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Editorial

# Stretching the limits of antiarrhythmic drug therapy: The promise of small-conductance calcium-activated potassium channel blockers☆

Atrial fibrillation remains a major health burden, negatively affecting the morbidity and mortality of >55 million patients worldwide [1]. Although much has been learned about the molecular basis of AF, many challenges remain in the translation of basic discoveries to clinical application [2,3]. There is increasing evidence that safe and effective rhythm control therapy (i.e., restoration and maintenance of normal sinus rhythm) may improve clinical outcomes of AF patients, particularly when initiated early, before AF-related remodeling renders the disease unresponsive to therapy [4]. Catheter ablation is more effective at maintaining normal sinus rhythm than currently available antiarrhythmic drugs (AADs) [1]. However, given the large number of AF patients, AADs will remain a cornerstone of AF therapy for many years to come [5]. Current AADs were developed in the absence of information on the heterogeneous mechanisms underlying AF initation and progression and are used in a one-size-fits-all manner, partially explaining their limited efficacy [5,6]. Moreover, these AADs do not discriminate between atrial and ventricular cardiomyocytes, resulting in a significant risk of ventricular proarrhythmia that, together with non-cardiac side effects, greatly limits their use in clinical practice [1,5]. Thus, there is a clear need for safer, more effective AADs for rhythm control of AF.

Atrial-selective AADs, targeting ion channels primarily expressed in the atria or exploiting differences in channel gating due to differences in resting membrane potential between atrial and ventricular cardiomyocytes, are expected to be devoid of ventricular proarrhythmic side effects [5,7]. Moreover, given the lower proarrhythmic proclivity of atrial-selective AADs, it may be possible to employ higher doses to increase antiarrhythmic efficacy. Several targets have been explored, including a number of repolarizing potassium channels primarily expressed in the atria [6,7]. Inhibition of these channels prolongs the atrial effective refractory period (ERP), destabilizing AF-maintaining reentry. Blockers of the ultra-rapid delayed-rectifier potassium current ($I_{Kur}$) were the first prototypical atrial-selective AADs. Although $I_{Kur}$ blockers showed promise in cellular and animal models, prolonging atrial ERP without significant effect on ventricular repolarization, their antiarrhythmic effects in clinical studies were disappointing [5,7]. Similarly, blockers of the acetylcholine-activated inward-rectifier potassium current ($I_{K,ACh}$), which develops calcium-dependent constitutive (receptor-independent) activity in AF [8–10], contributing to proarrhythmic shortening of atrial ERP, have shown antiarrhythmic effects in some animal models [7]. However, the compounds tested to date were either not effective in humans or were limited in their use because of adverse central nervous effects [7]. Thus, the antiarrhythmic potential of atrial-selective $I_{K,ACh}$ inhibition still requires direct clinical verification.

More recently, small-conductance calcium-activated potassium (SK or $K_{Ca}2.X$) channels, encoded by the *KCNN1-3* genes, have been proposed as targets for atrial-predominant rhyhm-control therapy [7]. Indeed, common variants in both *KCNN2* and *KCNN3* have been associated with AF in genome-wide association studies [11] and inhibition of SK channels prolongs atrial repolarization [12]. Besides the bee-venom toxin apamin, often used to identify $I_{SK}$ experimentally, several SK-channel inhibitors with different modes of action have significant antiarrhythmic effects in various animal models [6,7]. For example, SK-channel inhibitors prolong atrial ERP and reduce the duration of acutely induced AF in pigs subjected to 1 week of atrial tachycardia remodeling [7,13]. Moreover, SK-channel inhibition could terminate a more persistent, vernakalant-resistant form of AF obtained using long-lasting rapid atrial pacing protocols and could prevent reinduction of AF under these conditions in pigs [13], suggesting a potential future use for long-term rhythm-control therapy. However, in a horse model of persistent AF treatment with the SK-channel inhibitor NS8593 was unable to induce cardioversion [14], indicating that species differences and AF induction mechanism may play a critical role in SK-channel inhibitor efficacy.

In the present issue of the *International Journal of Cardiology Heart and Vasculature*, Yan et al. [15] investigated the antiarrhythmic effects of the SK-channel inhibitor N-(pyridin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine (ICA) in an *ex-vivo* rabbit atrial model with balloon-mediated atrial dilatation. The authors show that ICA prolongs atrial repolarization duration and reduces the stretch-induced shortening of atrial ERP. Moreover, total AF duration increased linearly with balloon pressure and SK-channel inhibition reduced the occurence of burst pacing-induced AF during stretch. As such, these data further support the notion that SK-channel inhibition may be an effective rhythm control strategy in AF patients.

