NASPE HISTORY

Antiarrhythmic Drugs: Past, Present, and Future
DAN M. RODEN
From the Division of Clinical Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee

The Antiarrhythmic Drug Landscape When NASPE Was Founded

When the North American Society of Pacing and Electrophysiology (NASPE) was founded 25 years ago, treatments were empiric and targeted diseases or symptoms whose underlying mechanisms were poorly understood, if at all. Therapies available and widely used for arrhythmias in the late 1970s included pacemakers, external defibrillation for cardiac arrest, and drugs: lidocaine, procainamide, quinidine, and disopyramide.1 Generally accepted indications for antiarrhythmic drug therapy included prevention (of recurrent cardiac arrest, of recurrent atrial fibrillation [AF]) and treatment of symptoms. Frequent premature ventricular contractions (PVCs), whether symptomatic or not, were a common indication for therapy since ventricular ectopy was by then becoming established as a marker for an increased risk of sudden death following myocardial infarction (MI). Few drugs were available, and these were incompletely effective at best, plagued by a high incidence of serious and nuisance adverse affects, and the mechanisms whereby they actually suppressed arrhythmias were poorly defined. Efficacy was judged by clinical anecdotes, like acute termination of an ongoing tachyarrhythmia by drug administration, and extrapolation to other settings. Few large controlled clinical trials had been performed. Studies had shown that lidocaine administered in the coronary care unit reduced the incidence of ventricular fibrillation but survival appeared unaffected;2 later analysis of much larger databases suggests an adverse effect of lidocaine on survival in this setting.3 Studies of β-blockers, including some of the first cardiology megatrials,4,5 suggested antiarrhythmic efficacy in some settings. Similarly, the striking efficacy of verapamil in supraventricular arrhythmias was beginning to be appreciated, and it was supplanting “traditional therapies,” like phenylephrine or physostigmine for acute termination of what was then termed PAT.6

NASPE: The Early Years

The increasing appreciation of ventricular arrhythmias as a marker of underlying heart disease, and therefore a potential drug target, led to development of multiple new antiarrhythmic molecules in the late 1970s and early 1980s. A common animal model used to screen for antiarrhythmic activity was the “Harris dog” that demonstrates extremely high frequency ventricular ectopic activity after two-stage coronary artery ligation. This arrhythmia is especially sensitive to sodium channel blockers, and so the first wave of new antiarrhythmics were drugs derived from existing structures, and demonstrating activity in this and other models (i.e., primarily sodium channel blockers). The backbones on which these new molecules were constructed were procainamide (leading to flecainide and encainide), lidocaine (leading to mexiletine and tocainide), and propranolol (leading to propafenone). While the lidocaine analogs improved on the parent molecule by being orally bioavailable, they shared lidocaine’s propensity to cause tremor.7,8 Early clinical trials showed enhanced efficacy along with reduced adverse effects in nonsustained ventricular arrhythmias when mexiletine and quinidine were combined.9 It now seems likely that the combination produced at least additive sodium channel blockade, and limited drug-specific noncardiac adverse effects by using reduced doses. In vitro studies showed that mexiletine and tocainide also blocked the action potential prolonging effects of quinidine,10,11 thereby presaging the increasing appreciation of the use of mexiletine and other sodium channel blockers in some of the long QT syndromes.12–14

The procainamide analogs encainide and flecainide (and many others with similar electrophysiological properties that never reached the market, including indecanide, lorcanide, and trancainide) shared common, and at the time highly distinctive and unusual, clinical features. These include marked PR and QRS duration prolongation at clinically useful doses, near-total suppression of ventricular ectopic beats, few if any noncardiac adverse effects, and a serious problem with proarrhythmia. The lack of serious noncardiac effects likely reflects the potency with which these drugs block cardiac sodium channels,
compared to other electrophysiological effects that they may exert. The principle that high potency block of a single pharmacologic target is desirable because it minimizes the side-effects that come with nonspecific drugs is now well-established near-dogma in drug development circles of all types. The experience with encainide and flecainide points to the advantages of this strategy (few side-effects that are not a direct extension of the drug’s targeted pharmacology) and the potential drawbacks. The conduction slowing exerted by these agents in and below the atrioventricular (AV) node likely also reflects sodium channel block as does the suppression of nonsustained ventricular arrhythmias.

