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Antiarrhythmic drugs for atrial fibrillation: Imminent impulses are emerging

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ABSTRACT

Rhythm and rate strategies are considered equivalent for the management of atrial fibrillation (AF). Moreover, both strategies are intended for improving symptoms and quality of life. Despite the clinical availability of several antiarrhythmic drugs (AAD) the alternatives for the patient with comorbidities are significantly fewer because of the concern regarding many adverse effects, including proarrhythmias. The impetuous development of AF ablation gave rise to a false impression that AAD are a second line therapy. All these statements reflect, in fact, the weakness of the classical paradigm and classification regarding AAD and the gap between the current knowledge of AF mechanism and determinants and the "classical" AAD non-discriminatory action. A new paradigm in development of effective and safe AAD is based on modern knowledge of *vulnerable* parameters involved in the genesis and perpetuation of AF. New AAD will target specific triggers of AF and ion currents which are expressed preferentially in fibrillatory atrium. Such targets will include repolarizing currents and channels, as ultrarapid potassium current, two pore potassium current, the acetylcholine-gated potassium current, small-conductance calcium-dependent potassium channels, but, also, molecular targets involved in intracellular calcium kinetics, as Ca^{2+}-calmodulin–dependent protein kinase, ryanodine receptors and non-coding miRNA. New mechanistic discoveries link AF to inflammation and modern anti-cytokine drugs. There is still a long way to win between basic research and clinical practice, but, without any doubt, antiarrhythmic drug therapy will remain and develop as a cornerstone therapy for AF not in conflict, but complementary and alternative to interventional therapy.

1. Introduction

The 2016 the European guideline of atrial fibrillation (AF) management [1] indicates two main therapeutic and outcome endpoints in AF: actions designated to improve life expectancy and those intended to improve quality of life. If stroke prevention belongs to the first category, rate/rhythm control strategies, irrespective if pharmacological or interventional, belong to the second one. Such considerations might be interpreted to suggest that sinus rhythm is expected to not associate with a better survival. In fact, an analysis from the AFFIRM trial [2] suggested that sinus rhythm positively influences survival, while antiarrhythmic drugs (AADs) do not; therefore, preserving sinus rhythm is a better strategy if not obtained with currently available AADs. Moreover, more recently, the CAMERA-MRI study [3] showed that successful AF catheter ablation, particularly in atria with less fibrosis, is associated with a significant improvement in left ventricular performance compared with pharmacological rate control.

The 2016 AF management guideline [1] offers several pharmacological options for drug conversion to sinus rhythm and its maintenance; however, these options are very limited for the majority of cases with structural heart disease such as heart failure (HF), ischemic heart disease (IHD) or significant myocardial hypertrophy. Amiodarone, with its multiple extra-cardiac side effects, remains the most efficient anti-arrhythmic drug. Although less efficient, other options for selected cases, are sotalol, dronedarone or vernakalant [4]. Several non-antiarrhythmic drugs demonstrated preventive abilities especially when applied for risk factors (upstream therapy). Recently the RACE 3 study [5] demonstrated that this therapy is feasible and effective in patients with AF and heart failure. The ESC 2016 AF management guideline recommend ACE-Is, ARBs and beta-blockers to be considered for prevention of new-onset AF in patients with heart failure and reduced ejection fraction with class IIa indication.

There is an important translational gap between currently available AADs and contemporary practical expectations. The tremendous development of AF ablation widened this gap even more and created a hypothetical competition between interventional and pharmacological rhythm control strategies. However, it is more than obvious that

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catheter ablation alone cannot be applied to the 33 million patients with AF expected in the next ten years [6,7], if we take into account the limited availability of specialized human resources, the very large costs, eminent procedure limitations, and contraindications or patient's preferences. Also, as demonstrated by a contemporary European registry, the ablation success is increased by AAD reinforcement therapy [8] from 63% to 83% and the residual AF risk remains high after ablation. AF ablation represents a possible cure only for paroxysmal arrhythmia with pulmonary vein bound triggers. However AF ablation is by definition not able to cure all the critical components (i.e. at molecular level) of the arrhythmic substrate and most importantly, as with the AADs, the impact of AF ablation on mortality was not yet proven. Two ambitious new studies, CASTLE-AF [9], and the very recent CABANA trial, communicated during the 2018 HRS congress, failed to dispel the uncertainty or to prove the superiority concerning hard end-points of AF ablation compared with pharmacological therapy [10].

