

Atrial Remodeling in Permanent Atrial Fibrillation: Mechanisms and Pharmacological Implications

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Abstract

Atrial fibrillation (AF), the most prevalent rhythm disorder in clinical practice, is currently significantly contributing to morbidity and mortality of the ageing population. In the past decades, a tremendous amount of research resulted in valuable insights into AF pathophysiology, with a primary focus on atrial remodeling. Defined as a persistent change in atrial function and structure, remodeling has the intrinsic properties to enhance the probability of focal (ectopic) and/or re-entrant pursuits, thus supporting AF persistence. The hallmark of structural remodeling is represented by atrial fibrosis, a multifactorial process involving an interaction between neurohormonal and cellular mediators. This paper provides a brief summary of the recent knowledge with respect to electrical and structural remodeling and novel insights into the pathogenesis of atrial fibrosis. Since current drug options for AF treatment are far from being optimal we also discuss the therapeutic principles and current alternatives for counteracting atrial fibrosis, and thus preventing arrhythmia recurrence.

Keywords: Atrial fibrillation; Atrial electrical remodelling; Atrial fibrosis; Antifibrillatory drugs

Introduction

Atrial fibrillation (AF) has a prevalence of 1.5-2% in general population and represents a major cause of morbidity and a socio-economic burden that is expected to grow worth in coming decades mainly in the developed countries. The arrhythmia is associated with high risk of stroke due to thromboembolism, of congestive heart failure and, also accounts for the highest rate of hospitalization among all types of arrhythmia, especially with advancing age [1].

AF is initiated when an atrial ectopic beat encounters during propagation an anatomical and/or functional obstacle and triggers the re-entry of the excitation wavefront. The classic mechanisms underlying the ectopic activity are represented by: (i) increased automaticity and (ii) triggered activity expressed as early (EAD) or delayed afterdepolarizations (DAD). It is nowadays proven that atrial cardiomyocytes in the pulmonary sleeve veins may present increased automaticity/pacemaker activity; they represent ectopic foci responsible for the initiation of single or multiple reentry circuits [2,3]. There are 2 main theories that explain the persistence of AF, namely: (i) the 'leading circle' theory implying the existence of single/multiple reentry circuits [2] and, more recently, (ii) the cardiac electric rotors theory [4]. Figure 1 depicts the pathophysiological changes that are involved in the initiation of AF.

Persistent or recurrent AF is constantly associated with the phenomenon of *atrial remodeling* characterized by electrical and structural changes of cardiomyocytes that are responsible for arrhythmia self-perpetuation and resistance to sinus rhythm conversion. The changes that contribute to atrial remodeling in AF include: (i) alterations of ion channels, gap-junctions, and extracellular matrix and, (ii) neurohumoral dysregulation, in particular of the renin-angiotensin-aldosterone system (RAAS) and the autonomic nervous system.

The paper briefly presents novel insights into the pathophysiology of atrial remodeling with particular emphasis on atrial fibrosis. The

currently available therapeutic options and strategies for developing novel pharmacologic agents capable to prevent/treat atrial remodelling are also discussed.

Mechanisms of Atrial Remodeling

Remodeling in AF lies at the very core of the progressive nature of the arrhythmia. During the past decades the phenomenon has been thoroughly characterized at cellular level with respect of three major components: electrical, contractile and structural remodeling that synergistically contributes to the generation of the vulnerable substrate [5].

Electrical remodeling is due to alteration of several ion channels with the subsequent shortening of the action potential (AP) and membrane hyperpolarization [6]. The changes are due to the downregulation of the plateau currents and upregulation of several repolarizing currents (Figure 2). In this respect, three major changes have been described in the past decade to underlie the AP triangularization: (i) downregulation of inward current $I_{Ca,L}$, (ii) upregulation of the inward rectifier current IK1, and (iii) activation of $I_{K,Ach}$, respectively [7-10].

Electrical remodeling (shortening of the atrial refractoriness) is reversible after the sinus rhythm restoration; however, with AF persistence, calcium overload is the main intracellular signal responsible

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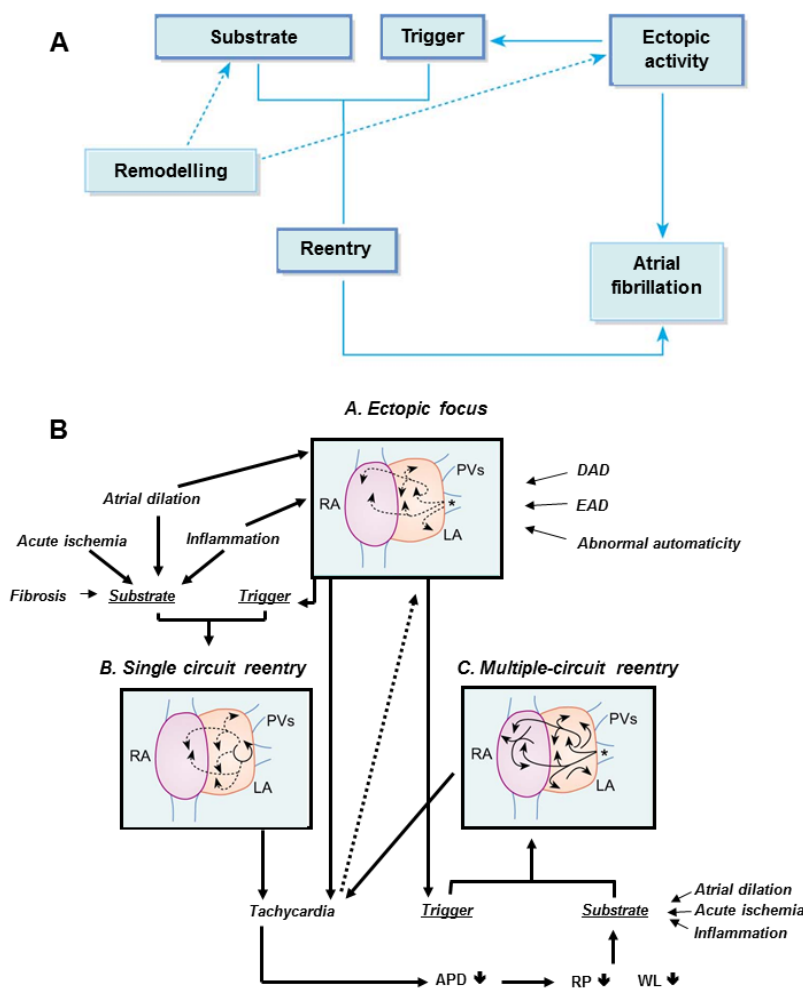


