ATRIAL FIBRILLATION

REVIEW ARTICLE

Modern Pharmacologic Strategies in the Management of Atrial Fibrillation

JOEL A. LARDIZABAL, MD, GRACE HUANG, DO and PRAKASH C. DEEDWANIA, MD, FACC, FAHA

Division of Cardiology, Department of Medicine, University of California – San Francisco School of Medicine, Fresno Medical Education Program, Fresno, CA

UCSF School of Medicine, Veterans Affairs Central California HCS, Fresno, CA

ABSTRACT. Atrial fibrillation (AF), the most prevalent clinically-significant arrhythmia, is associated with high burden in terms of morbidity, mortality and socioeconomic consequences. The maintenance of sinus rhythm is an attractive therapeutic goal, but this strategy has failed to result in net clinical benefit in multiple clinical trials due to the relative inefficacy and toxicity of the classic antiarrhythmic drugs. New agents, like dronedarone and vernakalant, have shown promise and have emerged as viable options for AF pharmacotherapy. However, concerns regarding their efficacy and safety still limit their clinical utility. As such, a rate-control strategy to AF management is remains the standard. Recent data has shown that the strict heart rate (HR) control of HR may not be as beneficial as previously thought, and a more lenient approach to HR control is now considered a reasonable initial treatment goal. Stroke thromboprophylaxis is also an integral aspect of AF management. The CHA2DS2-VASc score is a new risk stratification scheme that is purported to be a superior to the classic CHADS2 scoring system in terms of predictive value, although this assertion has yet to be verified in a randomized trial. Novel classes of drugs have emerged in an attempt to simplify treatment and improve compliance to antithrombotic therapy. Dabigatran, an oral direct thrombin inhibitor, has recently been added as a first-line alternative to warfarin in high-risk patients. Dual antiplatelet therapy with combination aspirin-clopidogrel has also become a viable treatment option in patients not suitable for warfarin anticoagulation. Other emerging agents, such as oral Factor Xa inhibitors and novel vitamin K antagonists, are currently under investigation and are showing promise. However, more definitive data regarding their efficacy, safety, and cost-effectiveness are clearly required before they become part of the pharmacologic armamentarium for AF therapy.

KEYWORDS. atrial fibrillation, antiarrhythmic therapy, antithrombotic strategy, pharmacotherapy.

Background

Atrial fibrillation (AF) is the most common clinically significant arrhythmia encountered in modern medical practice, with a prevalence of nearly 2.7 million in the USA. The condition is closely linked to aging, and with an incidence of over 75,000 new cases each year, the number of AF cases is projected to exceed 12 million by year 2050 as the demographic proportion of elderly individuals increases.1 AF is associated with significant rates of morbidity and mortality, accounting for over 500,000 hospitalizations and nearly 100,000 deaths annually. AF, whether paroxysmal or persistent, independently increases the risk of stroke nearly 5-fold, and is estimated to be responsible for at least 15–20% of all ischemic strokes.2 In addition, AF is also associated with increased hospitalization and mortality from coronary heart disease and heart failure.3

The authors report no conflicts of interest for the published content.

Manuscript received March 25, 2011, final version accepted April 8, 2011.

Address correspondence to: Prakash C. Deedwania, MD, FACC, FAHA, Chief of Cardiology, Veterans Affairs Central California HCS, 2615 E. Clinton Avenue, Fresno, CA 93703. E-mail: pdeedwania@fresno.ucsf.edu
The high AF burden served as the impetus for the development of more effective and efficient strategies of managing this disease and its associated conditions. Surgical and catheter-based invasive approaches to AF therapy, including Maze and ablative pulmonary vein isolation procedures, have dramatically improved in recent years. Despite the rapid increase in the popularity and safety of these invasive procedures, however, pharmacologic therapy remains the first-line treatment for AF. Modern advances in drug research and design have resulted in state-of-the-art medications that have significantly increased the safety, effectiveness and efficiency of AF pharmacotherapy.