2. The beginning of the end and the end of the beginning

The first warning signal for current AADs was the report of the CAST trial results [11,12] demonstrating an increase in mortality with encainide, flecainide and moricizine in patients with structural heart disease. The management of ischemic heart disease changed since then, and flecainide proved to be safer than initially believed [13]. However, repeated meta-analyses and systematic reviews showed that current AADs have moderate to low efficacy in controlling sinus rhythm at the expense of frequent side effects including severe proarrhythmia and a high withdrawal rate [14]. The main explanation for classic "AAD failure" was clearly revealed by the *Sicilian Gambit* investigators [15] in a new paradigm, unfortunately "[considered] to be clinically unwieldy and … never fully accepted" [16]. The classical approach was a drug-centered rather a patient's arrhythmia-centered strategy based on the "*one fits all*" Singh-Vaughan-Williams incomplete and exclusive electrophysiological classification. The antiarrhythmic treatment is therefore empirical, potentially explaining the limited efficacy of currently available AADs. Moreover, each classical AAD combines target (therapeutic) effects with off-target (side) effects, blunting the global efficacy and safety profile [17]. For example, potassium channel blockers (class III) are beneficial in reversing the arrhythmogenic shortening of the action potential duration (APD), but deleterious because they may induce early afterdepolarizations (EADs)-mediated triggered activity. Calcium channel blockers (class IV) and sodium current blockers (class I) are beneficial in preventing delayed afterdepolarizations (DAD) as AF triggers and perpetuators, but deleterious in contributing to further shortening of the APD or promoting slow heterogeneous conduction.

A new AAD paradigm should be based on clear understanding of the individual arrhythmic mechanism, evaluating its critical components and revealing the arrhythmia's most *vulnerable* parameter as the target for the specific AAD. Moreover AF is increasingly considered as the consequence of a progressive atrial cardiomyopathy that also needs interruption (in addition to AF) in order to reach a higher therapeutic success rate [18]. Therefore, if considered, a new paradigm should be based on an arrhythmia and patient approach with the aim to increase both efficacy and safety. AF reentry initiation and perpetuation is dependent on a vulnerable substrate (in turn favored by predisposing conditions such as age, hypertension, heart failure etc.) and on triggers (activated by acute initiating factors such as inflammation or neurohormonal imbalance). In the classical paradigm the reentry and effective refractory period (ERP) are targeted by class III AAD; novel targets include atrial-specific channels (see below) [19]. Similarly, if the classical targeting of triggers (excitability, abnormal automaticity and ectopic activity) involved class I AAD, newer drugs such as vernakalant or ranolazine among the others, target some atrial-selective channels or intracellular calcium handling. And finally, if classical drugs targeting substrate remodeling involve upstream therapy (renin-angiotensin-aldosterone system inhibition, statins or beta-blockers), novel targets may include calcium signaling molecules, transient receptor potential (TRP) channels or miRNA [20,21].

A drug considered as a transition from traditional to modern AADs is vernakalant. This drug inhibits potassium channels and also sodium channels (both peak and late sodium current) prolonging ERP, increasing excitation threshold, decreasing conduction and lowering the risk of proarrhythmias due to APD prolongation [22]. Vernakalant, a frequency- and voltage-dependent blocker, is not an atrial-selective ion-channel blocker; however, because the atrial resting membrane potential is more positive (depolarized) than that of the ventricle and this difference further increases during AF, vernakalant acts as an atrial-selective AAD. Its rapid onset/offset kinetics confer a low proarrhythmic risk. Four randomized control trials (RCT) demonstrated the very rapid conversion of AF (but not flutter) with vernakalant (ACT I–III and CRAFT) [23]. The AVRO study [24] confirmed its superior efficacy compared to amiodarone for the cardioversion of recent-onset AF. However, vernakalant loses its efficacy if AF persists for more than 2 days, which suggests that this drug cannot be useful in patients with long-term AF-induced atrial remodeling.

