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New developments in atrial antiarrhythmic drug therapy

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Abstract

Atrial fibrillation (AF) is a growing clinical problem associated with increased morbidity and mortality. Currently available antiarrhythmic drugs (AADs), although highly effective in acute cardioversion of paroxysmal AF, are generally only moderately successful in long-term maintenance of sinus rhythm. The use of AADs is often associated with an increased risk of ventricular proarrhythmia, extracardiac toxicity, and exacerbation of concomitant diseases such as heart failure. AF is commonly associated with intracardiac and extracardiac disease, which can modulate the efficacy and safety of AAD therapy. In light of the multifactorial intracardiac and extracardiac causes of AF generation, current development of anti-AF agents is focused on modulation of ion channel activity as well as on upstream therapies that reduce structural substrates. The available data indicate that multiple ion channel blockers exhibiting potent inhibition of peak I_{Na} with relatively rapid unbinding kinetics, as well as inhibition of late I_{Na} and I_{Kr}, may be preferable for the management of AF when considering both safety and efficacy.

Introduction

Atrial fibrillation (AF) is the most commonly encountered sustained arrhythmia, affecting an estimated 2.3 million people in the US alone.[1] Advancing age is a major risk factor for AF and the prevalence of this condition is rising at an alarming rate with ageing of the population.[1] Of the two principal options for the management of AF, rhythm control—which aims to restore and maintain sinus rhythm—is believed to be preferable to rate control, in which ventricular rate is regulated while the atria continue to fibrillate.[1-3] However, currently available approaches for rhythm control have important limitations, which are discussed below, making rate control preferable in some cases, particularly in older patients with relatively few symptoms of AF.

Rhythm control of AF can be achieved with antiarrhythmic drugs (AADs), catheter ablation techniques, or electrical cardioversion. AADs are often successfully used to maintain sinus rhythm following catheter ablation or cardioversion.[4] Most AADs currently available for rhythm control of AF have poor safety profiles and inadequate long-term efficacy, making long-term pharmacologic rhythm control in patients with AF a challenge.[5,6] The results of a number of multicenter, randomized, and prospective clinical trials, including AFFIRM,[7] and the AF-CHF,[8] RACE,[9] and PIAF[10] studies, suggest that rhythm control strategy with AADs

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Review criteria We have attempted to cite the most relevant papers concerning the respective statements, arguments, and hypotheses discussed in this Review. These references were taken from searches of the PubMed database using appropriate terms, including “atrial fibrillation”, “anti-arrhythmic agents”, and “upstream therapy”. The literature search was limited to full-text articles in the English language. Because of space limitations, we have restricted our citations to the most pertinent publications.

is not superior to rate control in terms of survival, and may be associated with an increase in rate of hospitalization. Adverse effects of AADs, such as ventricular proarrhythmia and extracardiac toxicity, are likely to negate the limited ability of these agents to maintain sinus rhythm. The *post-hoc* analysis of the AFFIRM data showed that patients maintained in sinus rhythm had a better survival rate than those in whom AF persisted.[11]

Mounting evidence indicates that for some AF cases—particularly relatively young (<65 years of age) symptomatic patients—catheter ablation is superior to currently available AADs for long-term maintenance of sinus rhythm.[12,13] However, despite progress in catheter ablation technologies and improvements in the success of these techniques, AADs remain first-line therapy for rhythm control of AF[1] and are expected to do so for the foreseeable future.

AF is commonly associated with atrial electrical and structural abnormalities as well as with a constellation of intracardiac and extracardiac diseases, including heart failure, hypertension, coronary artery disease, myocardial infarction, and valvular heart defects, which can develop independently of AF but may promote and be aggravated by the arrhythmia. Each of these AF-associated abnormalities and diseases, as well as numerous mediating factors of these disorders, can also be pharmacological targets for AF treatment and may alter the safety and anti-AF efficacy of AAD therapy. Development of anti-AF medications, therefore, is currently focused on modulation of ion channel activity as well as on upstream therapies that target these intracardiac and extracardiac factors that induce or promote structural remodeling (Figure 1). Other preclinical investigations are directed at pharmacological modulation of gap junctions and intracellular calcium activity. In this Review, we discuss current and novel pharmacological approaches to rhythm control in patients with AF.

Modulation of ion channel activity

Most AADs in current clinical use exert their anti-AF actions via inhibition of cardiac ion channels, particularly during acute administration (Table 1). Chronic treatment can additionally remodel ion channel expression,[14] cause degradation of specific ion channels (for example, the ultra-rapid delayed rectifier potassium current [I_{Kur}] as reported with quinidine[15]), or influence atrial electrical and structural remodeling, as observed with amiodarone.[16,17] Anti-AF drugs can be very effective in the short term, with up to 80–90% efficacy for the termination of paroxysmal AF and some forms of persistent AF.[18-20] However, these agents are generally only moderately effective for long-term rhythm control of paroxysmal AF, and even less so in the case of persistent AF.[1] The long-term (1–1.5 years) efficacy of amiodarone, which is arguably the best available AAD for the maintenance of sinus rhythm, ranges from 34% to 65%.[12,21]

