Emerging drugs for atrial fibrillation

Atrial fibrillation is associated with excess morbidity and mortality, especially in the elderly. There are two approaches to the management of patients with atrial fibrillation: rate control or maintenance of sinus rhythm with antiarrhythmic medications. Depending on a patient's risk profile, both strategies may require anticoagulation. Management of atrial fibrillation may be challenging owing to side effects associated with drugs such as warfarin and antiarrhythmic agents. However, there are currently ongoing efforts to develop newer, safer and more tolerable drugs to treat this nuisance arrhythmia. This article deals with the emerging drugs as potential targets for the management of atrial fibrillation.

KEYWORDS: amiodarone ■ anticoagulants ■ atrial fibrillation ■ atrial selective channels ■ new antiarrhythmic agents

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Atrial fibrillation (AF) is associated with excess morbidity and mortality, and is the most common reason for arrhythmia-related hospitalization [1]. As a result of an aging population, the prevalence of AF is expected to rise over the next several decades, and as many as 6 million individuals may be affected by the year 2050 in the USA alone [2]. Greater awareness regarding the changing epidemiology, morbidity, mortality and public health burden associated with AF has intensified the focus on this arrhythmia. Recently, there has been an expansion in the available pharmacologic therapies directed at cardioversion, maintenance of sinus rhythm (SR), rate control and anticoagulation.

Currently in the USA, the most popular antiarrhythmic agents to convert AF include flecainide, propafenone and intravenous ibutilide. Although these drugs are effective at converting AF in an acute setting, their uses may be restricted to select patient populations (as with flecainide and propafenone) or associated with the need for hospitalization (as with ibutilide).

The most commonly prescribed antiarrhythmic, amiodarone, is used for both cardioversion and maintenance of SR. Although amiodarone is highly effective as a rhythm-control agent, its use is limited by its side-effect profile, which includes ocular, dermatologic, thyroid, pulmonary and hepatic toxicities.

One of the cornerstones of AF management is anticoagulant therapy to reduce the risk of thromboembolism, in particular ischemic stroke. Warfarin has been the mainstay of oral anticoagulant therapy among patients with AF. Despite abundant evidence that it attenuates stroke risk among patients with AF, warfarin use requires frequent monitoring, has multiple drug interactions and is associated with an increased risk of bleeding complications [3,4]. Few alternatives to warfarin therapy have emerged since its initial use in patients with AF in the early 1980s.

Owing to the limited choice and adverse side-effect profiles of the currently available medications for the management of AF, there have been aggressive searches for more effective and safer compounds. This article will highlight emerging drugs for the cardioversion and suppression of AF as well as oral antithrombotic agents.

Atrial selective channels

Traditionally, antiarrhythmic medications have been organized according to the Vaughn–Williams system, which classifies drugs based on their preferential effects on specific ion channels. While this framework is clinically useful, it belies the complex electrophysiological properties of many of the antiarrhythmic agents and the arrhythmias that they are used to treat. Growing insights into the cellular and molecular mechanisms underlying various arrhythmias has allowed for a more rational drug design. This, in turn, has yielded antiarrhythmic drugs with more precise mechanisms of action.

Along these lines, drugs that target selective atrial channels for the suppression of AF have been a recent subject of attention. One major advantage of these drugs is that they do not alter the electrophysiological properties of the ventricle and, thereby, reduce the adverse effects of proarrhythmia, such as torsades de pointes.

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Targets include the ultra-rapid delayed rectifier current (IKur) and the acetylcholine (IkACh) channels that are confined solely to the atrium. Inhibition of these two currents prolong the shortened atrial action potential associated with AF and, thereby, increase the chance of AF termination and suppression. Currently there are several atrial-selective antiarrhythmic drugs in clinical trials, including AVE-0118 and AZD7009.

Vernakalant is a relatively atria-specific agent that blocks multiple channels, including Ikur, Ito, INa and Ikr. In three clinical trials, vernakalant has been shown to be effective in the termination of AF as compared with placebo [5–7]. In a Phase III trial, the impact of vernakalant on the primary end point of AF conversion for at least 1 min within 90 min of drug infusion was evaluated. A total of 336 patients were enrolled and classified according to their duration of AF (short duration, 3–7 days and long duration, 8–45 days). Among patients with short-duration AF, vernakalant at 3 mg/kg was more effective at converting AF than placebo (52 vs 4%, respectively, p < 0.001) (Figure 1) [6]. A statistically significant difference in AF conversion was not observed among patients with long-duration AF (7.9 vs 0%, p = 0.09).