Another potential molecule is ranolazine, which was designed initially as an anti-anginal drug. It blocks the late sodium current (I_{NaL}), which increases during ischemia, long QT syndrome and is augmented with oxidative stress, causing cellular sodium overload [25,26]. The net effect of increased I_{NaL} is a diminished repolarization reserve, increased repolarization dispersion and enhanced EAD incidence. Moreover, because of the increased intracellular sodium, the NCX acts in a "reverse-mode" thereby increasing calcium influx and diastolic calcium levels, which may cause sarcoplasmic reticulum (SR) calcium release (SR calcium leak) along with DAD-mediated triggered activity [27]. Overall, ranolazine showed decent antiarrhythmic effects at the ventricular level. Besides this it also blocks the atrial-selective ultrarapid delayed-rectifier potassium current I_{KUR} pointing to potential anti-AF properties of this drug. Two comprehensive meta-analyses confirmed the efficacy of ranolazine for rhythm strategy and AF prevention [28,29]. Ranolazine could be combined with low-dose dronedarone for positive effects on efficacy (increasing rate-dependent block of I_{Na} and I_K) and safety (minimizing the effect on L-type calcium current and thereby reducing the negative inotropic effect of dronedarone). The phase 2 HARMONY trial [30] confirmed the synergistic action of ranolazine and low-dose dronedarone in reducing AF burden, with a positive safety profile. However, the newer I_{NaL} blocker eleclacine (also known as GS-6615), which was recently clinically used in different patient populations (LQTS-3, hypertrophic cardiomyopathy, and patients with ventricular tachycardia and ventricular fibrillation who also have implantable cardioverter-defibrillators - ICD), failed to show a reduction of ICD shocks and pacing events in patients with ventricular tachycardia and ventricular fibrillation when compared to a placebo (press releases only: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/02/WC500221764.pdf). Because of lack of efficacy the development program of this drug was discontinued; thus it is very unlikely that in the future the concept of I_{NaL} inhibition as an antiarrhythmic principle will be applied to AF.

3. Great expectations with additional approaches

An attractive target for rhythm control in AF is represented by some atrial-selective currents which show up-regulation during AF (arrhythmia-specific approach). Besides targeting a vulnerable parameter of arrhythmia determinants, drugs blocking these atrial-selective channels will be at least conceptually deprived of ventricular proarrhythmic effects.

I_{KUR} was among the first atrial-selective targets; blocking this current (overlapping with the transient outward potassium [I_{to}] current) is expected to prolong APD and destabilize reentrant arrhythmias [17]. Several compounds were investigated in phase 2 trials (e.g. MK-0448, XEN D0101, XEN D0103, BMS-394136, BMS-919373) demonstrating prolonged APD with increased rate and suppression of action potential

at higher rates; however, there is a shortening of APD in sinus rhythm with the risk of reinitiating AF [31–33]. Moreover, there is a strong risk of proarrhythmia with excessive blockade. In addition, the reduction of this current in some patients with chronic AF, may limit the efficacy of the drug [34].

The two-pore-domain potassium current I_{K2P} is driven by a large variety of channels [35] regulated by different signals including pH, stretch or temperature [31]. The TASK-1 ($K_{2p}3.1$) is abundant in human atria but not in the ventricles and is up-regulated in AF [36,37]. Pharmacologic blockade of the TASK-1 current results in APD prolongation. Several classic AADs (amiodarone, dronedarone or carvedilol) are non-selective TASK-1 blockers. There are contemporary attempts to synthetize a selective TASK-1 blocker deprived of important side-effects (i.e. pulmonary hypertension) [17,32] and one caveat with this approach is that TASK-1 currents are reduced instead of increased in AF patients with heart failure [36], making it unlikely that inhibition of TASK-1 would be an efficient anti-AF approach in patients with structurally-remodeled atria.

In humans, the acetylcholine-gated potassium current ($I_{K,ACh}$), the major effector of vagal nerve activation in atria, is functional in the atrium but not in the ventricle. During sinus rhythm $I_{K,ACh}$ is elicited only by muscarinic receptor activation, whereas in AF there is a receptor-independent "constitutive" $I_{K,ACh}$ current component causing a reentry-promoting atrial refractoriness abbreviation [38,39]. Flecainide and dronedarone both block this current and although other moderately selective $I_{K,ACh}$ blockers prolong repolarization in humans, their overall efficacy is rather limited [17,31,40]. There is an ongoing search for selective $I_{K,ACh}$ blockers deprived of some neurological side effects and general toxicity or excessive proarrhythmogenic APD prolongation at very high frequencies [32]. Thus like with I_{Kur}, selective targeting of $I_{K,ACh}$ is still a viable option of unproven clinical efficacy.