Antiarrhythmic drug therapy

The conversion of AF to normal sinus rhythm is an attractive therapeutic goal, at least conceptually, because of the theoretical hemodynamic benefits. In actual clinical practice, however, pharmacologic strategies aimed primarily at arrhythmia suppression have not resulted in net benefit thus far. A large number of chronic AF cases have irreversible structural and electrophysiologic substrates that perpetuate the arrhythmia, making them resistant to antiarrhythmic therapy. In those who respond to treatment, on the other hand, whatever clinical advantage gained from AF drug therapy appeared to be counteracted by the adverse events resulting from the toxicity of the widely used standard antiarrhythmic agents like amiodarone, sotalol, and dofetilide, among others. Over the years, much endeavor has been invested towards the design of safer, more tolerable, and more effective antiarrhythmic medications. Two novel agents, dronedarone and vernakalant, have been under development during the past decade with the intent of achieving such end, and have just been recently released.

Dronedarone

In 2009, the US Food and Drug Administration (FDA) approved the use of dronedarone to reduce cardiovascular hospitalization in patients with AF who have high-risk features. Dronedarone, a benzofuran derivative, is similar in chemical structure to amiodarone. However, dronedarone is purported to have a better safety profile because it is devoid of iodine moiety, which is primarily responsible for the pulmonary and thyroid toxicities of amiodarone. Dronedarone exhibits properties belonging to all four Vaughan-Williams classes of antiarrhythmics, but the specific contribution of each of these activities to the drug’s clinical effects is not defined.

The antiarrhythmic efficacy of dronedarone was tested in the ADONIS (American–Australian–African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm) and EURIDIS (European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm) studies of over 1,200 patients with AF who were randomized to treatment with either dronedarone 400 mg twice daily or placebo. After 12 months of follow-up, dronedarone was shown to significantly reduce the recurrence of AF by 25%. In addition, dronedarone also decreased the average ventricular rates in patients whose AF subsequently recurred.

The multicenter ATHENA trial (A Placebo-Controlled, Double-Blind, Parallel Arm Trial To Assess The Efficacy Of Dronedarone For The Prevention Of Cardiovascular Hospitalization Or Death From Any Cause In Patients With Atrial Fibrillation/Atrial Flutter), on the other hand, enrolled over 4,600 high-risk patients with AF, who were randomized to treatment with either dronedarone 400 mg twice daily or placebo. After a median 22 months of follow-up, the study found a significant 24% reduction in cardiovascular hospitalization or death in those who received dronedarone. A 29% lowering of cardiovascular mortality was also noted, driven almost exclusively by reduction in arrhythmia-related deaths.

The clinical efficacy of dronedarone in AF suppression, however, appears inferior to that of amiodarone. In the DIONYSOS trial (Efficacy & Safety of Dronedarone versus Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation), for example, more than 500 patients with persistent AF were randomized to 7 months treatment with either dronedarone or amiodarone. On follow-up, patients who received dronedarone had a 34% higher AF recurrence after 12 months, as well as a 33% higher recurrence of AF after successful cardioversion, compared to those given amiodarone.

Despite its seemingly limited antiarrhythmic efficacy, the clinical utility of dronedarone in AF therapy appears to be justified by its relatively favorable safety profile. In the ADONIS, EURIDIS and ATHENA trials, the incidences of pulmonary, thyroid and liver toxicities with dronedarone were similar to placebo. Compared to amiodarone, dronedarone had a 20% lower incidence of major adverse events in the DIONYSOS trial, driven mainly by significant reductions in thyroid, neurologic, skin, and ocular events, resulting in less frequent drug discontinuation. It is estimated that for every 1,000 patients treated with dronedarone instead of amiodarone, approximately 228 more AF recurrences are to be expected in exchange for 10 fewer deaths and 62 fewer adverse events requiring drug discontinuation.

Although dronedarone is among the safest of antiarrhythmic agents, it is not completely benign, and proper selection of appropriate patients with appropriate indications is especially emphasized when using this particular agent. The Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA) randomized over 600 patients hospitalized for symptomatic systolic heart failure to either dronedarone and placebo, 38% of whom had AF. The study was prematurely terminated after a median follow-up period of just 2 months because of a 2-fold excess in mortality with dronedarone, primarily due to worsening heart failure. This was the basis for the FDA Black Box Warning, which listed severely symptomatic or recently decompensated heart failure as a contraindication to dronedarone therapy.
Additionally, several cases of hepatocellular injury and acute hepatic failure related to dronedarone therapy were just recently described. Two patients required liver transplantation, both of whom were females of approximately 70 years of age who developed fulminant hepatic failure at 4–6 months of dronedarone treatment. These events were reported voluntarily by the drug manufacturer as part of post-marketing surveillance, and as the treatment population size is unknown, the frequency of these events cannot be reliably estimated. Nevertheless, the FDA recommended periodic liver function testing during the first 6 months of dronedarone treatment, and that the drug should be discontinued if evidence of liver injury is found.11

