/year. Looking at these 5 specific risk factors, a scoring system was created (Table 1).

Those with $CHAD_2$ scores of $\geq 2$ were at moderate or high risk of thromboembolic complications (adjusted annual stroke rate > 4%) and warrant anticoagulation with warfarin (in the absence of prohibitive contraindications). Lower-risk patients with $CHAD_2$ scores of 1 (2.8%) can be treated with either aspirin or warfarin, and in those with scores of 0 (1.9%), aspirin alone is sufficient because the risk of thromboembolic stroke approximated the hemorrhagic risk of anticoagulation.[8,9] This paradigm should apply to all patients with nonrheumatic AF regardless of treatment strategy because multiple studies have shown that embolization occurs with equal frequency in both rhythm and rate control approaches, primarily when warfarin is stopped. Unfortunately, the currently available antiarrhythmic medications are not very

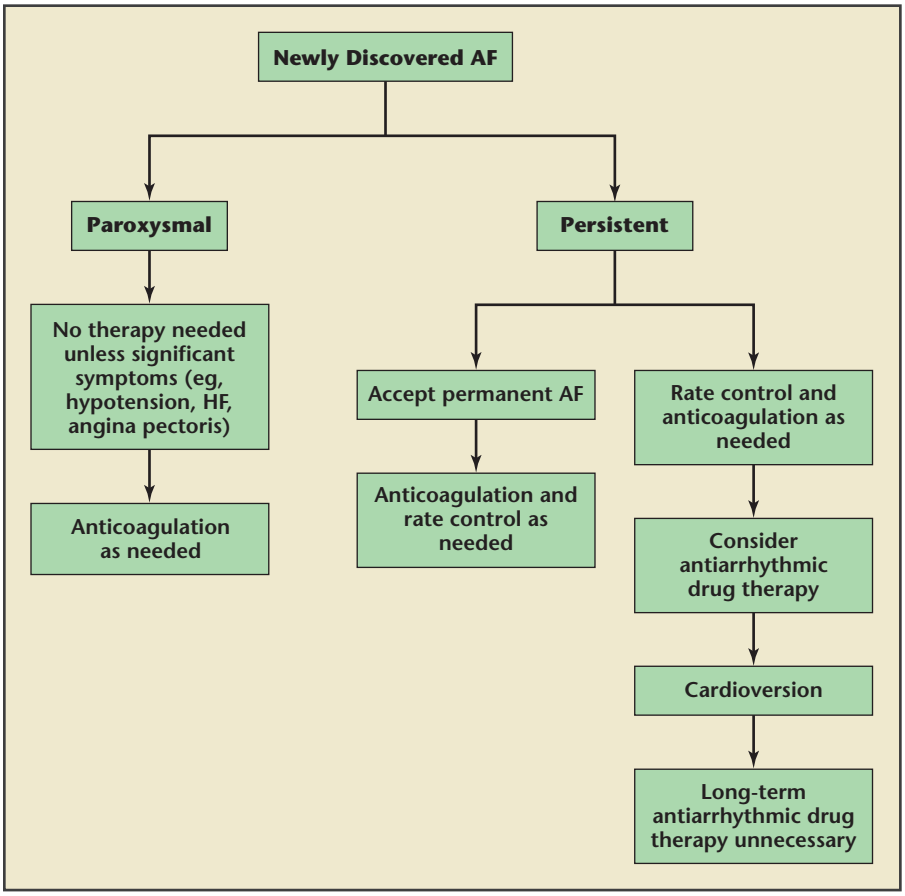



**Figure 2.** *Pharmacological management of patients with newly discovered atrial fibrillation. AF, atrial fibrillation; HF, heart failure.*

effective at maintaining sinus rhythm. It seems that the risk of stroke is mostly due to recurrent episodes of AF, which occur in 20% to 60% of patients on antiarrhythmic drugs (AADs) and in 70% to 80% of those with no therapy at 1 year. Up to 90% of these recurrent AF episodes are asymptomatic and therefore often undetected; as a result, even a seemingly successful rhythm control strategy should not be considered as a sole reason to discontinue anticoagulation.[10] Possible exceptions for discontinuation of anticoagulation may be long-term, continuous monitoring with either implantable loop recorders or in those patients who have pacemakers to monitor AF recurrences.

## Anticoagulation and Antiplatelet Therapy

Approximately one-third of patients with AF have coronary artery disease, and approximately 10% of patients referred for percutaneous coronary intervention (PCI) and stenting have a strong indication for long-term warfarin anticoagulation.[10,11] This high-risk group requires anticoagulant and antiplatelet triple therapy (warfarin, aspirin, and thienopyridine) and has demonstrated that the relative risk of major bleeding is 4 times higher with triple therapy as compared with dual antiplatelet therapy (aspirin + thienopyridine). Warfarin alone has not been shown to be of benefit for the prevention of stent thrombosis or restenosis; dual antiplatelet therapy has become the standard of care following stent implantation for the prevention of stent thrombosis. The treatment strategy for AF patients on anticoagulation undergoing PCI must be individualized for this high-risk group by carefully weighing the hemorrhagic and thromboembolic risk and risk of restenosis. The need for chronic anticoagulation may impact the decision of the interventional cardiologist to implant a bare metal stent (BMS) or a drug-eluting stent (DES) based on the difference in recommended duration of dual antiplatelet treatment. Appropriate treatment can be summarized as found in Figure 3.[12]

A practical approach would be to limit triple antithrombotic therapy use to 1 month for those with a BMS and to 12 months or less for those with certain DESs. Following this initial critical period of triple therapy, it would be reasonable to combine warfarin with aspirin for continuing therapy in the absence of contraindications. The reduction from triple therapy to warfarin and aspirin (81 mg) as soon as feasible will further reduce the risk of hemorrhagic complications in these patients.