The Atrial Arrhythmia Conversion Trial (ACT)II was a prospective, randomized double-blind placebo-controlled trial of vernakalant for the conversion of AF or atrial flutter following a coronary artery bypass graft and/or valvular surgery [7]. Patients were randomized to receive a 10-min infusion of vernakalant 3 mg/kg or placebo. Vernakalant was found to be superior to placebo with respect to the primary end point of conversion of AF or atrial flutter to SR within 90 min of dosing. A total of 47% of patients with AF who received vernakalant converted to SR compared with 14% of patients who received placebo (p < 0.001). The median time to conversion was 12 min.

In general, vernakalant appears to be well tolerated with a favorable side-effect profile as compared with placebo. In the Phase III trial mentioned previously, four serious adverse events were reported in three patients, (two hypotension, one cardiogenic shock and one complete heart block). The hypotensive effects of vernakalant appear to be transient. While vernakalant may prolong the heartrate-corrected QT interval it does not appear to be associated with torsades de pointes [6,7]. The most commonly reported side effects have been alteration in taste, sneezing, paresthesias and nausea.

Currently, vernakalant has been approved by the US FDA Cardiovascular and Renal Drugs Advisory Committee and is still awaiting final FDA approval. Other trials with vernakalant are still in planning. If approved, physicians will have a new option for the pharmacologic conversion of AF.

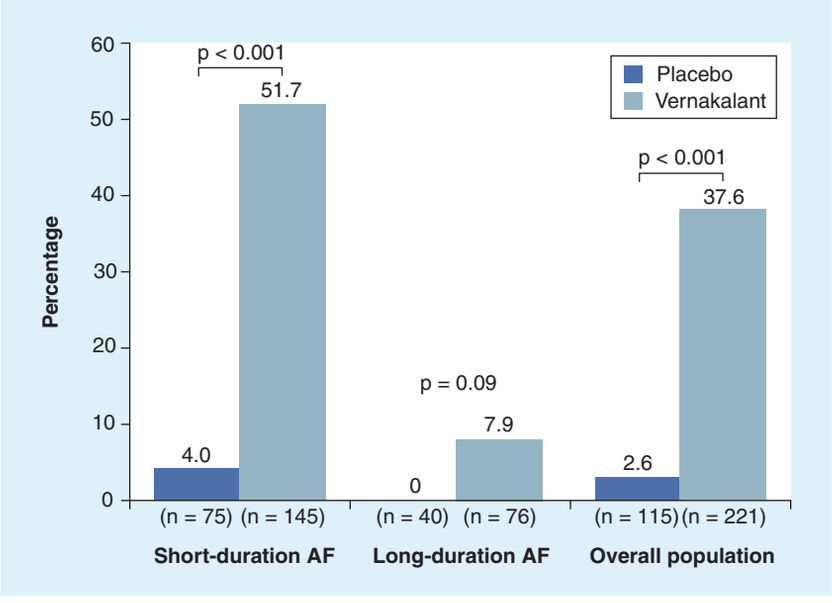


Figure 1. Conversion rates in the short, long and overall atrial fibrillation populations in vernakalant and placebo groups.
AF: Atrial fibrillation.
Reproduced with permission from [6].

Amiodarone congeners

Dronedarone is a congener to amiodarone but lacks its iodine content. Like amiodarone, it blocks similar channels – Ikr, Iks, ICa, Ito, INa, IkACh, as well as α and β receptors [8]. Dronedarone was specifically designed to lack an iodine moiety in order to render it less toxic than amiodarone. In the Dronedarone for Prevention of Atrial Fibrillation: A Dose-Ranging Study (DAFNE), a twice-daily dose of 400 mg dronedarone was found to posses the best combination of efficacy and safety for the prevention of AF recurrence [9]. Further testing in the European trial in AF patients receiving dronedarone (EURIDIS) and American–Australian–African trial with dronedarone in AF or atrial flutter patients for the maintenance of sinus rhythm (ADONIS) trials demonstrated that dronedarone was superior to placebo in preventing AF recurrences at 1 year [10]. However, recurrence rates were high in both groups and at 1 year 67.1% of patients on dronedarone versus 77.5% on placebo experienced AF recurrence (Figure 2).

