Update on medical management of atrial fibrillation in the modern era

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The management of atrial fibrillation involves control of the ventricular response rate, anticoagulation to reduce the risk of stroke and attempts to maintain sinus rhythm. The approach to patients with atrial fibrillation has become increasingly complex as therapeutic options have expanded. The ultimate reasons to treat atrial fibrillation include improvement in symptoms, reduction in adverse outcomes and improvement in survival. Despite increasing interest in non pharmacological approaches to treat and potentially cure atrial fibrillation, drugs remain the primary method to treat most patients. This review updates the present state-of-the-art regarding medical management of atrial fibrillation based on present and emerging evidence.

KEYWORDS Atrial fibrillation; Medical management; Rate control; Rhythm control; Anticoagulation

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Medical management of atrial fibrillation (AF) has become increasingly complex as greater understanding of the consequences of AF becomes evident and as treatment options expand. Treatment goals include, but are not limited to, symptom control, improvement in functionality, hemodynamic stabilization, stroke prevention, reduction in hospitalization, prevention of tachycardia-induced cardiomyopathy, and improved survival.[1] Drugs, the primary approach for treatment of most AF patients, are used to anticoagulate, control ventricular rate, and help maintain sinus rhythm. This review focuses on the nuances of present medical management of patients with AF with a view toward future strategies.

Anticoagulation

The long-term risk of thromboemboli can be high in patients with AF no matter what other medical therapy is prescribed. Warfarin anticoagulation can prevent stroke and death in AF patients. Prospective randomized controlled clinical trials show that warfarin significantly reduces risk of stroke (relative risk reduction 62%) and risk of death (relative risk reduction 26%) in "high-risk" AF patients.[2,3]

Despite risk of stroke, however, not all patients are at substantial risk, and the absolute benefit of warfarin can be quite small in some patient groups. The CHADS2 score (Congestive heart failure, Hypertension, Age >75, Diabetes, Stroke or transient ischemic attack, each counting as one point except stroke, which counts as two) was established as a method to discriminate patients at "high risk" (stroke risk >5% per year) who may benefit from anticoagulation from those at "low risk" (stroke risk <3% per year) who may not. However, the CHADS2 score is an imperfect method for determining which AF patients would benefit from warfarin who are at "intermediate risk" (stroke rate 3%–5% per year).

Current guidelines established on the basis of rate of stroke and on benefit from warfarin recommend warfarin anticoagulation for patients with a CHADS2 score ≥ 2 (annual risk of stroke 4%),[4] but better methods are needed to determine which AF patient requires anticoagulation. There is a need to distinguish between higher-risk and lower-risk AF patients with a CHADS2 score = 1. A study by Rietbrock et al[5] determined that the CHADS2 score could be more precise if it were modified by age, gender, and the reweighing of other risk factors.

Benefits of warfarin must be balanced against adverse effects, bleeding risk, drug–drug interactions, inefficacy, and difficulty maintaining an international normalized ratio (INR) between 2 and 3. Underutilization and overutilization of warfarin based on guideline recommendations occur commonly. Present recommendations are based on prospective controlled clinical trials that excluded nearly half of the patients,[6] often the elderly, who are at the highest risk for thromboembolic complications but also risk for bleeding from warfarin. Perhaps in light of the perceived risks, these patients at high risk for stroke often are not anticoagulated.[7]

In clinical practice, the risk of major hemorrhage from warfarin may be high. The elderly (age >80 years) appear to be at higher risk for bleeding from warfarin than are those younger than 80 years.[8] Due to safety concerns, warfarin

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may be discontinued, especially in elderly patients. The BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) trial evaluated elderly AF patients (age >75 years).[9] Compared with aspirin, warfarin anticoagulation was associated with improved outcomes except, perhaps, for the extreme elderly (>85 years) in a subgroup analysis.