The principal complication of all anti-AF drugs is that they are associated with an increased risk of life-threatening ventricular arrhythmias, induction of multi-organ toxicity, or worsening of coexisting disease.[1,22] Severe ventricular proarrhythmia has been observed with administration of sodium-channel blockers (class IC agents, such as flecainide and propafenone) in patients with structural heart disease.[23] Agents that potently inhibit the rapidly activating delayed rectifier potassium current (I_{Kr}) can produce long QT syndrome and related life-threatening polymorphic ventricular tachycardia (torsade de pointes [TdP]).[1] These drugs include class III agents such as dofetilide, ibutilide, and sotalol or class IA agents such as quinidine. Amiodarone is a class III drug that induces TdP only rarely, but is often associated with the development of extracardiac multi-organ toxicity with long-term use.[24,25] Amiodarone-associated death is caused largely by pulmonary complications.[26] The worsening of coexisting disease, such as heart failure, has also been associated with the use of AADs. In the ANDROMEDA study,[22] the use of dronedarone in patients with severe left ventricular (LV) systolic dysfunction increased mortality, apparently unrelated to AF or ventricular

proarrhythmia. Although amiodarone is generally not associated with excess all-cause mortality, the death rate for amiodarone use in patients with NYHA class IV heart failure was reported to be greater than for placebo in SCD-HeFT.[27] Notably, however, the prognosis of patients after a CHF-related hospitalization is very bad regardless of the therapy administered.[28] These adverse effects and limitations of currently available AADs restrict the scope of these agents in the management of patients with AF.

Atrial-selective ion channel block

The atrial-selective approach to the treatment of AF was conceived with the aim of reducing the risk of ventricular arrhythmias. The channels responsible for the I_{Kur}, the acetylcholine-regulated inward rectifying potassium current ($I_{K\text{-}ACh}$), and the constitutively active (CA)-$I_{K\text{-}Ach}$ (which does not require acetylcholine or muscarinic receptors for activation) are present in atria, but largely absent from the ventricles. These channels are, therefore, commonly referred to as being atrial-specific.[29,30] While this strategy is attractive in theory, the available data indicate that blockade of I_{Kur} alone might not effectively suppress AF.[31-33] Indeed, when administered at concentrations that effectively suppress AF, currently available I_{Kur} blockers potently inhibit other currents as well. For example, vernakalant and AZD7009 also block the early sodium current (I_{Na}) and AVE0118 also blocks the transient outward potassium current (I_{to}), $I_{K\text{-}ACh}$, Ca-$I_{K\text{-}ACh}$, and I_{Na}.[34-38] The anti-AF actions of AZD7009 and vernakalant appear to be largely the result of inhibition of I_{Na} rather than I_{Kur}.[32] AZD7009 reduces excitability and conduction velocity preferentially in the atria of dogs *in vivo*,[39] indicating atrial-selective sodium-channel block. While a number of other purported I_{Kur} blockers have been shown to produce atrial-selective effective refractory period (ERP) prolongation and to suppress experimental AF,[40] whether pure I_{Kur} block can effectively suppress AF has yet to be demonstrated.[30,33] Selective inhibition of I_{Kur} neither prevents nor terminates acetylcholine-mediated AF in canine atria.[41] Notably, I_{Kur} density is progressively reduced with acceleration of activation rate;[42] therefore, the contribution of this current in AF may be relatively small. However, under conditions associated with triangulation of atrial action potential morphology (electrical remodeling or rapid activation rates), I_{Kur} blockers promote prolongation of action potential duration at 90% repolarization (APD_{90}).[43] I_{Kur} density has also been reported to be reduced in cells isolated from the atria of patients with chronic AF.[37,44] By contrast to remodeled atria, where I_{Kur} block slightly prolongs APD_{90}, selective I_{Kur} inhibition abbreviates APD_{90} in healthy atria (Figure 2).[41,45] This finding could explain the occurrence of AF with I_{Kur} inhibition in 'healthy' canine atria[41] and the association between AF and a mutation in *KCNA5*, the gene that encodes the α subunit of the I_{Kur} channel.[46]

Vagal activity can contribute to the initiation of paroxysmal AF,[47,48] and so blocking parasympathetic activity could help maintain sinus rhythm in these patients. $I_{K\text{-}ACh}$ block with tertiapin-Q prolongs atrial APD and suppresses AF in experimental models.[49,50] Interestingly, CA-I_{KACh} is only marginally present in healthy nonfibrillating human or canine atria and is significantly increased in the atria of patients with chronic AF and in canine tachycardia-remodeled atria,[49,51-53] indicating that this current is not only atrial-specific, but is also a pathology-specific target.[54] At present, there are no available drugs that selectively block CA-I_{KACh}.

Atrial-selective multiple ion channel block

Several cardiac ion channels, including fast I_{Na} sodium channels[30,55] and I_{Kr} potassium channels, [56-64] respond in an atrial-selective or predominant manner when blocked with specific drugs, despite being present in both atria and ventricles. In canine coronary-perfused cardiac preparations, atrial-selective or predominant I_{Na} blockers, such as amiodarone (long-term treatment) and ranolazine, effectively suppress AF with little or no effects in the ventricles.[31,55,63,65] Ranolazine and amiodarone exert these actions by atrial-selective or atrial-

predominant depression of I_{Na}–dependent parameters leading to increased diastolic threshold of excitation and induction of postrepolarization refractoriness (Figures 3 and 4).[55,63,66,67] In superfused pulmonary vein preparations, both ranolazine and long-term amiodarone also effectively suppress intracellular calcium-dependent delayed (DAD) and late phase 3 early after depolarization (EAD)-induced triggered activity.[66,67] AZD7009 is also an atrial-selective I_{Na} blocker.[39] Although the clinical anti-AF efficacy of amiodarone, ranolazine, and AZD7009 has been documented,[19,25,68-70] the degree to which the efficacy of these multiple ion channel blockers depends on their potency to depress sodium-channel-dependent parameters remains to be elucidated.

