

FOCUS ISSUE: ATRIAL FIBRILLATION

Atrial-Selective Approaches for the Treatment of Atrial Fibrillation

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Atrial-selective pharmacologic approaches represent promising novel therapeutic options for the treatment of atrial fibrillation (AF). Medical treatment for AF is still more widely applied than interventional therapies but is hampered by several important weaknesses. Besides limited clinical efficacy (cardioversion success and sinus-rhythm maintenance), side effects like ventricular proarrhythmia and negative inotropy are important limitations to present class I and III drug therapy. Although no statistically significant detrimental survival consequences have been documented in trials, constitutional adverse effects might also limit applicability. Cardiac targets for novel atrial-selective antiarrhythmic compounds have been identified, and a large-scale search for safe and effective medications has begun. Several ionic currents (I_{KACH} , I_{Kur}) and connexins (Cx-40) are potential targets, because atrial-selective expression makes them attractive in terms of reduced ventricular side-effect liability. Data on most agents are still experimental, but some clinical findings are available. Atrial fibrillation generates a specifically remodeled atrial milieu for which other therapeutic interventions might be effective. Some drugs show frequency-dependent action, whereas others target structurally remodeled atria. This review focuses on potential atrial-selective compounds, summarizing mechanisms of action *in vitro* and *in vivo*. It also mentions favorable interventions on the milieu in terms of conventional (such as antifibrotic effects of angiotensin-system antagonism) and innovative gene-therapy approaches that might add to future AF therapeutic options. (J Am Coll Cardiol 2008;51:787–92) © 2008 by the American College of Cardiology Foundation

Invasive electrophysiological procedures such as pulmonary vein or left-atrial circumferential ablation represent promising approaches to atrial fibrillation (AF) treatment. Although these therapeutic options are being optimized, medical therapy remains the standard initial treatment for most patients (1). The impact of AF on public health is tremendous, given its influence on quality of life, morbidity, and mortality. Atrial fibrillation affects a constantly increasing number of individuals as populations age.

Pharmacologic approaches to AF have traditionally applied antiarrhythmic agents originally developed to treat ventricular arrhythmias. Perhaps because of this, they tend

to have prominent ventricular effects and risks of ventricular proarrhythmia.

Rationale for Atrial-Selective AF Therapy

Vaughan–Williams antiarrhythmic drug classes I and III might convert AF and prevent relapses after cardioversion, but clinical efficacy and tolerability are limited. Ventricular side effects that limit applicability include proarrhythmic events and negative inotropy. Although no overall detrimental effect on survival was found in AF-FIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management), a possible excess of non-cardiovascular deaths poses a potentially serious additional caveat (2).

Class I agents inhibit sodium (Na^+)-current and suppress AF by reducing excitability and destabilizing re-entrant rotors (3). Class III drugs like d,l-sotalol and amiodarone are used for AF-prevention after cardioversion with success rates of approximately 50% to 80% after 1 year (4). Except for amiodarone (for which noncardiac side effects are prominent), most class III agents have a significant risk of ventricular proarrhythmia (5). Class III drugs prolong action potential duration (APD) by blocking the rapid delayed-rectifier potassium current (I_{Kr}) (6). Rapid delayed-

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Abbreviations and Acronyms

- AF** = atrial fibrillation
- AP** = action potential
- APD** = action potential duration
- Cx** = connexin
- DPO** = diphenylphosphine oxide
- ERP** = effective refractory period
- I_{KACH}** = acetylcholine-regulated potassium current
- I_{Kr}** = rapid delayed-rectifier potassium current
- I_{Kur}** = ultrarapid delayed-rectifier potassium current
- I_{Na}** = sodium current
- SAC** = stretch-activated channel

rectifier potassium current is important for both atrial and ventricular repolarization, and blocking I_{Kr} increases the QT-interval and risks causing torsades de pointes arrhythmias.

Potential Targets for Atrial-Selective Therapy

Ion-channel targets. Modulation of atrially expressed ion-channel proteins has emerged as a novel therapeutic concept: anti-arrhythmic agents that target such channels/proteins are termed “atrial-selective” drugs. Currents like the ultrarapid delayed-rectifier (I_{Kur}) and acetylcholine-regulated current (I_{KACH}) are expressed in atrial but not ventricular cells and therefore are of potential interest (Fig. 1). Truly specific modulators

of cardiac ion-channels or structure are unavailable. Most drugs are 1 or 2 orders of magnitude more effective in inhibiting the target of interest (Fig. 2) compared with other potential targets.