Proton pump inhibitors (PPIs) can be recommended for patients at medium and high risk for gastrointestinal bleeding who are in need of triple therapy to prophylax against bleeding.[13] Pantoprazole has less interaction metabolically with clopidogrel and warfarin and therefore may be somewhat safer in patients who require a PPI. A target International Normalized Ratio (INR) 2.0 to 2.5 in patients on triple therapy with very close observation, clinical follow-up, and frequent measurement of prothrombin times appears to be a prudent choice for these patients.

**Table 1**
**Stroke Risk in Patients With Nonvalvular Atrial Fibrillation Not Treated With Anticoagulation According to the $CHADS_2$ Index**

| $CHADS_2$ Risk Criteria | Score |
|---|---|
| Prior stroke or TIA | 2 |
| Age > 75 y | 1 |
| Hypertension | 1 |
| Diabetes mellitus | 1 |
| Heart failure | 1 |

| Adjusted Stroke Patients (N = 1733) | Rate (%/y)[a] (95% CI) | $CHADS_2$ Score |
|---|---|---|
| 120 | 1.9 (1.2 to 3.0) | 0 |
| 463 | 2.8 (2.0 to 3.8) | 1 |
| 523 | 4.0 (3.1 to 5.1) | 2 |
| 337 | 5.9 (4.6 to 7.3) | 3 |
| 220 | 8.5 (6.3 to 11.1) | 4 |
| 65 | 12.5 (8.2 to 17.5) | 5 |
| 5 | 18.2 (10.5 to 27.4) | 6 |

$CHADS_2$, Congestive heart failure, Hypertension, Age > 75, Diabetes mellitus, and prior Stroke or transient ischemic attack; CI, confidence interval; TIA, transient ischemic attack.
[a]The adjusted stroke rate was derived from multivariate analysis assuming no aspirin usage.
Data from Gage BF et al.[9] and van Walraven WC et al.[35]

The rational approach to choosing a regimen can begin with an assessment of embolic risk and bleeding risk. For example, if the embolic risk is low (< 3%) in a patient with a BMS, aspirin + clopidogrel for 1 month followed by aspirin + warfarin following the first month is acceptable. If the patient has a DES, he or she should be treated with aspirin + clopidogrel for 12 months (or less depending on which DES is used), followed by aspirin + warfarin. However, if the embolic risk is medium (3%-5%) or high (> 6%), then the bleeding risk must be ascertained.

If the bleeding risk is high, one should avoid implanting a DES and instead use warfarin + aspirin + clopidogrel for 1 month, while giving consideration to adding a PPI such as pantoprazole. After that first month, warfarin + aspirin can be used indefinitely, or (in some instances) warfarin + clopidogrel can be used (although there is less evidence for this combination). In some patients with a high embolic risk and a high bleeding risk, coronary artery bypass grafting (CABG) might be considered.

If the bleeding risk is medium in a patient with a medium or high embolic risk, one should consider avoiding a DES if possible. If a BMS is implanted, a combination of aspirin + warfarin + clopidogrel for 1 month (with a PPI) should be used, followed by warfarin + aspirin after the first month, or, alternatively, aspirin + clopidogrel could be prescribed. If a DES is implanted, then warfarin + aspirin + clopidogrel for 12 months (with a PPI) should be considered, followed by warfarin + aspirin.

When the embolic risk is medium or high, and there is a low risk of bleeding, if the patient receives a BMS, then warfarin + aspirin + clopidogrel (with a PPI) should be considered for 1 month; then warfarin + aspirin should be prescribed. If a DES is used in this situation, warfarin + aspirin + clopidogrel for 12 months (+ a PPI) should be given, followed by warfarin + aspirin (refer to Figure 3 for a diagrammatic chart of these alternatives).

## Management Strategy: Rate Versus Rhythm Control

In addition to diagnosis, stabilization, determination of underlying cause, and anticoagulation, the next critical step of rate versus rhythm control must be addressed. AF requires a well-crafted treatment strategy because it can have negative consequences, such as systemic embolization, exacerbation of heart failure, loss of atrial contraction contribution, rapid ventricular rate, and reduced cardiac output, if left untreated. The latter effects can have significant negative effects on the patient's quality of life, leading to complaints of palpitations, easy fatigue, and dyspnea on exertion, with reduced exercise capabilities. The initial approach is determined mainly by hemodynamic stability in terms of adequate blood pressure control, systemic perfusion, and heart failure compensation. If the patient is hypotensive and has a significant CHF or angina, immediate electrical cardioversion should be considered. After stability is attained, attention is usually turned to other aspects of AF care and whether to achieve rate control or normalization of the underlying rhythm (Figure 1).