It should be emphasized that the nature and degree of atrial selectivity of AADs observed in normal hearts may be different in remodeled hearts or those associated with various pathologies, including myocardial infarction, long QT syndrome, heart failure, and hypertrophy. The pharmacological responses to sodium-channel and potassium-channel blockers can be very different, and even opposite (Figure 2), in healthy versus diseased atria and ventricles; both augmentation and reduction in blocking efficacy have been reported.[32,45,71] These altered substrates and pharmacological sensitivities could explain why atrial-selective agents (ranolazine, AVE0118, chronic amiodarone) can successfully suppress ventricular arrhythmias encountered under pathophysiological conditions.[24,68,72]

A number of factors are likely to contribute to the atrial selectivity of I_{Na} blockers, including a more depolarized resting membrane potential (RMP), more negative half-inactivation voltage ($V_{0.5}$), and more gradual phase 3 of the action potential in atrial cells as compared with ventricular cells (Figure 3).[32,55,73] As a consequence, a large proportion of sodium channels are inactivated at the normal RMP in atrial cells. The fraction of resting channels is, therefore, smaller in atrial cells than in ventricular cells at RMP. Atrial cells show a greater accumulation of use-dependent sodium-channel block, because much of the recovery from sodium-channel block commonly occurs during the resting state of the channel.[74,75] Rapid kinetics of recovery from inactivation is thought to contribute to the atrial selectivity of sodium-channel blockers. Drugs, such as propafenone, that exhibit slow dissociation from the sodium channel show little or no atrial selectivity, whereas agents that dissociate rapidly, such as ranolazine and amiodarone, tend to be highly atrial-selective in their inhibition of I_{Na}-dependent parameters.[55,76] Our current understanding of the mechanisms of atrial selectivity of I_{Na} blockers, as well as potential applications of atrial-selective I_{Na} block for rhythm control of AF, have been discussed in more detail eslewhere.[31,32,77] Mechanisms by which depression of I_{Na} by drugs with rapid unbinding kinetics lead to AF termination are discussed in an elegant study by Comtois and colleagues.[78]

Selective inhibition of I_{Kr} prolongs APD and ERP to a greater extent in the atria than in the ventricles at both normal and rapid heart rates (Figure 4).[56-62] Atrial-predominant prolongation of APD and ERP by ranolazine and chronic amiodarone (both I_{Kr} blockers) is thought to contribute to their atrial-selective, use-dependent inhibition of sodium-channel-dependent parameters in the atria by causing greater abbreviation of the diastolic interval (Figure 4). Much of the recovery of sodium channels from inactivation occurs during the diastolic interval and curtailment of this interval promotes accumulation of I_{Na} block. Under bradycardic conditions or following long pauses, however, it is the ventricles rather than atria that develop substantial APD prolongation, EADs, and TdP with selective I_{Kr} inhibition.[79,80] The proarrhythmic effects of I_{Kr} block can be counteracted with a concomitant block of late $I_{Na.}$ In remodeled atria, in which APD is abbreviated, prolongation of APD_{90} secondary to I_{Kur} block can promote accumulation of I_{Na} block preferentially by reducing diastolic interval in the atria but not in ventricles.[32] The reduced ability of I_{Kr} block to prolong APD in remodeled atria can be overcome with additional inhibition of I_{Kur}/I_{to}.[81]

Practical clinical experience indicates that multiple ion channel blockers that can block I_{Na} with rapid dissociation kinetics are generally better suited for rhythm control of AF than are selective ion channel blockers, because the former have a more favorable risk:benefit ratio.[32] With the exception of I_{Kr} blockers, such as dofetilide, currently used AADs (amiodarone, dronedarone, flecainide, propafenone) and promising investigational AADs (vernakalant and AZD7009) inhibit multiple ion channels. Notably, selective inhibition of I_{Na}, which at present can be achieved only with I_{Na} blockers with rapid binding and unbinding kinetics (for example, lidocaine and mexiletine), is not very effective in the clinical management of AF.[1]

Several anti-AF agents, including amiodarone, dronedarone, vernakalant, and ranolazine, are effective in the clinic and do not, or only rarely, produce ventricular proarrhythmia. These relatively safe AADs have two features in common; firstly they all inhibit I_{Na} with relatively rapid kinetics and, secondly, they all also block I_{Kr}. As discussed, rapidly dissociating I_{Na} blockers tend to be atrial selective, whereas slowly dissociating blockers are not.[32] These characteristics coupled with the ability of these drugs to inhibit late I_{Na}, which keeps the effects of their I_{Kr} block in check, adds to their electrical safety profile. Late I_{Na} inhibition plays a key role in the suppression of ventricular arrhythmias in a variety of pathological conditions, such as long QT syndrome, acute ischemia, and heart failure.[82-84] Slowly dissociating I_{Na} blockers, which also block late I_{Na},[85] promote arrhythmogenesis in structurally compromised ventricles because they slow conduction and induce unidirectional block, thus providing the substrate for the development of re-entry.[23]