There are other reasons why the recommendations are not followed. There can be difficulties in maintaining the INR within an accepted, rather narrow, therapeutic range for many patients. Patients are reticent to take warfarin. Physicians may be concerned about the clinical issue of dual or triple antithrombotic therapy in AF patients receiving stents or other implants (a growing problem in an aging AF population with concomitant vascular disease). Unfortunately in clinical practice, despite its potential benefits, warfarin may not be used as recommended, and persistence of therapy may be only as high as 70%.[10]

Patients and physicians would prefer a better drug than warfarin. Heparin, low-molecular-weight heparin, aspirin, and other drugs have been advocated for some patients and specific clinical situations. Few data support their use. Heparin and low-molecular-weight heparin still may have a role in the acute management of patients with AF around the time of cardioversion.[11,12] Any benefit of aspirin may simply be due to its effect on carotid and aortic plaques. The evidence suggesting that aspirin has benefits comes from limited data,[13,14] and other data do not suggest any clear benefit from aspirin.[3,15,16] Other platelet inhibitors appear ineffective. The ACTIVE W (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events) trial evaluated clopidogrel with aspirin in more than 6,000 AF patients. The combination was not as effective as warfarin.[17]

The hope for more effective and safe anticoagulants continues. The goal is to find a low-risk, universally effective drug that anticoagulates rapidly and effectively and has a modestly short half-life, no drug–drug and drug–food interactions, no need for patient-specific titration, and no serious side effects. Ximelagatran, a direct thrombin inhibitor with many of these desired features, was evaluated in two major trials and showed promise. Combined data from two large trials showed ximelagatran to be as good as (i.e., noninferior to) warfarin.[18–20] It was not approved by the Food and Drug Administration (FDA) due to concerns about safety.

Other anticoagulant regimens, including direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, idraparinux), have been or are being evaluated.[21–24] A trial that compared idraparinux to warfarin was stopped due to severe bleeding in the idraparinux arm (AMADEUS trial). Other factor Xa inhibitors may be tested. Dabigatran has been associated with an acceptable risk of bleeding and stroke; however, from currently available data, this effect may be highly dose dependent.

Questions remain. What is the best way to anticoagulate a patient acutely when cardioversion is considered? What is the best way to anticoagulate when an ablation is planned? Is dual or triple antithrombotic therapy safe and effective in AF patients with concomitant coronary artery and peripheral vascular disease? Who benefits from heparin? What is the role of transesophageal echocardiography? How long does warfarin need to be given to a patient with recurrent AF who requires cardioversion but has a low CHADS2 score? Is there a better way to risk stratify? Are there better methods for assessing risk for left atrial thrombus besides a transesophageal echocardiogram? Which patients with a negative transesophageal echocardiogram require anticoagulation?

There is much to be learned about effective anticoagulation in AF, but the bottom line is that warfarin, with all of its risks, has no reasonable substitute yet for patients at "high risk" for stroke. Better anticoagulants and better methods for assessing risk are needed. New thrombin inhibitors may become available. Left atrial appendage occlusion devices may prove beneficial and safe. At present, no convincing data exist to support discontinuation of anticoagulation in AF patients at increased risk for stroke. Long-term outcome studies of AF ablation ultimately may provide this much awaited information.

Rate control

Control of the ventricular response rate and its regularity in AF ("rate control") is an underemphasized and poorly defined component of the medical management of AF. Ironically, the importance of rate control, the best resting and exercise rate, the optimal acceleration and deceleration in rate with activity, and the best method for controlling rate are often not addressed carefully in clinical practice. Careful attention to rate control management in large prospective randomized trials, however, may explain similarities in outcomes between rate and rhythm control approaches.

Besides affecting symptoms and hemodynamics, persistent rapid ventricular rates during AF can cause cardiomyopathy.[25] Likely, tachycardia-induced cardiomyopathy is underrecognized. Although rate control can reverse tachycardia-induced ventricular dysfunction, in part, complete reversal of the dysfunction is uncertain and may not occur.[26,27] Conversely, AF can develop due to cardiomyopathy. Fast ventricular rates in AF can exacerbate heart failure.