Small-conductance calcium-dependent potassium channels (SK channels) are more abundant in the atria compared to the ventricles, contributing to atrial repolarization [41,42]. Calcium handling is importantly perturbed in AF patients [43–45] and as a consequence, the SK channels are activated [31], contributing to AF-related APD shortening [46] and triggered activity, particularly in the pulmonary veins [47]. Several molecules were synthetized to modulate the calcium sensor (e.g. NS8593 or AP14145) of SK channels, which mediates the calcium-dependent channel regulation, or to block the pore (e.g. apamin or ICAGEN) of SK channels [31] and the possible antifibrillatory effect of SK channel block was demonstrated in several models of AF [48]. The potential antiarrhythmic properties of SK channels block are under clinical evaluation for the cardioversion of AF to sinus rhythm and SK channels are - to the best of our knowledge - the only ion channel target not yet proven in the clinical setting.

There are important and complex alterations of atrial calcium handling in AF patients which contribute to the induction and maintenance of the arrhythmia [49] and promote the progression to persistent AF forms [50]. Therefore it is expected that identifying the precise physiopathological mechanisms could offer the basis for development of newer AADs targeting aberrant atrial calcium signaling. Ca^{2+}-calmodulin-dependent protein kinase (CaMKII)-induced hyperphosphorylation of RyR2 (increased diastolic SR calcium leak) and of phospholamban (disinhibition of SR calcium ATPase type-2a, increasing SR calcium load) both increase the incidence of DAD-mediated triggered activity [49,51,52]. Selective CaMKII blockers are under development [53]. Downregulation of calstabin (FKBP12.6), an endogenous stabilizer of RyR2 channels, also contributes to dysfunctional RyR2 [34]. Dantrolene, S107, and S44121 stabilize RyR2-FKBP12.6 binding, while others (including ivabradine) could enhance FKBP12.6 expression [17]. Other compounds directly block RyR2 channels in their closed state (e.g. tetracaine) or open state (e.g. flecainide or propafenone) [54]. R-carvedilol (deprived of β-adrenoceptor blocking properties) also inhibits RyR2 channels [55]. Overall the antiarrhythmic efficacy of some of these RyR2 modulators was already demonstrated in individuals with polymorphic catecholaminergic ventricular tachycardia [56]. However, it remains to be demonstrated that similar approaches could be effective in patients with AF.

Several investigators demonstrated the role of non-coding microRNAs (miR) in the pathophysiology of AF and their modifications during arrhythmia. They contribute to both initiation through APD modification and substrate remodeling through fibrosis activation. Some miRs such as miR-21 (up-regulated in AF), miR-29, miR-30, and miR-133 (all down-regulated in AF) are linked to increased atrial fibrosis, whereas alterations in other miRs like miR-1 and miR-26 appear to contribute to APD shortening. A better understanding of their role in AF will permit their use for the development of targeted therapies [57].

New mechanistic discoveries are expected to drive the development of antiarrhythmic approaches traditionally not considered effective in arrhythmias. Recent work identified an unexpected contribution of inflammatory signaling (NLRP3 inflammasome system) in atrial cardiomyocytes including the human to the evolution of electrical, structural and calcium handling remodeling which promotes AF induction, maintenance and progression [58]. This novel paradigm of disease-inducing NLRP3 inflammasome-mediated signaling in non-immune cells may offer great opportunities for AF treatment because antagonizing downstream effectors activated by the NLRP3 inflammasome (e.g. IL-1β), for which clinical options are already available (e.g. anakinra, or canakinumab, low-dose methotrexate, and colchicine [59–61]), may also be of value against AF. Clearly this will require direct demonstration in prospective clinical trials in the different AF subpopulation.

It is evident that we are lost in translation of basic research discoveries to the clinical practice, for which many obstacles exist [62,63]. The new paradigm moves our knowledge now from the "*reductionism*" concept of the "one drug one electrophysiologic target" to the more complex network interpretation of the patient with arrhythmias. Based on the actual arrhythmia phenotype, defined by biomarkers, non-invasive substrate determination/substratification including potential non-invasive detection of the predominant underlying molecular mechanisms [64], future AADs should target vulnerable arrhythmia determinants with emergent anticipated and unanticipated off-target effects [65]. The "war" against arrhythmias such as AF will be ultimately won by the conjunct effects of the knowledge progress of both pharmacological and interventional antiarrhythmic therapies. As Churchill said once "Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning".

Disclosures

Dr. Dobrev is a member of the scientific advisory board of OMEICOS Therapeutics GmbH, a company developing small-molecules mimicking the effects of omega-3 fatty acids, and of Acesion Pharma, a company developing selective blockers of small-conductance calcium-dependent potassium channels.

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