Recurrence of AF after return to sinus rhythm is common. Certain risk factors increase the likelihood of recurrence, including a left atrial size > 4.5 cm with poor atrial

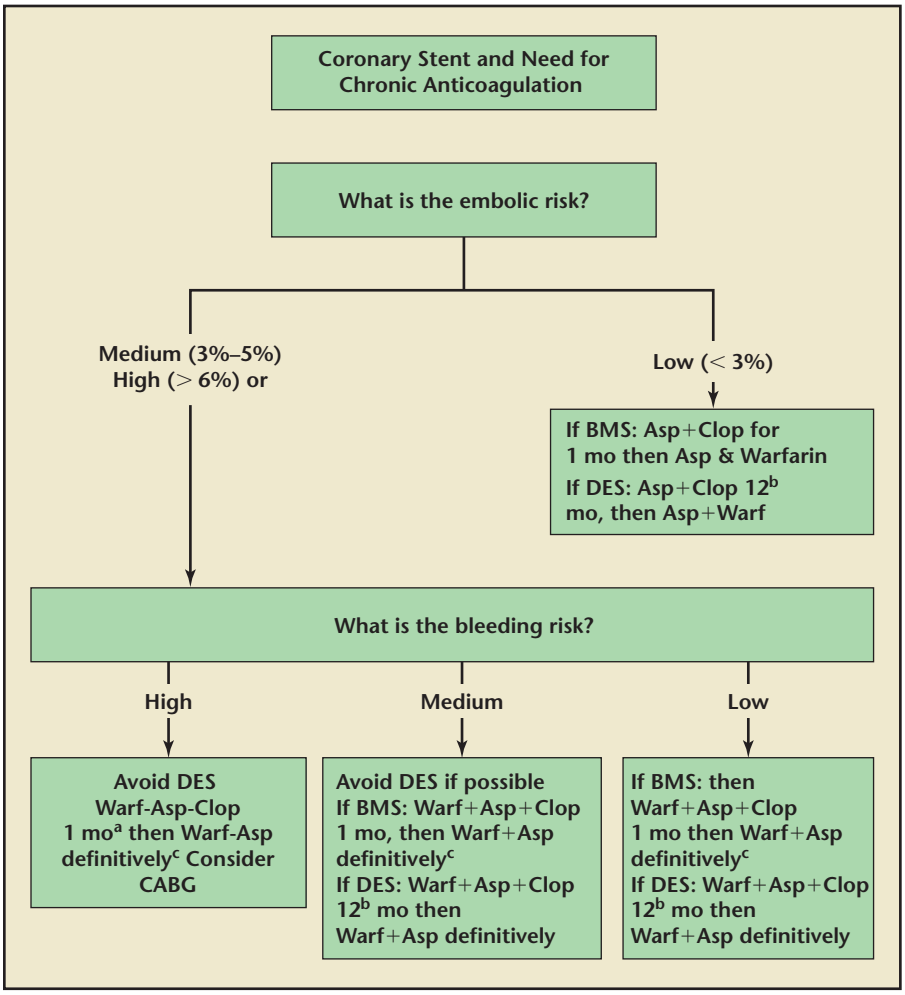



**Figure 3.** *Flow chart for the selection of appropriate treatment. [a]Consider adding a PPI to any combination that includes aspirin. [b]May be less than 12 months depending on which DES is used. [c]Alternatively, warfarin + clopidogrel (less evidence for this combination). [d]For acute coronary syndrome, warfarin + aspirin + clopidogrel for 12 months, then warfarin + aspirin. Asp, aspirin; BMS, bare metal stent; CABG, coronary artery bypass graft; Clop, clopidogrel; DES, drug-eluting stent; PPI, proton pump inhibitor; Warf, warfarin. Adapted with permission from Sourgounis A et al.*[12]

muscle contractility, long-standing AF, heart failure, and hypertensive heart disease (Figure 3). Therefore, drugs are often used to maintain sinus rhythm in certain patients with the theoretical basis of improving atrial remodeling, slowing the progression of disease, improving hemodynamics by returning atrial kick, and relieving symptoms, thereby improving quality of life and potentially reducing thromboembolic events. However, these benefits for rhythm control have not been shown in clinical studies that have focused on endpoints such as symptom control, quantity and quality of life, thromboembolic risk, rehospitalization rates, and exercise capacity.