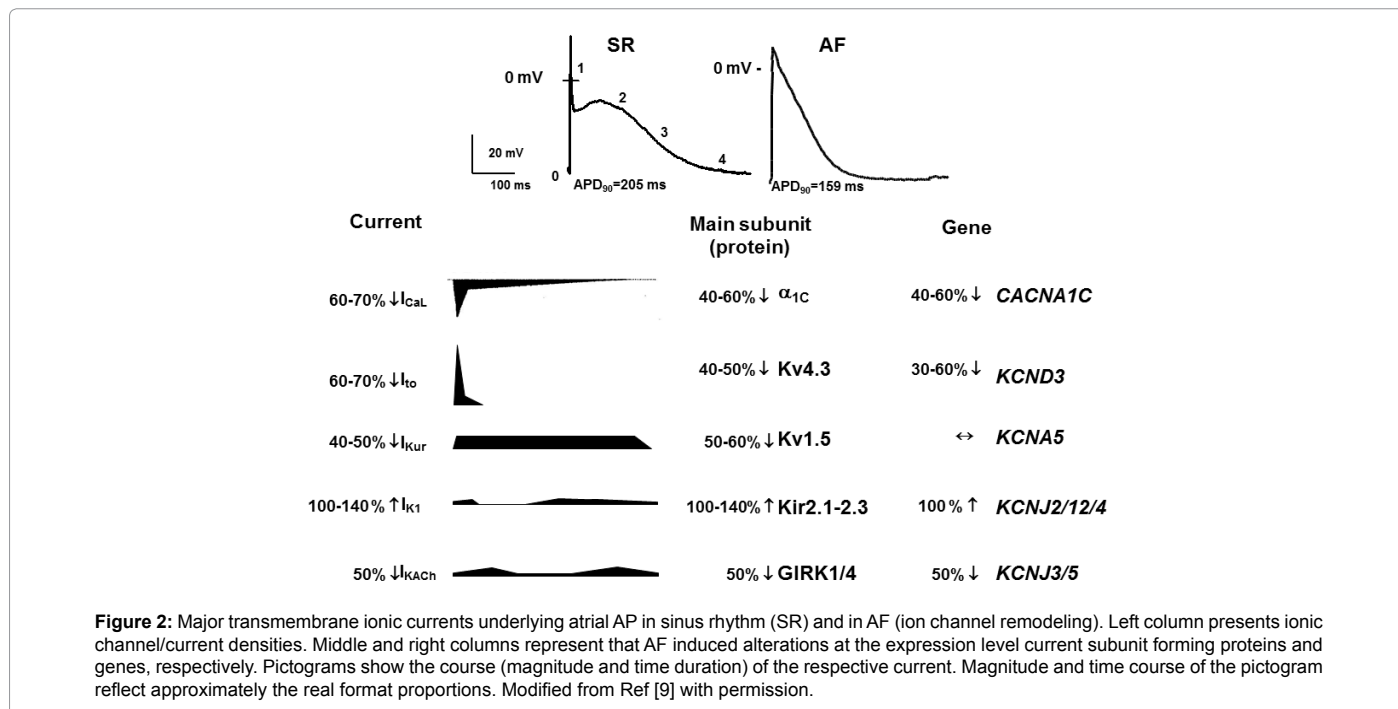
Figure 1: Panel (A) Principal factors involved in inducing and maintaining AF. **Panel (B)** AF is started by an extrasystole originated from a pacemaker region (commonly left upper pulmonary vein), initiated by atrial tachycardia remodeling (ATR induced APD shortening). The electrical perpetuator may be a single/mother wave and/or multiple wave/circuit re-entry. The main re-entry initiating factors are: atrial ischaemia and inflammation. The principal factors of structural/morphological remodeling: atrial (micro)fibrosis and left atrial dilation. List of abbreviations: AF=atrial fibrillation; RA=right atrium; LA=left atrium; EAD=early afterdepolarization; DAD=delayed afterdepolarization; PVs=pulmonary veins; APD=action potential duration; RP=refractory period; WL=wavelength). Modified from Ref [8] with permission.

for further promoting reentry [10]. Indeed, high Ca^{2+} concentration will bind calmodulin with the subsequent activation of calcineurin and trigger the signalling events responsible for perpetuation of the AP shortening and hyperpolarization, namely the increase in the previously mentioned potassium currents [10]. However, it is not clear whether electrical remodeling *per se* is relevant in clinical settings, since in a recent study no significant differences were found in the change in electrophysiological properties over 2 years between patients with and those without atrial tachyarrhythmias [11].

Calcium overload of atrial cardiomyocytes also lies at the origin of the Ca^{2+} sparks via the increased activation of the ryanodine receptors at the sarcoplasmic reticulum, an event that most probably contributes to the contractile remodelling [12]. Interestingly, in heart failure, one of the most frequent pathologic condition that predispose to AF, changes in intracellular Ca^{2+} handling preceding the onset of AF are different from those developing after the onset of AF [13]. Moreover, a recent report suggests a different dynamic for the alterations in intracellular

calcium during AF progression and after its termination, respectively. Accordingly, in the case of the former three stages occur: (i) Ca^{2+} overload, (ii) remodeling, and (iii) steady state, whereas during the latter, 'recovery' of calcium concentration also occurs in three steps: (i) calcium unloading, (ii) reverse remodeling and (iii) full recovery. In this respect, it is important to mention that the previously mentioned stage of remodeling is apparently associated with ' Ca^{2+} silencing' [14]. These observations are relevant for both the development of novel mechanism-based therapeutics agents acting as calcium 'stabilizers' and the timing of their administration [15].

Another direct consequence of altered calcium handling, referred as *contractile remodeling*, consists in loss of atrial contractility with subsequent increase in compliance and, finally, atrial dilation. One of the important consequences of atrial dilation has been classically related to the risk of atrial thrombosis even after sinus rhythm restoration [7]. However, this paradigm has been recently challenged by the group of Stanley Nattel who was not able to demonstrate the prothrombotic



effects of AF-associated remodeling in an elegant study performed in canines [16].

Chronic atrial stretch and geometric deformation are the major activators of the signalling pathways leading to cellular hypertrophy and diffuse and patchy interstitial fibrosis [17], collectively termed *structural remodeling*, the main mechanism responsible for the progression of AF. Structural remodeling refers to both the cellular and non-cellular components of the atrial tissue and results in local conduction heterogeneities that account for AF self-perpetuation. Predictably, structural remodeling will be less reversible as compared to the electrical one. However, it should be mentioned that structural remodeling is also the hallmark of heart failure and of other underlying chronic cardiac pathologies; therefore, the occurrence of AF is favoured in these settings.