I_{KACH} . The inwardly rectifying I_{KACH} mediates vagal influences on heart rate and atrial repolarization. Pore-forming Kir3 alpha-subunits are prominently expressed in sinus, atrio-ventricular nodes, and atrial myocardium but are largely absent in ventricles (7). The I_{KACH} activation shortens APD and causes hyperpolarization. Kir3.1 messenger ribonucleic acid (mRNA) is downregulated, and the response to acetylcholine is blunted in AF (8). In contrast, increases in the constitutively active (i.e., active in the absence of agonist) form of this current contribute to AF-related electrical remodeling (9–11). Because of this upregulation of constitutive I_{KACH} , I_{KACH} inhibition causes substantial APD prolongation and atrial tachyarrhythmia termination in the presence of atrial remodeling (11).

I_{Kur} . This current is called “ultrarapid” because it activates 2 orders of magnitude faster than I_{Kr} . Ultrarapid delayed-rectifier potassium current is carried by Kv1.5 alpha-subunits and is present in human atrial but not ventricular cells (12–14). One study demonstrated reduced I_{Kur} with human AF (15), which could limit the efficacy of I_{Kur} inhibition, but this result was not confirmed by subsequent investigations (16,17). The effects of I_{Kur} inhibition on atrial repolarization depend strongly on action potential (AP) morphology, with the brief, triangular APs during AF being particularly susceptible to prolongation by I_{Kur} inhibition (18).

Atrially expressed connexins. Connexin (Cx)-40 and Cx-43 are the 2 connexins present in the atrium: Cx-43 is expressed throughout the heart, but Cx-40 expression is restricted to atria and conducting system (19). Connexin-40 knockout-mice exhibit prolonged P waves and susceptibility to atrial arrhythmias (20). Cardiac-specific mutations in *GJA5* (encoding Cx40) lead to idiopathic AF (21). Connexins are remodeled in AF, but different studies have provided widely discrepant results (22).

Sodium current. Atrial sodium current (I_{Na})-block terminates AF by destabilizing AF-maintaining re-entrant rotors (3). Although atrial and ventricular Na^+ -channels have the same principal Na^+ -channel alpha-subunit (Nav1.5), differences in beta-subunits could convey drug selectivity. State-dependent I_{Na} -block could produce blocking selectivity for rapid rates like those of AF or for atrial APs (23). Some atrial-selective agents (like vernakalant) might achieve AF termination and atrial selectivity by rapidly unbinding I_{Na} antagonism (24).

Stretch-activated channels. Atrial fibrillation is commonly associated with conditions that increase left-atrial pressure like heart failure or valvular heart disease. Left-atrial enlargement is common in AF and makes the arrhythmia harder to control. Cellular stretch activates stretch-activated nonselective cation channels (SACs). The peptide SAC-inhibitor GsMTx4 (a tarantula-spider venom toxin) suppresses AF in a rabbit atrial-stretch model (25).

Nonion-channel targets. Modulation of atrial-structure changes associated with AF might represent an interesting approach to AF treatment devoid of proarrhythmic poten-

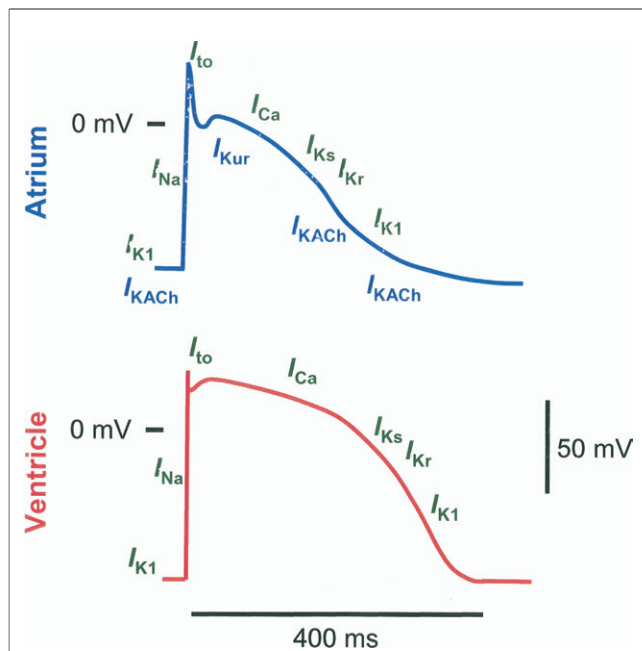


Figure 1 Regional Difference in Ionic Current Contribution to APs

Differences in key ion currents between atrial (blue) and ventricular (red) action potentials (APs). Atrial APs have smaller AP amplitude and less negative resting membrane potential. Currents (green) identified above the line illustrating the APs are present in both regions; atrially expressed ionic currents are illustrated below the AP schematic (blue). I_{KACH} = acetylcholine-regulated potassium current; I_{Kur} = ultrarapid delayed-rectifier potassium current; I_{Na} = sodium current.