**Vernakalant**

In 2010, the European Union approved the use of vernakalant, a novel antiarrhythmic agent for rapid conversion of new-onset AF in both non-surgical and post-surgical patients. Vernakalant is a mixed frequency-dependent sodium and atria-preferential potassium channel blocker. The drug selectively prolongs atrial refractory periods without significant effects on ventricular refractoriness, QT intervals, or hemodynamic parameters.12

The clinical efficacy of vernakalant in AF conversion was tested in the Atrial Arrhythmia Conversion Trial (ACT).13 In this study, over 300 patients with recent-onset AF were randomized to treatment with either placebo or vernakalant 3 mg/kg intravenous infusion. Within 90 min of drug infusion, AF was successfully terminated in 37.6% of patients who received vernakalant compared to 2.6% of those given placebo. Median time to arrhythmia termination was only 11 min with vernakalant. Clinical efficacy of the drug is most notable among patients with AF of short duration (within 7 days of onset), where the success rate for vernakalant was 51.7%, compared to 4% with placebo. A separate arm of the ACT study (ACT-II)14 compared intravenous vernakalant to placebo in 150 cardiac surgery patients with postoperative AF. Within 90 min of infusion, vernakalant was found to successfully terminate the arrhythmia in 47% of patients, as opposed to 14% in the placebo group. Onset of drug action was relatively quick, with a median time of 12 min to conversion.

The AVRO Trial (A Phase III Superiority Study of Vernakalant vs Amiodarone in Subjects with Recent Onset Atrial Fibrillation)15 compared the efficacy and safety of intravenous vernakalant to amiodarone in over 250 patients with short-duration AF (within 48 h of onset) in a randomized, double-blind fashion. The study found that within 90 min of infusion, vernakalant successfully converted 52% of patients with relatively rapid onset of action (median time of 11 min), compared to 5% in those who received amiodarone. At 4 h, vernakalant maintained its clinical superiority over amiodarone (54% versus 23% were in sinus rhythm, respectively). This resulted in a significant 39% higher rate of symptom relief with vernakalant.

In the ACT studies, vernakalant was well tolerated, although higher incidences of minor adverse events, hypotension and drug discontinuation were noted compared to placebo. In the AVRO Trial, rates of serious adverse effects and drug discontinuation, although uncommon, were higher with vernakalant compared to amiodarone. Questions linger regarding the safety profile of vernakalant, and the FDA has yet to approve its use in the USA until more data are available. In fact, the FDA has recently suspended the ongoing ACT-5 Trial because of cardiogenic shock-related mortality in one of the subjects who received intravenous vernakalant.16

The development of oral vernakalant is ongoing after phase 2 studies yielded favorable efficacy in AF therapy. A dose-ranging trial that randomized over 700 patients at risk for recurrent AF to either placebo or oral vernakalant found that 500 mg of the drug taken twice daily resulted in a significant reduction in the rate of AF relapse compared to placebo.17 As it is, the future of oral vernakalant in the treatment of AF will remain uncertain until phase 3 trials, which will take several more years, have been completed.

**Non-arrhythmic therapy**

Non-arrhythmic therapeutic alternatives to the conventional antiarrhythmic drugs have also been evaluated in AF management. Retrospective and epidemiologic data suggest that renin–angiotensin antagonists, statins, omega-3 fatty acids, antioxidants, anti-inflammatory agents, and ranozaline may favorably alter the natural course of AF by modulating the underlying structural, electrophysiologic, and neurohormonal substrates that fuel atrial arrhythmogenesis.18 Unfortunately, the clinical efficacy of these alternative therapies for AF has never been corroborated in large randomized trials. For example, in the ACTIVE-I Trial (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events),19 over 9,000 high-risk patients with AF were randomized to treatment with either irbesartan or placebo. After 4 years of follow-up, the study found no difference in the composite rates of cardiovascular events, hospitalizations, mortality, and stroke between groups. This suggests that renin–angiotensin blockade does not provide additional therapeutic benefit in patients with atrial fibrillation who are well controlled on current therapy.