In summary, the available data indicate that multiple ion channel blockers exhibiting potent inhibition of fast I_{Na} with relatively rapid unbinding kinetics, as well as inhibition of late I_{Na} and I_{Kr} seem to be best suited for the management of AF. The addition of I_{Kur} block to this cocktail is theorized to increase atrial selectivity and anti-AF ability in remodeled atria.[32] The long-term adverse effects of AADs are difficult to predict, as shown by the results of CAST,[23] and the SWORD[86] and ANDROMEDA trials.[22] However, agents, such as dronedarone and ranolazine, that have the above ion-channel profile seem to be relatively safe in the long-term for some,[87,88] but perhaps not all,[22] AF pathologies.

Improved derivatives of existing drugs

Another approach for the development of new drugs involves modification of molecules that have demonstrated anti-AF efficacy. Many AADs in current use are derivatives of existing drugs; for example, flecainide and propafenone stem from procainamide and propranolol, respectively. One notable example of this approach is dronedarone, which was approved by the FDA in July 2009 and is an amiodarone derivative lacking the iodine moiety believed to be responsible for the multi-organ toxicity associated with amiodarone use. Dronedarone has been found to be significantly more effective than placebo in maintaining sinus rhythm in patients with AF, and is largely free of extra-cardiac toxicity.[89] Dronedarone also has rate-control properties,[89,90] and AADs that have combined rhythm-control and rate-control effects may be of particular interest in future AAD development. The anti-AF efficacy of dronedarone, however, appears to be inferior to that of amiodarone.[88] In the landmark, randomized placebo-controlled study, ATHENA,[91] dronedarone substantially reduced incidence of cardiac hospitalization and cardiovascular-related death in patients with AF.[91] Of the enrolled patients, 21% had NYHA class II or III chronic heart failure, 12% had an LV ejection fraction of less than 45%, and 60% had coronary artery disease.[91] The amelioration of several comorbidities, including reduced incidence of AF, stroke, and acute coronary syndrome and a decrease in blood pressure, was observed with the use of dronedarone in ATHENA.[90,92] These dronedarone-related positive outcomes are likely to be interrelated and contribute to the decrease in cardiovascular-related hospitalization and death.[91,92] However, all-cause mortality was not statistically significantly reduced by dronedarone use in ATHENA (5% for

dronedarone versus 6% for placebo, $P = 0.18$).[91] In another large trial (ANDROMEDA),[22] dronedarone was associated with increased mortality in patients with severe heart failure and LV systolic dysfunction (NYHA class III and IV), which was likely to be the result of worsening chronic heart failure. Whether the increase in mortality in ANDROMEDA was related to dronedarone itself, or to unrelated confounding factors, remains unknown. The initially postulated hypothesis accounting for the increase in mortality in ANDREOMEDA (that is, discontinuation of treatment with angiotensin-converting-enzyme [ACE] inhibitors because of elevation in serum creatinine level) remains an issue of debate.[88] A negative inotropic effect of dronedarone resulting from inhibition of $I_{Ca\text{-}L}$[93] could have contributed to worsening of severe heart failure, leading to increased mortality.[88]

Other examples of efforts to improve existing AADs include AZD1305 and AVE1231, which are derivatives of AZD7009 and AVE0118, respectively.[94,95] AZD7009 has been found to be effective in acute cardioversion of both paroxysmal and persistent AF, with a small risk for induction of ventricular arrhythmias.[19,70] Although AVE0118 effectively suppresses AF in several experimental AF models,[36,38] its clinical efficacy turned out to be disappointing and its clinical use for long-term management of AF is limited by first-pass hepatic metabolism. These negative outcomes apparently explain the termination of the further development of AVE0118.

Gap-junction therapy

Conduction disturbances are associated with many forms of cardiac arrhythmia, including AF. Conduction abnormalities in the heart can occur as a consequence of disturbances in sodium-channel or calcium-channel activity, gap-junction abnormalities (impairing cell–cell communications), and structural changes in the myocardium.[96] Gap junctions—comprised of proteins called connexins (Cx)—are complexes that connect myocardial cells through low-resistance pathways. Cx40, Cx43, and Cx45 are found in the human heart. Cx40 is commonly recognized as a potential target for atrial-specific treatment of AF because it is found in atrial, but not ventricular, myocardium.[97] Cx40 is, however, present in the ventricular conduction system.[97]

To date, experimental studies have shown that improved conduction with the gap-junction modulator rotigaptide may exert antiarrhythmic action in some AF pathologies (models of chronic mitral regurgitation AF and acute ischemia AF), but not others (models of heart failure or atrial tachypacing).[98,99] GAP-134—a dipeptide that behaves similarly to rotigaptide by specifically enhancing gap-junction conductance—has been shown to improve conduction and to reduce inducibility of AF in canine experimental models.[100,101] The clinical applicability of this approach is yet to be determined.