The interesting differences between these newer drugs and older sodium channel blocking drugs were well explained in the framework of the “Modulated Receptor Hypothesis,” popularized in the early and mid-1980s. This hypothesis proposes that drugs bind to a common site on sodium channels but exhibit variable clinical effects because of variability in the rates at which drug binds to and dissociates from this site; in addition, as the sodium channel shuttles through its conformational states (primarily closed, open, and inactivated), affinity of the drug for its binding site changes. This framework can explain clinical and basic observations like the beneficial effects of certain drug combinations, variable conduction slowing at slow versus fast heart rates, and atrial versus ventricular selectivity. Notably, the concept emerged well before any ion channel had been cloned. A contemporary view of drug block of sodium channels (and indeed many other channels) supports the idea of a common drug binding site to which individual drugs gain access as a function of their own physicochemical properties and the specific structural and gating properties of the ion channel protein itself. Some ion channel blockers may bind to a site distant from the conducting pore to generate a structural change in the protein that then blocks current flow (an “allosteric” effect), while others do appear to bind within and, therefore, directly block ion flow within the conducting pore of a channel.

Despite the contemporary appeal of a single drug target strategy for drug development, the most effective antiarrhythmic compound is the “dirtiest” of drugs, amiodarone. Amiodarone was developed in the 1960s as an antianginal, entered clinical practice in South America and Europe as an antiarrhythmic in the 1970s, and percolated through to the United States in the 1980s. The major mechanisms whereby this drug suppresses a wide range of arrhythmias remain uncertain, but one key electrophysiological effect that was appreciated early was prolongation of the QT interval. Therefore, along with sodium channel blockers being developed in the 1980s, a second strategy was development of drugs that would prolong the QT interval. A proposed mechanism whereby QT prolongation by amiodarone (and bretylium) suppressed arrhythmias was by decreasing heterogeneity of action potential durations and, thereby, preventing reentry. The physiological heterogeneity that we now increasingly appreciate across the ventricular wall was not then understood, but heterogeneities of action potential durations between normal and infarcted tissue were well recognized and reduction of such heterogeneities were one proposed mechanism for the efficacy of these compounds that experimental data continues to support.

The Cardiac Arrhythmia Suppression Trial (CAST)

CAST represents a landmark trial result, not only for the arrhythmia community, but also for the drug development and regulatory communities at large. CAST tested the then-prevalent hypothesis that since ventricular ectopy following MI is a risk factor for sudden death, suppression of ventricular ectopy would reduce the incidence of sudden death. As is now well appreciated (Fig. 1), mortality among patients randomized to ventricular ectopic suppression with encainide or flecainide in CAST was approximately threefold higher than that of patients randomized to receive placebo. For physicians caring for patients this result in 1989 came as a bolt from the blue, and most physicians are now reluctant, at best, to initiate antiarrhythmic therapy for patients with few or no symptoms.

For basic and clinical scientists interested in arrhythmia mechanisms, the CAST result provided a strong impetus to further work that defined the way in which loss of sodium channel function could be arrhythmogenic, particularly in the damaged heart. The propensity of encainide and flecainide to “paradoxically” generate sustained arrhythmias in patients with baseline nonsustained arrhythmias, or to generate frequent, incessant, or occasionally uncardiovertible ventricular tachycardia in patients with rare episodes prior to drug, had been recognized in the early 1980s. However, the extent to which this or similar electrophysiological effects might translate into the recently ischemic heart had not been widely appreciated pre-CAST. One likely mechanism underlying the proarrhythmic effect of sodium channel block is conduction slowing, an effect that promotes reentry. More recently, human genetics has provided further evidence that loss of sodium channel function is proarrhythmic, with description of the Brugada syndrome and the proposal...
The consequences of the CAST result

- new indications for drug therapy
- new understanding of mechanisms
  - clinical
  - whole heart and whole animal
  - cellular
  - molecular
  - genetic
- targeting mechanisms in antiarrhythmic drug use and development (the "Sicilian Gambit")
- development of antiarrhythmics with alternate modes of action
- proarrhythmia as the centerpiece of
  - new antiarrhythmic drug development
  - clinical choice of antiarrhythmics in specific patients
- increased use of the multicenter trial
- focus away from surrogate endpoints in all pivotal studies of all new drugs

that loss of sodium channel function in this disease promotes transmural heterogeneity that similarly favors reentry.27