The largest and most quoted study is the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial.[14,15] This group studied 4060 patients randomly assigned to either rate or rhythm control. Rate control could be achieved with a β-blocker, a calcium channel blocker, or digoxin while patients were therapeutically anticoagulated with warfarin. The rhythm control group was given an AAD; the selection of these drugs was left up to the discretion of the investigator. The following drugs were acceptable for use according to the protocol: amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, combinations of these drugs, and dofetilide when it became available. Inclusion criteria were age > 65 years, no contraindications to the use of the pharmacologic agents, and ≥ 6 hours of AF during the previous 6 months, with a qualifying episode within the 12 weeks prior to enrollment. The 3 principal drugs used in the patients randomized to rate control were digoxin (51% of patients), β-blockers (49%), or calcium channel antagonists (41%). In the rhythm control arm, patients were predominantly treated using amiodarone (39%), sotalol (33%), and propafenone (10%). Ablation and pacemakers were also used in the rhythm control arm if necessary. The rate of warfarin use was 85% to 95% in the rate control arm and approximately 70% in the rhythm control arm. Patients in the rhythm control arm were permitted to discontinue anticoagulation therapy after normal rhythm had been achieved and maintained for 1 month. After being followed-up for 3.5 years there was no difference between the rate and rhythm control groups in incidence of arrhythmic death, cardiac death, or ischemic stroke.[15] The prevalence of sinus rhythm declined over time and at 5 years was approximately 60% in the rhythm control arm and approximately 40% in the rate control arm, thus confirming the limited efficacy of medical therapy to maintain sinus rhythm. The primary endpoint of AFFIRM was all-cause mortality and was observed in 25.9% of patients in the rate control

arm and 26.7% of patients in the rhythm control arm (hazard ratio [HR] = 1.15; $P$ = .08). The cumulative noncardiovascular mortality curves appeared to diverge after approximately 1.5 to 2.0 years in favor of a lower mortality with rate control. There was no statistically significant difference in the secondary composite endpoint of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest (32.7% vs 32%; $P$ = .33), functional status, or quality of life. The hospitalization rate was higher in the rhythm control arm (80% vs 73%; $P < .001$). There was no significant difference in occurrence of ischemic stroke, which occurred in 5.6% of those in the rate control arm and 7.1% of those in the rhythm control arm ($P$ = .79). Most strokes occurred in patients in whom warfarin therapy was discontinued, almost with equal frequency, regardless of whether a rate control or rhythm control strategy was pursued. Many strokes seemed to occur in patients who had asymptomatic recurrences of AF.

It should be noted that although rate control without AAD reduces the risk of proarrhythmia, it may be associated with persistent symptoms of palpitations, dyspnea, chest pain, fatigue, and fainting. Patients may not find these symptoms tolerable. It is notable that patients who could not tolerate these symptoms were not enrolled in the trial, and therefore the results of the AFFIRM trial may not apply to these symptomatic patients who seem unable to tolerate a rate control-only strategy. It is possible, but as yet untested, that ablation may be a solution for those patients who do not tolerate rate control or do not seem to respond well to or tolerate AADs. Subgroup analysis following the AFFIRM study supported the premise that the increased mortality with rhythm control was likely due to the deleterious effects of AADs, which more than offset the benefits of maintaining normal sinus rhythm (NSR).[16] It is now accepted that some of these agents, especially the class IC agents, should not be used in patients with structural and ischemic heart disease because of the risk of proarrhythmia.

When medications alone are insufficient to maintain sinus rhythm, a hybrid approach may be undertaken using the addition of cardioversion.

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The Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trial looked at its efficacy. This trial enrolled 532 patients who had atrial flutter or recurrent, persistent AF < 1 year's duration or who had required 1 or 2 cardioversions within the prior 2 years.[17,18] They were randomized to a strategy of rate control (n = 256) using β-blockers, digoxin, or calcium antagonists titrated to a heart rate of < 100 beats/min, or rhythm control (n = 266) with electrical cardioversion and AAD prophylaxis. Anticoagulation in the rate control arm was titrated to achieve an INR of 2.0 to 3.5. In the rhythm control arm, anticoagulation was given for 1 month before cardioversion was attempted and discontinued if chronic sinus rhythm was obtained. If the patient did not respond to sotalol, flecainide, or propafenone, the patient was then given amiodarone. At a mean follow-up of 2.3 years, the primary endpoint (a composite of cardiovascular death, thromboembolic complications, severe bleeding, pacemaker implantation, and severe adverse effects of therapy) occurred in 17.2% of patients in the rate control arm as compared with 22.6% of those in the rhythm control arm. This −5.4% absolute difference was within the 90% confidence interval (CI) of −11.0% to 0.4% and thus rate control met the criteria for noninferiority. Investigators concluded that there were no significant differences between the rate and rhythm control groups with regard to quality of life, which was similar to the findings of the AFFIRM trial.

Multiple smaller studies have also shown no difference in quality of life or composite endpoints, which included death, cerebrovascular accident, functional status, or thromboembolic events.[19,20] Aside from the toxicity of AADs confounding the positive effects of maintaining NSR, many have hypothesized that the lack of difference in these studies is often due to either the inability to maintain patients in NSR when a rhythm control strategy is chosen, or the increase in hospitalizations for side effects or titration of AADs.