Atrial stretch and associated dilatation are well-accepted risk factors for AF, with AF itself promoting further atrial dilatation. In the chronic setting, atrial stretch induces reentry-promoting structural remodeling and dilated atria provide a larger substrate that can sustain more drivers, making arrhythmia termination less likely. Moreover, acute stretch, which may be clinically relevant in postoperative AF [16], shortens atrial ERP and slows conduction via stretch-activated and stretch-

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modulated ion channels, acutely promoting atrial arrhythmogenesis. In addition, acute stretch is associated with alterations in intracellular calcium through calcium influx via stretch-activated channels (e.g., transient-receptor potential channels), stretch-dependent modulation of voltage-dependent calcium channels (including $Ca_v1.2$), or increased calcium leak from the sarcoplasmic reticulum via ryanodine receptor channels [17]. Subsequent activation of SK channels, which are located in the immediate vicinity of $Ca_v1.2$ and ryanodine receptor channels [18], may therefore directly contribute to proarrhythmic stretch-induced ERP shortening, potentially explaining the antiarrhythmic efficacy of SK-channel inhibition under these conditions. However, direct proof is still lacking and the significant prolongation of baseline ERP (in the absence of stretch) may already be sufficient to modulate the arrhythmogenic risk. Of note, the atrial burst-pacing used to induce AF in the current study [15] would also be expected to promote calcium loading and subsequent activation of SK-currents. In agreement, previous work has identified a role for SK-channels in the reinduction of ventricular tachyarrhythmias after cardioversion by creating a mismatch between short repolarization duration and large, long calcium transients [18]. These factors may contribute to an overestimation of the importance of SK channels in the work by Yan et al. [15].

Despite the promising results in various animal models with clinically relevant risk factors such as atrial stretch, the antiarrhythmic potential of SK-channel inhibition in patients remains uncertain. This may be in part due to the incomplete understanding of the complexity of SK-channel remodeling and its effects on atrial electrophysiology and arrhythmogenesis. $I_{SK}$ is upregulated in different animal models with atrial tachypacing [18], but results in humans are variable. A number of studies have reported downregulation of some of the *KCNN* genes in AF patients [19,20], but results may depend on the atrial chamber of interest (with *KCNN1* expression increased in the left atrium of patients with AF and heart failure, but decreased in the right atrium [21]), and presence of systemic modulators [22]. For example, in HL-1 mouse atrial cardiomyocytes, stretch and β-adrenergic stimulation decreased *KCNN1* mRNA levels, whereas tachypacing and hypoxia suppressed *KCNN3* expression. On the other hand, expression of *KCNN2*, the most abundant isoform in human atria, was specifically enhanced by hypoxia [22]. Importantly, mRNA levels may be poor indicators of functional SK-channel remodeling since experimental studies have indicated an important role for SK-channel trafficking in the AF-associated increase in $I_{SK}$ [18]. Both increased and decreased $I_{SK}$ have been reported in atrial cardiomyocytes from Chinese AF populations [23,24], but results in individuals with European ancestry are scarse, although one study reported a reduced repolarization prolonging effect of the SK-channel inhibitors NS8593 and ICAGEN in atrial cardiomyocytes from AF patients compared to sinus rhythm controls [19].

Taken together, the development of atrial-selective AADs remains a promising avenue for improving AF management. SK-channels are an interesting target, with numerous promising studies in a wide range of different animal models, including the data in the presence of acute atrial stretch presented by Yan et al. [15]. However, mechanisms of SK-channel remodeling, as well as antiarrhythmic efficacy and safety of SK-channel inhibition will need to be investigated in human atrial samples and appropriately designed clinical trials. Safety is a particular concern in light of the upregulation of *KCNN* expression in ventricular samples of heart failure patients [20] and ventricular proarrhythmic effects of SK-channel inhibition observed in animal models [18]. Furthermore, the metabolic relevance of SK2 and SK3 expression in mitochondria has to be evaluated in human samples to assess potential safety issues in patients with e.g., ischemic heart disease [25]. Results of initial ongoing (e.g., NCT04571385) and future clinical trials are eagerly awaited to see if the current boundaries of AAD therapy for AF can be stretched and the management of AF patients can be improved.

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D.D. is member of the Scientific Advisory Board of Acession Pharma, which develops drugs aimed to target SK channels.

## Declaration of Competing Interest

The other authors report no relationships that could be construed as a conflict of interest

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