The idea that drugs might "paradoxically" worsen arrhythmias had been recognized in other settings pre-CAST, including increasing ventricular ectopic frequency by drug administration28 and QT prolongation and induction of torsades de pointes, discussed further below. In fact, the word "proarrhythmia" first appears in a Medline search in 1986. It is safe to say that the issue of proarrhythmia had been an interesting sidebar in the arrhythmia world until CAST, when the notion that antiarrhythmic drugs might kill more people than they saved moved drug safety, and in particular the issue of proarrhythmia, to the key question in new drug development. Further, CAST demonstrated, in a particularly graphic and unambiguous fashion, that the use of surrogate markers of drug effect as a substitute for important biological endpoints was intrinsically risky unless the biology linking the surrogate to the "hard" disease endpoint was extremely well understood.29 The specific problem in CAST was that the complexity of the biology linking ventricular ectopy to sudden death was not well understood. As a result of CAST, trials evaluating cholesterol lowering treatments, antithrombotic interventions, antiheart failure treatments, and newer antiarrhythmic drugs, to name but a few, have now refocused on hard endpoints, like death, rather than on surrogate endpoints.

The CAST result also led to a new framework to consider antiarrhythmic drug indications and development, the "Sicilian Gambit." The concept proposes that identifying and targeting specific arrhythmia mechanisms should supplant the nonspecific or poorly understood drug actions used to date,30 a philosophy that now more than ever seems most appropriate for the treatment of arrhythmias as discussed below.

NASPE: The Recent Past

Another consequence of CAST was that development of sodium channel blocking drugs came to a rapid halt, and QT prolonging agents then assumed the limelight. Just as procainamide and lidocaine provided the structural starting point of a range of sodium channel blocking molecules, two compounds with prominent (although not terribly potent) action potential prolonging...
properties formed the starting point here: N-acetyl procainamide (NAPA) (the major metabolite of procainamide) and sotalol. Both compounds also lack sodium channel block, and spawned a generation of QT prolonging drugs: the non–beta-blocking dextrorotary isomer of sotalol (d-sotalol), dofetilide, almokalant, sematilide, E4031, MK-499, MS-551, WAY-123,398, and others.32 The screening assay to develop these agents was usually action potential prolongation in a guinea pig papillary muscle, and as with newer sodium channel blockers, these compounds were not synthesized to interact with a specific predefined molecular target. Nevertheless, it proved relatively straightforward to generate compounds with extraordinary potencies (low nanomolar). Such high potency generally denotes specificity for a single drug target molecule, an unanticipated effect given the increasing appreciation at the time of the multiplicity of individual ion currents that determine QT by flowing across the cell membrane during cardiac repolarization. Nevertheless, subsequent studies identified block of one specific potassium current, termed \( I_{Kr} \) (“the rapid component of the delayed rectifier \( I_K^d \)”), as the major mechanism underlying QT prolongation by antiarrhythmic drugs and by “noncardiovascular” agents like terfenadine, astemizole, and cisapride.33 As with encainide and flecainide, high potency translates into a low incidence of side-effects unrelated to the drugs’ primary pharmacologic actions. Unfortunately, the parallels between potent sodium channel blocking drugs and potent \( I_{Kr} \) blocking drugs extend beyond this. First, in both cases, the “natural extension” of the drugs’ pharmacology is proarrhythmia: torsades de pointes for the \( I_{Kr} \) blockers. Interestingly, early studies with NAPA31 and sotalol34 reported early afterdepolarizations at slow drive rates in canine cardiac Purkinje fibers, a now well-recognized in vitro arrhythmogenic correlate of torsades de pointes. Second, loss of \( I_{Kr} \) function is also associated with a genetic arrhythmia syndrome, the LQT2 form of the long QT syndrome. As torsades de pointes became recognized as an \( I_{Kr} \) related problem, theoretical arguments were put forward suggesting that drugs preferentially prolonging action potentials at fast rates might prove to be superior antiarrhythmic drugs.35 As a consequence, a number of companies launched a search for \( I_{Kr} \)-specific blockers (that might have this attribute), but these programs were uniformly suspended when mutations in the genes whose expression underlies \( I_{Ks} \) were found to cause the LQT1 form of the long QT syndrome.