In the past few years, with the rapid evolution of research in the field of microRNA (miRNA), a class of small, non-coding RNA molecules that silence gene expression at the post-transcriptional level, a role of miRNA in both AF associated electrical and structural remodeling has been described. Thus, in the case of the former, downregulation of miR-26 was associated with increased density of I_{K1}, whereas upregulation of miR-328 elicited I_{CaL} reduction in both animal and human atrial samples [18]. As concerning the latter issue, Shan et al. [19] reported, in a dog model of AF induced by nicotine administration and rapid pacing, a profibrotic response characterized by significant upregulation of expression of TGF-beta1 and TGF-betaR2 proteins together with a 60-70% reduction of the anti-fibrotic miR-133 and miR-590 levels. In the same line, knockdown of atrial miR-21 has been reported to suppress atrial fibrosis and duration of AF 8 weeks after experimental myocardial infarction in rats [20]. Recently, miR-499 was found to be significantly upregulated in atrial myocardium of 4 subjects with permanent AF, leading to the downregulation of the small-conductance calcium-activated potassium channel 3 (SK3) proteins [21]. Whether this finding might contribute to the electrical remodeling in AF remain to be established. In the same line, it has been recently reported that

miR29 was significantly decreased in patients with chronic heart failure and atrial fibrillation; moreover, miR29b knockdown in canine atrial fibroblasts elicited an increase in collagen expression thus contributing to atrial fibrotic remodeling [22]. Therefore the authors concluded that miR29 may be used in the future as potential biomarker and/or therapeutic target.

The past decade witnessed a huge resurgence of interest in the role of mitochondria in cardiovascular health and disease. In this line, a recent prospective study reported an association between pre-operative atrial mitochondria dysfunction and the occurrence of AF in patients with metabolic syndrome undergoing CABG surgery [23]. In permeabilized cardiac fibres, these authors demonstrated a decreased respiration of permeabilized fibres in the presence of pyruvate-malate and palmitoyl-L-carnitine (but not of succinate) and an increased sensitivity to calcium overload. We have recently performed a similar study aimed at assessing the respiratory function in permeabilized fibres of human right atrial appendages harvested from patients with coronary heart disease vs. patients with valvular disease and preserved ejection fraction that underwent non-emergency cardiac surgery. Similarly to the previously mentioned data, we also found in coronary patients (but not in valvular ones) a significant decline for the oxidative phosphorylation capacity and respiratory control ratio for mitochondria energized with complex I (but not with complex II) substrates [24]. These observations are in the line with previous reports suggesting that treatments aimed at supporting cardiac mitochondria function might be able to mitigate electrical dysfunction in the heart [25].

Causes and Consequences of Atrial Fibrosis

In the past decade the contributing role of the structural remodeling (for example fibrosis) in initiating and maintaining and of AF has been extensively investigated, with a major emphasis on the occurrence of *atrial fibrosis*.

Tissue fibrosis represents the common endpoint in diseased hearts from hypertensive, valvular, coronary, diabetic and failing patients.

	Drugs or investigational compounds	Effects	Preclinical studies	Clinical studies
Improvement of current antiarrhythmic agents	Azimilide (FDA approval)	Primarily I_{Kr} and I_{Ks} blocker but additionally blocks I_{CaL} and I_{Na} (multi-channel blocker)	Several <i>in vitro</i> and <i>in vivo</i> animal models [38-41]	ALIVE, A-STAR, A-COMET I and II Studies [42,43]
	HMR-1556	Highly selective I_{Ks} blocker	Several <i>in vitro</i> and <i>in vivo</i> animal models [44,45]	Not
	AZD7009	Primarily I_{Kr} and I_{Na} blocker, but additionally blocks I_{to} , I_{Kur} and I_{Ks} (multi-channel blocker)	Several <i>in vitro</i> and <i>in vivo</i> animal models [46-48]	Small centre clinical trial [49,50]
	Dronedaron (FDA approval)	Amiodarone like multichannel blocker (I_{Na} , I_{Ca} , I_{Kr} blocker)	Several <i>in vitro</i> and <i>in vivo</i> animal models [51-53]	ADONIS, ATHENA, EURIDIS etc. [54-58]
	Tedisamil	Multichannel blocker (I_{Na} , I_{to} , I_{Kr} , I_{Ks} , I_{KATP} blocker)	Several <i>in vitro</i> and <i>in vivo</i> animal models [60-62]	Small centre clinical trial [63,64]
Atrial selective therapeutic agents	AVE0118	Primarily I_{Kur} , I_{to} and $I_{K,ACh}$ blocker	Several <i>in vitro</i> and <i>in vivo</i> animal models [67-72]	not
	XEN-D0101	Highly selective I_{Kur} blocker	Several <i>in vitro</i> and <i>in vivo</i> animal models [73,74]	Small centre clinical trial [75]
	DP01	Highly selective I_{Kur} blocker	Several <i>in vitro</i> and <i>in vivo</i> animal models [76,77]	Not
	Vernakalant	Primarily I_{Kr} and I_{Na} blocker, but additionally blocks I_{to} , I_{Na} , I_{Kr} and I_{Ks} (multichannel blocker)	Several <i>in vitro</i> and <i>in vivo</i> animal models [78-80]	AVRO [81,82]
	Ranolazine (FDA approval)	Primarily I_{Naf} and I_{Nal} and I_{Kr} blocker, but additionally blocks I_{CaL} and I_{Ks} (multichannel blocker)	Several <i>in vitro</i> and <i>in vivo</i> animal models [85-88]	MERLIN-TIMI [89]
	NIP-142, NIP-152	Highly selective $I_{K,ACh}$ blockers	Several <i>in vitro</i> and <i>in vivo</i> animal models [93,94]	not
	tertiapin Q	Highly selective $I_{K,ACh}$ blocker	Several <i>in vitro</i> and <i>in vivo</i> animal models [9,90,96,97]	not
NCX modulators	KB-R7943	Initially developed as selective NCX blocker, but additionally blocks I_{to} , I_{K1} , I_{Na} and I_{CaL}	Several <i>in vitro</i> and <i>in vivo</i> animal models	not
	SEA-0400	Selective NCX blocker, but additionally blocks I_{CaL}	Several <i>in vitro</i> and <i>in vivo</i> animal models	not
	ORM-10103	Highly selective and potent NCX blocker	<i>in vitro</i> animal model [104]	not
Gap-junction therapy	Rotigaptide	Selective gap junction closer peptide	Several <i>in vitro</i> and <i>in vivo</i> animal models [108,109]	not
	GAP-134	Selective gap junction closer peptide	Several <i>in vitro</i> and <i>in vivo</i> animal models [110,111]	not

Table 1: New drugs and investigational compounds developed for treating AF.