**Current clinical practice on antiarrhythmic therapy in AF**

Both the US20 and European21 practice guidelines for the management of AF have recently been updated to incorporate the role of dronedarone in the treatment algorithm. In AF patients without significant cardiac structural abnormalities, dronedarone has become a first-line agent (along with flecainide, propafenone, and sotalol) in the maintenance of sinus rhythm (see Figure 1). Dronedarone is also a first-line treatment...
option (along with dofetilide and sotalol) in AF patients with coronary artery disease. Amiodarone has been relegated as the alternative antiarrhythmic agent in most patients with AF, except in the setting of heart failure or significant left ventricle hypertrophy where it remains the first-line option. Although vernakalant was briefly described in the European guidelines as a potential agent for the acute termination of recent-onset AF, its exact role in the management of AF still remains undefined. The guidelines also recognize the potential role of renin–angiotensin antagonists and statins in the long-term maintenance of sinus rhythm in high-risk patients; however, further clarification in randomized clinical trials is required before they can be routinely recommended.

Rate control strategy

Even with the advent of state-of-the-art drug therapy, the treatment approach primarily aimed at maintaining sinus rhythm in patients with AF (rhythm-control strategy) has not really translated into definite clinical benefit. The suboptimal clinical efficacy and the relative toxicity of the current antiarrhythmic agents are partly to blame, but, whatever the reason, clinical trials have time and again confirmed the lack of superiority of the rhythm-control strategy over simple rate control approach, even in AF patients with heart failure who were supposed to derive the most hemodynamic gain from conversion to sinus rhythm.4 As such, heart rate (HR) control remains the primary treatment strategy in the general management of patients with AF.

Strict versus lenient rate control

Treatment goals for the rate control strategy have been traditionally defined as target HR between 60–80/min at rest and 80–115/min with moderate exercise. The clinical utility of these arbitrary goals, however, has been recently challenged by the results of the Rate Control Efficacy in Permanent Atrial Fibrillation (RACE-II) trial.22 In this study, over 600 patients with permanent AF were randomized to either lenient (target resting HR <110/min) or strict rate control (target HR <80/min at rest, <110/min on moderate exercise). After 3 years of follow-up, the composite rates of death, heart failure hospitalization, stroke, systemic embolism, bleeding, and arrhythmic events were similar between the two groups. Furthermore, 31% more patients in the lenient-control group met the HR targets with fewer office visits.

Current clinical practice on rate control strategy

The recent guidelines20,21 assert that lenient-rate control may be adopted as a reasonable initial strategy in patients with permanent AF as it is generally more convenient to implement. However, the long-term impact on left ventricular (LV) function was not studied, so if a lenient-rate control strategy is chosen for these patients, monitoring of LV function is recommended.

Beta adrenergic agonists (e.g. metoprolol, atenolol, propranolol, bisoprolol, carvedilol, esmolol) and non-dihydropyridine calcium channel blockers (e.g. diltiazem, verapamil) remain the standard agents for long-term HR control in AF. Digoxin and amiodarone are also considered first-line drugs for rate control, especially in the setting of LV dysfunction. Intravenous formulations of these classes of drugs are also indicated in acute HR control in most patients with AF who do not have contraindications. In addition to its role in the maintenance of sinus rhythm, dronedarone has also been recently added as a viable option for long-term rate control in AF (see Table 1).21

---

**Figure 1:** Recommended treatment algorithm for the selection of antiarrhythmic therapy for the maintenance of sinus rhythm in atrial fibrillation. (Adapted from Circ 2011;123(1):111)
Antithrombotic therapy

Stroke, with its potentially devastating consequences, is perhaps the most feared complication of AF. As such, assessment of the thromboembolic risk is mandated for all patients with AF. Whether a rhythm-control strategy or a rate-control treatment approach is chosen, antithrombotic therapy has to be considered at all times in patients at risk.

Thromboembolic risk assessment

The CHADS2 scoring system has been the most widely used tool in the evaluation of AF thromboembolic risk, given its simplicity and validated clinical utility. In this system, five major risk factors (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and previous stroke) are taken into account. Each risk factor present in an AF patient is assigned a point, except for stroke, which receives a score of 2. A total CHADS2 score of 2 or above (maximum of 6) indicates a high thromboembolic risk, for which anticoagulation is indicated. A score of 1 identifies a moderate-risk individual, where antiplatelet therapy (e.g. aspirin) or anticoagulation may be chosen, depending on bleeding risk. A score of 0 is suggestive of a low-risk setting in which antithrombotic therapy may be deferred.