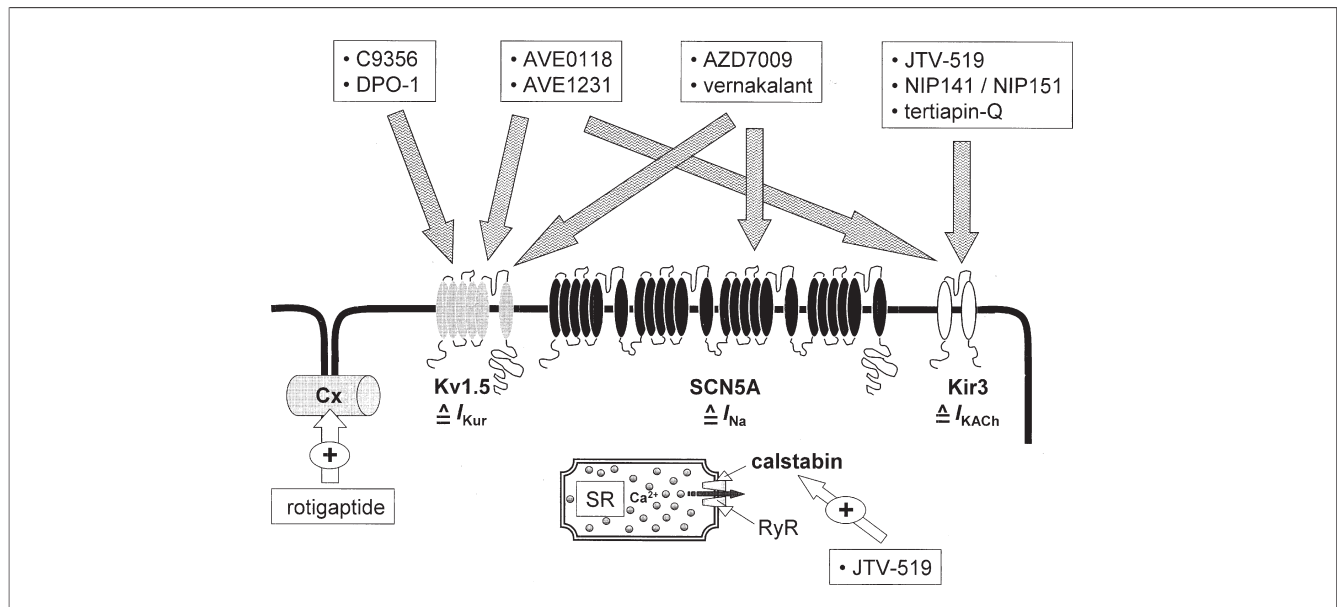


Figure 2 Targets of “Atrial-Selective” Antiarrhythmic Drugs

This figure presents a simplified cell with sarcolemmal membrane and ion currents and transporters that have served as targets for atrial-selective therapy shown. Pharmacologic agents discussed in the paper are presented in **boxes**, and **filled arrows** denote inhibition of specific currents. Rotigaptide is a connexin (Cx) activator—as illustrated by the “+” symbol. JTV-519 stabilizes ryanodine-receptor (RyR) and calstabin complexes. DPO = diphenylphosphine oxide; SR = sarcoplasmic reticulum; other abbreviations as in Figure 1.

tial. Tissue fibrosis is a prominent feature of AF-promoting remodeling in heart failure (26,27), with little reversal even after hemodynamic recovery (28). Atrial extracellular matrix remodeling is associated with AF persistence (29). Experimental and clinical studies suggest potential benefits of angiotensin-system inhibition, possibly via suppression of structural remodeling (30,31). Patients treated with the angiotensin-receptor antagonist irbesartan showed a dose-related reduction in AF recurrences (32,33). Very rapid atrial tachycardia, as accompanies AF, remodels atrial electrical properties and promotes AF; drugs that prevent such remodeling might be useful in AF management (22,23). Because of space limitations, this paper will not deal in detail with nonion-channel targets. The interested reader is referred to recent reviews (1,23,31,34).