Standard drugs used to control rate, alone or in combination, include beta-blockers, digoxin, calcium channel antagonists, and even amiodarone. Each drug has a unique mechanism of action for controlling rate and has a unique use based on the patient and comorbidities. The goals are to reduce risk of hemodynamic impairment, improve symptoms, and reduce risk of death and hospitalization. Few controlled trials show benefit of one drug over another. One controlled study compared digoxin, diltiazem, atenolol, digoxin plus diltiazem, and digoxin plus atenolol. The mean ventricular rate at rest and with exercise was most stringently controlled with digoxin plus atenolol. However, the study population was small (12 patients), and the ideal rate at rest and with exercise remained uncertain.[28]

In the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial, 2,027 patients randomized to the rate control arm were followed over 3.5 ± 0.3 years.[29] All drug options to control rate were allowed. Criteria for adequate rate control were measured at each follow-up visit and were prespecified. They included mean resting heart rate ≤80 bpm and rate ≤110 bpm on a 6-minute walk test or mean rate ≤100 bpm on 24-hour Holter monitor with no heart rate >100% maximum predicted age-adjusted exercise rate.

More than 80% achieved effective long-term rate control at rest and with exercise. As monotherapy, beta-blockers were most effective. The combination of digoxin and beta-blockers was highly effective. However, the optimal heart rate was not defined. In AFFIRM, when all drug options were available and frequent regimen changes were possible, rate control was achieved in most patients. AV junctional ablation and pacemaker implantation was used in 6%. Careful attempts to control rate may explain why rate control was as good as, if not better than, rhythm control in managing AF in controlled trials. Nevertheless, a stringent approach to rate control may not necessarily be the best.

The strict approach to rate control in AFFIRM was compared to a more lenient approach (resting heart rate <100 bpm) in the RACE (Rate Control Versus Electrical Cardioversion of Persistent Atrial Fibrillation) trial.[30] The actuarial event-free survival for the endpoint of this analysis (composite of mortality, cardiovascular hospitalization, and myocardial infarction) did not differ between studies, but there was a trend toward superiority in the lenient (RACE) approach. Although retrospective study comparisons are challenging, the best rate range at rest and with exercise remain uncertain. The prospective RACE II trial is comparing a lenient to a strict rate control approach.[31]

Rapid and slow rates in AF can affect many outcomes, but abrupt changes in rate and/or wide beat-by-beat swings in rate may be responsible for symptoms in AF. Most patients with AF are symptomatic intermittently. These symptoms may be due to inappropriate rate swings during AF that last for only a few seconds. AV junctional ablation with pacemaker implantation may be effective as these wide swings are eliminated.

Adequate rate control differs by patient population and underlying medical condition. For cardiac resynchronization therapy (CRT) to be effective, pacing is required. An observational, nonrandomized trial showed that, in patients with AF undergoing CRT, AV junctional ablation reduced heart failure deaths and improved overall survival (compared to rate control by drugs).[32] For CRT to benefit patients with AF, ventricular rate during AF must be controlled more stringently than if CRT pacing is not needed. Up to 70% of patients with AF require AV junctional ablation for CRT devices to pace over 85% of the time and be effective.[33]

The AVERT AF (Atrioventricular Junction Ablation Followed by Resynchronization Therapy in Patients with Congestive Heart Failure and Atrial Fibrillation) trial is an ongoing prospective, randomized, multicenter, double-blind trial of patients with New York Heart Association functional class II and III congestive heart failure and left ventricular ejection fraction ≤35%. The hypothesis is that AV junctional ablation with CRT pacing improves exercise capacity and functional status compared to rate control with drugs, irrespective of rate and QRS duration.[34] It is possible that AF ablation would succeed better than AV junctional ablation and CRT pacing for these patients.[35]

Rate control is vitally important and rarely assessed carefully. Care in medical rate control may improve outcomes. Adequate rate control should be achieved, but the optimal heart rate range for various activities and during rest is not known. AV junctional ablation is rarely needed but can be useful for controlling rate response and irregularity in rate and for controlling rate aggressively in patients with heart failure and AF who require CRT.

Rhythm control

Restoration and maintenance of sinus rhythm, so-called "rhythm control," with either electrical cardioversion and/or acute or chronic antiarrhythmic drug therapy are critical components in the medical management of AF. The purported value of sinus rhythm compared to intermittent or persistent AF is improved hemodynamics, increased cardiac output, reduced filling pressures, and enhanced autonomic balance, all of which could theoretically improve symptoms, hospitalization, quality of life, and survival. As discussed later, symptom improvement may be the only accepted indication for a strategy aimed primarily at rhythm control.

