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 initiation 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 rhythm-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 occurrence 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-
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_{v}, Ca_{2+} channels) and ryanodine receptor channels [17]. Subsequent activation of SK channels, which are located in the immediate vicinity of Ca_{v} and ryanodine receptor channels [17], 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 in 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 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 aorta, 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 scarce, 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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Declaration of Competing Interest
The other authors report no relationships that could be construed as a conflict of interest

References
[1] G. Hniddricks, T. Potpara, N. Dogen, E. Arbelo, J.J. Bax, C. Blomstrom-Lundqvist, et al., ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) for the ESC, Eur. Heart J. 42 (2021) (2020) 375-428.
[2] J. Hejtmaj, J.-B. Guichard, D. Dobrev, S. Nattel, Translational challenges in atrial fibrillation, Circ. Res. 122 (5) (2018) 752-773.
[3] S. Nettel, P.T. Sager, J. Huzer, J. Hejtmaj, D. Dobrev, Why translation from basic discoveries to clinical applications is so difficult for atrial fibrillation and possible approaches to improving it, Cardiovasc. Res. 117 (2021) 1616-1631.
[4] B. Reissmann, G. Breithardt, A.J. Camm, L.C. Van Gelder, A. Metzner, P. Kirchhof, The RACE to the EAST. In pursuit of rhythm control therapy for atrial fibrillation: a dedication to Harry Crijns, Europace 23 (2021) ii34-ii39.
[5] J. Hejtmaj, S.H. Hohnloser, A.J. Camm, Antiarrhythmic drugs for atrial fibrillation: lessons from the past and opportunities for the future, Europace 23 (2021) i14-i22.
[6] J. Hejtmaj, S. Ghazebbo, D. Dobrev, Investigational antiarrhythmic agents: promising drugs in early clinical development, Expert. Opin. Investig. Drugs 26 (8) (2017) 897-907.
[7] R. Peyronnet, U. Ravens, Atrial-selective antiarrhythmic drugs in need of alliance partners, Pharmacol. Res. 145 (2019), 104262.
[8] D. Dobrev, A. Friedrich, N. Voigt, N. Jost, E. Wettwer, T. Christ, M. Knaut, U. Ravens, The G protein-gated potassium current I_{SK} is constitutively active in patients with chronic atrial fibrillation, Circulation 112 (24) (2005) 3697-3706.
[9] N. Voigt, A. Maguy, Y.-H. Yeh, X. Qi, U. Ravens, D. Dobrev, S. Nettel, Changes in I_{SK} single-channel activity with atrial tachycardia remodelling in canine atrial cardiomyocytes, Cardiovasc. Res. 77 (1) (2008) 54-63.
[10] S. Makary, N. Voigt, A. Maguy, R. Waki, K. Nishida, M. Harada, D. Dobrev, S. Nettel, Differential protein kinase C isoform regulation and increased constitutive activity of acetylcholine-regulated potassium channels in atrial remodelling, Circ. Res. 109 (9) (2011) 1031-1043.
[11] C. Roselli, M.D. Chaffia, L.C. Weng, S. Aeschbach, G. Ahlborg, C.M. Albert, et al., Multi-ethnic genome-wide association study for atrial fibrillation, Nat Genet 50 (2018) 1225-1235.
[12] X. Y. Qi, J.G. Dinnes, B.J.M. Brundel, X.-B. Zhou, P. Naud, C.-T. Wu, H. Huang, M. Harada, M. Aflaki, D. Dobrev, M. Grunnet, S. Nettel, Role of small-conductance calcium-activated potassium channels in atrial electrophysiology and fibrillation in the dog, Circulation 129 (4) (2014) 430-440.
[13] J.G. Dinnes, J.E. Kirchhoff, T. Speerschneider, L. Ahlbgaard, N. Edvardsson, U. Sorensen, et al., The KCa2.2 channel inhibitor AP30663 selectively increases atrial refractoriness, converts vernakalant-resistant atrial fibrillation and prevents its reinduction in conscious pigs, Front. Pharmacol. 11 (2020) 159.
[14] M.F. Fenner, G. Gatta, S. Sattler, M. Kuiper, E.M. Hesselkilde, D.M.T. Adler, et al., Inhibition of small-conductance calcium-activated potassium current (I_{SK}) leads to differential atrial electrophysiological effects in a horse model of persistent atrial fibrillation, Front. Physiol. 12 (2021), 614483.
[15] Y. Yan, M.A. Skarsfeld, J.G. Dinnes, B.H. Bentzen, Small conductance calcium activated K’ channel inhibitor decreases stretch induced vulnerability to atrial fibrillation, Int. J. Cardiol. Heart Vasc. 37 (2021), 100898.
[16] D. Dobrev, M. Aguilar, J. Hejtmaj, J.B. Guichard, S. Nettel, Postoperative atrial fibrillation: mechanisms, manifestations and management, Nat. Rev. Cardio. 16 (2019) 417-436.
[17] Y. Zhang, Y. Qi, J.J. Li, L.W. He, X.H. Gao, Y. Zhang, et al., Stretch-induced sarcoplasmic reticulum calcium leak is causatively associated with atrial fibrillation in pressure-overloaded hearts, Cardiovasc. Res. 117 (2021) 1091-1102.
[18] X.-D. Zhang, P.N. Thai, D.K. Lieu, N. Chiamvimonvat, Cardiac small-conductance calcium-activated potassium channels in health and disease, Pfugers Arch. 473 (3) (2021) 477–489.

