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Atrial-selective sodium channel block for the treatment of atrial fibrillation

Alexander Burashnikov, PhD¹ and Charles Antzelevitch, PhD, FACC, FAHA, FHRS²

¹ Research Scientist, Masonic Medical Research Laboratory, 2150 Bleecker Street, Utica, NY 13501, USA

² Executive Director and Director of Research, Gordon K. Moe Scholar, Masonic Medical Research Laboratory, 2150 Bleecker Street, Utica, NY 13501, USA, Tel: +1 315 735 2217; Fax: +1 315 735 5648; E-mail: ca@mmrl.edu

Abstract

The pharmacological approach to therapy of atrial fibrillation (AF) is often associated with adverse effects resulting in the development of ventricular arrhythmias. As a consequence, much of the focus in recent years has been on development of atrial-selective agents. Atrial-selective sodium channel blockers have recently been shown to exist and be useful in the management of AF. This review summarizes the available data relative to current therapies, focusing on our understanding of the actions of atrial selective sodium channel blockers in suppressing and preventing the induction of AF and electrophysiological properties that confer atrial-selectivity to these antiarrhythmic drugs.

Keywords

arrhythmias; electrophysiology; pharmacology; sodium channel blocker

1. Background

Atrial fibrillation (AF) is the most prevalent sustained clinical arrhythmia associated with increased morbidity and mortality. The prevalence of AF is 0.4 – 1% in the general population and greater than 8% in individuals > 80 years of age. Approximately 2.3 million individuals in the North America and 4.5 million in Europe are affected by AF [1,2]. These numbers are projected to increase to 15 million in North America alone by 2050 [2] due largely to aging of the population. Although AF can occur in people with undetectable heart diseases (the so-called ‘lone or idiopathic AF’), this arrhythmia is normally associated with a number of clinical, often overlapping, conditions such as hypertension, heart failure, coronary artery disease and valvular heart disease, with an incidence of 80, 30, 25 and 17% in AF patients, respectively [2]. In terms of duration, AF is commonly defined as paroxysmal, persistent (lasting < 7 and ≥ 7 days, respectively), and permanent AF (which cannot be terminated or is not attempted to be terminated) [3]. AF is a progressive disease. If not treated appropriately, paroxysmal AF tends to recur progressively more often, last longer and transition to a persistent or permanent form. It is now well established that the longer the duration of AF, the more difficult it is to suppress the arrhythmia. The development of electrical and structural remodeling secondary to AF contributes to the tendency of AF to progress from paroxysmal to persistent and permanent. This progression has led to coining

of the phrase “AF-begets AF” by Allessie’s group in 1995 [4]. Another contributing factor is structural remodeling of the atria associated with aging, hypertension and heart failure.

Despite significant progress in non-pharmacological treatment of AF (largely due to the use of catheter ablation techniques), antiarrhythmic drugs (AADs) remain the first-line therapy for rhythm control of AF [1,3]. However, the efficacy and/or safety of AADs available for the treatment of AF are not optimal. Recent drug development has focused on the atrial-selective anti-AF medications, with the goal of avoiding the ventricular proarrhythmic effects of at present available drugs. We recently introduced the concept of atrial-selective sodium channel blockers as a novel strategy for the management of AF [5]. This review summarizes available data relative to current therapies and our understanding of the actions of atrial-selective sodium channel blockers in suppressing and preventing the induction of AF, as well as the biophysical properties that confer atrial-selectivity to AADs.

2. Unmet medical need and existing treatment

Effective and safe treatment of AF remains a major unmet medical need in our society. There are two principal options for the management of AF, that is, rate and rhythm control. Rate control, in which the atria is left fibrillating, is focused on reducing the number of beats crossing the atrioventricular node and thus preventing the detrimental effects on the ventricles, such as the development of cardiomyopathy and heart failure. The rhythm control strategy aims to maintain sinus rhythm, with its restoration when required (using AADs, catheter ablation or surgical techniques). Rate control and most rhythm control patients require anticoagulation therapy to reduce the risk of stroke [2,6].

Clinically available rhythm control anti-AF agents target the rapidly activating delayed rectifier potassium current (I_{Kr} , e.g., dofetilide and sotalol), the ‘early’ or ‘fast’ sodium current (I_{Na} , e.g., flecainide and propafenone) or several ion channels (potassium, sodium and calcium; e.g., amiodarone and dronedarone). The ability of AADs (both I_{Na} and I_{Kr} blockers) to acutely restore sinus rhythm is generally better with paroxysmal than persistent AF (ranging from 30 to 90% and 6 to 30% of AF patients, respectively) [2,6]. I_{Kr} blockade is generally more effective than I_{Na} blockade in the termination of persistent AF [1]. The efficacy of long-term maintenance of sinus rhythm (at 1 year) ranges between 40 and 50% with I_{Kr} and I_{Na} blockers and is up to 65% with amiodarone, perhaps the best available antiarrhythmic agent for the maintenance of sinus rhythm [6]. Unfortunately, the use of all currently available AADs is associated with a risk of induction of ventricular arrhythmias and/or organ toxicity. I_{Kr} blockers may induce acquired long QT syndrome and polymorphic ventricular tachycardia, known as Torsade de Pointes (TdP) [1]. Before 1989, agents that blocked I_{Na} were considered to be rather safe and were widely used for the treatment of both atrial and ventricular arrhythmias. In 1989, the Cardiac Arrhythmia Suppression Trail (CAST) revealed a shocking reality that potent I_{Na} blockers (Class IC) significantly increase total mortality in patients with previous myocardial infarction, presumably owing to severe ventricular arrhythmias [7]. As a consequence, the use of I_{Na} blockers for ventricular arrhythmias was significantly reduced and the development of new antiarrhythmic I_{Na} blockers was practically stopped. In contrast to ventricular arrhythmias, potent I_{Na} blockers such as flecainide and propafenone have been widely used before and after the CAST era for rhythm control of paroxysmal AF, with an important CAST-derived limitation of not using these agents in patients with structural heart diseases such as congestive heart failure, myocardial infarction or hypertrophy: these account for > 70% of all AF patients [2,6]. Although amiodarone is safe for use in patients with structurally-compromised ventricles, long-term administration of this agent can induce multi-organ toxicity and rare cases of TdP [8,9].