In 2/3 of cases AF is secondary to a pre-existent organic heart disease that contributes to the development of the vulnerable substrate for AF, whereas lone AF occurs in 1/3 of patients. Nevertheless, there is both experimental and clinical evidence that AF itself is able to promote fibrosis [26]. However, the timing of AF appearance is equally important since, in a recent study, prognosis in patients who developed AF before or consecutively with heart failure was less severe as compared with those who firstly developed heart failure [27].

Atrial fibrosis in the setting of AF is the result of complex interplay among profibrotic signalling pathways, inflammation and oxidative stress, the first two contributors being extensively studied. Indeed, profibrotic signalling pathways have been recently described and include the: (i) RAA system with angiotensin II acting on AT-1 receptors and aldosterone acting on the mineralocorticoid receptors, promoting both atrial and ventricular fibrosis, and the (ii) TGF-beta1 that stimulates collagen production via the SMAD pathway. Also, AF has been associated with high levels of inflammatory serum biomarkers and a positive effect of anti-inflammatory agents [28]. However, in an important population based case-control study, the use of non-aspirin NSAIDs has been reported to increase the relative risk of AF or flutter [29]. Atrial fibrosis results in electrical dissociation between adjacent muscle bundles with discontinuous transverse conduction and also,

between the epicardial layer and endocardial bundles leading to both focal and macro-reentry [30].

We will briefly mention some novel insights related to the role of oxidative stress in AF pathophysiology, since increased reactive oxygen species (ROS) production occurs with ageing as it does the AF prevalence. The major sources of ROS in the atria are: NADPH oxidases (NOX 1, 2 and 4), the electron transport chain (ETC), uncoupled NO synthase (NOS), and in some extent myeloperoxidase (MPO) [31,32]. Interestingly, the participation of ROS sources varies with the progression of the disease, an observation with important therapeutic implications. Thus, in both animals and humans, superoxide anion was reported to be NADPH oxidase (NOX2) dependent at 2 weeks of AF and NOS- and mitochondria-dependent after 6 months of AF [33]. These authors speculated that the early but transient increase of atrial NADPH oxidases may explain why statins (that inhibit NOX2) prevent postoperative AF but are less effective in the secondary prevention of the arrhythmia [33].

A second major source of superoxide anion which generates the highly reactive peroxynitrite is represented by NO synthases [34]. In a canine model of AF induced by seven days of tachypacing, induction of NOS isoform 2 (NOS2) has been reported [31].

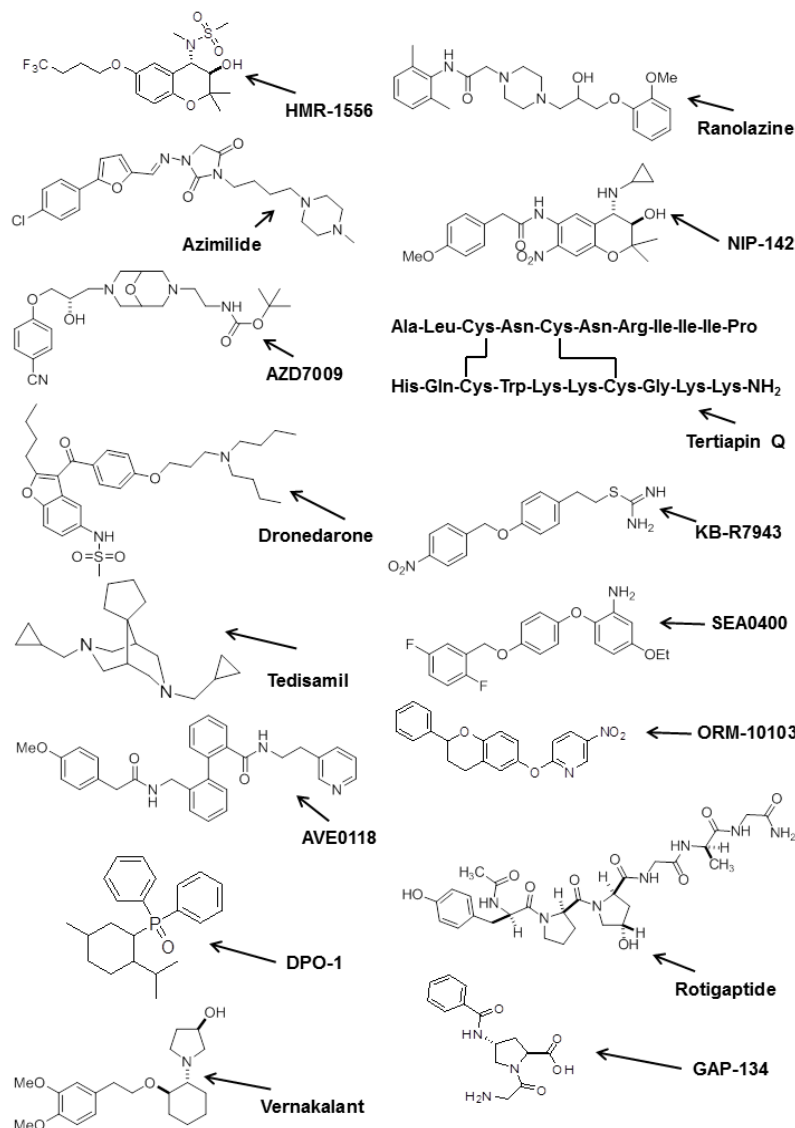


Figure 3: The chemical structures of the presented specific, multiple, atrial selective ion channel blocker drugs and of the newly developed gap-junction modulator antiarrhythmic peptides.

A third important source of ROS is the ETC at the inner mitochondrial membrane. In a mouse model of cardiac renin-angiotensin system activation (ACE8/8) presenting with a high rate of spontaneous ventricular tachycardia and reduction in connexin-43 level, administration of a mitochondrial antioxidant (MitoTempo) significantly decreased ventricular tachycardia inducibility, diminished elevated mitochondrial ROS, and increased connexin-43 and conduction at the gap junctions [35].

As for MPO, when released from polymorphs, it generates hypochlorous acid that further contributes to the tissue fibrosis via the activation of matrix metalloproteinases [31].

ROS elevation aggravates AF evolution by affecting ionic currents, gap junctions, inflammation and fibrosis (see [32] for a recent review); therefore, targeting oxidative stress is nowadays regarded as a potential “upstream therapy” [34], especially when considering the fact that many of the current pharmacologic therapies lack atrial specificity

or/and are proarrhythmic. Indeed, as recently suggested, primary prevention of AF and postoperative AF may benefit from NADPH oxidases inhibitors, whereas in persistent AF mitochondria-targeted antioxidants may prove to be most effective [32].