Potent \( I_{Kr} \) blocking antiarrhythmics were tested for a potential beneficial effect in patients at risk for sudden death, but these trials proved disappointing. Survival with the Oral d-Sotalol (SWORD) trial demonstrated that d-sotalol, like the potent sodium channel blocking drugs, also increased mortality.37 As in CAST, the mechanisms underlying this increased mortality in SWORD remained conjectural, but proarrhythmia due to the drug’s well-established propensity to cause torsades de pointes in some patients seems a likely candidate. Dofetilide is a drug with electrophysiological properties similar to those of d-sotalol, but in the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) studies dofetilide did not increase mortality.38 It seems likely that trial design issues, notably patient selection and patient monitoring, account for the difference between the outcomes with these two relatively similar compounds.

\( I_{Kr} \) is generated by expression of the Human Ether-a-go-go-Related Gene (HERG). Groundbreaking work for which the 2003 Nobel Prize in Chemistry was awarded describing the crystal structure of bacterial potassium channels has been combined with the electrophysiological characteristics of \( I_{Kr} \) block to identify features of the HERG protein, absent in other ion channels, that render it susceptible to inhibition by so many structurally and functionally unrelated drugs.17 The recognition of rare cases of torsades de pointes during treatment with “noncardiovascular drugs” like terfenadine, astemizole, cisapride, and others has been generalized into a new issue that development of all new drugs (regardless of indication) have to address: does a new agent have the potential to markedly prolong QT and cause torsades de pointes?24,43 Interestingly, astemizole and its metabolite desmethylastemizole, cisapride, and terfenadine are among the most potent HERG/\( I_{Kr} \)-blocking drugs yet described with potencies exceeding that of dofetilide.

One characteristic that newer sodium channel blocking or QT prolonging agents did share with older drugs was prominent interindividual variability in response: some patients appeared to derive striking symptomatic benefit, whereas others demonstrated apparently unpredictable adverse effects like bronchospasm with propafenone, torsades de pointes, or other proarrhythmia. Clinical studies have identified risk factors for these adverse events, and in many cases have provided a springboard for experiments to delineate underlying molecular mechanisms.44,45

The narrow margin between doses producing efficacy and those producing side-effects with older drugs like lidocaine and quinidine prompted the development of therapeutic drug monitoring as a strategy to optimize drug therapy. Extension of this approach with the newer drugs generated new findings that have proven important...
in clinical pharmacology in general. First, drug effects are mediated in some cases by generation of active metabolites: amiodarone, procainamide, propafenone, and encainide are examples. Second, some drugs are eliminated by a single pathway, whose inhibition, by genetic factors or by drug interactions, can lead to striking changes in plasma concentrations of drug and active metabolites, and serious and previously unexplained adverse reactions. Propafenone is a weak β-blocker that is metabolized by a specific hepatic enzyme, CYP2D6. In 5–10% of Caucasians and Africans, both CYP2D6 alleles encode nonfunctional enzyme; in these “poor metabolizer” subjects, propafenone elimination is slowed, plasma concentrations are markedly elevated, and beta-blocking actions are readily detected.47 Terfenadine and cisapride are eliminated by CYP3A4 to non-1Lkr-blocking metabolites; inhibition of CYP3A4 (by drugs like erythromycin or ketoconazole) led to dramatic increases in parent drug concentration and a torsades de pointes risk.48 The doubling of digoxin concentrations and development of toxicity with coadministration of a wide range of drugs (e.g., quinidine, amiodarone, itraconazole, cyclosporine, and many others) is now understood as a manifestation of inhibition of the major route of digoxin elimination, drug efflux by the transporter P-glycoprotein.49 This molecular approach to drug elimination is one facet of a view that the effects of drugs are determined by their interactions with a wide range of proteins, including not only those influencing pharmacokinetics, but also those determining drug targets, and the diseases that drug therapy is meant to treat. Pharmacogenomics, which studies how variations in the genes encoding these proteins can result in variable drug effects, arose in part from well-described examples in the arrhythmia field.50,51