A number of recent randomized, prospective and multi-center studies have provided compelling evidence that catheter ablation strategy, primarily targeting pulmonary vein regions of the left atrium, is more effective than AADs in the long-term maintenance of sinus rhythm in symptomatic and relatively young patients with paroxysmal AF in which at least one AAD had initially failed [10–12]. The long-term efficacy of catheter ablation for the treatment of persistent/permanent AF is generally lower than that of paroxysmal AF [3]. It is yet to be determined if rhythm control strategy based on catheter ablation method is superior to that based on AAD approach in terms of total mortality [2,13]. Notwithstanding the increasing efficacy of catheter ablation and the limitations of use of AADs, at the present time AADs remain the first-line therapy for rhythm control management of all types of AF patients, including symptomatic and relatively young patients with paroxysmal AF [1–3,6].

The results of a number of multi-center, randomized and prospective clinical trials (such as AFFIRM and AF-CHF) suggest that rhythm control strategy with AADs is not superior to rate control in terms of survival [14,15]. A common interpretation of these data is that the adverse effects of using AADs, secondary to extra-cardiac toxicity and ventricular proarrhythmia, exceed the benefit derived from a limited capability of these AADs to maintain sinus rhythm [2,6,16]. The maintenance of sinus rhythm with AADs was not achieved in all rhythm control patients and not all rate control patients were in AF all the time. When these considerations were taken into account, several *post hoc* analyses of the AFFIRM data showed that patients who were maintained in sinus rhythm had a better survival rate than those who were in AF [17–19]. It is generally believed that rhythm control with AADs would be preferable for most AF patients if safer and more effective anti-AF drugs were available [2,6,20].

Several novel pharmacological strategies aimed at improving the effectiveness and safety of AADs for AF rhythm control management have been proposed [20–22]. “Upstream therapy” is focused largely on non-ion channel targets designed to reduce and/or prevent atrial structural remodeling, hypertrophy, dilatation, hypertension, inflammation, oxidative injury and so on (i.e., factors believed to be involved in the generation of AF) [20,23]. “Upstream therapy” with angiotensin-converting enzyme inhibitors, angiotensin receptors blockers, statins, aldosterone antagonists and (ω -3 poly-unsaturated fatty acids has been shown to be of benefit for AF in some but not all studies [24,25].

Recent years have witnessed the development of novel ion-channel blockers that are atrial specific/selective in their actions as well as efforts to improve old anti-AF agents (e.g., dronedarone to replace amiodarone). Atrial-specific targets are those that are present exclusively or almost exclusively in atria and include the ultrarapid delayed rectified potassium current (I_{Kur}), the acetylcholine (ACh)-regulated inward rectifying potassium current (I_{K-ACh}), the constitutively active (CA) I_{K-ACh} (i.e., which does not require ACh or muscarinic receptors for activation) and connexin 40 (with a condition that connexin 40 is present in ventricular conduction system) [21,26,27]. Inhibition of both the conventional I_{K-ACh} and CA- I_{K-ACh} has been shown to exert antiarrhythmic actions in some types of experimental AF [28,29]. Gap junction activator rotigaptide produces antiarrhythmic actions in canine chronic mitral regurgitation AF model [30] and in the canine acute ischemia AF model [31] but did not affect AF development in AF models associated with heart failure or atrial tachypacing [30,31]. The clinical applicability of inhibitors of conventional and CA- I_{K-ACh} as well as enhancers of gap junctional conductance remains to be determined [27].

Among the atrial-specific approaches, the inhibition of I_{Kur} is the most investigated and widely considered to be the most promising for the treatment of AF [21,32]. However, at concentrations that effectively control AF, I_{Kur} blockers also potentially block other currents (e.g., I_{Na} by vernakalant and AZD7009 and I_{to}/I_{K-ACh} /CA- I_{K-ACh} by AVE0118) [33–36].

Although there are a number of other I_{Kur} blockers that have been shown to suppress experimental AF [32], it is yet to be proven that pure I_{Kur} block can effectively suppress AF (see section 4.1). Selective I_{Kur} inhibition can neither prevent nor terminate ACh-mediated AF in canine atria [37]. It has been reported that I_{Kur} density is progressively reduced with acceleration of activation rates [38] and that I_{Kur} density can be decreased in cells isolated from chronic AF atria [36,39]. It has been shown also that selective I_{Kur} reduction produces only minor (action potential duration) APD_{90} prolongation in human remodeled atria or canine ACh-treated atria (both showing a triangular action potential morphology and prone to develop AF) [37,40]. These data indicate that the relative contribution of I_{Kur} to atrial repolarization in remodeled atria may be relatively low, particularly at rapid activation rates. Although I_{Kur} block may contribute to the antiarrhythmic efficacy of the I_{Kur} blockers, I_{Kur} block alone may be insufficient to effectively suppress AF and inhibition of further currents may be required (e.g., I_{Na} , I_{Kr} , I_{to} , I_{KACh} , $CA-I_{KACh}$) [22,27,36,37,41]. In addition, I_{Kur} may actually predispose to the development of AF in non-remodeled atria [37,42]. In human and canine non-remodeled atria (displaying a plateau-shaped action potential morphology), selective I_{Kur} block abbreviates APD_{90} [37,40,43], a well-recognized pro-AF factor [44], and permits the development of AF in 'healthy' canine atria [37]. Consistent with these data, loss-of-function mutations in *KCNK5*, the gene that encodes the $K_v1.5$ channels responsible for I_{Kur} , was found to be associated with AF [42]. Note, however, that only one AF patient with the *KCNK5* mutation has been identified thus far.

