

Current and Emerging Antiarrhythmic Drug Therapy for Ventricular Tachycardia

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ABSTRACT

Ventricular arrhythmias, including ventricular fibrillation (VF) and sustained ventricular tachycardia (VT), are the principal causes of sudden cardiac death in patients with structural heart disease. While coronary artery disease is the predominant substrate associated with the development of VT, these arrhythmias are known to occur in a variety of disorders, including dilated cardiomyopathy, valvular and congenital heart disease, and cardiac ion channelopathies such as the long QT syndrome. In a minority of patients, VT occurs in the absence of structural heart disease. Despite the established mortality benefit of the implantable cardioverter defibrillator (ICD) in patients at risk of lethal arrhythmias, recurrent VT/VF

events continue to be a source of morbidity and impaired quality of life in such patients. Antiarrhythmic therapy is indicated in select patients to treat symptomatic VT episodes, to reduce the incidence of ICD shocks, and potentially to improve quality of life and reduce hospitalizations related to cardiac arrhythmia. The primary adverse effects of antiarrhythmic medications are related to both cardiac and extracardiac toxicity, including the risk of proarrhythmia. Current drug therapy for ventricular arrhythmia has been limited by suboptimal efficacy in many patients, resulting in recurrent VT/VF events, and by drug toxicity or intolerance leading to discontinuation in a large percentage of patients. Amiodarone and sotalol are the principal agents used in the chronic treatment of VT. In addition, dronedarone and dofetilide, agents approved for the treatment of atrial fibrillation, and ranolazine, an antianginal agent, have been demonstrated to be protective against ventricular arrhythmia in small clinical studies. Finally, advances in basic electrophysiology have uncovered new molecular targets for the treatment of ventricular arrhythmia, and pharmacologic agents directed at these targets

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may emerge as promising VT treatments in the future. The roles of these current and emerging therapies for the treatment of VT in humans will be summarized in this review.

Keywords: Antiarrhythmic medications; Ventricular fibrillation; Ventricular tachycardia

INTRODUCTION

Ventricular arrhythmias, including ventricular tachycardia (VT) and ventricular fibrillation (VF), are the leading cause of sudden cardiac death (SCD), which in turn represents about half of all cardiovascular mortality and accounts for over 350,000 deaths annually in the United States [1]. VT can be either sustained (lasting >30 s) or nonsustained, and can have a uniform QRS morphology (monomorphic) or a variable morphology (polymorphic). It is the most common wide complex tachycardia seen in association with structural heart disease [2]. The vast majority of VT is related to myocardial pathologic processes that promote cardiac fibrosis or inflammation, most commonly from coronary artery disease (CAD) in over 80% of patients [3]. However, myocarditis, dilated cardiomyopathy, congenital heart disease, cardiac infiltrative diseases, arrhythmogenic right ventricular cardiomyopathy, and hypertrophic cardiomyopathy are also known to contribute to an arrhythmogenic substrate. In about 10% of patients, VT occurs in the absence of structural heart disease [4]. This subset of VT is thought to be either idiopathic or related to primary electrical disease, such as the long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), or other cardiac ion channelopathies [5, 6].

The principal mechanisms of arrhythmogenesis in the heart are abnormal automaticity, triggered activity from after-depolarizations, and myocardial reentry [2]. Triggered activity and abnormal automaticity are the most important mechanisms of focal VT arising from the ventricular outflow tracts, although microreentrant circuits may also play a role. In the setting of myocardial scar from CAD, macroreentry is the most common mechanism contributing to VT [7, 8]. It is estimated that 1–5% of all patients with a history of previous myocardial infarction (MI) will develop VT. In the setting of acute MI, on the other hand, the incidence of VT/VF ranges from 2% to 10% [9, 10]. This upfront arrhythmic risk has been reduced by early coronary reperfusion strategies, such as thrombolytics and primary angioplasty, in the acute phases of MI [2, 11]. The electrical substrate for VT following acute MI is established as early as 2 weeks postinfarction, based on programmed ventricular stimulation studies, and presumably is present indefinitely [12]. The abnormal substrate is characterized by inflammation and fibrosis, cardiac hypertrophy, abnormal cell coupling, and ion channel expression in the myocardium that promote ventricular arrhythmia [5]. The subsequent development of VT in at-risk patients results from the interplay of the abnormal myocardial substrate and arrhythmogenic triggers. The roles played by the autonomic nervous system, hemodynamic stress, metabolic abnormalities, and ventricular premature depolarizations as proarrhythmic triggers have all been well described [6, 13].