The Present

The randomized, multicenter trial had become a key feature of the cardiovascular landscape by the early 1980s, notably with large β-blocker trials. One key consequence of CAST was the appropriate institutionalization of this approach to compare efficacy of alternate treatment strategies in arrhythmias. Landmark clinical trials that have moved the arrhythmia field forward include demonstrations of modest benefit with amiodarone in patients convalescing from MI (Canadian Myocardial Infarction Amiodarone Trial [CAMIAT] and European Myocardial Infarction Amiodarone Trial [EMIAT]).52,53 Studies showing significant survival advantages of implanted cardioverter/defibrillator devices in secondary prevention (Antiarrhythmic versus Implantable Defibrillators [AVID] trial and others)54–56 and in primary prevention (Multicenter Unsustained Tachycardia Trial [MUSTT], Multicenter Automatic Defibrillator Implantation Trial I [MADIT-I], and MADIT-II),57–59 and in comparisons of rhythm versus rate control in AF (Atrial Fibrillation Follow-Up Investigation of Rhythm Management [AFFIRM] study).60

At the birth of NASPE, drugs were the only option available for patients with tachyarrhythmias. Ablative therapies and devices have now become therapies of choice for many patients. This reflects the demonstrated efficacy of these approaches and the recognition of the inherent risks, and in particular the risk of proarrhythmia, with long-term use of antiarrhythmic drugs. In communities in which tertiary care is not readily available, drugs may still be used. Even here, however, a key criterion for selection of drugs is minimizing risk and this likely accounts for the widespread use of amiodarone, despite its potential for organ toxicity. In tertiary care settings, antiarrhythmic drugs are increasingly used as adjunctive therapy to nonpharmacologic approaches. These include hybrid pacing/ablation/drug therapies to prevent recurrent AF in patients with incompletely successful focal atrial tachycardia ablation61,62 and drug therapy to prevent ventricular arrhythmias leading to shocks in patients with ICDs.63,64 A particularly interesting example comes again from the proarrhythmia area: slow, drug-modified atrial flutter is one well-recognized outcome of sodium channel blocking drugs (including quinidine, flecainide, propafenone, and amiodarone) for AF. Ablation targeting isthmus dependent atrial flutter, with continuation of the drug to prevent AF, has been used successfully as hybrid therapy in some patients.65 Importantly, the use dependent properties of such sodium channel blockers can generate wide QRS complexes during 1:1 AV conduction of this arrhythmia, and this is likely one mechanism underlying early reports of flecainide induced ventricular tachycardia in patients receiving the drug for AF.66,67

The major unmet needs in antiarrhythmic drug therapy are in the management of AF (rate control and rhythm control) and in primary prevention of sudden death. Nonpharmacologic therapies have made significant impacts in both of these areas, but given the large and increasing numbers of patients at risk and the modest efficacy of available therapies, new treatments seem desirable, and are the focus of ongoing drug development programs. Drugs that are currently in relatively late phase development are listed in Table I.68–70 The hope of the ion channel blockers in development is that by not targeting Ik,r specifically, the risk of drug induced torsades de pointes may be reduced. Azimilide acts by blocking
multiple ion channels (including $I_{Kr}$, $I_{Ks}$ and perhaps calcium current) and in some trials has been effective in AF.$^{71-73}$ Azimilide, like doxetilide, showed a neutral effect in a large post-MI trial (Azimilide Post-Infarct Survival Evaluation trial [ALIVE]), although the incidence of AF was reduced. Bone marrow depression may be a problem. Dronedarone is an amiodarone analog developed in the hope that it would produce amiodarone-like efficacy without long-term organ toxicity.$^{74,75}$ Tedisamil was developed as an antianginal and turns out to block a number of potassium currents,$^{76,77}$ torsades de pointes has been elicited in experimental animals,$^{78}$ and diarrhea is a common adverse effect.$^{77}$ Piboserod is an antagonist of serotonin 5HT4 receptors that is being evaluated in AF (and has been examined in other settings like irritable bowel). Two compounds (DTI-0009 and tecadenoson [CVT-510]) act at adenosine receptors and are in development as new strategies to control atrial response in AF.$^{79,80}$ Amio-aqueous IV is a new formulation of amiodarone that may lack some of the adverse effects related to the current formulation.$^{81}$