In some instances, including aortic stenosis, hypertrophic cardiomyopathy, and diastolic or systolic dysfunction, sinus rhythm is critical for hemodynamic stability and patient functionality. Urgent cardioversion may be necessary if rate control is not possible, is ineffective, or is not adequate. For young patients with highly symptomatic paroxysmal or persistent AF, rhythm control is the only option.

For most patients with nonvalvular AF, however, especially those who are older and less active, the value of a long-term rhythm control medication strategy is less clear.[36–38] Prospective, randomized, controlled, clinical trials of patients with AF (mostly age >65 years and at risk for stroke) consistently have shown no benefit (and maybe harm) using a rhythm control approach. This includes patients with heart failure. Patients randomized to a rhythm control strategy had more cerebrovascular accidents,[36] higher hospitalization rates,[36–38] and no improvement in survival or quality of life.

No prospective study shows that antiarrhythmic drugs improve survival in AF patients. Retrospective data from AFFIRM indicate that patients with a history of AF but who are generally in sinus rhythm have a better survival (hazard ratio 0.53, confidence interval [CI] 0.39–0.72), but this may not be due to any specific therapy.[39] In AFFIRM, patients in the rate control arm had an approximately 40% chance at 5

years of maintaining sinus rhythm.[36] Likewise, data from the DIAMOND (Danish Investigations of Arrhythmia and Mortality on Dofetilide) trial showed that patients with impaired left ventricular function who converted to sinus rhythm with dofetilide or placebo had a lower mortality rate than did those who remained in AF or atrial flutter (risk ratio 0.44, CI 0.30–0.64, $P < 0.0001$).[40] These data are based on *post hoc* analyses. Whether the benefit is derived from sinus rhythm alone or if AF marks a patient population with a greater burden of disease who has a higher mortality rate is unclear.

Based on data from AFFIRM, there are predictors indicating which patients will maintain sinus rhythm.[41] Predictors include being in the rhythm control arm of the study, having a first episode of AF on enrollment, having an episode of AF lasting <48 hours, and having a small left atrial size. It makes sense that this population may have a better prognosis. Mitral regurgitation and reduced ejection fraction were not associated with maintenance of sinus rhythm.

For patients in whom rhythm control appears to be the best strategy, treatment options include electrical or pharmacologic cardioversion and intermittent or long-term antiarrhythmic drug treatment. Therapies are individualized based on patient need, clinical presentation, presence of underlying heart disease, comorbidities, and their associated risks and benefits.

Occasional outpatient electrical cardioversion without antiarrhythmic drug use is a safe and effective approach to help maintain sinus rhythm in those with infrequent episodes of AF.[42] Medical cardioversion of recent-onset AF with intravenous ibutilide may be useful[43,44] if a patient prefers medical conversion or if the patient has early recurrence of AF after electrical cardioversion attempts. Ibutilide can prevent acute recurrences of AF, but the risk of torsades de pointes, the expense, and monitoring limit its use. Similarly, there is a role for oral loading with a class IC antiarrhythmic drug to facilitate conversion of occasional episodes of acute-onset AF ("pill in the pocket").[45,46]

A Cochrane database review of 45 randomized controlled studies involving 12,559 patients evaluated various antiarrhythmic drugs used for maintenance of sinus rhythm and their effect on mortality, thromboembolic events, adverse effects, and proarrhythmia.[47] Class IA (disopyramide, quinidine), IC (flecainide, propafenone), and III (amiodarone, dofetilide, dronedarone, sotalol) drugs showed a significant reduction in AF recurrence (odds ratio 0.19–0.60, number needed to treat: 2–9) compared to placebo, but none improved mortality. Class IA drugs were associated with increased mortality. All drugs studied, except propafenone and amiodarone, increased the risk of proarrhythmia.