Modalities for Prevention and Therapy of Atrial Remodeling

Restoration of sinus rhythm versus rate control

The rhythm control is the optimal therapeutic option and intervention to suppress atrial fibrillation, i.e. to re-establish the normal sinus rhythm (SR). The rate control can be reached by several therapeutic approaches including to prolong atrioventricular nodal refractoriness and/or to slow of AV node conduction. These can be assessed by application of various types and classes of antiarrhythmic drugs from which we highlight especially the β -blockers, the Ca^{2+} -channel blockers or the golden standard, the amiodarone [36]. It was demonstrated that ectopic

triggers originating from pulmonary veins are sources of extrasystoles and, consequently, of AF. Eliminating the excitability of these ectopic triggers can terminate AF and, hence, provide rhythm control. This goal can be reached by several classical antiarrhythmic drugs which include especially the Na⁺ channel blockers or by multiple ion channel blockers (for example amiodarone). Based on the commonly accepted wavelet concept [2], short effective refractory periods and slowed conduction will enhance the probability of inducing re-entries. According to this theory, by counteracting either of them the conduction in the respective tissue will be enhanced (consequently that re-entrant wavefront will find the tissue still in refractory status).

Novel pharmacological agents and investigational compounds surmounting AF

The palette of currently existing antiarrhythmic agents for the treatment of AF are in principle far from being ideal, since, many of them have serious problems regarding not only their efficacy but also safety concerns. In general, all antiarrhythmic drugs combating ventricular arrhythmias may successfully suppress AF by lengthening atrial ERP and by slowing atrial tissue conduction, but it is expected that their atrial selectivity to minimize ventricular proarrhythmic effects. This was referred as the 'atrial selective drug concept', which means these drugs are expected to target currents existing in the atria but not or only minimal the ones present in the ventricles. In addition these drugs must lack cardiac or extra cardiac organ toxicity and should be tolerable in patients having heart complications as for example coronary artery disease.

There are several possibilities to design drugs for combating AF. The novel compounds can block: (i) specific or multiple ion channels, (ii) preferably in an atrial-selective manner, (iii) they can be directed at non-ion channel targets including upstream inflammatory or infiltrative processes or (iv) they may influence gap-junctions (the latter being considered the most modern pharmacological therapeutic approach of AF). We will briefly address further all these issues. At the end of this section Table 1 summarizes again all important data of the presented drugs.

Drugs with specific and multiple ion channel blocking effects

The principal target for these drugs is to lengthen repolarization (i.e., class III compounds). During last two decades there were reported several novel compounds or investigational drugs; however, majority of them have been abandoned, because of the risk of ventricular proarrhythmic potency, especially of inducing *Torsades de Pointes* type tachyarrhythmias.

Selective I_{Ks} blockers

Azimilide (Procter & Gamble, specific I_{Kr} and I_{Ks} blocker, Figure 3). The drug was designed based on an elegant developing idea from the mid-nineties (so called *Sanguinetti's* hypothesis [37]). Accordingly, it was presumed that I_{Ks} blockers would be free of reverse rate-dependency. However, the data showed that azimilide blocked not only I_{Ks} but I_{Kr} as well. Based on these results it was expected to be specifically effective during tachycardia which commonly associates with AF. Some reports showed that azimilide, like amiodarone, possesses calcium and use-dependent sodium channel blocking effects [38,39]. However, we must emphasize that after some encouraging studies in AF [40,41], the initial optimism disappeared and the modest results of several studies (e.g., the ALIVE study) ended up with the conclusion that azimilide will never become a powerful tool for treating AF [42,43].

HMR-1556 (IKs blocker, Figure 3). HMR-1556 is a pure I_{Ks} selective blocker and was designed based on the *Sanguinetti's* hypothesis [37], which turned the attention of the pharmaceutical industry to I_{Ks} blockers. HMR1556 is the first powerful and highly selective I_{Ks} blocker that was tested as novel antiarrhythmic drug, and the results demonstrated that indeed effectively blocks I_{Ks}, and only at higher concentration also inhibits I_{to}, the sustained outward current I_{sus}, and I_{CaL} currents [44]. In a canine model of vagal AF, HMR1556 prolonged the atrial effective refractory period (AERP) and exerted a modest effect on the duration of induced AF only in the presence of intact β-adrenergic stimulation. However, we must emphasize that in the last years several reports made questionable the efficacy of I_{Ks} blockers, especially in certain conditions, such as the long QT syndrome 1 and in other circumstances where repolarization reserve is compromised [45].

AZD7009 (Astra Zeneca, I_{Kr} and I_{Na} blocker, Figure 3). The pharmacological profile of AZD7009 includes a combined block of I_{Kr} and rate-dependent block of I_{Na} at micromolar concentrations. In addition later studies revealed that, in higher concentrations, the compound blocked other repolarizing currents such as I_{to}, I_{Kur} and I_{Ks} [46,47]. In dog atria, AZD7009 concentration-dependently reduced V_{max} and increased APD. In addition, the suppression of V_{max}, but not APD prolongation, showed used frequency-dependence also [48]. New clinical trials demonstrated AZD7009 to be successful in SR conversion in persistent atrial fibrillation [49,50]. It is presumable that the latter effect is the result of the favourable ion channel blocker profile of the compound.

Amiodarone-like multichannel blockers

The undoubted success of amiodarone promoted the concept that a simultaneous blockade of several specific inward and outward currents may result in a more favourable electrophysiological profile than that obtained through the use of single channel blockers [51].

Dronedarone (Sanofi Aventis, Figure 3) is so far the most promising recently drug developed based on this idea. The originating point for designing the dronedarone molecule was amiodarone but without containing an iodine. It is generally accepted that the iodine molecule of amiodarone is responsible for the severe extra-cardiac (pulmonary, thyroid, hepatic and ocular) toxicity of amiodarone [51]. The *in vitro* electrophysiological results showed that dronedarone possesses quite similar acute and chronic electrophysiological effects as known to amiodarone [52,53]. In dog ventricular preparations, dronedarone indeed was multi-channel blocker. Accordingly the drug blocked I_{CaL} and I_{Kr}, and reduced the maximum upstroke velocity in a frequency-dependent manner [51]. Based on these promising preclinical investigations dronedarone has been recommended for combating atrial arrhythmias, including in intensive clinical treatment.

Two large trials, ADONIS and EURIDIS, also showed the superiority of dronedarone over placebo. Accordingly dronedarone did not significantly lengthen the QT interval and had very low ventricular proarrhythmic effects (lack of causing *torsades de pointes* [54,55] arrhythmias). Later ATHENA (phase III randomised trial) investigators reported also encouraging results, from which we should emphasize the prolonged time to first cardiovascular hospitalization or death from any cause (the primary endpoint) by 24% compared to placebo [56]. Despite of these positive reports, it should be emphasized that dronedarone is still far from being a new golden antiarrhythmic drug. Several clinical reports indicated that the antiarrhythmic potential of the starting molecule amiodarone remains net superior to that of dronedarone [57,58]. After the results of the ATHENA trial, the

Food and Drug Administration (FDA) in U.S. approved dronedarone as secondary endpoint for the prevention of hospitalizations due to recurrent AF. Based on this rather unusual approval label dronedarone is not allowed to be marketed in US as primary anti-AF agent [58]. Recently, the administration of dronedarone was accompanied by severe extra-cardiac side effects, from which we must stressed out some recent cases of near fatal liver toxicity making immediate liver transplantation necessary [59].