The only intervention demonstrated to improve survival in patients at risk of SCD from ventricular arrhythmias is the implantable cardioverter defibrillator (ICD). It is indicated for secondary prevention in patients with a

history of sustained VT/VF, and for primary prevention in patients with a history of heart failure or previous MI and left ventricular ejection fraction (LVEF) of 35% or less [14]. There are several limitations, however, with the ICD as primary therapy for VT/VF. First, and most important, is that although the ICD effectively terminates ventricular arrhythmias, it does not prevent them. Second is the morbidity associated with both appropriate and inappropriate ICD shocks. Third, the current selection criteria for ICD candidacy are imperfect, as many ICD recipients never receive appropriate ICD therapy for VT/VF, whereas many other patients with LVEF greater than 35% who are not eligible for the ICD go on to experience SCD [15]. In addition, the benefit of the ICD is not established in the early post-MI period; despite an increased risk of arrhythmic death in this population, there was no difference in total mortality in patients within 6 and 40 days of acute MI treated with the ICD vs. medical therapy in a randomized trial [16].

Antiarrhythmic drug therapy is commonly used as adjunctive treatment in ICD recipients for the suppression of VT/VF episodes. In the Antiarrhythmic Versus Implantable Defibrillator (AVID) trial of secondary prevention ICD therapy, the 1-year arrhythmia event rate was 90% in the ICD arm, and was reduced to 64% with concurrent antiarrhythmic therapy [17]. Overall, up to 70% of patients with an ICD receive adjuvant antiarrhythmic drug therapy, even though there is no medication formally approved for this indication [18]. The indications for adjunctive antiarrhythmic therapy are: to reduce the incidence of appropriate and inappropriate ICD shocks; to slow the rate of spontaneous VT episodes to improve their hemodynamic tolerance and to facilitate pace termination by the ICD; to treat symptomatic VT episodes; to improve quality of life; and

potentially to reduce hospitalizations related to cardiac arrhythmia [18].

Current antiarrhythmic therapy for VT is limited by its potential for both cardiac and extracardiac toxicity, including the risk of proarrhythmia, and by its limited efficacy. In the Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) trial, amiodarone and sotalol were each significantly more effective in preventing ICD shocks compared to beta-blockers alone, but 1-year shock rates were still 10% in the amiodarone arm and 24% in the sotalol arm, with drug-related adverse effects leading to discontinuation in one in five patients [19]. No new antiarrhythmic agents have yet been approved for the treatment for VT in the past decade; however, novel concepts in the understanding of ventricular arrhythmogenesis have the potential to deliver new therapeutic targets for VT that balance antiarrhythmic efficacy against the risks of organ toxicity, negative inotropy, and proarrhythmic effects seen with contemporary drug therapy.

Several clinical trials have evaluated the efficacy and safety of various antiarrhythmic medications used for the treatment of VT in patients with established cardiovascular disease. This review will summarize their findings and discuss more recent data on emerging pharmacotherapies for ventricular arrhythmia.

METHODS

The following review article incorporates data from clinical trials, review articles, and textbooks to provide a comprehensive and up-to-date summary of antiarrhythmic drug therapy for VT. Emerging antiarrhythmic therapies include those agents that have not yet been approved for clinical use in VT but

have been tested in clinical investigations or early phase clinical trials in humans in the past decade (2002–2012).