The ATHENA trial was designed to assess the impact of dronedarone on the combined primary

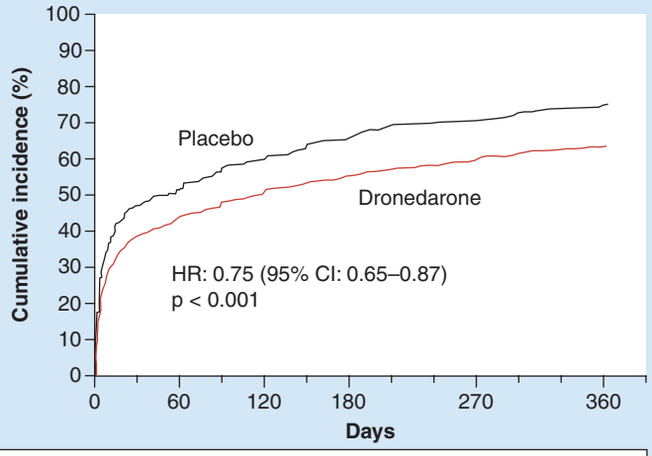
end point of cardiovascular hospitalization or all-cause mortality in patients with a recent or current history of nonpermanent AF [11]. Compared with placebo, dronedarone significantly reduced the risk of CV hospitalization or death as compared with placebo over a follow-up period of 21 months. The primary outcome occurred in 734 patients (31.9%) in the dronedarone group and in 917 patients (39.4%) in the placebo group (RR 0.76; 95% CI: 0.69–0.84) (FIGURE 3). It is worth noting that it was a decrease in AF-related admissions that drove the reduction in the primary end point. No statistically significant difference in all-cause mortality was observed (RR 0.84; 95% CI: 0.66–61.08).

In a *post-hoc* analysis of the ATHENA trial, dronedarone was also associated with a reduction in stroke in patients with AF who were randomized to dronedarone (1.8 vs 1.2% per year, hazard ratio 0.66, 95% CI: 0.46–0.96) [12]. However, one must interpret results from this retrospective analysis with caution and further trials will need to be conducted to determine dronedarone's impact on stroke.

A multicenter double-blinded randomized controlled trial (ANDROMEDA) enrolled patients with recently symptomatic or decompensated heart failure (New York Heart Association [NYHA] class II–IV) to assess dronedarone's impact on the combined end point of all-cause mortality or hospitalization for heart failure [13]. A history of AF was not required for entry into the study and at the time of randomization, AF was only present in 23.2% of the patients in the dronedarone group and 26.8% in the placebo group. The trial was terminated prematurely by the data and safety monitoring board owing to excess mortality among patients assigned to dronedarone (FIGURE 4). The excess mortality appeared to be predominantly related to worsening heart failure, although arrhythmia or sudden death may have contributed to this finding as well. While the mechanisms underlying this apparent increase in mortality have not yet been elucidated, the FDA has issued a black-box warning against dronedarone's use in NYHA class IV heart failure and NYHA class II–III heart failure with a recent decompensation.

Among patients with mild or no heart failure, dronedarone appears to be well tolerated. Its main side effects include diarrhea, nausea, vomiting and rash. There is no evidence of a proarrhythmia with only one case of torsades de pointes identified so far. Unlike amiodarone, dronedarone has no impact on oral anticoagulation management; however, it has been shown to affect cardiac glycoside levels and patients on digoxin should have their dose decreased or discontinued [14].

Although a great deal of attention has been given to the emergence of this new antiarrhythmic, its precise role in the management of AF remains ill-defined. In general, dronedarone's



No. at risk						
Placebo	409	192	156	133	112	90
Dronedarone	828	450	389	347	307	262