Tedisamil (Figure 3) was initially developed by Solvay Pharma-Kali Chemie AG as an anti-ischemic and bradycardic drug. Originally was supposed to be a selective I_{to} blocker, but later studies revealed that tedisamil possesses multichannel blocker effects. Indeed, the drug blocks several cardiac K⁺ currents (I_{to}, I_{Kur}, I_{Kr}, I_{Ks} and I_{KATP}) and produces a negative chronotropic effect by increasing gap junction conductance and conduction velocity. This later may be extremely useful by preventing the fast ventricular rates, which characterize the atria in the case of AF recurrence [60-62]. Tedisamil probable due to its “amiodarone-like” multichannel blocker properties, lacks in atrial tissue from reverse use-dependency effects. In spite of these apparent positive electrophysiological profile, preliminary clinical studies showed modest efficacy results and relatively high proarrhythmic risk (several documented cases of ventricular tachycardia), thereby tedisamil seems to unlikely to be beneficial in combating AF [63,64]. The drug has not received approval from FDA.

Atrial selective ion channel blocker drugs

The most promising and effective strategy in AF is the development of drugs known as “atrial selective drugs”, thus avoiding the proarrhythmic ventricular side effects. This concept exploits the differences between electrophysiological and expression patterns of ion channels between atrial and ventricular myocytes.

Accordingly, the development of atrial specific ion channel blockers can be reached by designing compounds that affect (block or activate) atrial selective transmembrane currents. Atrial specific targets suitable for developing novel treatment include: (i) the ultra-rapid delayed rectified potassium current (I_{Kur}), (ii) the acetylcholine-sensitive inward rectifier potassium current (I_{K,ACh}), (iii) the constitutively active I_{K,ACh} (i.e., which are active without initial activation of acetylcholine or muscarinic receptors), and, (iv) gap-junction constituent connexins (connexin 40, Cx40). In the light of the current knowledge, the channels responsible for I_{Kur} and I_{K,ACh} are exclusively or near exclusively present in atria and largely absent in ventricles, thereby they are perfect targets for atrial selective ion channel blocker (or atrial repolarization delaying agent, ARDA) drugs. In addition, there are other ion channels present both in atria and ventricles, but due to their specific kinetic properties, the selective modulation of them may produce larger effect in atria than in ventricles, consequently they also correspond to the atrial selective antiarrhythmic drug criteria. In particular, sodium channels responsible for fast I_{Na} current correspond to this concept.

I_{Kur} blockers

Firstly described by Wang et al. [65], the ultra-rapid component of the delayed rectifier current (I_{Kur}) is considered the typical atrial selective transmembrane current. Subsequently, the pharmaceutical industry has invested large efforts in developing selective I_{Kur} blockers as novel pharmacological agents for suppressing AF. Indeed, several new purportedly selectively I_{Kur} blocking compounds were developed and investigated in the last decade, from which the most investigated were AVE0118, ISQ-1, DPO-1, XEN-D101, vernakalant; AZD7009;

NIP-141, NIP-142, acacetin, etc). Of note, some reports, such as the one by Wettwer et al. [66] questioned the effectiveness of I_{Kur} blockers.

AVE0118 (Figure 3) was developed by Sanofi-Aventis. The biphenyl derivative AVE0118 blocks I_{Kur} at micromolar concentrations as reported in native atrial myocytes and in Kv1.5 cloned transgenic systems as well. In addition at similar concentration range the drug presented blocking effects on I_{to} and I_{K,ACh} currents as well [67,68]. AVE0118 shortened APD and ERP in atrial tissue originating from patients in SR, whereas it prolonged APD/ERP in AF patients [69]. Experimental studies in large animals (dogs and goats) have demonstrated the potency to prolong the atrial ERP and convert AF to SR. This property was associated with only little effect on ventricular refractoriness and QT interval and had no proarrhythmic side effect. The atrial refractoriness effect presented a regional heterogeneity since appeared to be more pronounced in the left atrium, than in the right one. In normal goat atria, AVE0118 lengthened rate-dependently atrial ERP. In experimentally instrumented permanent AF model, after 48 h of continuous AF, AVE0118 successfully prolonged the atrial ERP to the pre-remodelled level, and was able to prevent induction of AF in the majority of the experiments [70-72]. There are no clinical studies performed with AVE0118 and seems that its development has probably been stopped.

XEN-D0101 (chemical structure not disclosed) was developed by a small R&D company (Xention Ltd, UK). XEN-D0101 seems to be the only really highly selective Kv1.5 channel blocker that has been developed so far. Several reports showed that XEN-D0101 effectively and selectively blocked I_{Kur} channels, prolonged the atrial ERP and decreased the duration of AF in humans and dogs [73,74]. Clinical studies with this compound to maintain sinus rhythm after cardioversion in patients with persistent AF are under way and preliminary reports support its efficacy in combating atrial arrhythmias [75].

DPO-1 (Diphenylphosphine oxide, Figure 3). DPO-1 In isolated human atrial myocytes, DPO-1 rate-dependently blocks I_{Kur} at nanomolar concentrations. The drug blocks other currents as I_{to} only at micromolar concentrations. In human atrial tissue, DPO-1 induces plateau elevation and shortening (in SR) and prolongation (in AF) of APD. These effects were clearly atrial selective, since the compound had neutral effect in ventricular tissue preparations. The compound has been studied in non-human primates and suppressed atrial flutter by increasing atrial ERP by 13-15% [76,77].

Vernakalant (RSD1235, Cardiome and Astellas, Figure 3) is the atrial selective drug in the most advanced phase of investigation; it has been recently approved by the FDA for intravenous conversion of AF [3,78]. Vernakalant effectively blocked I_{Kur} in a positive frequency-dependent manner; however, in higher concentrations other currents including I_{to}, and I_{Na} were also blocked, so it may be referred as a multichannel blocker than a selective I_{Kur} (ARDA) blocker. The drug slowed conduction velocity within the atrium and prolonged the ERP recovery. Due to Na-channel properties, vernakalant possesses fast offset kinetics, thereby it is unlikely to cause conduction disturbances and proarrhythmia at low heart rates [79,80]. Recently, the AVRO study (phase III clinical study) demonstrated that vernakalant when compared to amiodarone, possesses superior efficacy for acute conversion of recent-onset AF [81,82].