[19] L. Skhsbye, C. Poulet, J.G. Diness, B.H. Bentzen, L. Yuan, U. Kappert, et al., Small-conductance calcium-activated potassium (SK) channels contribute to action potential repolarization in human atria, Cardiovasc. Res. 103 (2014) 156–167.

[20] E. Darkow, T.T. Nguyen, M. Stolina, F.A. Kari, C. Schmidt, F. Wiedmann, et al., Small conductance Ca\(^{2+}\)-activated K\(^+\) (SK) channel mRNA expression in human atrial and ventricular tissue: comparison between donor, atrial fibrillation and heart failure tissue, Front. Physiol. 12 (2021), 650064.

[21] A.-K. Rahm, T. Wieder, D. Gramlich, M.E. Müller, M.N. Wunsch, F.A. El Tahry, et al., Differential regulation of K\(_{Ca}\) 2.1 (KCNQ1) \(K^+\) channel expression by histone deacetylases in atrial fibrillation with concomitant heart failure, Physiol. Rep. 9 (11) (2021) e14835, https://doi.org/10.14814/phy2.14835.

[22] A.K. Rahm, D. Gramlich, T. Wieder, M.E. Müller, A. Schoeffel, F.A. El Tahry, et al., Trigger-specific remodeling of K\(_{Ca}\) 2 potassium channels in models of atrial fibrillation, Pharmacogenomics. Pers Med. 14 (2021) 579–590.

[23] H. Wang, T. Li, L. Zhang, Y. Yang, X.R. Zeng, Effects of intracellular calcium alteration on SK currents in atrial cardiomyocytes from patients with atrial fibrillation, Zhongguo Ying Yong Sheng Li Xue Za Zhi 30 (2014) 296–300, 5.

[24] T. Yu, C. Deng, R. Wu, H. Guo, S. Zheng, X. Yu, Z. Shan, S. Kuang, Q. Lin, Decreased expression of small-conductance Ca\(^{2+}\)-activated K\(^+\) channels SK1 and SK2 in human chronic atrial fibrillation, Life Sci. 90 (5-6) (2012) 219–227.

[25] D.F. Stowe, A.K. Gadicherla, Y. Zhou, M. Aldakkak, Q. Cheng, W.-M. Kwok, M. T. Jiang, J.S. Heuser, MeiYing Yang, A.K.S. Camara, Protection against cardiac injury by small Ca\(^{2+}\)-sensitive K\(^+\) channels identified in guinea pig cardiac inner mitochondrial membrane, Biochim. Biophys. Acta 1828 (2) (2013) 427–442.

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