Intracellular calcium homeostasis

A growing body of evidence implicates abnormal intracellular calcium homeostasis in the development of AF, and normalization of sarcoplasmic reticulum (SR) calcium release as a potential therapeutic approach.[102-105] Abnormal intracellular calcium handling can promote AF by directly inducing intracellular calcium-mediated DAD, EAD, and late phase 3 EAD-induced triggered activity, modulating electrical remodeling, and affecting a number of signaling cascades involved in structural remodeling.[105] An increase in spontaneous SR Ca^{2+} release, as well as a significant SR calcium leak, have been observed in atrial myocytes isolated from AF patients and dogs with tachypacing-induced atrial remodeling.[103,104] This SR calcium leak may be mediated by protein kinase a hyper-phosphorylation and calstabin2 (a ryanodine receptor inhibitory subunit, FKBP12.6).[104]

Although pharmacological modulation of these arrhythmogenic mechanisms might be of benefit, the challenge is to regulate SR calcium release and intracellular calcium loading, without compromising myocardial contractility. Ranolazine limits sodium loading, primarily via inhibition of early I_{Na}, and so can also reduce calcium loading associated with conditions that predispose to the development of AF, and suppress triggered AF activity induced by DAD, EAD, and late phase 3 EAD.[66] Amiodarone has been reported to exert similar actions to ranolazine in both atria and pulmonary veins.[63,67] Other sodium-channel-blocking agents used in the management of AF, including vernakalant, flecainide, propafenone, AZD7009, as well as β-blockers, are thought to act in part by modulating calcium homeostasis and suppressing triggered activity.

‘Pill-in-the-pocket’ approach to therapy

The idea of limiting AAD administration to critical times was introduced because the chance of an adverse reaction is more likely with long-term administration of these agents. Acute termination of paroxysmal AF with class IC agents has proved to be a reasonable approach in some patients with AF.[18] This has been labeled a ‘pill-in-the-pocket’ approach. Preliminary results indicate that a single dose of ranolazine (2 g) is effective for this strategy.[106] In addition, ranolazine is safe in patients with structural heart diseases,[87] pointing to a much wider potential applicability of the pill-in-the-pocket approach in patients with AF. Short-term administration of AADs is also used for maintenance of sinus rhythm following cardioversion (electrically or by catheter radiofrequency oblation) or postoperatively.[4,107] Short-term application of an AAD can be of a greater benefit than risk in some, but not all patients with AF. All-cause mortality and the rate of AF recurrence have been shown to be greater in patients treated with amiodarone episodically when compared with those who received amiodarone continuously (patients with NYHA class III and IV chronic heart failure were excluded from the study).[108]

Upstream therapy

The recognition that atrial structural remodeling can lead to the induction of AF[109] has led to the development of ‘upstream therapies’, which target arrhythmogenic structural remodeling in the atria, factors that promote such remodeling, or both.[110,111] Structural remodeling encompasses a number of pathological changes, including increased interstitial fibrosis, fibroblast proliferation, dilatation, hypertrophy, pathological collagen accumulation and its abnormal distribution or redistribution, and is often associated with stretch, oxidative stress, inflammation, or ischemia.[112,113] These factors are in turn induced by, or associated with, hypertension, heart failure, or coronary artery disease.[110-113] Studies of drugs designed to directly or indirectly mitigate these precipitating factors, such as ACE inhibitors, angiotensin II receptor blockers (ARBs), omega-3 polyunsaturated fatty acids, and statins, have yielded variable results.[110,111,114-117] The precise value of upstream therapy in the treatment of AF varies substantially by AF pathology.[111,116-118] Preoperative statin and omega-3 therapy has been consistently associated with a reduction in postoperative AF.[119-121] A number of clinical studies have indicated that ARBs and statins might be of particular benefit for patients with AF and severe ventricular dysfunction and heart failure,[122-124] but not in those without heart disease.[114,125,126]

Most of the current clinical data on upstream AF therapy are, however, derived from observational studies that were not sufficiently powered, and these findings do not warrant rejection or widespread use of any of the approaches.[111,115-117] The results of several large randomized placebo-controlled trials are now available. In the GISSI-AF trial,[114] treatment with the ARB valsartan did not reduce the recurrence of AF (only 8% of the enrolled patients had chronic heart failure or LV systolic dysfunction). In another large clinical trial (ACTIVE-I), the ARB irbesartan also did not substantially reduce the composite of stroke, myocardial

infarction, and vascular death in patients with AF and hypertension, but this agent was associated with a reduced rate of hospitalization from heart failure.[127] Several large, randomized placebo-controlled trials testing the anti-AF efficacy of various types of upstream therapy are underway, including studies assessing antiarrhythmic ability of omega-3-acid ethyl esters[115] and olmesartan (the ANTIPAF trial)[128] in the prevention of recurrence of paroxysmal AF. Interestingly, because atria commonly develop structural remodeling to a greater extent than do the ventricles,[129-133] structural remodeling is a potential atrial-selective target for upstream therapy of AF.[134]

Future directions

The ultimate goal of pharmacological therapy for AF is to improve patient morbidity (and, thus, quality of life) and reduce mortality. To date, all large, placebo-controlled, randomized clinical trials evaluating the ability of anti-AF AADs to improve all-cause mortality have yielded neutral outcomes at best.[1,89,90,135,136] However, morbidity (and quality of life) of patients with AF can be significantly improved with the use of AADs.[90,137] The results of ATHENA, which demonstrated significant reductions in cardiovascular-related morbidity and mortality in dronedarone-treated patients with AF,[91,92] may encourage a change of focus in the management of AF, from electrocardiographically-derived measures (that is, rhythm control and rate control) toward more general end points (such as morbidity and mortality).[138] This novel paradigm is related to the fact that the positive outcomes with dronedarone can be achieved in spite of the rather limited ability of this agent to maintain sinus rhythm. In the combined analysis of EURIDIS and ADONIS, AF recurrence (after 1 year of follow-up) occurred in 64% patients randomly assigned to dronedarone, as compared with 75% patients taking placebo.[89]