Figure 2. Kaplan–Meier estimates of first recurrence of atrial fibrillation or flutter in the EURIDIS and ADONIS trials (combined analysis).
HR: Hazard ratio.
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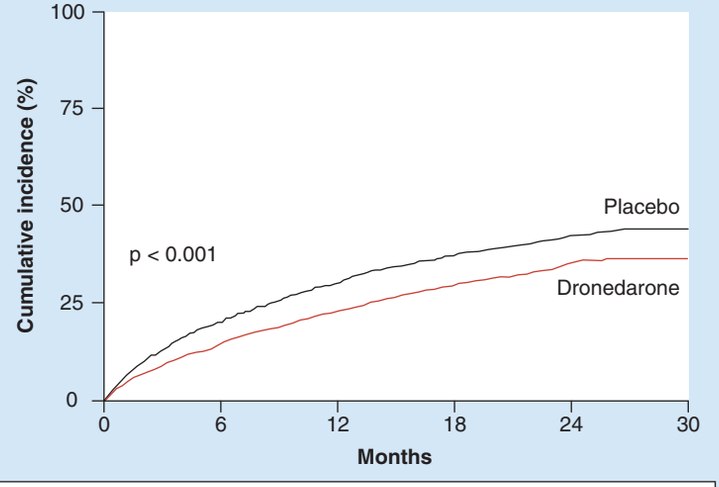


No. at risk						
Placebo	2327	1858	1625	1072	385	3
Dronedarone	2301	1963	1776	1177	403	2

Figure 3. Kaplan–Meier cumulative incidence of the primary study outcome in the ATHENA trial (first hospitalization due to cardiovascular events or death from any cause).
Reproduced with permission from [11].

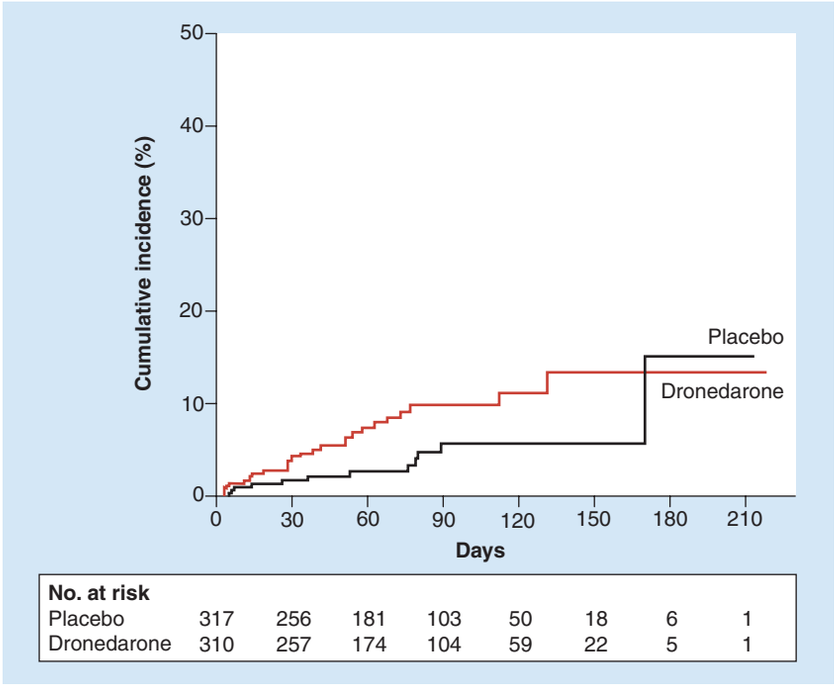


Figure 4. Kaplan–Meier cumulative incidence of all-cause mortality in dronedarone and placebo groups.
Reproduced with permission from [13].

modest efficacy as an antiarrhythmic combined with its safety concerns in patients with heart failure may relegate it to a second- or third-line agent for the management of AF.

Budiodarone (AT1–2042) is another amiodarone congener that possesses an iodine content. It has a shorter half-life than amiodarone with reduced dependence on the CYP450 system. In the Paroxysmal Atrial Fibrillation Study with Continuous Atrial Fibrillation Logging (PASCAL) trial, 72 patients with paroxysmal AF and dual-chamber pacemakers with electrogram storage capabilities were randomized to placebo or budiodarone [15]. After 12 weeks, AF burden was significantly reduced by budiodarone from baseline in a dose-dependant fashion (54 and 74% reduction in disease burden with the 400 and 600 mg doses, respectively, p = 0.0001). Although the drug was well tolerated, studies of longer duration will be needed to fully assess its safety profile and efficacy.

Finally, Celivarone is a noniodinated amiodarone with similar electrophysiologic properties. It is used once daily. Clinical trials are currently in progress to assess the role of this compound in the management of AF.