Recent experimental studies have identified atrial-selective or predominant I_{Na} blockers that can effectively suppress AF with little or no effect in the ventricles [5,45–47]. Based on these proof-of-concept experiments, we have proposed a novel investigational atrial selective sodium channel block strategy for AF treatment. We refer to atrial-selective or predominant targets as those that are present in both chambers of the heart, but whose inhibition produces greater effects in atria versus ventricles. In these cases, block of I_{Na} leads to atrial-selective depression of excitability and conduction as well as the development of post-repolarization refractoriness (PRR) in multicellular cardiac preparations or *in vivo*.

3. Current research goals

Data relative to atrial-selective sodium channel block as a strategy for the management of AF appeared only in 2007 [5], and so a number of critical questions remain to be answered. Among these are: What properties of sodium channel blockers (kinetics and modes of binding and unbinding, lipid solubility, molecular size and chemical structure) determine their atrial selectivity? How does electrical and structural remodeling in both atria and ventricles modify atrial selectivity and anti-AF potential of I_{Na} blockers? What factors/conditions may promote atrial selectivity and anti-AF efficacy of sodium channel blockers? What specific types of AF pathologies can be treated most effectively and safely with atrial selective I_{Na} blockers? Are acute and chronic effects of atrial selective I_{Na} blockers on the heart similar? Are atrial selective I_{Na} blockers safe in the short and long term, particularly in structurally compromised hearts (both in terms of proarrhythmia and extra-cardiac toxicity)? To what extent can data on atrial selectivity of I_{Na} blockers obtained from dog be applied to humans? What is the genetic basis for the atrioventricular difference in biophysical properties of sodium channel and how do these differences in biophysical properties contribute to atrioventricular distinctions in pharmacologic response? Can these genetic differences be applied to the development of atrial-specific treatments of AF? Current research is focused on finding answers to these and related questions. The remainder of the review attempts to summarize the available information regarding these issues.

4. Scientific rationale

4.1 Atrial-selective depression of sodium channel-mediated parameters

The emergence of the atrial selective sodium channel block as a strategy for AF therapy derives from experimental findings that ranolazine predominantly depresses atrial versus ventricular sodium channel-dependent parameters and suppresses AF at concentrations producing little to no effect in the ventricles (Figures 1 and 2) [5]. Similar atrial selective properties were revealed later with chronic amiodarone [45]. Ranolazine and chronic amiodarone reduce maximum rate of rise of the action potential upstroke ($V_{\max}$), prolong conduction time (CT), increase diastolic threshold of excitation (DTE) and induce PRR specifically or predominantly in the canine isolated atrial versus ventricular coronary-perfused preparations (Figures 1 and 3) [5,45]. Induction of PRR is a unique feature of I_{Na} blockers, occurring when the effective refractory period (ERP) is prolonged without prolongation of action potential duration (APD_{70-90}) or to a greater degree than APD_{70-90} . Lidocaine exerts mild atrial-predominant effects on these I_{Na} -mediated parameters, whereas ranolazine and chronic amiodarone are strongly atrial-selective in their suppression of I_{Na} -dependent parameters [5,45]. In contrast, propafenone depresses $V_{\max}$ and CT, decreases DTE and induces PRR in a chamber-independent manner at a pacing cycle length of 500 ms, but become a bit more atrial-selective at a basic cycle length of 300 ms (see Section 4.2) [48].

Interestingly, although lidocaine is a specific I_{Na} blocker, ranolazine and amiodarone are not. Ranolazine, first recognized as an antianginal and then as an antiarrhythmic agent, in therapeutically relevant concentrations (1 – 10.0 μ M) blocks early I_{Na} , late I_{Na} , I_{Kr} and late I_{Ca} [5,49]. Amiodarone has likewise been shown to inhibit several cardiac ionic currents (I_{Kr} , I_{KS} , I_{Na} , late I_{Na} , I_{to} , I_{Ca-L} , I_{Ca-T} , I_{K1} , $I_{K(ACh)}$ and $I_{K(ATP)}$ as well as to block α - and β -adrenoceptors [8,50].

AZD7009 decreases excitability (i.e., DTE) and conduction velocity preferentially in atria of dogs *in vivo* [51], indicating that its atrial selectivity is due in part to its inhibition of I_{Na} giving rise to an atrial selective prolongation of ERP [34,51].

A prominent I_{Kur} blocker, AVE0118, also inhibits I_{Na} (decreases $V_{\max}$) in an atrial selective manner and its atrial selectivity in ERP in non-remodeled atria is owing to sodium channel inhibition [52]. This atrial selectivity of AVE0118 and its I_{Na} blocking potency is weaker compared to ranolazine. Vernakalant, another I_{Kur} blocker, also potently blocks I_{Na} [33]. ISQ-1 and TAEA, two more I_{Kur} blockers, slow conduction velocity in atria but not in ventricles [53], suggesting an ability to block I_{Na} in an atrial selective manner. Interestingly, in non-remodeled atria, I_{Kur} blockers abbreviate or produce no change in APD_{70-90} [37,40,43,54], but apparently always prolong ERP in both non-remodeled and remodeled atria [32], which can be explained with the induction of sodium channel-dependent PRR (as has been demonstrated for AVE0118 in canine non-remodeled atria [52]). Of note, the effects of most I_{Kur} blockers on I_{Na} - or I_{Na} -mediated parameters have either not been studied or studied under conditions that may not unmask their atrial selectivity (i.e., in ventricular myocytes at slow pacing rates) [55,56].