Because no difference in strategy results is seen in the above studies, the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial addressed the question of whether there would be benefit to the specific population of patients with heart failure and depressed ejection fraction that is possibly sensitive to smaller alterations in cardiac hemodynamics.[21,22] This randomized trial compared rate control with rhythm control in patients with left ventricular ejection fraction (LVEF) ≤ 35%, CHF symptoms, and a history of AF; asymptomatic patients were enrolled if they had a prior hospitalization for CHF or an LVEF ≤ 25%. At baseline, 31% of patients had New York Heart Association class

III or IV heart failure with a mean LVEF of 27%; persistent AF was seen in the majority of patients (69%), with 31% having paroxysmal episodes. By trial design, rhythm control was predominantly achieved with amiodarone (82%), with less frequent use of sotalol (1.8%) or dofetilide (0.4%). In the rate control group, β-blockers and digoxin were used in 88% and 75% of patients, respectively. Crossover occurred in 21% of the rhythm control group and in 10% of the rate control group. There was no difference in the primary endpoint of cardiovascular death between the groups (26.7% of the rhythm control group vs 25.2% of the rate control group [HR 1.06; 95% CI, 0.86-1.30; $P$ = .59]). Total mortality, worsening CHF, and stroke were similar between the 2 groups, as was the composite endpoint of cardiovascular death, worsening CHF, and stroke. There was also no difference in total mortality (31.8% vs 30.8%; $P$ = NS). Bradyarrhythmias were more common in the rhythm control group (8.5% vs 4.9%; $P$ = .007). Outcomes in the 2 groups relating to death from cardiovascular causes, death from any cause, worsening heart failure, stroke, or risk of heart failure were comparable. No significant differences between the 2 strategies were found in any of the subgroups. The AF-CHF investigators concluded that because the death rate from cardiovascular causes was not reduced by a rhythm control strategy, rate control should be considered as a primary approach for patients with CHF and AF.

The trials are reasonably consistent in that they found no decided advantage of rhythm control over rate control in patients with or without CHF. Further, there are disadvantages to a rhythm control approach with AADs, including not only the adverse effects, but the necessity of hospitalization or office testing for dosage and medication changes, and prolonged monitoring if termination of anticoagulation is considered. In many, there is still the need for long-term anticoagulation and therefore continued follow-up for therapeutic anticoagulation, which reduces quality of life, continues the risk of bleeding, and affects even a successful rhythm control strategy. Additionally, there are contraindications to some AADs in patients with depressed LVEF, LV hypertrophy, and prior myocardial infarction, which can lead to increased mortality (Figure 4).[6,16] For this reason, rate control is preferred as an initial approach in order to minimize adverse reactions to the AADs (Table 2).[23]

## Drug Therapy to Maintain Sinus Rhythm

If a pharmacologic rhythm control approach is deemed the best option for a specific patient, there is good evidence that amiodarone is the most effective AAD for maintaining regular sinus rhythm, especially in patients with heart failure, as it has very little negative inotropic effect.[23] Oral amiodarone prolongs the atrial refractory period much more than the intravenous form and is therefore effective for persistent AF. In a meta-analysis of antiarrhythmic efficacy, amiodarone was reported to maintain sinus rhythm in over 60% of patients after cardioversion at 1 year. Dofetilide showed a similar efficacy at 1 year (58%) in the Symptomatic Atrial Fibrillation Investigation Research on Dofetilide (SAFIRE-D) trial.[24] Although class IC drugs (propafenone and flecainide) and sotalol are as effective and better tolerated than class IA drugs (quinidine), their 6-month efficacy rates of maintaining sinus rhythm after cardioversion are about 50%, whereas it is only 25% in untreated patients or those on placebo (Figure 4).[25,26]

Potential side effects from AADs such as quinidine can include even more rapid ventricular response from a vagolytic effect or slowing of the atrial rate, allowing more impulses to penetrate the atrioventricular (AV) node. This can also be seen with class IA and IC agents. This can be prevented by concurrent administration of AV nodal blocking agents. QRS widening with class IC agents mimicking ventricular tachycardia can be seen. There can be worsening sinus node function, AV nodal conduction, or His-Purkinje conduction, resulting in symptomatic bradycardia. Class I (sodium channel blocking) and class III (potassium channel blocking) agents can also cause QT prolongation and torsades de pointes (TdP), whereas class IC agents may precipitate ventricular arrhythmias in patients with a history of prior myocardial infarction, depressed ejection fraction (EF), or significant LV hypertrophy. End-organ toxicity can also occur with procainamide-induced neutropenia, quinidine-induced thrombocytopenia, amiodarone-induced thyroid toxicity, or pulmonary fibrosis.[25]

## Nonpharmacologic Approach

From the nonpharmacologic standpoint, there are surgical and electroablative procedures to restore sinus rhythm. These interventional and surgical procedures theoretically have the advantage of improving the