Gap junctions

Gap junctions connect myocardial cells and facilitate electrical conduction between cardiac myocytes. Each gap junction consists of two channels called connexons constructed from membrane proteins known as connexins. Abnormal expression of connexin proteins due to ischemia, mutation or conditions of stress, may lead to abnormal coupling of cardiac myocytes and serve as the basis for arrhythmogenesis. This logic has prompted the development of compounds known as gap-junction enhancers, which promote enhanced cellular communication and preserve gap-junction integrity.

Rotigaptide is a gap-junction modifier that has been demonstrated to prevent the slowing of atrial conduction velocity under conditions of stress [16]. In canine models, rotigaptide has been demonstrated to reduce vulnerability to AF under certain conditions [17,18]. Future trials will be needed to test the clinical usefulness of compounds such as rotigaptide.

Renin–angiotension–aldosterone system

Activation of the renin–angiotensin–aldosterone system is thought to promote AF by functional, structural and electrical remodeling. In a *post-hoc* analysis of randomized trials, the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers were demonstrated to be associated with lower rates of new onset as well as recurrent AF [19,20].

However, in a randomized controlled trial designed to assess the impact of valsartan on recurrent AF, no differences were observed between treatment and control groups [21]. Strictly speaking, this study was a secondary prevention trial and the role of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for primary AF prevention remains uncertain.

Statins

Numerous retrospective studies and small randomized trials have demonstrated that the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has been associated with the suppression of AF. In the Atorvastatin for Reduction of Myocardial Dysrhythmia After cardiac surgery (ARMYDA)-3 trial, postoperative patients were randomized to atorvastatin or placebo 7 days prior to cardiac surgery. Atorvastatin was associated with a 61% relative risk reduction of AF episodes (p = 0.01) [22]. The data regarding statin use for prevention of AF in the general population are less robust. One meta-analysis suggests that statins are significantly associated with a decreased risk of incidence or recurrence of AF among patients with a history of previous AF [23]. However,

a large-scale randomized controlled trial is needed to conclusively establish the role for statins in the suppression of AF.

Miscellaneous

Ranolazine is currently approved in the USA for use in patients with chronic stable angina. However, this compound is also electrophysiologically active and blocks late INa, late ICa, Iks and Ikr currents. Ranolazine has been found to prolong the action potential duration in the atrium and suppress AF in canine and porcine models [24–26]. In the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) trial, ranolazine was associated with a reduction in ventricular arrhythmias [27]. There was also a trend toward a reduction in new-onset AF among patients assigned to ranolazine. While these results are thought provoking, they should be considered hypothesis-generating until the impact of ranolazine on AF can be prospectively assessed.

Tedisamil was designed primarily as an antianginal drug but has been found to block multiple ion channels, including Ikr, Iks, Ikur Ito and Ik_{ATP}. It prolongs the atrial refractory period and may possess anti-AF activity. At two doses of 0.4 and 0.6 mg/kg, intravenous tedisamil was superior to placebo in conversion to SR [28]. However, there have been safety concerns with tedisamil, including increased adverse events among women, proarrhythmia, hypotension and bradycardia. In February of 2007, the FDA Cardiovascular and Renal Drugs Advisory Committee voted against its approval for use in the cardioversion of AF. The future of this compound is uncertain at this time.

Anticoagulants

Tecarfarin (ATI-5923) is a novel vitamin K antagonist and structural analog of warfarin. However, unlike warfarin, it is not metabolized via the P450 system and, therefore, is expected to have fewer interactions with commonly used drugs. In a small open-label study, tecarfarin was used to treat patients with AF and low-to-moderate risk of stroke [29]. Nearly all the patients were taking warfarin at the time of enrollment and were switched to tecarfarin therapy. After an initial 3 weeks of dose titration, the international normalized ratio was within target range 71.4% of the time, a finding that compares favorably with standard warfarin therapy. Further studies will need to be performed to establish tecarfarin's role in the management of AF.

