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Clinical Use and Future Perspectives on Antiarrhythmic Drugs

Juan Carlos Estrada, MD and Dawood Darbar, MD

Divisions of Cardiovascular Medicine and Clinical Pharmacology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN

Abstract

Cardiac arrhythmias are associated with significant morbidity and mortality. Antiarrhythmic drug therapy was traditionally the mainstay of arrhythmia treatment; however, the limited efficacy and proarrhythmic potential of conventional antiarrhythmic drugs has generated interest in new approaches to the treatment of arrhythmias. Over the last decade there has been improved characterization of the molecular pathways that culminate in arrhythmias. By analyzing mechanisms that increase susceptibility to arrhythmia in individuals with genetic syndromes, it might be possible to not only improve current therapies but also to develop novel approaches to treat and prevent common arrhythmias.

Cardiac arrhythmias remain a major source of morbidity and mortality in developed countries. In the past decade the treatment of arrhythmias has been dramatically altered by the development of non-pharmacological therapies such as targeted ablation of arrhythmogenic tissues and implantable cardioverter defibrillators (ICDs) as well as the limited efficacy and proarrhythmic potential of conventional antiarrhythmic drugs. Efficacy of antiarrhythmic drugs in suppressing the most common arrhythmia, atrial fibrillation (AF), is generally between 30 to 60% and no single agent shows superiority with the possible exception of amiodarone. Between 0.5 million and 1 million North Americans and Europeans die each year of sudden cardiac death (SCD), which causes 10–20% of all deaths among adults in the Western world [1,2]. The most common underlying cause for SCD is ventricular fibrillation (VF). SCD most often occurs in patients with underlying coronary artery disease (CAD). Thereby, as the prevalence of CAD increases worldwide, so will the incidence of SCD. Although identification of patients at high risk for SCD is possible by evaluating those with heart disease, in about half of all cases SCD is the initial presenting symptom of heart disease [2,3]. In those judged to be at high risk of SCD, ICDs are often used. These devices are highly effective at terminating life-threatening arrhythmias if they occur, but they do not prevent arrhythmia.

There are other forms of arrhythmias besides AF and VF but, these stand out because they are common and serious forms of arrhythmias and because safe and effective therapies have not yet been developed. Here, we initially focus on current antiarrhythmic drugs and their limitations, then, we go on to discuss how emerging understanding of underlying arrhythmic mechanisms, especially in rare genetic arrhythmia syndromes, might inform the development of improved therapies.

Ablation for arrhythmic cure

Ablation for arrhythmic cure is predicated on an understanding of underlying mechanisms. The development of an understanding of the precise locations of fixed macro-reentrant circuits,

notably in the Wolff-Parkinson-White (WPW) syndrome, allowed surgeons, and subsequently electrophysiologists, to permanently interrupt circuits and to cure patients. Radiofrequency (RF) catheter ablation techniques have had a dramatic impact on the approach to the treatment of a variety of cardiac arrhythmias. This is especially evident in the case of WPW syndrome and atrio-ventricular (AV) nodal reentrant tachycardia, where RF catheter ablation of accessory pathways and AV nodal slow pathways has become first-line therapy. More recently, RF catheter ablation has been applied successfully in patients with atrial tachycardias and atrial flutter. However, catheter ablation of more complex arrhythmias including many forms of intra-atrial reentry, many ventricular tachycardias (VTs) and AF continues to pose a major challenge. Arrhythmias for which ablation is most effective (accessory pathways, AV nodal reentrant tachycardia, typical atrial flutter, right ventricular outflow tract [RVOT] VT) depend primarily on anatomically well-defined substrates. Accordingly, approaches to mapping and ablation of these arrhythmias are anatomically directed (e.g. accessory pathways along the annuli, RVOT VT), if not completely determined by anatomic location (AV nodal reentrant tachycardia, typical atrial flutter).