Atrioventricular differences of the response to I_{Na} blockers are poorly investigated and controversial (for review see [47]). Failure to reveal the atrial selectivity of I_{Na} blockers in some studies may be due to the use of superfused atrial and ventricular preparations [34,57–61]. In general, whereas ventricular superfused preparations display electrophysiological characteristics and pharmacological responses similar to those of coronary-perfused preparations [5,49], atrial superfused tissue preparations do not [5,43]. Superfused atrial preparations typically display action potentials with a triangular morphology, whereas

coronary-perfused atria have action potentials with a prominent plateau [43]. Ventricular action potentials display a plateau in both superfused and coronary-perfused preparations. Atrial APD is much briefer than ventricular APD in superfused preparations, but comparable in coronary-perfused preparations [5,57,58]. Because the efficacy of I_{Na} blockers is critically dependent on the duration of the action potential and diastolic interval (with the latter being a function of the former) [62,63], data from superfused atrial preparations should be interpreted with great caution. Semi-quantitative assessment of atrial selectivity of I_{Na} blockers is shown in Figure 4.

4.2 Atrial selective prolongation of APD₉₀ by I_{Kr} block promotes atrial selective I_{Na} block

Ranolazine, propafenone and chronic amiodarone (all possessing I_{Kr} blocking activity), but not lidocaine, produce a greater prolongation of APD₉₀ in canine atria versus ventricles [5,45,47]. Selective I_{Kr} blockers such as E-4031 also preferentially prolong atrial APD₉₀ [45]. These data are consistent with a number of experimental and clinical studies demonstrating a preferential prolongation of ERP in atria versus ventricles by I_{Kr} blockers (such as sotalol, d-sotalol, dl-sotalol, dofetilide, WAY-123,398, ibutilide, MK499 and almokalant) at pacing rates equivalent to the resting sinus rhythm [64–70]. However, under bradycardic conditions or with long pauses, these agents produce a greater APD prolongation and early afterdepolarizations leading to the development of TdP arrhythmias in the ventricles rather than the atria [71,72]. Rate-dependent atrioventricular differences in response to I_{Kr} inhibition are not well appreciated and underlying mechanisms of these differences remain undefined.

The atrial-predominant APD prolongation leads to a greater abbreviation of diastolic interval or its elimination at rapid rates in atria versus ventricles. (Figure 3B) The progressive elimination of the diastolic interval in atria at rapid rates leads to greater accumulation of drug-induced sodium channel block in atria than in ventricles because recovery from sodium channel block generally occurs during the diastolic interval [73]. This mechanism is thought to contribute to greater atrial selectivity of ranolazine and amiodarone versus lidocaine [5]. Thus, I_{Kr} inhibition may exert anti-AF activity through a direct effect to prolong APD/ERP as well as by an indirect influence to promote I_{Na} blockade in an atrial-predominant manner. The contribution of I_{Kr} block to the atrial-selective actions of ranolazine and amiodarone is clearly owing to its potentiation of their action to depress V_{Max} and CT or increase ERP, PRR and DTE through inhibition of sodium channel current. Indeed, ranolazine-induced PRR is much longer than the ranolazine-induced APD₇₅ prolongation (Figure 1).

4.3 Cellular and ionic mechanisms of atrial selectivity of I_{Na} blockers

I_{Na} blockers generally bind more effectively to open and/or inactivated sodium channels (i.e., during the action potential) than to resting sodium channels (i.e., during the diastolic interval). Unblocking is largely associated with the resting state of the sodium channel [63,73]. Acceleration of activation rates promotes the development of sodium channel blockade by increasing the proportion of time that the sodium channels are in the open/inactivated state and reducing the time that the channels are in the resting state. There are no 'pure' open or inactivated state I_{Na} blockers. As a general rule, predominantly inactivated-state blockers are I_{Na} blockers having rapid unbinding kinetics ($\tau < 1$ s; i.e., Class IB agents) and predominantly open-state blockers are I_{Na} blockers having medium or slow unbinding kinetics ($\tau > 1$ but < 12 s and > 12 s; Class IA and IC agents, respectively) [62,73]. Depolarization of the resting membrane potential (RMP) normally promotes and abbreviation of APD reduces the efficacy of I_{Na} block.

Available data suggest that open versus inactivated state block of the sodium channel does not determine the potential for atrial selectivity. Although both propafenone and ranolazine

are predominantly open state blockers [63,74] (Nesterenko *et al.*, unpublished), amiodarone and lidocaine are predominantly inactivated state blockers [63]. Rate of dissociation of drug from the sodium channel, on the other hand, is thought to contribute to atrial selectivity. Ranolazine and amiodarone, both atrial-selective sodium channel blockers, possess relatively rapid dissociation kinetics (unbinding $\tau = 0.2 - 1.6$ s) [5,75] whereas propafenone, which shows little to no atrial selectivity, displays slow dissociation kinetics (unbinding $\tau = 8$ s) [63]. Validation of this hypothesis awaits assessment of the atrial selectivity of other 'slow' I_{Na} .

The 'atrial-selective' properties of I_{Na} blockers are owing to atrioventricular differences in the biophysical properties of the sodium channel and differences in the morphology of atrial and ventricular action potentials (Figure 5) [5,45,47]. The RMP is intrinsically more depolarized in atrial versus ventricular myocytes, presumably owing to a weaker I_{K1} in atria [76]. The steady-state inactivation curve of the atrial versus ventricular I_{Na} is shifted to the left, with the half inactivation voltage ($V_{0.5}$) in atrial myocytes being 9–14 mV more negative than that of ventricular myocytes [5,77,78]. As a consequence of the more depolarized RMP and more negative $V_{0.5}$, a larger fraction of sodium channels are in the inactivated state in atrial versus ventricular cells. The fraction of resting sodium channels is, therefore, smaller in atrial versus ventricular cells at the RMP. Because much of the recovery from sodium channel block commonly occurs during the resting state of the channel [62,73], atrial cells should show a greater accumulation of use-dependent sodium channel block. Atrial-selective APD prolongation (owing to I_{Kr} block) may also importantly promote atrial selective depression of sodium channel-dependent parameters (discussed in Section 4.2).