## The Future

A hundred years ago, indications for drug treatment of any kind were nonspecific: weakness, jaundice, anemia, fainting, or palpitations. In our current evidence-based climate, such approaches to therapy are inappropriate, and we seek instead specific diagnoses: atrial flutter, ventricular ectopic activity, sustained ventricular tachycardia, sudden cardiac death due to ventricular fibrillation. Single drugs that provide safe and effective therapy for each of these conditions represent the goal of contemporary antiarrhythmic drug development. However, we also increasingly recognize that these arrhythmia diagnoses are, themselves, rather nonspecific. When NASPE was founded, the treatment of atrial flutter was lumped with that for AF; we now recognize that both drug and ablative therapies are generally quite different for the two arrhythmias.$^{82,83}$ AF may be related to heart failure, may represent focal activity in pulmonary vein(s) or elsewhere, or may represent the consequence of atrial fibrosis that comes with age or with maintained AF.$^{84}$ Each of these entities is likely to respond to a different form of drug therapy. Thus, just as a single drug to “cure cancer” is an irrational goal, because “cancer” represents a wide spectrum of pathophysiologies, the concept of a single drug to cure large numbers of patients with arrhythmias is intrinsically flawed because of our increasing recognition of the diversity of mechanisms that can generate arrhythmias. Further, if experience has taught us nothing else in the lifetime of NASPE, it has shown us that tinkering with the electrophysiological substrate to cure one arrhythmia runs the great risk of generating the substrate for another (occasionally more serious) one. This diversity in arrhythmia mechanisms is further compounded by genetic variants that determine drug elimination and drug actions; screening individual patients for important variants that would then influence choice of drug or dose is an appealing vision whose implementation is the goal of modern pharmacogenomics.$^{50,51}$

Is there then no prospect for new effective antiarrhythmic drugs? Two strategies are now being developed that should hold some promise. The first is the development of drugs that target atrial tissue only, thereby holding the promise of efficacy in AF but avoiding ventricular proarhythmia.$^{85,86}$ One such molecular target is the potassium channel gene Kv1.5 (now known as KCNA5), whose expression underlies the ultrarapid delayed rectifier current, $I_{Kur}$. In humans, KCNA5 expression is much greater in atrium than in ventricle,$^{87}$ and $I_{Kur}$ is readily recorded in atrium but not ventricle.$^{88}$ However, the gene is also expressed in extracardiac tissues (brain, endocrine organs) so

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<tr>
<th>Drug</th>
<th>Indication</th>
<th>Mechanism of Action</th>
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<tbody>
<tr>
<td>Amio-aqueous IV</td>
<td>As for IV amiodarone</td>
<td>As for IV amiodarone</td>
</tr>
<tr>
<td>Azimilide</td>
<td>Maintenance of sinus rhythm in AF</td>
<td>Block of multiple $K^+$ currents</td>
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<tr>
<td>Dronedarone</td>
<td>Maintenance of sinus rhythm in AF</td>
<td>Block of multiple $K^+$ currents</td>
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<tr>
<td>DTI-0009</td>
<td>Rate control in AF</td>
<td>Adenosine receptor blocker</td>
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<tr>
<td>Piboserod</td>
<td>Maintenance of sinus rhythm in AF</td>
<td>Block of atrial serotonin in 5HT4 receptors</td>
</tr>
<tr>
<td>RSD1235</td>
<td>Maintenance of sinus rhythm in AF</td>
<td>Atrial selective action potential prolongation</td>
</tr>
<tr>
<td>Tecadenoson (CVT-510)</td>
<td>Rate control in AF</td>
<td>Adenosine receptor blocker</td>
</tr>
<tr>
<td>Tedisamil</td>
<td>Maintenance of sinus rhythm in AF</td>
<td>Block of multiple $K^+$ currents</td>
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### Table I.

New Antiarrhythmic Drugs Currently in Clinical Trials
extracardiac adverse effects might arise with a Kv1.5 blocker. Whether contemporary molecular biological approaches, like microarray or other large scale genomic experiments, can define suitable targets, like molecules expressed only in atrium, or better yet molecules expressed only in diseased but not healthy atrium, remains to be determined. Further studies of the molecular basis of arrhythmias will assist in identifications of such new targets.