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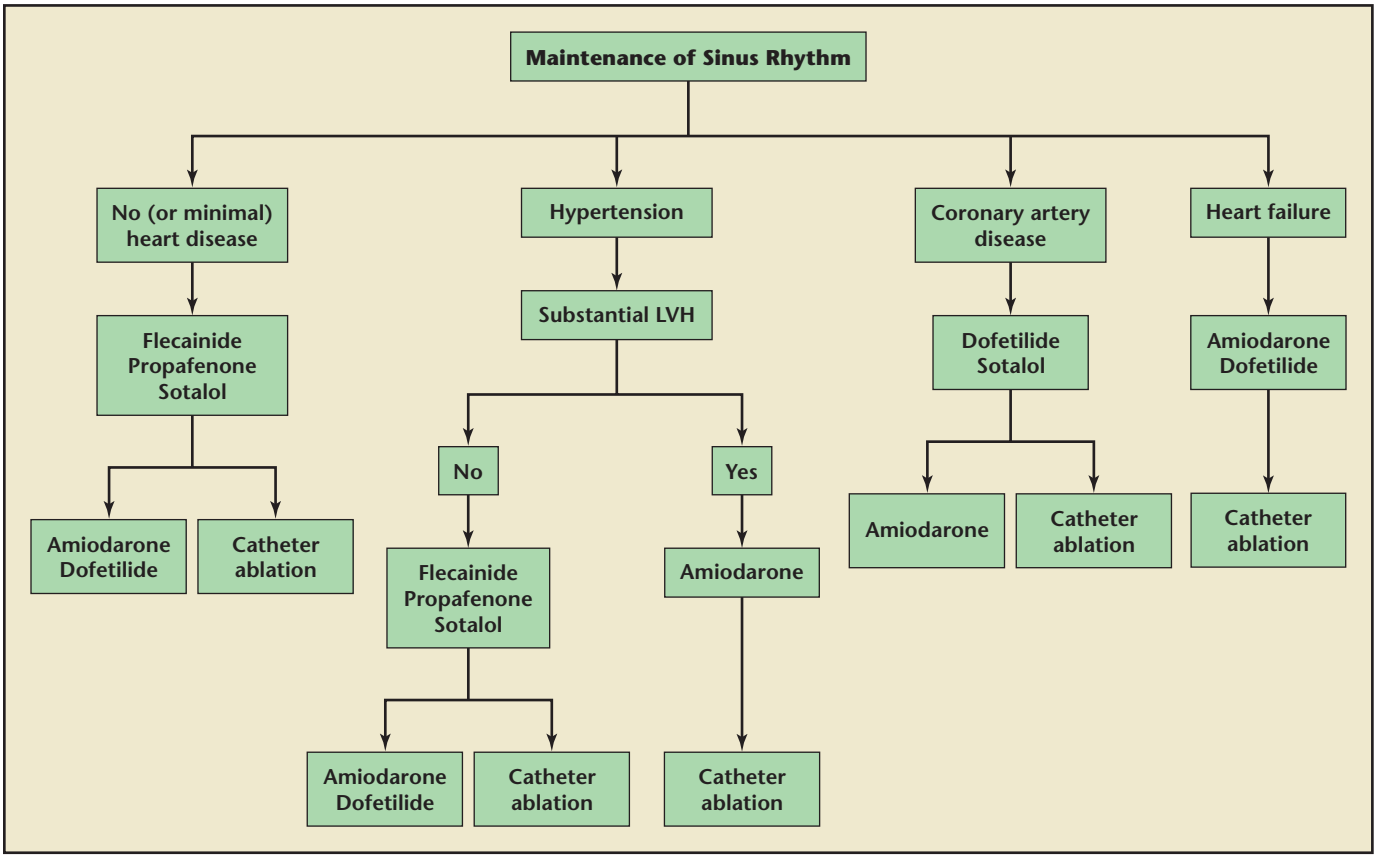


**Figure 4.** *Antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation. Within each box, drugs are listed alphabetically and not in order of suggested use. The vertical flow indicates order of preference under each condition. The seriousness of heart disease proceeds from left to right, and selection of therapy in patients with multiple conditions depends on the most serious condition present. LVH, left ventricular hypertrophy. Data from ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation.*[6]

patient's prognosis, symptom control, and quality of life by maintaining NSR without the deleterious side effects of AADs, particularly in patients who have structural heart disease and CHF. The most important reason to pursue the restoration and maintenance of NSR (rhythm control) is to control the symptoms associated with AF; however, the randomized trials have not shown any significant outcome endpoint advantage to a pharmacologic rhythm control approach. In most trials, drugs were not able to maintain NSR in the majority of patients, and as a result the patients in the rhythm control arms really did not achieve adequate rhythm control. Additionally, although NSR was associated with a survival advantage, this advantage was offset by the adverse effects of AADs (eg, increased hospitalization rates), which can decrease quality of life, along with adverse effects (such as proarrhythmia or exacerbation of heart failure from negative inotropic effects), as most were composite endpoints that included one of the above.

## Clinical Recommendations

The 2 largest clinical trials, AFFIRM and RACE, demonstrate that both rate and rhythm control are generally acceptable approaches. The correct strategy for a particular patient will depend on his or her individual needs and sound clinical judgment. Additionally, the choice of AADs varies depending upon the clinical situation and the general medical condition of the patient with regard to the metabolism and side effects of the AAD, as well as his or her cardiac condition (Figure 4 and Table 2). All patients should receive anticoagulation based on the $CHAD_2$ criteria, irrespective of the treatment strategy chosen.