The factors contributing to atrial-selective depression of sodium channel-dependent parameters at rapid activation rates include: i) A more negative half-inactivation voltage in atria, which reduces the availability of sodium channels and the fraction of resting sodium channels; ii) A more depolarized RMP in atria, which further reduces the availability of sodium channel and potentiates the effect of sodium channel blockers; iii) Greater drug-induced slowing of Phase III in atria (owing to I_{Kr} block), which results in failure of the action potential to achieve maximum resting potential at rapid rates, thus, leading to a depolarized take-off potential, further reducing the availability of sodium channels (Figure 3); iv) The slower Phase III also leads to elimination of the diastolic interval in atria but not ventricles, thus, reducing the rate of dissociation of sodium blockers from the channel (Figure 3); and v) Recovery from inactivation of the sodium channel is slower in atrial cells [78].

It is noteworthy that I_{Na} density is much greater in atrial versus ventricular cells (Figure 5) [5,78]. The higher density of I_{Na} in atrial cells [5,78] may offset the lower availability of sodium channels in atrial versus ventricular cells. The time constants for sodium channel activation and inactivation are also twice as rapid in atrial as in ventricular myocytes [78], indicating that the total open time of the sodium channels during each action potential should be shorter in atrial cells.

4.4 Atrial-selective multiple ion channel block for the management of AF with the sodium channel as the prime target

Although the promise of selective ion channel block for the management of AF has been attractive in theory, practical clinical experience and experimental evidence suggest that 'dirty' drugs affecting several ion currents, such as amiodarone, are generally more effective. Clinical data indicate that selective I_{Na} blockers, such as lidocaine or mexiletine (Class IB agents), which have rapid binding/unbinding kinetics, are not very effective in suppressing AF [1]. All clinically effective anti-AF Class I agents inhibit several currents

(such as I_{Kr} , I_{Ks} , I_{to}) and have relatively slow binding/unbinding kinetics from the sodium channel (e.g., flecainide or propafenone, Class IC; and quinidine, Class IA). It is not clear whether 'pure' I_{Na} block, independent of dissociation kinetics, is capable of suppressing clinical AF at therapeutic concentrations of I_{Na} blockers. Experimental and theoretical data have shown that 'pure' I_{Na} inhibition with rapid kinetics (with high concentrations of lidocaine and TTX) can effectively suppress 'acute' ACh-mediated AF in non-remodeled isolated preparations [79,80]. Although pilsicainide has been proclaimed to be a pure sodium channel blocker with slow kinetics and shown to be effective in AF suppression [81], this agent also inhibits HERG and occasionally produces long QT syndrome [82].

Ranolazine, propafenone and chronic amiodarone are effective in the suppression of ACh-mediated AF in canine isolated coronary-perfused right atria [5,45,48]. A major difference between ranolazine and propafenone is that at clinically relevant concentrations, which effectively suppress AF (10.0 and 1.5 μ M, respectively), ventricular electrophysiological parameters are strongly affected by propafenone but not ranolazine. Ranolazine has been shown also to potently suppress isoproterenol-mediated AF associated with ischemia and reperfusion in canine isolated right atria [5]. Chronic amiodarone (40 mg/kg day for 6 weeks) prevents ACh-mediated AF, although causing moderate electrophysiological changes in canine isolated coronary-perfused left ventricular preparations [45]. The antiarrhythmic efficacy of lidocaine (at 21 μ M, also a clinically relevant concentration) in this ACh-mediated AF model is relatively poor and its electrophysiologic effects in the ventricles are much greater than those of ranolazine [5]. Ranolazine or chronic amiodarone produce a greater prolongation of PRR than of APD, suggesting that their anti-AF effect is due largely to I_{Na} inhibition rather than I_{Kr} block. The ability of I_{Kr} block alone to suppress ACh-mediated AF is relatively poor.

The effectiveness of ranolazine to suppress AF in experimental models is consistent with the results of the MERLIN-TIMI 36 clinical study in which ranolazine treatment was associated with reduced incidence of supraventricular arrhythmias and a 30% reduction in new onset AF in patients with non-ST segment elevation acute coronary syndrome [83]. In a recent single-center study, ranolazine was effective in maintaining sinus rhythm in a cohort of AF patients (most of them with structural heart diseases) in whom more established AADs had failed [84]. AZD7009 has been shown to terminate AF and atrial flutter in 100% of cases in the canine sterile pericarditis model [51]. In a randomized, double-blind, placebo-controlled and multi-center study, the success rate of AZD7009 to terminate AF or atrial flutter in humans was impressive indeed (up to 70% in patients with mean AF duration of 43 days (2 – 90 days) and up to 52% in patients with AF lasting > 1 week) [85]. In another clinical study, conversion rate of AF of < 30 day duration with AZD7009 was comparable to DC cardioversion (82 versus 83%, respectively) [86]. For comparison, the success rate of cardioversion of paroxysmal AF (< 7 day duration) with vernakalant is 51% [87]. Chronic amiodarone is arguably the best AAD for the maintenance of sinus rhythm [9]. Although the anti-AF mechanisms of chronic amiodarone is quite complex [87], in canine ACh-model it is likely to be largely owing to the sodium channel blockade [45]. We are not aware of any clinical study in which the issue of atrial selective I_{Na} blockade has been specifically investigated.

Clinical data indicate that agents with relatively 'slow' (τ of $\sim$ 6 s) [63,73] sodium channel dissociation kinetics are capable of inducing ventricular fibrillation (VF) and ventricular tachycardia in structurally-compromised hearts (e.g., encainide, flecainide and propafenone) [7]. Atrial-selective I_{Na} blockers such as ranolazine and amiodarone have relatively rapid kinetics (unbinding τ = 0.2 – 1.6 s) [5,50], which may account for their safety in patients with structurally compromised hearts [8,83,88]. Despite their ability to inhibit I_{Kr} these agents either do not (ranolazine) or very rarely (amiodarone) induce TdP. The two drugs

differ with respect to extra-cardiac toxicity. Chronic amiodarone is notorious for induction of extra-cardiac toxicity [8], whereas acute and chronic use of ranolazine has been shown to be safe [88].