DISCUSSION

Current Antiarrhythmic Therapy

Classification of Antiarrhythmic Agents

The most common classification scheme for antiarrhythmic agents is the Vaughan Williams classification, which characterizes drugs based on their ability to block specific ion currents or cell receptors [20]. Table 1 summarizes these agents and their use in the treatment of ventricular arrhythmias, and Table 2 summarizes the results of select clinical trials with these medications. Class I agents are sodium channel blockers, further divided into Class IA (quinidine, procainamide and disopyramide), Class IB (lidocaine, mexiletine), and Class IC (flecainide, propafenone). Class II agents are beta-adrenergic receptor blockers, such as propranolol. Class III agents are potassium channel blockers, such as amiodarone, sotalol, dofetilide, and dronedarone. Class IV agents are calcium channel blockers, such as verapamil. The Vaughan Williams classification does not, however, account for the complex actions of certain antiarrhythmics, such as amiodarone, which is known to have multichannel blocking properties [38].

Beta-Blockers

Beta-blockers are considered first-line therapy for patients with systolic heart failure and following acute MI for their established survival benefit in these populations [30, 31, 39, 40]. In addition, beta-blockers are indicated in the treatment of certain ion channelopathies,

such as congenital long QT syndrome and CPVT [41].

In the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), bisoprolol reduced all-cause mortality by 34% and sudden cardiac death by 44% in patients with heart failure [30]. The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) randomly assigned over 45,000 patients to either a combination of intravenous and oral metoprolol or placebo within 24 h of acute MI, and showed that the use of early beta-blocker therapy reduced the risk of VF development, although this was counterbalanced by an increase in cardiogenic shock, especially during the first day after admission [31]. Overall, a meta-analysis of beta-blocker studies in post-MI patients suggests a significant relative benefit in preventing SCD and all-cause mortality [42].

Amiodarone

Amiodarone is an iodinated benzofuran derivative that is highly lipophilic. It combines properties of all Vaughan Williams classifications, possessing sodium channel, potassium channel, calcium channel, and beta-adrenergic receptor blocking activity. It accumulates in a variety of organ tissues, including adipose, leading to an elimination half-life of over 30 days. In fact, amiodarone can be detected in plasma up to 9 months after discontinuation [22].

In the pre-ICD era, amiodarone had an established use for the prevention of SCD in high-risk patients with a history of previous MI or aborted SCD [43]. Meta-analysis showed a modest reduction in all-cause mortality with amiodarone vs. placebo [44]. A pooled analysis of the European Amiodarone Myocardial Infarction Trial (EMIAT) and the Canadian Amiodarone Myocardial Infarction Trial (CAMIAT) that evaluated amiodarone use in