### *Patients With Normal Ejection Fraction*

These patients are potential candidates for all AADs and rate control drugs, and the main question is whether they are symptomatic. For those who are truly asymptomatic, rate control with anticoagulation may be the best option because there

**Table 2**
**Recommended Doses of Drugs Proven Effective for Pharmacologic Cardioversion of Atrial Fibrillation**

| Drug[a] | Route of Administration | Dosage[b] | | Potential Adverse Effect |
|---|---|---|---|---|
| Amiodarone | Oral | Inpatient: 1.2-1.8 g/d divided dose until 10 g total, then 200-400 mg/d maintenance or 30 mg/kg as single dose | | Hypotension, bradycardia, QT prolongation, TdP (rare), GI upset, constipation, phlebitis (IV) |
| | | Outpatient: 600-800 mg/d divided dose until 10 g total, then 200-400 mg/d maintenance | | |
| | IV | 5-7 mg/kg over 30-60 min, then 1.2-1.8 mg/d continuous IV or in divided oral doses until 10 g total, then 200-400 mg/d maintenance | | |
| Dofetilide | Oral | Creatinine clearance (mL/min) | Dose (μ bid) | QT prolongation, torsades de points; adjust dose for renal function, body size, and age |
| | | > 60 | 500 | |
| | | 40-60 | 250 | |
| | | 20-40 | 125 | |
| | | < 20 | Contraindicated | |
| Flecainide | Oral | 200-300 mg[c] | | Hypotension, atrial flutter with high ventricular rate |
| | IV | 1.5-3.0 mg/kg over 10-20 min | | |
| Ibutilide | IV | 1 mg over 10 min; repeat 1 mg when necessary | | QT prolongation, TdP |
| Propafenone | Oral | 600 mg | | Hypotension, atrial flutter with high ventricular rate |
| | IV | 1.5-2.0 mg/kg over 10-20 min | | |
| Quinidines[d] | Oral | 0.75-1.5 g divided dose over 6-12 h, usually with a rate-slowing drug | | QT prolongation, TdP, GI upset, hypotension |

AF, atrial fibrillation; bid, twice daily; GI, gastrointestinal; IV, intravenous; LV, left ventricular; TdP, torsades de pointes.
[a]Drugs are listed alphabetically.
[b]Dosages given in the table may differ from those recommended by the manufacturers.
[c]Insufficient data are available on which to base specific recommendations for the use of one loading regimen over another for patients with ischemic heart disease or impaired LV function and these drugs should be used cautiously or not at all in such patients.
[d]The use of quinidine loading to achieve pharmacologic conversion of AF is controversial and safer methods are available with the alternative agents listed in the table. Quinidine should be used with caution.
Data from ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation.[6]

are fewer side effects associated with this strategy. A symptom-targeted approach is appropriate in those whose symptoms are due to rapid ventricular rates with shortness of breath and decreased exercise tolerance. For those who feel palpitations from irregular rates or are unable to tolerate rate control medications due to blood pressure–lowering effects or ineffectiveness of digoxin, AADs are an option. The first-line drugs used in those without structural heart disease are propafenone and flecainide because of their safety profile, lack of end-organ toxicity, and low proarrhythmic risk. Sotalol is also a good option for similar reasons. Amiodarone is usually reserved as a second-line option and often in an older subset of patients due to the cumulative effects of end-organ toxicity associated with long-term use. For those who remain symptomatic or refractory to medications, another possible option is AV node ablation and pacemaker placement, or surgical and catheter-based ablation procedures.

*Heart Failure*

In clinical practice a common goal has been to cardiovert AF to NSR to improve cardiac function in patients with heart failure. As previously described in the AF-CHF trial, it was found that a routine strategy of rhythm control did not reduce the rate of death from cardiovascular

causes compared with a rate control strategy.[21,22] Although there still may be some quality of life benefits,[23] the effect of maintaining NSR to benefit patients with CHF may be better served by nonpharmacologic approaches for maintenance of NSR, which avoids the adverse effects of the AADs.

It appears clinically reasonable to pursue a rhythm control approach in systolic heart failure patients who remain sufficiently symptomatic despite adequate rate control, to relieve symptoms and improve quality of life, even though longevity may not be positively affected. For the CHF population, options are limited to amiodarone and dofetilide, which have neutral survival study results in this patient population.[25-28]

*Paroxysmal Versus Persistent AF*

Another distinguishing feature in treatment decisions is whether the AF is paroxysmal or persistent. Often those with paroxysmal episodes tend to be more symptomatic and may prefer rhythm control to minimize occurrences. These patients can be treated essentially with any of the AADs as long as they have normal baseline conduction. If their episodes are infrequent (2-3/y) a *pill-in-the-pocket* strategy may be useful. This strategy utilizes a higher-dose AAD given at the onset of an episode to acutely convert the patient. This may be preferred as opposed to daily chronic suppressive therapy. Medications used for the pill-in-the-pocket approach are propafenone, 600 mg, or flecainide, 300 mg, and have conversion rates as high as 70% to 80% within 12 hours of administration in episodes of recent onset.[26,27] Intravenous ibutilide is another option for acute conversion, but is given intravenously. Its efficacy is 35% to 40% conversion of patients within 1 hour of administration. There is a 2% to 3% higher risk of TdP with ibutilide in patients with low ejection fraction (< 20%), and patients do need to be monitored for at least 4 hours after administration.[27] Additionally, the patients with paroxysmal AF episodes typically have better success rates with ablation than those with persistent AF, probably due to greater atrial myopathy. The persistent AF patients need to be treated based on both their symptoms and their heart function stratification, as just described.