The low proarrhythmic potential and antiarrhythmic efficacy of ranolazine and amiodarone in the ventricle is probably related to their ability to significantly block late I_{Na} [89,90]. A balanced inhibition of outward I_K and inward late I_{Na} prevents the development of an exaggerated dispersion of repolarization as well as the induction of early afterdepolarizations, thus, averting both the substrate and trigger for development of TdP arrhythmias [89,91]. Late I_{Na} inhibition plays a key role in suppression of ventricular arrhythmias in a variety of pathological conditions such as long QT syndrome, acute ischemia and heart failure [89,91,92].

A combination of both atrial-selective I_{Na} block and atrial-specific I_{Kur} block is expected to exert a more potent effect than either approach alone for the management of AF. In remodeled atria, prolongation of APD₉₀ secondary to I_{Kur} block can promote accumulation of I_{Na} block preferentially in atria by reducing diastolic interval in atria but not in ventricles, thus, contributing to the anti-AF effects of these agents. Interestingly, although the ability of I_{Kr} block alone to prolong APD and suppress AF is significantly reduced in remodeled goat atria, further inhibition of I_{Kur}/I_{To} restores their effectiveness, pointing to a synergism of this drug combination [93].

It is yet to be determined whether ranolazine preserves its atrial-selectivity for block of I_{Na} with chronic administration. Amiodarone seems to produce atrial-selective depression of I_{Na} -mediated parameters with both acute and chronic applications [45]. Our preliminary data indicate that acute effects of amiodarone on sodium channel-mediated parameters studied in canine coronary-perfused atrial and ventricular preparations are atrial predominant as well (Burashnikov *et al.*, unpublished).

The available data suggest that agents with combined inhibition of early I_{Na} (as the prime target, with relatively rapid kinetics), late I_{Na} , I_{Kr} and I_{Kur} could be atrial-selective and effective in suppressing AF without exerting a proarrhythmic effect in ventricular myocardium.

4.5 Atrial selectivity of I_{Na} blockade in remodeled atria

AF is normally associated with electrical and structural remodeling, which can significantly modify pharmacologic response of atria to sodium and potassium channel blockers [40,94,95]. In this respect, it is important to recognize that the atrial selectivity of I_{Na} blockers has been demonstrated in 'healthy atria and ventricles' [5,45,47]. Fibrillating atria or atria susceptible to AF normally display short APDs and a depolarized RMP, which reduce and promote the effectiveness of I_{Na} block, respectively [63]. The ability of ranolazine, chronic amiodarone, lidocaine and propafenone to suppress sodium channel-dependent parameters is reduced in ACh-treated canine atrial preparations, possessing an abbreviated APD [5,45,48]. Alterations in I_{Na} density have been reported in remodeled canine [96], but not human [97], atria. Conduction velocity is not changed in remodeled atria of the goat [4]. V_{05} of I_{Na} inactivation is shifted by +10 mV in cells isolated from AF versus sinus rhythm patients [97], which may reduce atrial sensitivity to I_{Na} blockers. This may account for the lower antiarrhythmic efficacy of I_{Na} block in persistent AF [1]. This limitation may apply to atrial selective I_{Na} blockers as well. Note, however, that the potency of Class IC agents was not altered by atrial tachypacing-induced remodeling in goats [98].

4.6 Influence of atrial-selective agents on ventricular arrhythmias

Ventricular arrhythmias commonly occur under pathophysiological conditions associated with ischemia, infarction, long QT syndrome and hypertrophy. These conditions can importantly modulate the response to sodium and potassium channel blockers. This may explain why atrial-selective agents (as determined by their actions in 'healthy hearts') can exert significant electrophysiological and antiarrhythmic actions in 'abnormal' ventricles. For example, the atrial selective I_{Kur}/I_m blocker AVE0118 effectively suppresses ventricular arrhythmias occurring in the setting of ischemia in dogs [99]. Ranolazine reduces the incidence of ventricular arrhythmias associated with acute coronary and long QT syndrome, an effect attributed to the action of ranolazine to block late I_{Na} [83,89,100]. Although generally used to treat atrial arrhythmias, amiodarone can effectively suppress ventricular arrhythmias [9].

4.7 Molecular biology and genetics of cardiac sodium channels

The genetic basis for the atrioventricular difference in biophysical properties of the sodium channel is not fully understood. Whereas the α -subunit of the cardiac sodium channel (SCN5A) is the same in atrial and ventricular cells, chamber-specific differences in the stoichiometry of auxiliary subunits may exist and contribute to the distinct characteristics of atrial and ventricular sodium channels. Four β sub-units of the sodium channel have been identified in the heart (*SCN1B*, *SCN2B*, *SCN3B* and *SCN4B*) [101]. *SCN3B* is present in the ventricles but not in the atria of sheep and rat hearts [102,103]. *SCN1B* was found both in atria and ventricles of guinea pigs, rat and humans [102–104]. *SCN1B* is more strongly expressed in atria versus ventricles in human [104]. The expression level of *SCN1B* is much greater than that of *SCN3B* in the human heart [104]. Interestingly, co-expression of *SCN3B* and *SCN5A* in *Xenopus* oocytes shifts the h-curve to the right, compared to *SCN5A* alone or *SCN5A* + *SCN1B* [102]. This may contribute to the atrioventricular difference in the steady-state inactivation curves (Figure 5). In contrast, co-expression of *SCN5A* and *SCN3B* in TSA201 cells shifts the h-curve to the left, compared to *SCN5A* alone or *SCN5A* + *SCN1B* co-expression [105]. A left-ward shift of h-curve was also observed when *SCN5A* is co-expressed with *SCN3B* in Chinese hamster ovary cells [103]. *SCN1B* null mice have an increased $Na_v1.5$ protein expression and acutely isolated ventricular myocytes from these mice have an increased early I_{Na} and late I_{Na} [106]. It is recognized that β -subunits of various channels can interact with each other, affecting phenotypical manifestations of the channels. I_{Na} may be influenced by *KChIP2* (a β subunit of $K_v4.3$ channels, producing I_{to}) and *SCN1B*, in turn, may affect I_{to} parameters [107].