Sodium channel blockers

According to the “modulated receptor hypothesis” it is known that fast sodium channel blocker (for example Class IA antiarrhythmics)

drugs displays preferential binding to open (activated) or closed (inactivated; resting) states of the Na^+ -channel [83]. Since fast sodium channel is highly expressed in ventricular tissue, it is not obviously to explain and understand the atrial selectivity properties of Na^+ channel blockers. Based on the hypotheses formulated by Antzelevitch and co-workers we may assume that the atrial selectivity of I_{Na} blockers is probable due to two important differences of the atrial tissue in comparison with the ventricles: (i) atrial tissue has a slightly more positive (depolarized) resting potential; (ii) a more negative potential for half-maximum inactivation of I_{Na} . Due to more depolarized membrane potential during diastole, unlike in ventricles, fewer Na^+ channel will recover faster from inactivation in the atria; consequently I_{Na} blockers known to bind more preferentially to the inactivated channel state will exhibit larger Na^+ channel blockade in the atria as compared to the ventricles [84].

Ranolazine (Figure 3) was initially developed as an antianginal drug, but was soon recognized also to successfully suppressing ventricular EADs and to reduce transmural dispersion of APD [85]. *In vitro* electrophysiological investigations revealed that ranolazine blocks primarily late I_{Na} but several other currents as I_{Kr} , I_{Ks} , and even possibly L-type calcium current (I_{CaL}) [86]. Ranolazine was shown to reduce ischemic intracellular sodium and calcium overload, and to effectively suppress triggered activity, such as EADs. These properties were associated with the late I_{Na} current inhibiting properties. In order to determine whether I_{Na} blockade may be effective in suppressing arrhythmias, extensive investigations were performed in isolated canine single (ventricular myocytes) and multicellular (wedge) preparations [87]. Ranolazine reduced the transmural dispersion of repolarization, a known proarrhythmic substrate [84]. Recent experiments in canine isolated perfused atrial and ventricular preparations have suggested that ranolazine shows a stronger affinity to atrial sodium channels than that of ventricular ones [88]. However, we must emphasize that clinical studies showed only moderate results when testing the effect of ranolazine in counteracting AF [89].

Atrial acetylcholine-sensitive potassium current ($\text{I}_{\text{K,ACh}}$) blockers

Blockade of another atrial-selective current, the acetylcholine activated inward rectifier K^+ current, $\text{I}_{\text{K,ACh}}$, is expected to exert a useful effect in vagally induced atrial fibrillation. Since $\text{I}_{\text{K,ACh}}$ is also absent in ventricles, the $\text{I}_{\text{K,ACh}}$ blockers, similar to I_{Kur} blockers, are also real ARDAs. Numerous investigations reported that activation of $\text{I}_{\text{K,ACh}}$ by vagal stimulation will parallel shorten atrial ERP and increase the availability of the Na^+ channel, thereby can create of re-entry substrate based on the dispersion of atrial repolarisation. At high frequencies characteristic to AF, these reentries may create rotors, which consequently promote the increased duration of AF episodes [90]. Several investigations reported that vagal activity can contribute to the initiation of paroxysmal AF [91,92], thereby some authors proposed the hypothesis that blockade of parasympathetic activity may have beneficial effects and could help to maintain SR; therefore, selective $\text{I}_{\text{K,ACh}}$ blockade may be a promising atrial selective therapeutic strategy [90].

NIP-142 (Figure 3) and NIP-151 (chemical structures not disclosed). NIP-142 is a benzopyrane derivative compound, which was synthesized as highly selective blocker of $\text{I}_{\text{K,ACh}}$. Accordingly with the hypothesis, investigational results demonstrated that NIP-142 could prevent the acetylcholine-induced, arrhythmogenic AP shortening [93]. The congener derivative NIP-151 seems to be even more potent and more selective compound than NIP-142. A recent investigation reported

performed in dogs, NIP-151, in an atrial selective manner, significantly lengthened atrial ERP and prevented vagally- and aconitine induced AF [94].

Constitutively active $\text{I}_{\text{K,ACh}}$ channels (CI- $\text{I}_{\text{K,ACh}}$)

Recently, it has been shown that in atrial tissue originating from patients in permanent AF, the $\text{I}_{\text{K,ACh}}$ channels are opened and active without direct ligand stimulation, *i.e.* they are constitutively active ($\text{CC-I}_{\text{K,ACh}}$) [90,95]. In this study it was hypothesised that in long term chronic AF constitutively active $\text{I}_{\text{K,ACh}}$ current is one of main responsible for APD abbreviation and triangularization, thus making the atria susceptible for reentry based tachyarrhythmias [90]. A logic conclusion of this observation was that selective blockade of $\text{CC-I}_{\text{K,ACh}}$ current may have potent antiarrhythmic/antifibrillatory effects [93]. However, due to lack of selective CI- $\text{I}_{\text{K,ACh}}$ antagonists, direct control of this hypothesis is not possible yet. However, in a recent study, this hypothesis was at least questioned. Indeed, in an experimentally induced tachypaced dog model of permanent AF (ATR), we have revealed that the real magnitude of the outward repolarizing CI- $\text{I}_{\text{K,ACh}}$ does not seem to be large enough to substantially contribute to the atrial ERP shortening and thus to the APD shortening [9,96,97]. Therefore, in this study [9] we have proposed the following new concept: in normal *in vivo* physiological condition a “background” vagal stimulation is always present, thereby, consequently it is probable that an acetylcholine-dependent $\text{I}_{\text{K,ACh}}$ exists in atrial myocytes either in SR or AF. In permanent AF the CI- $\text{I}_{\text{K,ACh}}$ can also be activated, and its effect will add to the vagally stimulated $\text{I}_{\text{K,ACh}}$, so the resulting net outward current may become large enough to contribute to the atrial ERP/APD shortening. Consequently, blockade of this combined basal $\text{I}_{\text{K,ACh}}$ and $\text{CC-I}_{\text{K,ACh}}$ current may prevent AF. Indeed, in a series of recent experiments we have clearly demonstrated the presence of CI- $\text{I}_{\text{K,ACh}}$ in atrial cardiomyocytes isolated from ATR dogs, near of a clear presence of cholinergic activated $\text{I}_{\text{K,ACh}}$ currents [9]. Selective blockade of combined $\text{I}_{\text{K,ACh}}$ current with low nanomolar concentrations of Tertiapin Q (Figure 3) successfully prevented experimentally induced AF in conscious ATR dogs [9,96,97]. However, further investigations are performed presently to test this hypothesis.