Recent advances in our understanding of AF have led to development of catheter ablation techniques that could feasibly achieve a cure for AF. Catheter ablation for AF was first reported more than a decade ago and stemmed from the success of the surgical Maze procedure. The latter is a surgical method based on mapping studies of animal and human AF that has been reported to successfully control AF in more than 90% of selected cases [4]. A key advance has been the recognition that the pulmonary veins are a common source of arrhythmogenic foci with abnormal automaticity that induce paroxysmal AF [5]. Modifications of the Maze procedure (Maze III) involve encircling the pulmonary veins, and may prevent initiation of AF by isolating such potentially arrhythmogenic foci. Surgeons currently tend to use the procedure for patients who have drug-refractory AF undergoing surgery for concomitant cardiac disease (frequently mitral valve disease). Given the success of the surgical approach, several ablation strategies have been designed. Ablation of these foci eliminates or reduces the frequency of recurrent AF in more than 60% of patients, although there is still a small recurrence rate following the procedure, necessitating the need for antiarrhythmic drugs [6,7]. Although catheter-directed ablation of AF represents a substantial achievement that promises better therapy for a large number of patients presently resistant to pharmacological or electrical conversion to sinus rhythm, the limited available studies suggest that this approach offers benefit to selected patients with AF. Furthermore, these studies do not provide convincing evidence of optimum catheter positioning or absolute rate of treatment success [8]. For now, pulmonary vein isolation may best be considered for patients resistant to pharmacological treatment, especially those who are younger and have lone AF.

Historical Perspective on Current Antiarrhythmic Drugs and Their Limitations

Drugs that are currently marketed as antiarrhythmics were initially developed in whole-animal models by screening for their effects on normal cardiac electrophysiology. However, decades elapsed before the initial use of older antiarrhythmic drugs in humans and more importantly the definition of their molecular mechanisms of action. Antiarrhythmic drugs are only partly effective and have many adverse effects. The most important of these is the potential to generate new life-threatening arrhythmias (proarrhythmia).

The increasing appreciation of ventricular arrhythmias as a marker of underlying heart disease and, therefore, a potential drug target, led to the development of multiple new antiarrhythmic drugs in the late 1970's and early 1980's. An early animal model that was used to screen for antiarrhythmic activity was the "Harris dog," which demonstrates extremely high-frequency ventricular ectopic activity after two-stage coronary artery ligation. As ventricular arrhythmias are especially sensitive to sodium channel blockers, so the first wave of new antiarrhythmics

were drugs that were derived from existing structures and demonstrated activity in this and other models, i.e., primarily sodium channel blockers.

The Cardiac Arrhythmia Suppression Trial (CAST) represents a landmark trial result, not only for antiarrhythmic drug development but for drug development in general. CAST tested the then-prevalent hypothesis that because ventricular ectopy following myocardial infarction is a risk factor for SCD, suppression of ventricular ectopy would reduce the incidence of SCD. As is now well appreciated, mortality among patients randomized to ventricular ectopic suppression with encainide or flecainide in CAST was approximately three-fold higher than that of patients randomized to receive placebo [9]. It also emphasized the importance of a randomized, placebo-controlled trial with a primary ‘hard’ endpoint, such as death, as opposed to a surrogate end point, such as ectopic-beat suppression, in order to sort out if a drug was beneficial or not. The drugs tested in CAST turned out to be potent sodium-channel blocking agents.

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 was arrhythmogenic. It is thought that blocking sodium channels increases the risk of SCD by slowing conduction and/or increasing the heterogeneity of repolarization, both of which can be arrhythmogenic, especially in diseased hearts [10,11]. More recently, human genetic studies have provided further evidence that loss of sodium channel function can be proarrhythmic with description of the Brugada syndrome and the proposal that loss of sodium channel function in this disease promotes transmural heterogeneity that favors reentry [12]. 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 [13], a philosophy that now more than ever seems most appropriate for the treatment of arrhythmias as discussed later.

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 action potential-prolonging properties formed the framework here: N-acetyl procainamide (NAPA) and sotalol. Both compounds also lack sodium channel block [14,15] and gave rise to a generation of QT-prolonging drugs: d-sotalol, dofetilide, almokalant, sematilide and others [16]. Although the screening assay to develop these agents usually was 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, subsequent studies identified block of one specific potassium current, termed I_{Kr} , (the rapid component of the cardiac delayed rectifier potassium current), as the major mechanism underlying QT prolongation by antiarrhythmic drugs. I_{Kr} is encoded by *KCNH2* (also known as *HERG*). However, blocking I_{Kr} carries the risk of marked QT-interval prolongation and a distinctive form of polymorphic ventricular tachycardia, termed torsades de pointes. Indeed, potassium-channel blocking antiarrhythmic drugs have been tested in CAST-like trials and did not prevent more deaths than a placebo [17–19]. Moreover, the same mechanism underlies the development of torsades de pointes in response to ‘non-cardiovascular’ drugs such as certain antihistamines, antibiotics and antipsychotics [20].

