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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