Several major questions about the pharmacological management of patients with AF need to be addressed in future studies. Because the primary end point of ATHENA was unique (time to first cardiovascular hospitalization or death), future studies need to determine if dronedarone is superior to the other AADs in prolonging survival free of cardiovascular hospitalization. Of note, secondary analysis of data from DIAMOND[137] suggests that dofetilide reduces hospitalization in patients with AF and chronic heart failure without improving all-cause mortality. In addition, amiodarone significantly reduced arrhythmic death compared with placebo in patients with myocardial infarction (LV ejection fraction ≤40%), but did not improve all-cause mortality in EMIAT[139] and CAMIAT.[140]

The introduction of atrial-selective sodium-channel blockade for the management of AF needs to be further explored and developed as an approach to achieving safe and effective rhythm control.[32,141] Available studies suggest that although novel agents demonstrating anti-AF efficacy are multiple ion channel blockers, they potently inhibit early I_{Na} (for example, vernakalant, dronedarone, AZD7009, ranolazine)[34,35,55,142] and most, if not all, are atrial-selective I_{Na} blockers. We have reviewed this subject elsewhere.[32] Studies have revealed a unique synergism when predominantly inactivated-state and activated-state I_{Na} blockers are combined. The combination of long-term therapy with amiodarone[63] and acute administration of ranolazine,[55] both of which are atrial-selective ion channel blockers, resulted in a profound atrial-selective use-dependent inhibition of I_{Na} and depression of I_{Na}-dependent parameters in isolated canine atria, leading to a potent effect of the drug combination for the prevention of AF.[143] Studies of the molecular differences between atrial and ventricular sodium-channels are needed to enable us to better understand the basis for atrial selectivity of pharmacological agents and design ever more selective drugs. Experimental observations suggest that studies specifically designed to evaluate the potential clinical role of atrial-selective sodium-channel blockers, such as ranolazine and amiodarone, as antiarrhythmics are warranted.

Conclusions

The ultimate goal of AF therapy is to improve patient quality-of-life and reduce mortality. Ongoing research aimed at development of new pharmacological strategies for the management of AF includes a wide range of approaches, targeting both AF-related electrical and nonelectrical (intracardiac and extracardiac) abnormalities. While success to date has been modest, the identification of atrial-selective agents and targets, as well as the development of upstream therapies, hold promise for the development of effective and safe new treatments.

Key points

- Atrial fibrillation (AF) is a growing clinical problem associated with increased morbidity and mortality
- Currently available antiarrhythmic drugs (AADs) can be highly effective in acute cardioversion of AF, but are only moderately successful in long-term maintenance of sinus rhythm and may induce adverse effects
- AF is commonly associated with atrial electrical and structural abnormalities as well as extracardiac disease, which may induce or promote AF and determine the efficacy and safety of AAD therapy
- Current development of anti-AF agents is focused on alteration of ion channel activity as well as upstream therapies that reduce structural substrates
- Multiple ion channel blockers exhibiting inhibition of fast I_{Na} and late I_{Na}, I_{Kr}, and I_{Kur} are likely to be atrial-selective and may be best suited for the management of AF
- Preventing or reversing atrial structural remodeling (‘upstream therapy’) seems to be beneficial for some AF pathologies, such as postoperative AF or AF associated with severe heart failure

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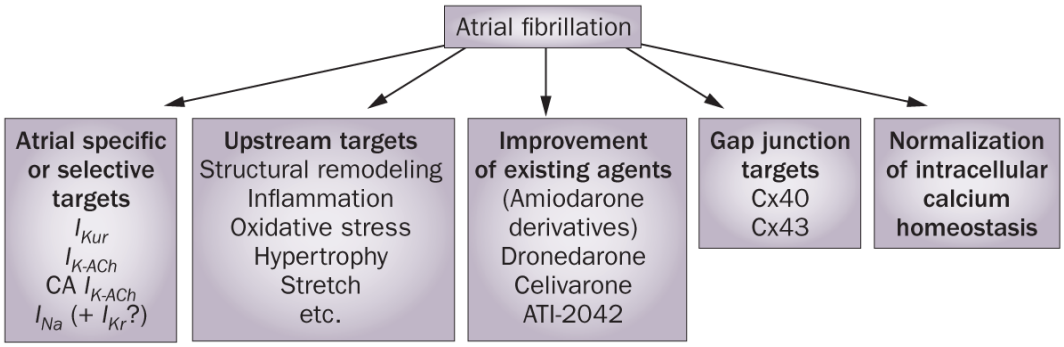

Figure 1.
Current prominent investigational strategies for rhythm control of atrial fibrillation. Abbreviations: CA, constitutively active; Cx, connexin; $I_{K\text{-}ACh}$, acetylcholine-regulated inward rectifying potassium current; I_{Kr}, rapidly activating delayed rectified potassium current; I_{Kur}, ultra-rapid delayed rectifier potassium current; I_{Na}, early sodium current. Modified from Burashnikov, A. & Antzelevitch, C. *Ann. Noninvasive Electrocardiol.* **14**, 290–300 (2009).