Targeting Signaling Pathways for Treatment of Arrhythmias

Traditional antiarrhythmic drugs target a single molecular target, such as sodium channels or *KCNH2* channels. However, in a complex biological system such as the cardiomyocyte, it is

perhaps not surprising that these agents have unintended electrophysiological consequences. Thus, the development of antiarrhythmic drugs that target activation of abnormal arrhythmogenic pathways, which are absent or minimally active in normal tissue, could be a safer and more effective way to drug development. Indeed, β -blockers, which do not directly target ion channels, have not shown serious proarrhythmic effects and can reduce the incidence of SCD [21,22]. In addition, animal experiments and clinical trials have identified other pharmacological interventions that seem to have antiarrhythmic properties but do not target ion channels [23].

Structural myocardial changes such as cavity dilation, hypertrophy of myocytes, and/or interstitial fibrosis appear to be morphologic substrates or triggers for some arrhythmias. Therefore, components of signal transduction pathways responsible for these structural changes could serve as non-ion-channel drug targets to improve therapy for arrhythmias. Recent large randomized clinical trials have described striking effects on SCD of several interventions not yet developed as targeting arrhythmia triggers or substrates. GISSI-Prevenzione (Gruppo Italiano per lo Studio della sopravvivenza nell'Infarto Miocardico-Prevenzione) prospectively evaluated the effect of n-3 polyunsaturated fatty acid (n-3 PUFAs) supplementation in more than 11000 patients with recent (<3 months) acute myocardial infarction and found a 53% reduction in SCD at 4 months [24]. These findings are only partially explained by their beneficial effects on lipids. The n-3 PUFAs reduce VF in animal models, reduce Na^+ and L-type Ca^{2+} currents, modify eicosanoid production, and likely alter membrane fluidity [25]. In addition, there is increasing evidence for antioxidant/anti-inflammatory properties. Although a reduction in mortality and serious ventricular tachyarrhythmias in patients with ICDs has not been demonstrated, initial studies suggest a beneficial effect on AF [26]. The n-3 PUFAs reduce isoproterenol-induced asynchronous contractions in isolated atrial myocytes [27]. In the Cardiovascular Health Study, consumption of tuna or baked/broiled fish in persons aged ≥ 65 years was associated with a reduction in the risk of AF, although two other studies failed to show a beneficial effect [25,27]. Recently, n-3 PUFAs were shown to reduce postoperative AF [25].

Similar unexpected large effects of 'non-antiarrhythmic' drugs on SCD have been seen in trials of angiotensin-converting-enzyme (ACE) inhibitors [28], HMG-Co-A reductase inhibitors (statins) [29], and aldosterone receptor antagonists [30]. Although 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 requires further exploration. Retrospective analyses suggest that ACE inhibitor therapy is associated with a lower incidence of AF and a placebo-controlled trial found a similar beneficial effect of adding the angiotensin-receptor blocker irbesartan to amiodarone [31]. Inhibition of the renin-angiotensin-aldosterone system (RAAS) appears to prevent the development of AF by suppressing electrical and structural cardiac remodeling; this is supported by experimental data on ventricular tachypacing-induced heart failure and the canine rapid atrial pacing model [32].

Oxidative stress

Environmental stress such as inflammation, renin-angiotensin-aldosterone system (RAAS) activation, and aging can cause oxidative damage in the atrium [33]. Oxidative changes are present in the atrial tissue of patients with AF, accompanied by mitochondrial DNA damage and upregulation of genes involved in the production of reactive oxygen species. In a porcine model of AT and in human AF, atrial superoxide production is increased, with a major contribution from NAD(P)H oxidase [33]. The water-soluble antioxidant ascorbate has proven beneficial in animal models and early clinical trials [27,33]. Ascorbate can attenuate electrical modeling and oxidative damage in the canine AT model (although one study showed no

benefit), reduce postoperative AF, and decrease early AF recurrence and CRP after cardioversion [33].