A new scoring scheme has recently been proposed to improve the predictive accuracy of thromboembolic risk stratification in AF patients. The CHA2DS2-VASc scoring system, a refinement of the 2006 Birmingham/National Institute for Health and Clinical Excellence stroke risk stratification schema, reclassified and incorporated additional risk factors. The new scheme adopted the classic CHADS2 system, but assigned an additional point to age ≥75 years. In addition, three other risk factors for stroke are considered (history of vascular disease, age 65–74, and female sex), each assigned 1 point. Like the CHADS2 system, total CHA2DS2-VASc scores of 0, 1, and ≥2 (maximum of 9) correspond to low, moderate, and high thromboembolic risks, respectively. In a real-life cohort of over 1,000 patients with AF, the Euro Heart Survey compared the CHADS2 and the CHA2DS2-VASc scoring systems, and found that the new scheme had a modestly enhanced predictive value, showing progressive increase in event rates corresponding with increasing scores.

Table 1: Pharmacologic agents recommended for heart rate control in atrial fibrillation (Adapted from Europace 2010;12(10):2399)

<table>
<thead>
<tr>
<th>Pharmacologic agents</th>
<th>β-Blockers</th>
<th>Non-dihydropyridine calcium channel antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intravenous administration</td>
<td>Usual oral maintenance dose</td>
</tr>
<tr>
<td>Metoprolol CR/XL</td>
<td>2.5–5 mg</td>
<td>100–200 mg o.d. (ER)</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>N/A</td>
<td>2.5–10 mg o.d.</td>
</tr>
<tr>
<td>Atenolol</td>
<td>N/A</td>
<td>25–100 mg o.d.</td>
</tr>
<tr>
<td>Esmolol</td>
<td>10 mg</td>
<td>N/A</td>
</tr>
<tr>
<td>Propranolol</td>
<td>1 mg</td>
<td>10–40 mg t.i.d.</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>N/A</td>
<td>3.125–25 mg b.i.d.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Digitals glycosides</th>
<th>Verapamil</th>
<th>Calcium channel antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 mg</td>
<td>40 mg b.d. to 360 mg (ER) o.d.</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>N/A</td>
<td>60 mg t.d.s. to 360 mg (ER) o.d.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Others</th>
<th>Amiodarone</th>
<th>Dronedarone9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 mg/kg in 1 h. and 50 mg/h maintenance</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>100 mg–200 mg o.d.</td>
<td>400 mg b.i.d.</td>
</tr>
</tbody>
</table>

J A Lardizabal, G Huang, and P C Deedwania

The Journal of Innovations in Cardiac Rhythm Management, May 2011
The European practice guidelines have recently incorporated the CHA2DS2-VASc scheme in AF management treatment recommendations (see Figure 2). Whether or not this new scoring method will gain widespread clinical acceptance remains to be seen. Prospective, randomized, controlled trials may be required to establish its superiority over the classic CHADS2 risk stratification system.

Standard antithrombotic regimen

Anticoagulation using the oral vitamin K antagonist (VKA) warfarin and antiplatelet treatment using aspirin have been the mainstay of antithrombotic therapy for stroke prophylaxis in AF. Aspirin offers a modest 19% reduction in stroke compared to placebo, and, as such, is indicated only for individuals at low or moderate risk. Warfarin is three times more effective than aspirin, with a 62% stroke risk reduction in patients with AF, and is the preferred antithrombotic agent in moderate- to high-risk individuals.

The widespread use of warfarin has been credited for significantly cutting down the rates of ischemic stroke by more than half over a ten-year period, from 47% in 1992 to just 20% in 2002. Unfortunately, less than half of high-risk patients with AF are actually on anticoagulant therapy. Warfarin interacts with certain food and medications, resulting in impaired compliance. It also requires frequent monitoring of coagulation profile and dose adjustment. In a meta-analysis of 21 trials involving nearly 6,300 individuals with AF who were actually on chronic anticoagulation, patients on average spent only 61% of time within the target therapeutic range. They were under the therapeutic range 26% of the time and were supratherapeutic 13% of the time.

Efforts have been directed at developing new pharmacologic agents and strategies that are simpler, more convenient, and more efficient than the current standard therapies that would increase compliance to thromboprophylaxis and reduce stroke rates in AF even further. Those efforts have led to the design of oral direct thrombin inhibitors and the use of dual antiplatelet therapy, novel drugs, and approaches intended to supplant warfarin.