There are mutations or rare variants in *SCN5A* that have been associated with familial AF [108,109]. These mutations or polymorphisms in *SCN5A*, however, are likely to account for only a minority of AF cases [108–110]. It is not known whether atrial-selective I_{Na} blockers will be of benefit or harm in AF patients with *SCN5A* mutations. However, because I_{Na} blockers apparently have never been shown to induce AF *de novo* (in contrast to VF) it is not clear whether I_{Na} block will promote AF. It is, however, noteworthy that *SCN5A* mutations have been associated with AF in patients with Brugada [111].

5. Competitive environment

The concept of the atrial selective block of I_{Na} for the management of AF is relatively new [5]. Few atrial selective I_{Na} blockers have been identified until now. AADs thus far shown to depress sodium channel-dependent parameters in a atrial-selective manner in experimental models and to effectively suppress AF (in experimental models and in the clinic) are ranolazine, chronic amiodarone and AZD7009 (Table 1) [5,45,51,83–86,112]. Vernakalant, by virtue of its effect to block I_{Na} with rapid kinetics and to inhibit I_A [33] may

also prove to be an atrial-selective I_{Na} blocker. Vernakalant, a cardiome product, has received an approval letter for acute termination of AF and is undergoing Phase III clinical trials for maintenance therapy. We are not aware of any programs specifically designed for the development of atrial-selective I_{Na} blockers.

6. Potential development issues

The chemical structure contributing to atrial-selective depression of I_{Na} -dependent parameters is not known. Accordingly, there is no clear directive for development of safe and effective drugs with this unique feature. Because long-term use of ranolazine has been found to be free of significant intra- or extra-cardiac adverse effects [88], the chemical structure of ranolazine may be a 'safe model' to use for the development of atrial-selective I_{Na} blockers.

7. Conclusion

A growing body of experimental and clinical evidence suggests that atrial-selective sodium channel blockers may offer a safe and effective strategy for the management of AF. These agents, which include ranolazine, amiodarone and AZD7009, are effective in suppressing AF and/or preventing its re-induction, without the risk of with a low risk of induction of ventricular tachycardia/VF or TdP [83–86,112]. The degree to which the clinical effectiveness of these multi-ion channel blockers depends on their potency to depress sodium channel-dependent parameters remains to be explained. Available data suggest that the two principal factors contributing to atrial selectivity are: i) rapid dissociation of the drug from the sodium channels; and ii) atrial selective APD prolongation secondary to inhibition of I_{Kr} and I_{Kur} . The clinical observations coupled with recent experimental data suggest that further studies specifically designed to evaluate the potential role of atrial-selective sodium channel blockers as antiarrhythmics are warranted.

8. Expert opinion

The cellular and molecular mechanisms responsible for the initiation and maintenance of AF are multi-factorial and pathology- and stage-specific. Dynamic factors such as autonomic influences are well-known to promote AF [113]. The development of AADs has been empiric, in part due to: i) our relatively poor understanding of cellular and molecular mechanisms of AF under different pathophysiological conditions; and ii) incomplete knowledge of the optimal chemical structure needed to appropriately interact with anti-AF targets without inducing ventricular arrhythmias or extra-cardiac adverse effects.

Two principal factors have recently been suggested as contributing to atrial selectivity of sodium channel blockers: i) relatively rapid dissociation of the drug from the sodium channels; and ii) atrial predominant APD prolongation secondary to inhibition of I_{Kr} and I_{Kur} . The most effective anti-AF agent amiodarone, initially introduced as an anti-anginal agent in 1962 [8], was recently shown to possess both of these actions and to be an atrial-selective sodium channel blocker [45]. Ranolazine, an antianginal agent with a ion channel profile similar to that of amiodarone, also possesses these two key factors and has been shown to be highly selective in its ability to suppress I_{Na} -mediated parameters [5]. Vernakalant and AZD7009, recently developed as I_{Kur} blockers, also potentially inhibit I_{Na} and I_{Kr} and their anti-AF efficacy may be largely owing to I_{Na} block rather than I_{Kur} block [22,37]. Anti-AF efficacy of another purported selective I_{Kur} blocker AVE0118 may be largely due with its inhibition of $CA-I_{K-ACh}$, as well as inhibition of I_{Na} , rather than I_{Kur} . [36,52]. Although a great deal of effort has been devoted to development of specific I_{Kur} blockers [32], it remains to be determined if inhibition of I_{Kur} alone is sufficient to effectively suppress AF (see sections 2.0 and 4.1 for discussion) [27,41,47].

Interestingly, many of the prominent new investigational anti-AF agents block I_{Na} (such as dronedarone, vernakalant, AZD7009, ranolazine, AVE0118). All three agents investigated for depressing sodium channel-dependent parameters (i.e., ranolazine, AZD7009 and AVE0118) do so in an atrial-predominant manner [5,51,52]. Atrioventricular differences of the effects of vernakalant and dronedarone on sodium channel-dependent parameters have not been studied. However, vernakalant, like ranolazine and amiodarone, blocks I_{Na} with rapid kinetics and inhibits I_{Kr} [33]. Dronedarone is an analogue of amiodarone possessing ion channel block profile similar to its predecessor. Although the anti-AF effectiveness of amiodarone has been ascribed to a large number of factors, including APD/ERP prolongation, reduction of dispersion of repolarization, induction of PRR, prolongation of excitable gap, suppression of triggered activity, inhibition of atrial electrical and structural remodeling and blocking of (β -adreno-receptors [114], recent studies suggest that the drug's actions to depress sodium channel-dependent parameters may predominate [45].