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, confer cardiovascular benefits beyond cholesterol-lowering effects, at least in part because of reduced oxidative stress and inflammation. Recent studies indicate that statins prevent remodeling and AF promotion in the canine AT and sterile pericarditis models [34]. In most large clinical trials to date, statins have been shown to reduce AF (and in some cases, CRP and/or atrial oxidative damage) in patients with coronary artery disease, LV dysfunction, and age greater than 65 years as well as after cardioversion, CABG, and non-cardiac thoracic surgery [27,33]. As for RAAS inhibition, large-scale prospective randomized, double-blind, placebo-controlled trials have as yet not been performed.

The mechanisms by which these interventions, which are not reported to have proarrhythmic potential, exert antiarrhythmic effects is an area of intense investigation because identification of the responsible molecular pathways could lead to the development of more specific, effective and safe antiarrhythmic drugs.

A Mechanism-based Approach to Antiarrhythmic therapy

One universal principle of pharmacologic therapy is that the best treatment is that targeted specifically to disease mechanisms. In arrhythmia therapy, a good example is cure of arrhythmias in the WPW syndrome by bypass tract ablation. As our understanding of the molecular and cellular basis of arrhythmias has evolved, so too has the list of arrhythmias for which specific mechanisms have been defined, and therefore specific antiarrhythmic drug therapies may be indicated (Table 1). Thus, the role of adrenergic triggering in RVOT VT makes beta-blockers a rational mechanism-based therapy. Recognition of the critical role of slow conduction within the AV node or orthodromic reciprocating tachycardia makes adenosine a rational, mechanism-based choice of therapy for the acute termination of these arrhythmias. However, it is the recent advances in our understanding of molecular mechanisms in specific rare inherited monogenic arrhythmia syndromes that has provided insight into common arrhythmias which may also prompt consideration of specific mechanism-based therapies.

Monogenic arrhythmia syndromes

Monogenic diseases are caused by single genetic defects, follow Mendelian inheritance, and are classified as autosomal dominant, autosomal recessive, or X-linked. Over 5000 monogenic diseases have been identified, and more than 1000 genes responsible for these disorders are known. The prevalence of monogenic diseases ranges from 1 in 1000 individuals in the most common forms to 1 in 200,000 in the rarest. The identification and study of the genetic substrate of these diseases are important not only because they contribute to the development of diagnostic tests for affected individuals but also help understand the function of different proteins in humans. Consequently, genetic testing is currently applied not only for diagnostic evaluation, but also as a research tool for the study of pathophysiology of inherited arrhythmia syndromes. In cardiology, there are two major clusters of monogenic disorders: [1] The cardiomyopathies due to alterations in sarcometric and in cytoskeletal proteins and [2] the arrhythmogenic diseases that are caused by mutations in ion channels and ion channel-controlling proteins such as the congenital long-QT syndromes (LQTS), the Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), Andersen-Tawil syndrome and AF.

The earliest description of a familial disease characterized by QT-interval prolongation on an electrocardiogram, a structurally normal heart and an increased risk of SCD was in the late

1950's. However, the LQTS and other rare genetic diseases that cause arrhythmias remained electrophysiologic curiosities until the identification of large numbers of kindreds through registries allowing a comprehensive description of clinical features, and more importantly, the identification of disease-associated genes. Concurrently, familial diseases in patients presenting with cardiomyopathy were also described, and disease-associated genes were identified. Importantly, all familial cardiomyopathy syndromes are associated with increased susceptibility to arrhythmias, and in many cases arrhythmias such as AF, SCD due to VF or profound bradyarrhythmias can be the presenting symptoms that lead to the diagnosis of heart disease in the patient or a family member.