Drugs in Development

$I_{K_{ACh}}$ inhibitors. Purely selective $I_{K_{ACh}}$ inhibitors are currently unavailable for clinical use. Tertiapin-Q is a nonoxidizable derivative of the naturally occurring peptide-toxin tertiapin that selectively and potently inhibits Kir3 and Kir1 channels (35,36). Because there are no significant cardiomyocyte Kir1 channels, the drug is highly selective for $I_{K_{ACh}}$ (Kir3.1/3.4) in cardiac tissue. The background inward-rectifier current I_{K1} (Kir2 channels) remains unaffected (36). Tertiapin-Q inhibits constitutively active $I_{K_{ACh}}$ at low-nanomolar concentrations (9,10). Tertiapin-Q terminates atrial tachyarrhythmias in tachycardia-remodeled preparations without altering ventricular repolarization (9,11). Intravenous tertiapin terminates vagally induced and

aconitine-dependent AF in dogs (37). The practical development of $I_{K_{ACh}}$ -blockers for AF therapy will require avoidance of collateral vagolytic side-effects due to $I_{K_{ACh}}$ inhibition in other systems.

NIP-142 inhibits heterologously expressed Kir3.1/3.4 current (reconstituting $I_{K_{ACh}}$) as well as Kv1.5 current (38,39). It terminates vagal AF and prevents AF reinduction (40). NIP-141 (a hydrochloride-bound form of NIP-142) blocks human atrial transient outward current (I_{to}) and I_{Kur} with low-micromolar half-inhibitory concentration (IC_{50}) (41). Although combined $I_{K_{ACh}}$ and I_{Kur} block make this drug interesting, it is not strictly atrial-selective, possibly because of I_{Kr} and I_{to} inhibition (40). NIP-151 is a more selective $I_{K_{ACh}}$ -blocker with interesting preliminary evidence for efficacy against experimental AF (23).

JTV-519 (also known as K-201) is a drug with vasodilating properties that also has $I_{K_{ACh}}$ -blocking actions and an ability to stabilize calstabin-ryanodine receptor-binding (23). JTV-519 suppresses AF inducibility while prolonging atrial effective refractory period (ERP) (42,43). However, the drug also has actions on I_{Na} , I_{Ca} , I_{K1} , and I_{Kr} (44).

I_{Kur} inhibitors. I_{Kur} was the first ion-channel proposed as an atrial-selective target (12), and a series of I_{Kur} -blocking drugs has been developed.

AVE0118 targets I_{to}/I_{Kur} and has additional $I_{K_{ACh}}$ -blocking properties (45,46). AVE0118 decreases left-atrial vulnerability to AF induction and AF reinducibility after cardioversion from persistent AF without prolonging QT intervals (47,48), but its clinical development has been stopped for undisclosed reasons. AVE1231 is a congener

with improved pharmacokinetics and similar Kv1.5-blocking properties that also exhibits atrial selectivity (49).

Diphenylphosphine oxide (DPO) compounds inhibit heterologous hKv1.5 currents as well as human atrial I_{Kur} at low-micromolar concentrations (50). The DPO-1 inhibits I_{Kur} approximately 20-fold more effectively than I_{Kr} or I_{Ks} and approximately 8-fold more than I_{to} , while selectively prolonging human atrial versus ventricular APs. In an animal model of atrial flutter, DPO-1-induced atrial-ERP prolongation terminates arrhythmia without affecting QT intervals (51).

The synthesis of many other Kv1.5-inhibiting substances has recently been described. Experimental characterization of such agents, including 2-aminoalkylethers, aryl-sulfonamide-indane, and psoralen derivatives, has been initiated (52-54).

Cx activators. Abnormalities in connexin expression and function accompany AF-promoting remodeling due to heart failure and atrial tachyarrhythmias (23). Atrial fibrillation is a recognized complication of myocardial infarction (55,56), and acute atrial ischemia promotes AF maintenance (56). Ischemia-induced cellular acidification causes arrhythmogenic gap-junctional uncoupling (57). The peptide rotigaptide enhances gap-junction conductivity and prevents intercellular uncoupling (57). In AF related to atrial dilation, rotigaptide reversed atrial conduction slowing but failed to prevent AF (58). Recent work in canine AF models shows no efficacy for AF related to electrical and structural remodeling but effectiveness in ischemic AF and mitral-valve disease (59).