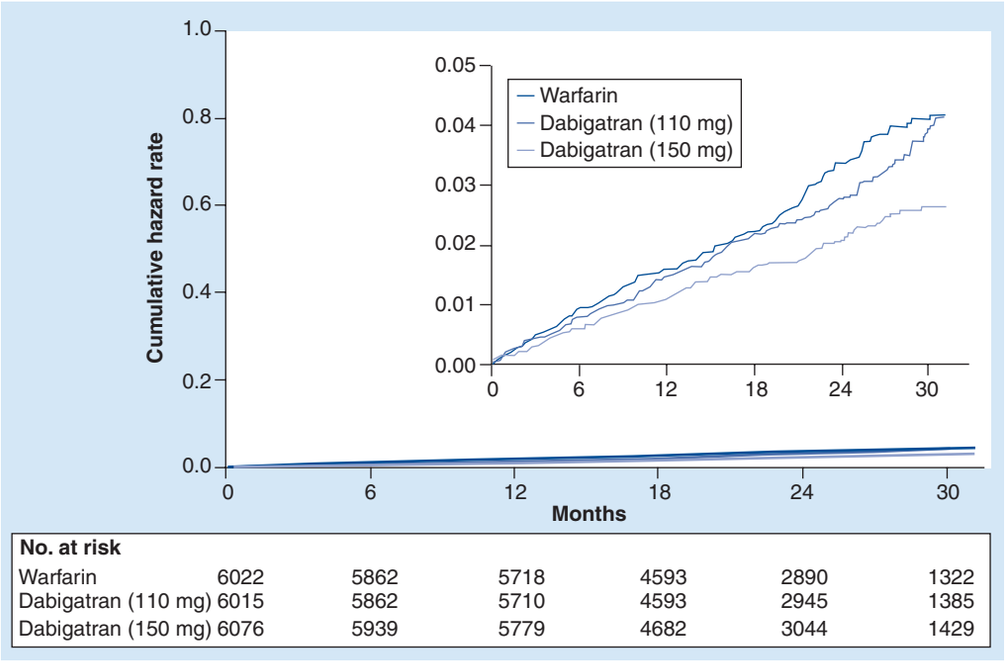
Dabigatran is a new oral direct thrombin inhibitor that does not require therapeutic monitoring. In a multicenter trial enrolling 18, 113 patients with AF, 110 and 150 mg of dabigatran was compared with warfarin therapy to assess its impact on the primary end point of stroke or systemic embolism [30]. Both dabigatran doses were noninferior to warfarin with respect to the primary end point. The 150 mg dose of dabigatran was superior to warfarin with respect to stroke or systemic embolism, and the 110-mg dose was superior to warfarin with respect to major bleeding (FIGURE 5).

No significant difference in major bleeding was observed comparing the 150 mg dose of dabigatran to warfarin. However, there was a significantly increased likelihood of gastrointestinal bleeding in the dabigatran 150 mg group as compared with warfarin (RR 1.50; CI: 1.19–11.89, $p < 0.001$). No evidence of hepatotoxcity was observed in this trial. Dyspepsia was more commonly reported among patients taking dabigatran (11.8 and 11.3% with the 110 and 150 mg doses, respectively, vs 5.8% taking warfarin). While the safety profile of dabigatran appears to be favorable, additional studies will need to be conducted to establish its long-term effects.

The emergence of an effective oral anticoagulant that does not require frequent blood monitoring may be a landmark achievement in the management of AF. Prior studies of compounds that function as safe and effective alternatives to warfarin for patients with AF have been disappointing [31–33]. Drugs such as ximelagatran and idraparinux appeared effective as anticoagulants, but were limited by their untoward side effects. The combination of clopidogrel and aspirin, while better than aspirin alone, has been found to be inferior to warfarin therapy for the prevention of vascular events in patients with AF [33,34]. The emergence of dabigatran may, therefore, help to fill a longstanding void in the management of AF.

Conclusion

There have been a great number advances in the development of agents used for the suppression and conversion of AF as well as anticoagulation therapy. While primacy of a rhythm control over rate control has not been substantiated by clinical trials, there are many compelling reasons to strive for rhythm control among highly symptomatic



No. at risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran (110 mg)	6015	5862	5710	4593	2945	1385
Dabigatran (150 mg)	6076	5939	5779	4682	3044	1429

Figure 5. Cumulative hazard rate for primary outcome (stroke or systemic embolism) according to treatment group.
Reproduced with permission from [30].

patients with AF. The use of antiarrhythmics in patients with AF requires a calculated trade-off between the risks of the antiarrhythmic therapy and its potential benefits. As the number of patients with AF continues to rise, so will the need for antiarrhythmic compounds that offer favorable safety/efficacy profiles. Drugs such as the ones mentioned in this article may help to fill this niche. In addition, the need for anticoagulation among patients at moderate-to-high risk for stroke persists whether a rhythm- or rate-control strategy is desired. The availability of drugs that serve as safe and effective alternatives to warfarin has been long awaited. At least two emerging drugs, tecarfarin and dabigatran, appear to hold promise in this area. Finally, while other new advances in AF treatment, such as ablative therapy and mechanical atrial appendage occluders, may no doubt change the landscape of AF management, the need for pharmacological agents in the management of AF will remain. Whether as primary or adjuvant therapy, drugs are likely to remain a cornerstone of management for this common arrhythmia.