Dual antiplatelet therapy

The efficacy of combination aspirin–clopidogrel therapy in AF thromboprophylaxis was tested in the ACTIVE trials (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events). The ACTIVE-W Trial enrolled over 6,700 moderate- to high-risk patients with AF who were randomized to treatment with either oral anticoagulation or combination aspirin–clopidogrel. The study was terminated prematurely after just 1.3 years of follow-up because of a clear superiority of warfarin over dual antiplatelet therapy (4.9% versus 7% rates of major thromboembolic events, respectively). Furthermore, bleeding events were not reduced by dual antiplatelet therapy, and, in fact, the rates of minor bleeding were lower with warfarin.

The ACTIVE-A Trial, on the other hand, enrolled over 7,500 high-risk AF patients who were unsuitable for warfarin therapy, and randomized them to treatment with either aspirin alone or combination aspirin–clopidogrel. After 3.6 years of follow-up, dual antiplatelet...
therapy was found to reduce stroke risk by 28% compared to aspirin alone. Although it was associated with higher risk of major bleeding, combination aspirin-clopidogrel treatment appears to be a viable therapy in AF patients at high risk for stroke.

**Oral direct thrombin inhibitors**

Ximelagatran was the first drug to be developed among the oral direct thrombin inhibitors (DTI), a new class of anticoagulants that can be administered without coagulation monitoring or dose adjustment, significantly simplifying treatment compared to warfarin. Pooled data from the SPORTIF (Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation) trials showed that fixed-dose ximelagatran was as effective as well-controlled, adjusted-dose warfarin for prevention of stroke and systemic embolic events.\(^{31}\) Combined rates of minor and major bleeding were significantly lower with ximelagatran (18% relative reduction). However, the drug was associated with significantly higher rates of liver toxicity. Ximelagatran was rejected by the FDA and was subsequently pulled out of the European market because of these adverse effects.

Dabigatran was the next oral DTI to be extensively evaluated clinically. This drug, conveniently taken at a fixed dosage without need for coagulation monitoring, does not require hepatic metabolism and has no significant interaction with food. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial\(^{32}\) randomized over 18,000 high-risk patients with AF into treatment with either dabigatran or warfarin. After 2 years of median follow-up, lower-dose dabigatran (110 mg twice daily) was found to be non-inferior to warfarin in terms of antithrombotic efficacy, but it was significantly associated with a 19% reduction in bleeding events. Higher-dose dabigatran (150 mg twice daily) was associated with a 34% significantly lower rate of stroke and embolic events, with similar bleeding rates compared to warfarin. The FDA approved dabigatran (150 mg twice daily dosing) in late 2010, with a primary indication of prevention of stroke and embolic events in patients with AF.

**Oral Factor Xa inhibitors**

Another new class of oral anticoagulants, the oral Factor Xa (FXa) inhibitors, has emerged. Originally designed for prophylaxis against venous thromboembolism (VTE), this new class of agents (which includes rivaroxaban, apixaban, betrixaban, and edoxaban) is currently being tested in the setting of AF. Like oral DTIs, oral direct FXa inhibitors are given at a fixed dose without the need for coagulation monitoring.

The ROCKET-AF trial (Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) randomized nearly 14,300 high-risk AF patients to treatment with either rivaroxaban 20 mg daily or warfarin. Preliminary results after 2.6 years of follow-up showed that rivaroxaban was not inferior to warfarin in terms of efficacy (stroke and embolic events) and safety (bleeding events).\(^{33}\) Full trial data have yet to be published, but rivaroxaban may potentially become a first-line alternative to warfarin or dabigatran in AF thromboprophylaxis if its desirable clinical efficacy and safety profile is confirmed.

The clinical efficacy of the oral FXa inhibitor apixaban in AF was also evaluated in the AVERROES (Apixaban versus Acetylsalicylic Acid to prevent Strokes) Trial,\(^{34}\) which randomized 5,600 high-risk patients with AF who were unsuitable for warfarin therapy into treatment with either apixaban 5 mg twice daily or aspirin. The trial was terminated early after 1.1 years of mean follow-up because of clear benefit in favor of apixaban. Apixaban significantly reduced rates of stroke or embolic events by 55% compared to aspirin. It also reduced mortality by 21%, but increased major bleeding by 13%. It remains unclear how apixaban would fare against dual antiplatelet therapy, which has also shown benefit in AF patients who are unsuitable for warfarin treatment. An established role for apixaban in AF therapy is unlikely to be defined until its clinical efficacy is compared against standard warfarin therapy. This is currently being tested in the ongoing ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation) Trial.