There are several common features of familial diseases that have important implications for the diagnosis and therapy of arrhythmias. First, the familial arrhythmia syndromes are more common than was once appreciated. Early estimates of LQTS prevalence of 1 in 10,000 have been replaced by estimates of 1 in 1,000–2,000 [35]. Second, the identification of disease-associated genes provides a starting point for studies of molecular mechanisms of arrhythmias. Third, elucidation of these mechanisms may lead to the identification of genetic markers of increased risk of AF or SCD in the general population. Knowledge of genetic variants may also be useful in identifying individuals who will respond particularly well or poorly to drugs or other therapies. Fourth, insight into the molecular mechanisms of arrhythmias may deter commercialization of certain drug class actions. For example, loss-of-function mutations in the genes whose expression underlies I_{Kr} and I_{Ks} cause LQTS; drugs that block these currents phenocopy the congenital LQTS and thus can be proarrhythmic (Table 1). Last, these common features reinforce the notion that arrhythmia therapies are most effective when targeted to underlying disease mechanisms. The concept of a mechanism-based approach to treatment of arrhythmias was first proposed over 20 years ago by a Task Force of the Working Group on Arrhythmias of the European Society of Cardiology and is known popularly as the Sicilian Gambit [13]. Table 1 extends this concept to suggest mechanism-based molecular therapies for congenital and acquired diseases associated with increased risk of arrhythmia. Thus, whereas blocking I_{Kr} and I_{Ks} has the potential to be deleterious in most patients, in a small subgroup with arrhythmias caused by gain-of-function mutations in the underlying genes, potassium-channel blockers may be curative. Recently, a patient with early-onset AF and the commonest form of the LQTS (type 1 with a defect in I_{Ks}) was successfully treated with mexiletine with complete suppression of the AF [36]. It is possible that in the presence of decreased repolarization reserve mediated by a potassium channel loss-of-function mutation, as in LQT1, unopposed physiologic late sodium current is pathogenic and therefore may represent a strategic target for antiarrhythmic therapy.

Insight into arrhythmia mechanisms from monogenic arrhythmia syndromes

The identification of genes responsible for the inherited arrhythmia syndromes has contributed greatly to our understanding of arrhythmia mechanisms. The monogenic arrhythmia syndromes have several common features. First, with few exceptions, these syndromes are transmitted in an autosomal dominant manner with variable penetrance. Very rarely, an individual inherits two abnormal disease-associated alleles (usually one from each parent) presents with a severe phenotype as compared to individuals with one disease-associated allele [37]. Second, patients with these syndromes and structurally normal hearts are generally classified as 'diseases of the action potential', with mutations typically affecting ion channels, although there are exceptions. Similarly, hypertrophic cardiomyopathy can be viewed as a disease of sarcomere, dilated cardiomyopathy a disease of the cardiac cytoskeleton, and arrhythmogenic right ventricular cardiomyopathy a disease of cardiomyocyte-cardiomyocyte adhesion. Third, although almost all studies in this field have focused on mutations in the germ line, it is possible that somatic mutations might predispose some individuals to arrhythmias. Recently, in one small case series of patients with AF, a mutation was detected in *GJA5*, which encodes the gap

junction protein connexin-40, in atrial cells but not in the germ line [38]. The role of such somatic mutations in determining the mechanisms of arrhythmias remains unexplored.

Despite these unifying themes however, the clinical phenotype can be heterogeneous and varies not only by broad disease category but also by disease-associated gene. Thus, in patients with certain forms of LQTS, SCD occurs predominantly with exercise. By contrast, for other forms of LQTS it occurs predominantly when patient are at rest [39]. Similarly, some studies suggest that mutations in myosin-binding protein C tend to cause symptoms later in life in patients with hypertrophic cardiomyopathy than do mutations affecting other genes [40]. In addition, when large numbers of families have been studied, mutations affecting specific domains or specific amino-acid residues have been implicated in a better or worse prognosis [41].

Common genetic variants

Genetic variation constitutes the uniqueness of each individual. A polymorphism is defined as a discontinuous genetic variation that results in the occurrence of several different forms or types of individuals among the members of a single species. The most obvious example of polymorphism is the separation of higher organisms into male and female sexes. A polymorphism that persists over many generations is usually maintained because no one form has an overall advantage or disadvantage over the others in terms of natural selection. However, genetic variations in genes that encode proteins important for cellular physiology and function such as ion channel regulation and flux may be deleterious and could be selected against in a population. Usually, when genetic variation exists in a gene, there is a predominant form (allele) in the population, with one or more minority forms (alleles). Although genetic variations could arise *de novo* in a founder individual, it takes many generations before they will be randomly and equally distributed in a population. The second explanation for unequal population frequencies for certain genetic variants is that specific variations may carry a selection disadvantage with regards health and disease.