Future perspective

As the prevalence of AF continues to rise over the next several years, so too will our understanding regarding the mechanisms that predispose patients to this arrhythmia. Enhanced understanding concerning the risk factors for AF will result in a greater emphasis on prevention. Even so, AF will continue to be a common arrhythmia and enact a significant burden on healthcare systems around the world.

It is likely that rate-control strategies and risk-based anticoagulation will continue to suffice for the majority of patients. However, for many symptomatic patients, rhythm control will be necessary, and many more options will be available for clinicians and patients who opt to pursue this strategy.

Further insight into the electrophysiological properties of AF will lead to the continued development of antiarrhythmic drugs with greater specificity. 'Dirty' drugs like amiodarone (currently the most commonly prescribed drug for AF) will likely be used as a last resort. Rationally-designed drugs that specifically target AF and/or the atria will likely result in greater antiarrhythmic efficacy without the problems of proarrhythmia. Despite advances in other areas of AF treatment, antiarrhythmic drugs will continue to be a cornerstone in AF management.

The most feared and serious consequence of AF will continue to be ischemic stroke from thromboembolism. Further refinement of risk-stratification schemes to predict stroke may result in more tailored anticoagulation therapy. However, even the best risk-stratification schemes will cast a wide net and millions of individuals will continue to require anticoagulation

to reduce the risk of this complication. Warfarin will likely be relegated to a second- or third-line agent for patients who are unable to tolerate newer anticoagulants that do not require frequent monitoring.

Mechanical devices, such as atrial appendage occluders, may prove to be effective at attenuating stroke risk and might represent a viable option for individuals who are unable or unwilling to take anticoagulant therapy. In theory, devices such as these could be combined with ablative therapy and perhaps even obviate the need for anticoagulation in select patients.

Advances in catheter ablation are likely to dominate the landscape of AF management over the next 5–10 years. The basic and translational research that informs our understanding of AF will continue to expand and, in turn, enable us to modify AF substrate with greater precision. More streamlined approaches to AF ablation will develop as more robust clinical data and long-term follow-up is generated. For some patients, particularly those with paroxysmal AF and no structural heart disease, we may be able to offer something never before available – a cure.

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Executive summary

- There are a number of emerging pharmacologic therapies for the treatment of atrial fibrillation (AF).
- Antiarrhythmic drugs that specifically target atrial tissue demonstrate promise in suppressing AF while avoiding proarrhythmia. The atria-specific drug vernakalant has been shown, in clinical trials, to be safe and effective for the chemical cardioversion of AF as compared with placebo.
- Amiodarone congeners are biologically and structurally similar to amiodarone. The most extensively studied of these is dronedarone. In clinical trials dronedarone was modestly better than placebo for the maintenance of sinus rhythm as compared with placebo. It has also been shown to reduce cardiovascular hospitalization related to AF. It should be avoided in patients with significant heart failure as it may increase mortality in this population.
- Gap junctions represent another potential molecular target for the suppression of AF. Rotigaptide is a gap-junction modifier that reduces AF susceptibility in animal models.
- Although retrospective data suggested that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may suppress AF, a randomized controlled trial that examined valsartan's impact on recurrent AF found no difference between treatment and placebo groups.
- Statins may be effective at suppressing AF in the postoperative setting. However, their effectiveness in reducing AF in the general population has not been conclusively established.
- The antianginal drug ranolazine is an eletrophysiologically active compound. In animal models and *post-hoc* analysis of one clinical trial, it was associated with decreased vulnerability to AF.
- The need for safe and effective alternatives to warfarin for patients with AF and moderate-to-high risk for stroke is paramount. The direct thrombin inhibitor dabigatran, shows promise as a candidate drug to fill this niche. In one large randomized controlled trial it was at least as effective as warfarin for the prevention of stroke, and did not result in increased major bleeding. If approved, it will be the first oral anticoagulant that does not require therapeutic monitoring.

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