*For the risk of subdural hematoma to outweigh the risk of thromboembolic stroke in the average elderly patient, a patient must actually fall in excess of 295 times per year before the risk of anticoagulation with warfarin outweighs its benefits.*

## The Elderly: Octogenarians and Beyond

The elderly account for approximately one-third of all patients with AF in clinical practice, but are usually under-represented in clinical trials. Patients in this group often have contraindications as well as potential hazards to the use of warfarin anticoagulation, such as falls and other trauma. Counterbalancing these potential complications is the fact that these elderly patients are at the highest risk for thromboembolic complications such as stroke and derive the highest benefit from stroke prevention with warfarin anticoagulation. Both the AFFIRM and RACE trials showed no decrease in the incidence of thromboembolization with a rhythm control approach, making it inadvisable to discontinue warfarin in many cases.[29,30] The risk of falling must be carefully assessed and focused on serious complications such as subdural hematoma when weighing warfarin continuation against a serious complication such as stroke. Interestingly, for the risk of subdural hematoma to outweigh the risk of thromboembolic stroke in the average elderly patient, a patient must actually fall in excess of 295 times per year before the risk of anticoagulation with warfarin outweighs its benefits.[30]

## Young Patients or Those With Lone AF

Younger patients were also somewhat under-represented in the RACE and AFFIRM trials, and therefore it is somewhat uncertain whether young patients would benefit from a more aggressive rhythm control approach.[31] There is also some continued uncertainty as to whether all patients with primary true paroxysmal lone AF are destined to progress to more persistent forms or only those with a yet-to-be-identified progressive atrial myopathy. If the AF is progressive, it may be worthwhile to target these patients earlier and eliminate their AF prior to its further advancement of underlying heart disease and resultant consequences.

## Novel Agents

Additional pharmacologic agents that are not considered conventional AADs have been investigated and used in AF: (1) Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)—both have been shown to prevent new-onset AF and recurrent AF by possibly regressing fibrosis and preventing adverse remodeling by decreasing atrial stretch. (2) In immediate postoperative CABG patients correction of magnesium deficiency and treatment with

vitamin C has been shown to reduce the incidence of postoperative AF; and (3) Some evidence shows that statins may prevent the occurrence of AF in patients with lone AF, ischemic heart disease, and following cardiac bypass surgery.[31]

## Future Pharmacologic Directions

The benefits of maintaining NSR with currently available antiarrhythmic medications are offset by adverse reactions to these medications. To allow patients to appreciate and enjoy the benefits of the improved prognosis from NSR, new agents with reduced adverse reactions must be developed.

Dronedarone, a benzofuran derivative related to amiodarone, has shown promise in some groups with favorable therapeutic reaction profiles and a better safety profile then amiodarone. Trials comparing dronederone versus amiodarone for safety and efficacy in the maintenance of NSR have been held.[32] However, in patients with CHF and an EF of less than 35%, the Andromeda Study showed increased mortality in the dronedarone-treated group and was terminated early.[33] Other new agents are now in development to overcome the existing adverse side-effect profiles presented by the current medications.[34]

## Conclusions

The strategy for rhythm control has been pushed forward in a significant way by interventional and surgical therapy that has overcome a lot of the adverse side effects and proarrhythmic shortcomings associated with the drugs used for rhythm control. The "cure being worse than the disease" problem for AADs has begun to be answered by electrophysiologists. A key point clarified by the trials reviewed here is the need for continued anticoagulation in high-risk patients despite the reestablishment of NSR, even while they are still taking medication. Considering the state of flux of AF management, patients and their physicians must be flexible, not only with regard to considering rate versus rhythm control and changing approaches, but also with regard to switching from pharmacologic rate and rhythm control strategies to surgical and ablative strategies. ■

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## Main Points

- Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults and accounts for approximately one-third of all arrhythmias requiring admission to the hospital, and approximately 36% of all strokes in individuals aged 80 to 89 years are attributable to AF.
- Recurrence of AF after return to sinus rhythm is common; therefore, drugs are used to maintain sinus rhythm in some patients, potentially reducing thromboembolic events, although the efficacy of medical therapy to maintain sinus rhythm is limited.
- Although rate control without antiarrhythmic drugs (AAD) reduces the risk of proarrhythmia, it may be associated with persistent symptoms of palpitations, dyspnea, chest pain, fatigue, and fainting. However, if a pharmacologic rhythm control approach is deemed the best option for a specific patient, there is good evidence that amiodarone is the most effective AAD for maintaining regular sinus rhythm, especially in patients with congestive heart failure (CHF).
- From the nonpharmacologic standpoint, there are surgical and electroablative procedures to restore normal sinus rhythm (NSR) for patients who do not tolerate rate control or do not tolerate AADs. These interventional and surgical procedures have the advantage of improving the patient's prognosis, symptom control, and quality of life by maintaining NSR without the deleterious side effects of AADs, particularly in patients who have structural heart disease and CHF.

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