Early-phase clinical evaluation of the other oral FXa inhibitors betrixaban and edoxaban appears promising.\(^{35,36}\) However, data from large-scale randomized trials comparing their clinical efficacy with standard treatment, which are still ongoing, are clearly required.

**Other emerging antithrombotics**

Another novel class of antithrombotics, the indirect FXa inhibitors, has briefly emerged but no definitive role in the treatment of AF has been found so far. Idraparinux, the first in its class, has a rapid onset and long duration of half-life, given as a weekly subcutaneous injection. Idraparinux was originally studied for VTE, but has also been recently evaluated in AF patients in the AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients with Atrial Fibrillation) Trial.\(^{37}\) After randomizing over 4,500 patients with high-risk AF, the study found that idraparinux was non-inferior to warfarin in clinical efficacy. However, the trial was stopped prematurely because of significantly higher rates of major and intracranial bleeding with idraparinux. Idrabiaptarinux, a similar once-weekly, subcutaneously administered indirect FXa inhibitor, was also investigated in high-risk patients with AF in the BOREALIS-AF (Biotinylated Idraparinux Versus Oral Adjusted-dose Warfarin to Prevent Stroke and Systemic Thromboembolic Events in Patients with Atrial Fibrillation) Trial, but was terminated prematurely by its sponsor for non-safety-related reasons.\(^{38}\)

Tecarfarin, a new-generation oral VKA, is currently being investigated as a potentially safer and more reliable alternative to warfarin in AF. Early-phase test results suggested that tecarfarin therapy resulted in high
rates of achievement of therapeutic coagulation levels and very low rates of supratherapeutic toxicity. This was later confirmed in the EmbraceAC trial, in which patients at high risk for thromboembolic events were treated with oral anticoagulation (warfarin at goal INR = 2–3). Moderate-risk individuals may be treated with either aspirin or warfarin, depending on bleeding risk (although warfarin is preferred). Antithrombotic therapy may be deferred in low-risk patients, who may also be treated with aspirin (although no therapy is preferred).

Recent updates to these guidelines added dual antiplatelet therapy using combination aspirin–clopidogrel as a viable therapeutic option in patients unsuitable for warfarin treatment. Perhaps the most significant of the updates is the recommendation that dabigatran be added as a first-line alternative to warfarin in AF thromboprophylaxis.

The role of the novel oral FXa inhibitors and other emerging classes of drugs in the antithrombotic therapy of patients with AF remains undefined, pending reliable data on their clinical efficacy and safety. In addition, the cost-effectiveness of these emerging pharmacotherapeutic agents needs to be closely scrutinized before they are considered as viable alternatives to the current standard treatment.

Conclusion

AF is a highly prevalent disorder with significant morbidity, mortality, and socioeconomic implications. Antiarrhythmic therapy has failed to result in net clinical benefit in multiple clinical trials, perhaps due to the relative inefficacy and toxicity of the classic antiarrhythmic drugs. Newer agents, like dronedarone and vernakalant, have shown promise and have emerged as viable options for AF pharmacotherapy in the most recently updated practice guidelines. However, concerns regarding the efficacy and safety of these novel drugs still remain, which may limit their clinical utility. As such, a rate-control strategy to AF management is still the standard. Recent data has shown that the strict control of HR may not be as beneficial as previously thought. A more lenient approach to HR control is now considered a reasonable initial goal. Stroke thromboprophylaxis is an integral aspect of AF management. A new, more detailed risk-stratification scheme, the CHA2DS2-VASc score, is being proposed to supplant the classic CHADS2 scoring system. Also, novel classes of drugs have been designed in an attempt to simplify treatment and improve compliance to antithrombotic therapy. Dabigatran, an oral DTI, has recently been added as a first-line alternative to warfarin in high-risk patients. Dual antiplatelet therapy with combination aspirin–clopidogrel has also become a viable treatment option in patients unsuitable for warfarin. Other emerging agents, such as oral FXa inhibitors and novel VKAs, are currently under investigation and are showing promise. However, more definitive data regarding their efficacy, safety, and cost-effectiveness are clearly required before they are considered feasible options in AF therapy.

References


22. J A Lardizabal, G Huang, and P C Deedwania