Table 1 Summary of antiarrhythmic medications used for ventricular tachycardia

Drug [reference]	V-W class	Dosage (oral)	Metabolism	Adverse effects	Drug–drug interactions
Quinidine [21]	IA	324–648 mg q8h (gluconate) 300–600 mg q6h (sulfate)	Hepatic (CYP3A4) and renal	Diarrhea, stomach cramps, tinnitus, fever, rash, thrombocytopenia, hemolytic anemia, QT prolongation, torsades	↓ digoxin dose by 50%; ↓ warfarin and beta-blocker dose; amiodarone, cimetidine and verapamil may ↑ quinidine levels
Disopyramide [21]	IA	150–300 mg q6h (150 mg q12–24h in moderate–severe CKD)	Primarily renal	Urinary retention, blurred vision, constipation, dry mouth, QT prolongation, torsades	Phenytoin may ↓ disopyramide levels; use caution with co-administration of other QT prolonging medications
Mexiletine [21]	IB	150–300 mg q8h	Hepatic (CYP2D6)	Nausea, stomach cramps, tremor, blurred vision, ataxia, confusion	Cimetidine and quinidine may ↑ mexiletine levels
Flecainide [21]	IC	50–200 mg q12h (50–200 mg q24h in significant CKD)	Hepatic (CYP2D6) and renal	Tremor, blurred vision, headache, ataxia, PR and QRS prolongation, proarrhythmia	Amiodarone, cimetidine, propranolol and quinidine may ↑ flecainide levels
Propafenone [21]	IC	150–300 mg q8h	Hepatic (CYP2D6, 3A4, 1A2)	Constipation, dizziness, headache, metallic taste, bronchospasm, bradycardia, PR and QRS prolongation, proarrhythmia	↓ digoxin dose by 25–50%; cimetidine and quinidine may ↑ propafenone levels
Amiodarone [22]	III	Loading dose 400 mg q6–12h for 10 g Maintenance dose 200–600 mg/day	Hepatic (CYP3A4)	Pulmonary toxicity, hypo/hypothyroidism, hepatic toxicity, neuropathy, corneal deposits, bradycardia, prolongation of PR, QRS, QT	↓ digoxin and warfarin dose by 25–50%
Sotalol [22]	III	Start 80 mg q12h (80 mg q24h if moderate CKD) Maintenance dose 80–160 mg q12h (40–80 mg q12h in CKD). Avoid in severe CKD	Renal	Bradycardia, fatigue, bronchospasm, heart failure, QT prolongation, torsades	Use caution with co-administration of other QT prolonging medications

Table 1 continued

Drug [reference]	V-W class	Dosage (oral)	Metabolism	Adverse effects	Drug–drug interactions
Dofetilide [23–25]	III	500 µg q12h if CrCl >60; 250 µg q12h if CrCl 40–60; 125 µg q12h if CrCl 20–39. Avoid in severe CKD	Renal and hepatic (CYP3A4)	Headache, chest pain, dizziness, respiratory tract infection, dyspnea, nausea, QT prolongation, torsades	Do not administer dofetilide with cimetidine, ketoconazole, prochlorperazine, megestrol, verapamil, trimethoprim or hydrochlorothiazide
Dronedarone [26, 27]	III	400 mg q12h	Hepatic (CYP3A4)	Diarrhea, nausea, stomach cramps, QT prolongation, bradycardia, heart failure, hepatic toxicity	Verapamil and diltiazem may ↑ dronedarone levels; dronedarone may ↑ digoxin, beta-blocker and simvastatin levels
Ranolazine [28, 29]	IB	500–1,000 mg q12h	Hepatic (CYP3A4)	Dizziness, headache, nausea, QT prolongation	Ranolazine may ↑ digoxin and simvastatin levels; diltiazem and verapamil may ↑ ranolazine levels

CKD chronic kidney disease, CrCl creatinine clearance, CYP cytochrome P450, q6h, q8h, q12h, q24h dosing every 6, 8, 12, 24 h, respectively, V-W Vaughan Williams

Table 2 Summary of clinical trials of antiarrhythmic medications

Study [reference]	Population	N	Agent(s) studied	Follow-up	Primary endpoint	Results
CIBIS II [30]	Heart failure with NYHA Class 3 or 4 symptoms, ejection fraction $\leq 35\%$	2,647	Bisoprolol vs. placebo	Mean of 1.3 years	All-cause mortality	Mortality was lower with bisoprolol compared to placebo (11.8% vs. 17.3%; hazard ratio 0.66, $P < 0.0001$). Sudden death was lower with bisoprolol compared to placebo (3.6% vs. 6.3%; hazard ratio 0.56, $P = 0.0011$)
COMMIT [31]	Acute MI patients within 24 h of suspected onset	45,852	Metoprolol (IV plus oral) vs. placebo	28 days	1. Death, reinfarction, or cardiac arrest 2. Death from any cause	No significant difference in either primary outcome. Fewer patients had ventricular fibrillation with metoprolol vs. placebo (2.5% vs. 3.0%; odds ratio 0.83, $P = 0.001$) but more developed cardiogenic shock (5.0% vs. 3.9%; odds ratio 1.30, $P < 0.00001$)
OPTIC [19]	Secondary prevention ICD recipients	412	Amiodarone + beta-blocker vs. sotalol vs. beta-blocker	1 year	ICD shock for any reason	Fewer shocks with amiodarone + beta-blocker (10.3%) compared to sotalol (24.3%) or beta-blocker alone (38.5%)
Pacifico et al. [32]	Secondary prevention ICD recipients	302	D,L-sotalol vs. placebo	1 year	Death or ICD shock from any cause	Lower risk of death or ICD shock with sotalol over placebo (reduction in risk, 48%, $P < 0.001$). Sotalol also reduced the mean frequency of shocks due to any cause (1.43 vs. 3.89 shocks per year, $P = 0.008$)