Atrial-selective agents of uncertain mechanism. Several agents have atrial-selective action of uncertain ionic mechanism. AZD7009 is a multi-channel blocker that terminates experimental AF in a sterile pericarditis model with minor QT interval prolongation (approximately 9%) (60). AZD7009 is approximately equally potent at inhibiting hKv1.5 and hKv4.3/hKChIP2.2-currents (61) and is also an open-channel HERG (I_{Kr})-current blocker (62). A combined in vivo and in vitro evaluation of AZD7009 showed APD prolongation and evidence of frequency-dependent I_{Na} inhibition (63). Atrial ERP was prolonged in vivo with marginal (nonsignificant) effects on ventricular tissue. However, clear ventricular effects in vitro raised questions about atrial selectivity. AZD7009, azimilide (inhibitor of I_{Ks} , I_{Kr} , and $I_{Ca,L}$), and AVE0118 reduce AF inducibility to the same extent in acutely dilated rabbit atria (64). AZD7009 increased atrial ERP more in dilated than nondilated atria, possibly owing to I_{Na} inhibition, and has proven safe and effective in cardioverting persistent clinical AF (65).

Vernakalant (formerly RSD1235) blocks Kv1.5, I_{to} , HERG, and Na^+ current (24). I_{Na} -block shows rapid resting-state unbinding and is frequency-dependent. Despite its large pharmacologic spectrum of activity, experimental data suggest that vernakalant's AF-selective actions might be based on state-dependent I_{Na} blockade (23). In a randomized, placebo-controlled study of patients with

<72-h duration AF (66), vernakalant terminated AF in 61% of subjects with a median conversion time of 14 min (vs. 5% and 162 min for placebo). The QTc and QRS duration were nonsignificantly prolonged. Intravenous vernakalant is in late-stage clinical development, and an oral formulation is in phase II trials.

Gene Therapy

Gene therapy approaches promise greater selectivity than classical small-molecule drugs and represent a rapidly expanding field of research. Proof-of-principle for gene therapy in AF was provided by studies showing that transferring the gene encoding constitutively active inhibitory G-protein into the AV node controls ventricular response-rate and reverses tachycardiomyopathy in pigs with AF (67). Selective transmural atrial-refractoriness prolongation has been achieved by a novel approach to local application of an adenovirus carrying a dominant-negative mutated HERG construct (68).

MicroRNA (mir) represents another recently discovered gene-therapy target. Mir-1 seems involved in regulating cardiac conduction and modulates *KCNJ1* and *GJA1* transcription in human coronary artery disease (69,70). Because *GJA1* encodes Cx43, it might be relevant to AF, and microRNA designed to enhance Cx40-expression could be valuable for atrial-selective therapy. Modulation of cardiac ion-channel genes (*KCNQ1*, *KCNE1*, *HCN2*, *HCN4*) by mir-1 and -133 might represent an alternative approach to regulation of AV-nodal conduction or atrial excitability (71,72). This emerging field needs to be explored further before therapeutic applications are fully appreciated.

Many obstacles to gene therapy remain to be overcome, including effective local gene-delivery approaches, stable gene incorporation, control over the level and distribution of gene expression, avoidance of inflammatory reactions and other adverse effects of vectors, and so forth. Nevertheless, gene therapy remains a very novel and potentially promising therapeutic approach.

Summary and Conclusions

The development of novel antiarrhythmic agents promises to expand the range of AF pharmacotherapy. Although purely selective atrial antiarrhythmic agents are not available, many candidate drugs demonstrate relative selectivity. Some ion-channels, notably I_{Kur} and I_{KACH} , are selectively expressed in atrium versus ventricle, but it remains to be shown that blocking them conveys antiarrhythmic action with a desirable lack of side effects in man. Connexin modulation might be interesting, but efficacy depends strongly on AF mechanisms, and thus far the requirement for intravenous administration limits applicability. State-selective I_{Na} blockade might allow AF-suppression without the proarrhythmic complications that plagued classical I_{Na} -blockers. Some drugs have atrial-selective actions and antiAF efficacy of uncertain mechanism; further research

might provide useful mechanistic clues for novel-compound development. Gene-therapy approaches are still in their infancy but might provide important advantages.

It is too early to be sure whether the concept of atrial-selective drug therapy will translate into safer and more effective ways of maintaining sinus rhythm, but the range of novel targets under investigation provides hope for the future. Most studies to date have been experimental but have paved the way for clinical trials that will hopefully soon confirm the safety, efficacy, and applicability of this approach.

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