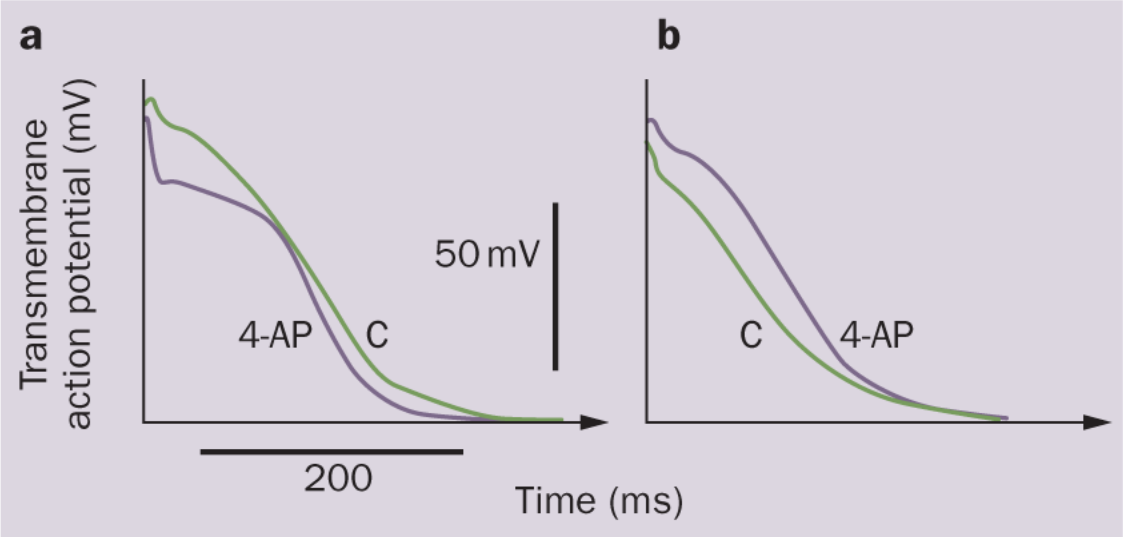

Figure 2.

Opposite effect of I_{Kur} inhibition on the action potential in healthy and remodeled atria. Block of I_{Kur} with 4-aminopyridine (50 μM). APD_{90} is abbreviated in **a** | 'healthy' (plateau-shaped action potential), but prolonged in **b** | 'remodeled' (triangular-shaped action potential) canine coronary-perfused atrial preparations. Abbreviations: 4-AP, 4-aminopyridine; APD_{90}, action potential duration at 90% repolarization; C, control. Modified from Burashnikov, A. & Antzelevitch, C. *Heart Rhythm* **5**, 1304–1309 (2008) and Burashnikov, A. *et al. Am. J. Physiol. Heart Circ. Physiol.* **286**, H2393–H2400 (2004).

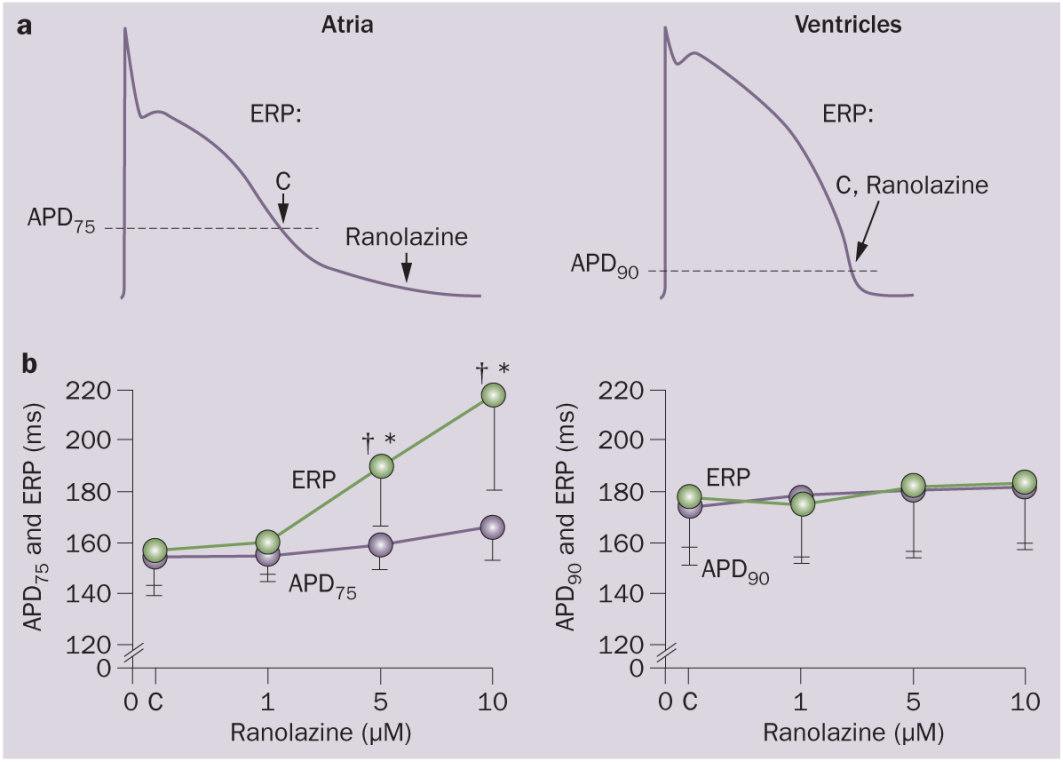

Figure 3.