NCX modulators

The $\text{Na}^+/\text{Ca}^{2+}$ exchanger current (NCX) exchanges one intracellular Ca^{2+} ion for three extracellular sodium ions. During rapid atrial rates caused by AF or pacing, the larger entrant intracellular sodium relative to calcium may cause the bidirectional exchanger to work in the reverse mode, consequently elevating the intracellular Ca^{2+} level and thus contributing to the shortening of the action potential. These may increase the incidence of DAD (elicited by NCX1 activity) that in turn can trigger AF. Therefore, it has been postulated that NCX blockers as useful antiarrhythmic drugs [98,99]. Lack of potent and selective NCX blockers made impossible to unequivocally prove this hypothesis so far. During last decade several NCX blockers were developed and investigated but to date no true potent and selective NCX blocker has been reported.

KB-R7943 (Kanebo, Figure 3) preferentially inhibits the reverse mode of the NCX. Several studies revealed also that this effect was associated by a clear blocking potency on sodium, potassium and calcium channels (I_{to} , I_{K} , I_{K1} , I_{Na} , and I_{CaL}). In anesthetized dogs, KB-R7943 prevented atrial ERP shortening caused by pacing-induced AF [100,101], but obviously this effect cannot be associated strictly to NCX blocking properties of the drug.

SEA0400 (Taisho Pharmaceutical, Figure 3) is another NCX

inhibitor which is more selective and potent than KB-R7943, and for several years this was the most investigated NCX blocker compound. It was reported that SEA0400 effectively blocks NCX in both forward and reverse mode at micromolar concentrations; however, the drug also effectively suppressed the L-type Ca current (I_{CaL}) at comparable concentrations [102]. In a recent study in humans where SEA0400 has been applied as a tool to identify NCX current, it was reported that the NCX current is significantly upregulated in AF as compared to SR [103]. In spite of many published reports that showed that NCX blockade with SEA0400 may suppress ectopic automaticity in pulmonary veins, we must emphasize that these observations remains questionable due to the lack of trusted selective NCX blocking effect [99].

ORM-10103 (Orion Pharmaceutical, Figure 3) is a novel developed, and purportedly the most selective and highly potent NCX blocker. In a recent study it was reported that ORM-10103 significantly reduced both the inward and outward NCX currents at submicromolar concentration. The drug did not significantly change the main repolarisation K currents (I_{to} , I_{Kr} , I_{Ks} , I_{K1}), the L-type Ca^{2+} current, the Na^+/K^+ pump or the maximum rate of depolarization (dV/dt_{max}), indicative of the fast inward Na^+ current even at the high concentration of 10 μM ORM-10103, suggesting that, indeed, this is the firstly reported highly selective NCX blocker [104]. The amplitude of pharmacologically induced early and delayed afterdepolarizations were significantly decreased by ORM-10103 (3 and 10 μM) in a concentration-dependent manner [104].

Gap junctions modulators

Electrical and structural remodelling caused by permanent AF involves significant changes in junctions at the atrial intercalated discs. These may include fascia adherens, the desmosomes, and recently, the gap junction proteins (N-cadherin, desmoplakin, and connexins). Cardiac connexins present two major isoforms: one with the molecular weight of 40 and 43 kDa, respectively. Atrial myocardium and conduction system express particularly connexin 40, while connexin 43 is also present in conductive tissue [105]. There are some studies reporting that acute ischemia may close the gap junctions and slow conduction velocity. Therefore, it has been suggested that specific gap junctions' modulators that prevent closing of cardiac gap junctions may possess antiarrhythmic effect against AF [106,107].

Rotigaptide (GAP-486, ZP123, Figure 3) is the firstly reported substance developed for protecting against the closing of the gap junctions. Rotigaptide is a peptide developed by applying the original antiarrhythmic peptide structure, where the d-isomers have been substituted for l-isomers. In acute coronary artery occlusion, rotigaptide was shown to effectively attenuate the conduction velocity slowing and ventricular arrhythmogenesis, while being neutral in controls [108,109].

GAP 134 (Figure 3) was designed with the specific aim to reduce atrial conduction velocity [110]. However, in a recent investigation performed in the acute dog model of permanent AF the drug did not prove to have either strong antiarrhythmic or AP lengthening potential [110,111]. We may summarize that gap junction modulators may be indeed novel and potentially efficacious pharmacological targets against AF, but several investigations are required to establish their real potential.

Other possible ion channel targets for novel antiarrhythmic drugs

There are several attempts for targeting other ion channels such as the: two pore-domain potassium channels [K2P] [112], transient receptor channels [TRP] [113], mechanosensitive, stretch activated

channels [114], calcium activated K^+ -channels [115] etc. Based on the information of several investigations in native (especially ventricular) and transgenic systems many of them may be useful targets for antiarrhythmic exploitation; however, until now there are no or very few promising results suggesting that modulators of these channels may provide beneficial effects in preventing AF.

Non ion-channel blockers – upstream therapy of AF

In addition to the ion channel-based AF therapy, there is a rapid development of non ion-channel approaches, aimed at reducing or reversing structural remodeling, inflammation, and oxidative stress injury associated with AF. These approaches are collectively referred to as “upstream therapies” [116,117].

As previously mentioned several pathophysiological processes, such as inflammation and oxidative injury, promote structural remodeling, including fibroblast proliferation, accumulation and/or redistribution of collagen, chamber dilation, and hypertrophy that are associated to AF. Proarrhythmic actions of atrial structural remodeling are generally related to conduction disturbances, which promote re-entrant arrhythmias. Several experimental and clinical studies have shown that the so-called “upstream therapy” drugs affecting structural remodeling, inflammation, and/or oxidative stress, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and statins may reduce the occurrence of AF [118,119]; while in contrary, other studies questioned the efficacy of such therapies in AF [120]. However, we must emphasize that numerous clinical trials proved that the use of statins was significantly associated with a decreased risk of atrial fibrillation in patients with sinus rhythm. The highest benefit was seen for the prevention of postoperative atrial fibrillation and in secondary prevention of atrial fibrillation, with a high heterogeneity, explained by differences in statin types, patient populations and surgery types [121,122].

We must also emphasize that the contribution of inflammation and oxidative stress in the development of AF is still not fully understood and varies significantly among different AF pathologies [36,123,124].

Conclusions

The past decades witnessed an enormous amount of research aimed at deciphering the mechanisms underlying atrial remodeling in AF and developing methods to counteract it. Both ion channel and non ion-channel therapeutic approaches are envisaged in order to improve the management of AF. A great deal of attention is currently paid to novel antiarrhythmic drugs that possess high affinity for atrial myocardium or target multiple ion channels. Whether the use of these antiarrhythmic agents will translate into improved prognosis of patients with AF remains to be confirmed in larger-scale prospective trials.

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