Table 2 continued

Study [reference]	Population	N	Agent(s) studied	Follow-up	Primary endpoint	Results
SWORD [33]	Previous MI, ejection fraction $\leq 40\%$	3,121	D-Sotalol vs. placebo	Mean of 148 days	All-cause mortality	Higher risk of death with D-sotalol over placebo (5.0% vs. 3.1%; relative risk 1.65, $P = 0.006$). Arrhythmic deaths accounted for the increased mortality
EMIAT/CAMIAT pooled analysis [34]	Survivors of acute MI with either ejection fraction $\leq 40\%$ (EMIAT), or with frequent ventricular ectopy (CAMIAT)	2,687	Beta-blockers + amiodarone, beta-blockers alone, amiodarone alone vs. placebo	2 years	All-cause mortality, cardiac death, arrhythmic cardiac death, nonarrhythmic cardiac death, arrhythmic death, or resuscitated cardiac arrest	Event rates were significantly lower for patients receiving beta-blockers + amiodarone compared to beta-blockers alone, amiodarone alone, or placebo
CAST [35]	Survivors of acute MI with frequent ventricular ectopy	1,498	Encainide or flecainide vs. placebo	Mean of 10 months	All-cause mortality	Increased mortality with encainide or flecainide compared to placebo, including both arrhythmic death ($P = 0.0004$), and nonarrhythmic cardiac death ($P = 0.01$)
SHIELD [36]	ICD recipients with history of VT/VF	633	Azimilide vs. placebo	1 year	1. All-cause shocks plus symptomatic tachyarrhythmias terminated by antitachycardia pacing 2. All-cause shocks	All-cause shocks plus symptomatic ventricular tachycardia terminated by antitachycardia pacing were significantly reduced by azimilide (hazard ratio 0.43, $P = 0.0006$ on 75 mg dose; hazard ratio 0.53, $P = 0.0053$ on 125 mg dose). The reductions in all-cause shocks on azimilide were not statistically significant

Table 2 continued

Study [reference]	Population	N	Agent(s) studied	Follow-up	Primary endpoint	Results
ALPHEE [37]	ICD recipients with history of VT/VF and ejection fraction $\leq 40\%$	486	Celivarone vs. placebo	Median of 9 months	ICD therapy for VT/VF or sudden death	No significant difference in the primary outcome with celivarone vs. placebo

ICD implantable cardioverter defibrillator, MI myocardial infarction, N number of patients, NYHA New York Heart Association, VF ventricular fibrillation, VT ventricular tachycardia

patients recovering from MI (EMIAT enrolled patients with LVEF $\leq 40\%$ and CAMIAT enrolled patients with frequent or repetitive ventricular ectopy) found that incidences of cardiovascular death and arrhythmic death or resuscitated cardiac arrest were significantly lower in patients receiving both beta-blockers and amiodarone than in those not receiving beta-blockers, with or without amiodarone [34]. Conversely, in the era of the primary prevention ICD, amiodarone did not confer a survival benefit over placebo in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) of symptomatic heart failure patients with LVEF of 35% or less [45].