Ranolazine induces atrial-selective prolongation of the ERP and development of PRR. The PRR is the difference between ERP and APD_{75} in atria and between ERP and APD_{90} in ventricles. ERP corresponds to APD_{75} in atria and APD_{90} in ventricles. Cycle length, 500 ms. Schematic illustration of induction of postrepolarization refractoriness with ranolazine in the atrium but not in the ventricle. **a** | The arrows illustrate the position on the action potential corresponding to the end of the ERP in atria and ventricles and the effect of ranolazine to shift the end of the ERP in atria but not ventricles. Summary data of the effect of ranolazine to induce PRR in atria but not in ventricles. **b** | **P* <0.05 versus control. ‡*P* <0.05 versus APD_{75} values in atria and APD_{90} in ventricles; (*n* = 5–18). Abbreviations: APD_{90}, action potential duration at 90% repolarization; C, control; CL, cycle length; ERP, effective refractory period. Modified from Burashnikov, A. *et al. Circulation* **116**, 1449–1457 (2007).

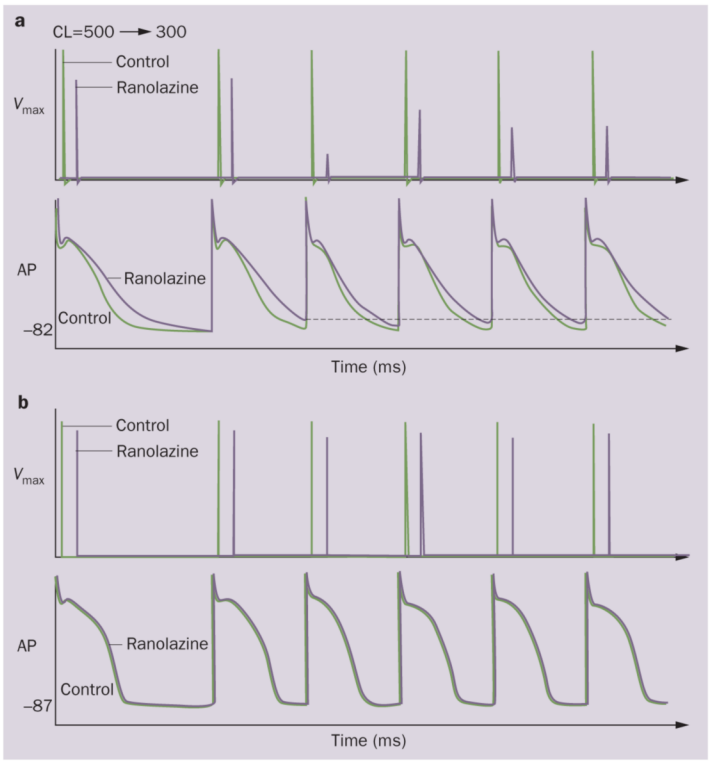

Figure 4.

Ranolazine produces a much greater rate-dependent inhibition of the maximal action potential upstroke velocity (V_{max}) in atria than in ventricles. Shown are V_{max} and action potential recordings obtained from coronary-perfused canine right atrium **a** | and left ventricle **b** | before (C) and after ranolazine (10 μM). Ranolazine prolongs late repolarization in the atria, but not in the ventricles (due to I_{Kr} inhibition) and acceleration of rate leads to elimination of the diastolic interval, during which much of the recovery from sodium-channel block occurs, contributing to the atrial selectivity of the drug. Abbreviations: AP, action potential; CL, cycle length. Modified from Antzelevitch, C. & Burashnikov, A. *J. Electrocardiol.* **42**, 543–548 (2009).

Table 1

Drugs used for rhythm control in atrial fibrillation

Agent	Primary mechanisms of action	Primary indication	Current status
Amiodarone	Multiple ion channel block. Atrial-selective peak I_{Na} block	Maintenance of sinus rhythm	Off-label use
Dronedarone	Multiple ion channel block	Maintenance of sinus rhythm, reduction of cardiovascular hospitalization	FDA approved
Dofetilide	I_{Kr} block	Acute cardioversion and maintenance of sinus rhythm	FDA approved
Sotalol	I_{Kr} block	Maintenance of sinus rhythm	FDA approved
Ibutilide	I_{Kr} block	Acute cardioversion	FDA approved
Propafenone	Peak I_{Na} block	Acute cardioversion and maintenance of sinus rhythm	FDA approved
Flecainide	Peak I_{Na} block	Acute cardioversion and maintenance of sinus rhythm	FDA approved
Vernakalant	Peak I_{Na} and I_{Kur} block	Acute cardioversion	Investigational
Ranolazine	Atrial-selective peak I_{Na} and I_{Kr} block	Acute cardioversion and maintenance of sinus rhythm	Off-label use
AZD7009	Atrial-selective peak I_{Na} and I_{Kr} block	Acute cardioversion	Investigational, abandoned
AVE0118	Atrial selective I_{Kur}, I_{to}, $I_{K\text{-}ACh}$ block	Maintenance of sinus rhythm	Investigational, abandoned