A second newer approach to development of antiarrhythmic drugs is to recognize the dangers, described here, of ion channel-active agents. A contemporary view would hold that arrhythmias arise as a consequence of perturbed cell biology, on a genetic and/or structural basis. An increasingly recognized link in the pathway between an initial molecular lesion and the manifestation of an arrhythmia is the process generically known as “electrophysiologic remodeling,” which in this context is taken to mean the cascade of events that translates a molecular stimulus to a transiently, semipermanently, or permanently altered substrate that with appropriate triggers then develops arrhythmias. As the molecular details of this sort of framework are increasingly well worked out, the upstream molecular events that generate the abnormal substrate may be identified, and might then be superior molecular targets. We have had in the antiarrhythmic world extensive experience with one class of drugs that appear to do just this: β-blockers. These drugs are not terribly effective in suppressing arrhythmias like ventricular ectopic activity, yet they are the most effective “antiarrhythmic” agents as a class in the prevention of sudden death. Perturbed intracellular calcium control is a common feature of the hypertrophic heart failure arrhythmic myocyte phenotype. Indeed, new evidence suggests that β-blockers may correct one aspect of this dysregulation, hyperphosphorylation of the SR calcium release channel.89 In addition, activation of the calcium dependent calmodulin kinase, CaMKII, appears to be an early upstream molecular event in generating the hypertrophic heart failure arrhythmic phenotype and CaMKII inhibition has been shown in proof-of-principle animal experiments to prevent arrhythmias in mouse and rabbit models.90,91 Similarly, inhibition of sodium-hydrogen or sodium-calcium exchange have blunted the remodeling that accompanies AF in animal models.92,93

Recent megatrials in cardiovascular medicine have described striking effects on sudden death of a number of interventions not developed, or even conceived of, as targeting arrhythmia triggers or substrates. The Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Mio-cardico (GISSI)-Prevenzione trial prospectively evaluated the effect of n-3 polyunsaturated fatty acids (fish oil) supplementation in >11,000 patients with recent (<3 months) acute MI, and found a 53% reduction in sudden death at 4 months.94 Similar unexpectedly large effects of “nonantiarrhythmic” drugs on sudden death have been seen in trials of angiotensin-converting enzyme (ACE) inhibitors,95 HMG CoA reductase inhibitors (statins),96 and aldosterone receptor antagonists.97 While an overall beneficial effect on plaque stability and the progression of coronary disease may underlie these drug actions, a direct modulatory effect on heretofore poorly understood signaling pathways that generate the arrhythmic substrate is a hypothesis that deserves further exploration; further understanding of the way in which these pathways affect arrhythmogenesis may point to entirely new and specific antiarrhythmic interventions.

Along the same lines, a number of studies now point to oxidant stress as a common feature of AF (especially in the postoperative period)98,99 and clinical trials are now underway to test the effect of antioxidant intervention by vitamin C in this patient population. Retrospective analyses of trials of ACE inhibitors have shown a marked reduction (>50%) in the development of AF.100,101 A similar (albeit smaller) effect was reported when patients with recurrent AF receiving amiodarone were randomized to the AT1 receptor blocker irbesartan or matching placebo.102 One study in dogs suggested that the beneficial effects of ACE inhibition were related to suppression of monophasic action potential (MAP) kinase activation that was associated with remodeling.103

**Conclusion**

Antiarrhythmic drug therapy has, over the lifetime of NASPE, progressed from a handful of poorly tolerated, relatively ineffective drugs with incompletely understood mechanisms of action to rational drug selection based on an improved understanding of risks and benefits derived from clinical trials and mechanistic studies. The drugs themselves are an improvement, but serious side-effects continue to be a major problem. The development of any single new drug entity that was modestly effective and yet not characterized by proarrhythmia or other side-effects would represent a huge advance. Whether such drugs could, or should, supplant nonpharmacologic therapies is not so clear. Nonpharmacologic therapies are curative in many instances, and it is difficult to conceive of situations in which patients at high risk of sudden death would be better served by a drug than the implantable cardioverter defibrillator. As is often the case, only development of such
novel compounds and appropriate clinical trials will establish their place in primary and tertiary cardiovascular care.

Understanding the mechanisms of arrhythmias and a critical evaluation of the efficacy and mechanisms of action of drugs used to treat them has been a key characteristic of the electrophysiological community over the last 25 years. These studies have provided striking advances for our patients. This intimate relationship between basic science and clinical science, between molecular and clinical genetics, between drug development and clinical drug trials, and between an understanding of mechanisms and application of mechanisms in clinical practice has been the distinguishing feature of the electrophysiological community that continue to make it a model for other disciplines.

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