The prolongation of APD/ERP or depression of I_{Na} -mediated parameters by AADs may not necessarily correlate with the ability of these agents to suppress clinical persistent AF, due in part to the fact that long-standing AF is associated with important structural remodeling. The ability I_{Na} blockers to suppress persistent AF is significantly reduced [1], despite the fact that the ability of the drugs to depress Independent parameters is not altered, at least in tachypacing-induced remodeled goat atria [94,98]. I_{Kr} block (dofetilide) is most effective in terminating clinically persistent AF [1], despite the fact that its ability to prolong APD/ERP is significantly reduced in remodeled atria [94].

There are major differences in the proarrhythmic liability of early I_{Na} or I_{Kr} blockers in the atria versus ventricles of the heart. I_{Na} blockers are capable of readily inducing severe proarrhythmia in the ventricles (e.g., VF), but apparently never (AF) or rarely (e.g., atrial flutter [115]) in atria. The proarrhythmic action of I_{Na} block in the ventricles is believed to be owing to conduction slowing. Why then can I_{Na} blockers slow conduction in atria without inducing AF? I_{Kr} blockers also readily induce TdP arrhythmias in ventricles, but not in atria [72,116]. The mechanisms underlying protection of atria from AAD-induced proarrhythmias are poorly understood and await further investigation. This information may be of benefit in the design of safer and more effective drugs for the management of AF.

The stigma of the CAST [7] resulted in pharmaceutical companies shying away from the development of I_{Na} blockers as antiarrhythmics for nearly 20 years. Inhibition of I_{Na} has proven to be effective in a variety of AF pathologies [1,117]; however, its proarrhythmic actions in structurally compromised ventricles have limited the utility of this approach. The advent of atrial-selective I_{Na} blockers may offer an important new strategy for the safe and effective management of AF under a wide variety of pathophysiological states associated with AF.

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Figure 1. Ranolazine specifically induces prolongation of the ERP and development of post-repolarization refractoriness in atria (the difference between ERP and APD₇₅ in atria and between ERP and APD₉₀ in ventricles; ERP corresponds to APD₇₅ in atria and APD₉₀ in ventricles)

CL= 500 ms. The arrows in panel A 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. Panel B includes summary data for the ranolazine induced changes in ERP and APD in atria and ventricles.

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* $p < 0.05$ versus control. $^{\dagger}p < 0.05$ versus APD₇₅ values in atria and APD₉₀ in ventricles; (n = 5 – 18).

APD: Action potential duration; C: Control; CL: Cycle length; ERP: Effective refractory period.

Figure 2. Ranolazine suppresses AF and/or prevents its induction in two experimental models involving isolated arterially-perfused right atria at concentrations producing little to no effects in ventricles

Persistent ACh-mediated AF (A.) and Iso-induced AF (C.) are suppressed by ranolazine. B. Ranolazine prevents rapid-pacing induction of AF following pretreatment with ACh (0.5 $\mu\text{mol/l}$). ERP is 140 ms at a CL of 500 ms (left panel). Acceleration of pacing rate from a CL of 500 to 200 ms permits a 1:1 response only during the first seven beats (right panel). In both models, ranolazine causes prominent use-dependent reduction of excitability and induction of PRR.

From Burashnikov *et al.* [5] with permission. Copyright of the American Heart Association. ACh: Acetylcholine; AF: Atrial fibrillation; CL: Cycle length; ERP: Effective refractory period; Iso: Isoproterenol; PRR: Post-repolarization refractoriness.

Figure 3. Ranolazine produces a much greater rate-dependent inhibition of the maximal action potential upstroke velocity ($V_{\max}$) in atria than in ventricles

A. Normalized changes in $V_{\max}$ of atrial and ventricular cardiac preparations paced at a CL of 500 ms. **B.** Ranolazine prolongs late repolarization in atria, but not ventricles and acceleration of rate leads to elimination of the diastolic interval, resulting in a more positive take-off potential in atrium and contributing to atrial selectivity of ranolazine. The diastolic interval remains relatively long in ventricles. “Atria” represent combined crista terminalis and pectinate muscle data. “Ventricles” represent combined epicardial and M-cell data from left ventricular wedge preparations.

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* $p < 0.05$ versus control. * $p < 0.05$ versus respective values of ventricles and Purkinje ($n = 7 - 21$).

CL: Cycle length.

Figure 4. A semi-quantitative assessment of atrial selectivity of I_{Na} blockers based on studies conducted in atrial and ventricular Cor-perfused and superfused (tissues) preparations, isolated myocytes and *in vivo*.

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Cor-perfused: Coronary-perfused.

Figure 5. Activation and steady-state inactivation in atrial versus ventricular myocytes

A. Current-voltage relation in ventricular and atrial myocytes. Voltage of peak I_{Na} is more positive and current density is larger in atrial versus ventricular myocytes. **B.** Summarized steady-state inactivation curves. **C.** Steady-state inactivation curves before and after addition of 15 μ M ranolazine.

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Table 1
Agents that suppress I_{Na}-dependent parameters in an atrial-selective manner and are effective against atrial fibrillation.

Compound	Company	Structure	Indication	Stage of development	Mechanisms of action
Ranolazine	CV Therapeutics		Anti-ischemic; proposed for rhythm control of AF	At present approved as an anti-anginal agent; clinical trial for AF indication is planned	Blocks I _{Na} and I _{Kr}
Amiodarone	Sanofi-Aventis		Rhythm control in AF patients	The most widely used anti-AF agent (used off-label)	Blocks I _{Na} , I _{Kr} , I _{Ks} , I _{Ca} and I _{K-ACH} α- and β-adrenergic blockade
AZD7009	AstraZeneca		Termination of AF	Phase II clinical trial was terminated owing to extra-cardiac side effect	Blocks I _{Na} , I _{Kr} and I _{Kur}

AF: Atrial fibrillation.