Amiodarone plus beta-blockers was shown to be superior to monotherapy with sotalol or beta-blockers in the OPTIC trial for the reduction of shocks in secondary prevention ICD recipients [19]. As a result of its greater efficacy, amiodarone is the most common antiarrhythmic agent used for suppression of VT in patients with structural heart disease and ICDs. In the AVID trial, nearly twice as many patients in the ICD arm who ultimately received adjuvant antiarrhythmic therapy were treated with amiodarone compared to either sotalol or mexiletine [17].

Amiodarone has a low risk of proarrhythmia, despite causing prolongation of the action potential duration and QT interval, probably because it reduces heterogeneity of depolarization. Torsade de pointes occurred in less than 1% in the EMIAT and CAMIAT trials [46, 47]. Extracardiac toxicity, however, is well described, and is related to both a daily and cumulative dose effect of amiodarone. Clinical hypothyroidism occurs in up to 32% of patients, and may require thyroxine supplementation even after drug discontinuation [22]. Hyperthyroidism can also occur, but is less common in the western world where dietary

iodine intake is adequate. Pulmonary toxicity is less common but is among the most serious adverse drug reactions, presenting as chronic interstitial pneumonitis, bronchiolitis obliterans with organizing pneumonia, or the acute respiratory distress syndrome. Corneal deposits, skin photosensitivity, neuropathy, and gastrointestinal side effects have also been reported [22].

Sotalol

Sotalol is a potassium channel blocker that prolongs action potential duration and is a Vaughan Williams Class III agent. It is a racemic mixture of D-sotalol, which has pure Class III antiarrhythmic activity, and L-sotalol, which has Class III and beta-blocker effects. Doses less than 120 mg twice daily appear to have a primary beta-blocker effect, with higher doses producing significant Class III activity [22].

A placebo-controlled trial in 302 ICD recipients showed that treatment with racemic sotalol significantly reduced the risk of death or ICD shock (34% incidence with sotalol vs. 54% with placebo) at 1 year [32]. However, the rate of drug discontinuation in the sotalol arm was 27%. A similar finding was noted in the OPTIC trial, with nearly a quarter of patients discontinuing sotalol therapy due to drug intolerance [19]. The most common adverse reactions in these trials were related to the beta-blocking effects of the drug; symptomatic bradycardia and torsade de pointes were rare. Of note, in the Survival With Oral D-Sotalol (SWORD) trial, D-sotalol, which does not have significant beta-blocking effects, was associated with increased mortality and proarrhythmia in patients with post-MI left ventricular dysfunction [33].

The most significant adverse reaction associated with sotalol is torsade de pointes, seen in 2–3% of patients; especially at risk are women and patients with heart failure or

chronic kidney disease (because of its significant renal drug elimination) [48]. For this reason, it is common practice to initiate sotalol therapy in the inpatient setting with continuous ECG monitoring during the loading phase for five doses in patients at higher risk. QT interval prolongation and bradycardia can presage the development of proarrhythmia and may warrant a reduction of the sotalol dose. Other adverse effects include fatigue, bronchospasm, dyspnea and heart failure. Unlike amiodarone, these effects are related to the daily dose but not the cumulative dose, making sotalol a more attractive first-line therapy for younger patients or those for whom longer-term treatment is anticipated [22].

Class I Antiarrhythmic Agents

The Cardiac Arrhythmia Suppression Trial (CAST) compared Class IC agents to placebo in post-MI patients with impaired LVEF (40% or less) for the suppression of ventricular ectopy, and was terminated prematurely due to excess mortality in the antiarrhythmic arm [35]. Both all-cause mortality and arrhythmic death were increased with both encainide and flecainide treatment. As such, Class IC antiarrhythmic agents are no longer recommended therapy for patients with ischemic heart disease or left ventricular dysfunction from any cause. Conversely, the risk of ventricular proarrhythmia with Class IC agents in the absence of structural heart disease is low; however, in patients with atrial arrhythmias, flecainide or propafenone may promote 1:1 atrioventricular nodal conduction with acceleration of the ventricular rate and a wide QRS tachycardia [21].