Amiodarone, even in low doses, is the most effective drug for maintaining sinus rhythm.[48,49] Risk of adverse clinical events was similar with amiodarone, sotalol, or propafenone in CTAF (Canadian Trial of Atrial Fibrillation), but stroke was lowest with amiodarone. These trials did not explore other important clinical endpoints such as hospitalization rates or cost of therapy. Although less effective, class IC (flecainide, propafenone) and III (sotalol, dofetilide) antiarrhythmic drugs still have a role in the attempt to maintain sinus rhythm. Amiodarone is a highly effective drug, but concern about complexity of use, adverse effects, drug–drug interactions, and long-term toxicity limit its use.

Antiarrhythmic drug toxicity and lack of efficacy are ready explanations for lack of benefit from a rhythm control standpoint, but this explanation may be incorrect. Consider heart failure patients treated with amiodarone, as in the AF-CHF (Atrial Fibrillation and Congestive Heart Failure) trial.[38] Amiodarone was able to maintain sinus rhythm in 60% to 70% of these patients (vs 20%–30% in a rate control group). Reported toxicity was low, and this has been supported by data from other trials of heart failure patients in whom amiodarone use was compared to placebo.[38,49–54]

For those patients who may benefit from a medication to help maintain sinus rhythm, guidelines have been developed recommending specific antiarrhythmic drugs based on clinical presentation.[4] The recommendations are based on drug efficacy and, most importantly, on drug safety. For patients with no evidence of ischemia and minimal or no heart disease, flecainide, propafenone, or sotalol is first-line therapy, followed by amiodarone, dofetilide, or catheter ablation. For patients with hypertension and substantial left ventricular hypertrophy, amiodarone is recommended. For patients with coronary artery disease, dofetilide or sotalol is first-line therapy, followed by amiodarone or catheter ablation. For patients with heart failure, amiodarone or dofetilide is first-line therapy, followed by catheter ablation.

"Upstream" therapies may reduce the risk of AF.[55] Based on the results of 11 studies of 45,457 patients, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for treatment of hypertension and heart failure reduce the risk of AF (relative risk reduction 0.52, CI 0.35–0.79).[56] Statins, used to treat hyperlipidemia, are associated with reduced risk of AF. Fish oil has been associated with a reduction in risk of postoperative AF.[57] Randomized controlled clinical trials are ongoing. Partial fatty acid oxidation inhibitors and peroxisome proliferator-activated receptor (PPAR) antagonists are under investigation.

New drugs are being developed.[58–60] A relatively selective IK_{ur} blocker, vernakalant, appears effective in converting AF and may be safer than less specific potassium channel blockers.[61] Multichannel blockers such as tedisamil (an I_{Kr} and I_{Ks} blocker), azimilide,[62] connexin modulators, 5-HT_4 antagonists, I_{KAch} blockers, Na^+/H^+ inhibitors, Na^+/Ca^{2+} inhibitors, and stretch-activated channel blockers, to name a few,[63] are under investigation, but their role in treating AF is far from clear.

One new drug, dronedarone, may emerge as a novel rhythm control drug that will change the approach to rhythm control. It is chemically similar to amiodarone but appears to be devoid of its toxicities. Dronedarone is somewhat

effective in maintaining sinus rhythm. It also may control the ventricular rate in AF. Dronedarone is the first rhythm control drug to be associated with substantial improvement in cardiovascular survival of patients with AF.[64] This may not be true for all patients. Dronedarone is associated with increased risk of mortality in patients with recent heart failure and ventricular dysfunction.[65] The exact role of the drug has not been defined.

Although catheter ablation continues to be recognized as a method for treatment of AF,[66] medical therapy for AF actually is on the increase. Better drugs and better approaches are needed.

Conclusion

Drugs are the primary method for treatment of most patients with AF. The goal—to reduce symptoms and improve outcomes related to AF—is within reach. Management involves drugs for rate control, rhythm control, and anticoagulation. Medical management is complex and evolving as new drugs become available and as ablation takes a bigger role in the care of these patients. Meanwhile, there is rapid progress with ablation techniques. A hybrid approach involving ablation and drugs may someday transform the hope for a cure to a reality.

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