Polymorphisms associated with increased risk of arrhythmias

It is now generally accepted that many common polymorphisms, usually defined as a population frequency greater than 1%, have physiological or functional consequence. For a long time it was assumed that development of polymorphic VT upon exposure to a QT prolonging drug was deemed an adverse reaction (so called 'acquired long QT syndrome'). However, the observation that mutations in a number of ion channel genes are responsible for familial or congenital LQTS raised the possibility of the influence of population variants of these genes in the 'acquired' form of long QT syndrome. Yang and colleagues [42] investigated the role of genetic variants in modulating the risk of torsades de pointes and found sub-clinical long QT syndrome mutations in 10–20% of subjects who develop this arrhythmia. We have proposed the idea of 'repolarization reserve' which suggests that multiple mechanisms contribute to normal repolarization, so that removal of any one of these (by disease, subclinical mutation or polymorphism in an ion channel or other gene) may be without consequence until a drug is added at which point the 'reduced repolarization reserve' becomes evident by marked QT prolongation and torsades de pointes [43].

In one report, a variant allele for the cardiac sodium channel gene *SCN5A* (S1102Y) was found to be widespread among African Americans (13%) and African Caribbeaners (19%), whereas it is not found in either Asians or whites [44]. This polymorphism was associated with prolongation of the QT interval and drug-induced arrhythmias. More recently, in the first genome-wide association study of AF, a strong association was discovered between AF and two single nucleotide polymorphisms (SNPs) on chromosome 4q25 [45]. Although the mechanism for this observed association remains unknown, both variants are adjacent to the *PITX2* gene, which is critical for cardiac development [46]. Similarly, variability in the normal

QT interval has been reproducibly associated with polymorphisms in *NOS1AP*, which encodes a subunit of nitric-oxide synthase 1 (also known as nNOS) [47,48].

Future Directions

The past decade has seen remarkable changes in our approach to patients with cardiac arrhythmias. Clearly, the incomplete efficacy and proarrhythmic potential of traditional antiarrhythmics have generated interest in not only novel pharmacologic approaches to arrhythmias but also non-pharmacologic treatments such as catheter ablation. Studies of familial syndromes have identified molecules whose dysfunction leads to arrhythmias and provided a better understanding of fundamental mechanisms underlying arrhythmias. Thus, a mechanism-based approach for the treatment of patients with these syndromes is now possible. However, the bigger challenge now is to apply the same approach to common types of arrhythmias such as AF and SCD. In large populations the identification of common variants that predispose individuals to arrhythmias hold promise for early detection and intervention in asymptomatic patients at high risk.

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Table 1**A mechanism-based approach to antiarrhythmic drug therapy**

Arrhythmia	Mechanism-based therapy	Mechanism targeted
AV nodal reentry AV reentry	Adenosine Verapamil	Macro-reentry utilizing the AV node
Outflow tract VT	Beta-blockers Verapamil, Diltiazem	Adrenergic stimulation
Fascicular VT	Beta-blockers Verapamil, Diltiazem	Reentry within the His-Purkinje system
Torsades de pointes due to drugs	Pacing Isoproterenol K ⁺ supplementation (to 4.5–5 mEq/L)	I _{Kr} block leading to bradycardia-dependent EADs and unstable intraventricular reentry due to heterogeneity of repolarization
Congenital long QT syndrome, type 1	β-blockers	Failure of the adrenergically-activated K ⁺ current I _{Ks} to maintain action potentials short during adrenergic stimulation
Congenital long QT syndrome, type 2	K ⁺ supplementation to 4.5–5 mEq/L	Abnormal action potential prolongation and heterogeneity due to loss of I _{Kr} function
Congenital long QT syndrome, type 3	Sodium channel block: mexiletine; flecainide	Abnormal action potential prolongation and heterogeneity due to increased inward sodium current during the action potential plateau
Brugada syndrome	I _{TO} block: quinidine, sotalol	Increased heterogeneity of action repolarization due to loss of sodium channel function and maintained I _{TO}
AF, VF, or T-wave oversensing in Short QT Syndrome	Quinidine, sotalol	Increased outward current, leading to shortened action potentials, due to abnormally increased I _{Ks} , I _{Kr} , or I _{K1} .
Catecholaminergic polymorphic VT	β-blockers	Leaky sarcoplasmic reticulum leading to after depolarization-mediated arrhythmias with heart rate increases due to adrenergic stimulation

AF, atrial fibrillation; AV, atrio-ventricular; EADs, early after-depolarization; VF, ventricular fibrillation; VT, ventricular tachycardia.