Earlier studies that examined Class I agents for secondary VT/VF prevention in post-MI patients showed they were inferior in efficacy to both amiodarone and sotalol [49, 50]. The

most commonly used Class I agent in this setting is mexiletine, used in 20% of patients who received adjuvant antiarrhythmic treatment in the ICD arm of the AVID trial [17]. As a Class IB antiarrhythmic agent, it does not seem to carry the increased mortality risk associated with the Class IC drugs, based on observational data with the Class IB drug lidocaine from the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-I and GUSTO-IIb) trials [51].

Quinidine, procainamide, and disopyramide are Class IA antiarrhythmic agents that have intermediate sodium channel blocker activity (compared to Class IC agents) and also prolong action potential duration via potassium channel blockade. They are indicated in the treatment of supraventricular arrhythmias and VT. Unfortunately, use of these agents is limited by the risk of torsade de pointes (seen in 0.5–8%) and the poor tolerability of these agents, including drug-induced lupus with procainamide, anticholinergic effects with disopyramide, and a host of gastrointestinal, dermatologic and neurologic side effects seen with quinidine use [21].

While the lower efficacy and poor tolerability of the Class I agents has relegated them to third-line therapy for the prevention and treatment of ventricular arrhythmia, there is evidence that combination therapy with a Class I and a Class III agent may be more effective than monotherapy with either agent [43]. Common combinations include amiodarone or sotalol plus mexiletine.

Emerging Antiarrhythmic Therapy

Dronedarone

Dronedarone is a recent addition to the antiarrhythmic armamentarium. A Vaughan Williams Class III agent, dronedarone is a

multichannel blocker similar in structure to amiodarone but noniodinated. It was developed with the potential to achieve antiarrhythmic efficacy similar to that of amiodarone, without the extracardiac toxicity seen with long-term amiodarone therapy [26, 52]. It is approved for the treatment of atrial fibrillation, largely based on results of A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation (ATHENA), a placebo-controlled, double-blind, parallel arm trial to assess the efficacy of dronedarone 400 mg b.i.d. for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation or atrial flutter, which demonstrated significant reductions in the composite endpoint of all-cause mortality and cardiovascular hospitalization with dronedarone vs. placebo [26]. In two earlier randomized trials of dronedarone in patients with atrial fibrillation or flutter, rates of pulmonary, thyroid, and hepatic adverse effects were not significantly greater with dronedarone than with placebo at 1 year follow-up [27]. After its approval in the United States, however, subsequent reports of severe liver toxicity led to a warning by the US Food and Drug Administration, recommending that prescribing physicians follow hepatic function tests routinely [53].

Although dronedarone has not been studied specifically for the treatment of VT/VF, animal studies have demonstrated antiarrhythmic properties on ventricular myocardium, and subsequent reports in humans have supported its efficacy in select cases [54–56]. In addition, in ATHENA, patients on dronedarone showed a reduction in arrhythmic death [26]. The use of dronedarone in patients with heart failure, however, is controversial in light of the Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity

Decrease (ANDROMEDA) trial, whose results suggest dronedarone may lead to worsening heart failure symptoms and a two-fold increase in mortality in this population [52]. As such, dronedarone is contraindicated in Class IV heart failure patients or in those who have had a recent hospitalization for decompensated heart failure. The ANDROMEDA study authors recommend that “dronedarone should not be used in patients with heart failure and reduced left ventricular systolic function.” A more recent placebo-controlled trial of dronedarone in patients with permanent atrial fibrillation and major vascular risk factors (including CAD and heart failure) was stopped prematurely due to a two-fold excess in cardiovascular mortality [57]. Stroke, hospitalization for heart failure, and arrhythmic deaths were also significantly increased in the dronedarone arm of the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) [57]. While some of these adverse findings were unexplained, it was postulated that the negative inotropic effects of dronedarone, along with its drug–drug interactions (notably with vitamin K antagonists and with digoxin) and potential proarrhythmic effects, may have contributed.

In summary, while dronedarone has been shown to be effective in suppressing ventricular arrhythmia in animal studies and in case reports of patients with refractory VT/VF episodes, the results of ANDROMEDA and PALLAS have raised doubts about the safety of this medication in patients with structural heart disease.

Dofetilide

Dofetilide is a Class III antiarrhythmic agent and a selective blocker of the rapid delayed rectifier potassium current, I_{Kr} [58]. It is approved in North America for the treatment of atrial fibrillation; however, it has been shown

to have efficacy in the treatment of ventricular arrhythmia. A randomized trial of patients with CAD and sustained VT showed that oral dofetilide was equally as effective as oral sotalol in the prevention of recurrent ventricular arrhythmias and arrhythmic death at 1 year [59]. A more recent study in 30 ICD recipients with drug-refractory VT/VF episodes showed a significant reduction in both monthly ventricular arrhythmia episodes (from 1.8 ± 4.5 to 1.0 ± 3.5 , $P = 0.006$) and monthly ICD therapies (from 0.9 ± 1.4 to 0.4 ± 1.7 , $P = 0.037$) after treatment with dofetilide. In addition, 83% of patients had complete suppression of VT/VF during their first month of treatment [60].

Dofetilide is very well tolerated, although inpatient monitoring for 3 days is required during the loading phase, given the risk of QT prolongation and the potential for torsade de pointes (seen in 1–3%) [23, 24]. Dofetilide dosing is based on calculated creatinine clearance, as a result of its renal drug elimination. The safety of dofetilide has been established in patients with left ventricular dysfunction and CAD [24, 25], and on the basis of limited clinical experience in the treatment of ventricular arrhythmia, it may be an alternative antiarrhythmic agent for such patients with VT/VF events refractory to amiodarone and/or sotalol therapy.

Ranolazine

Ranolazine is a novel antianginal drug with multiple ion channel blocking antiarrhythmic activity. It is a piperazine derivative with a chemical structure similar to lidocaine, and its most potent ion channel blocking effect is on late sodium current [28, 29, 61, 62]. It is thus considered a Vaughan Williams Class IB agent. Ranolazine also has effects on the delayed rectifier current (I_{Kr}) and prolongs action

potential duration, with corresponding QT interval prolongation on electrocardiography. It has been shown in experimental animal models to have antiarrhythmic effects in the ventricle [61, 62]. In the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 36 trial (MERLIN-TIMI 36), ranolazine was shown clinically to reduce arrhythmia episodes, including nonsustained VT, on ambulatory cardiac monitoring in patients presenting with acute coronary syndrome [29]. It has subsequently been used in the suppression of ectopic ventricular activity [63] and for the reduction in VT burden and prevention of shocks in ICD recipients [64].

Ranolazine in particular works synergistically with the Class III antiarrhythmic agents, most commonly with amiodarone [65]. This has been demonstrated in animal models to have an antiarrhythmic effect in both the atrium and ventricle. In rabbit hearts treated with both ranolazine and a Class III agent, there was no increase in early after-depolarizations or ventricular proarrhythmia associated with the addition of ranolazine [61]. In addition, in the MERLIN-TIMI 36 trial, despite causing modest QT prolongation, ranolazine use was not associated with an increased risk of SCD compared with placebo [66]. Based on limited but positive clinical experiences with ranolazine, it appears to be beneficial as add-on therapy in patients with recurrent VT events while on a Class III antiarrhythmic agent.

Azimidide

Azimidide is an investigational Class III antiarrhythmic agent that blocks both the rapid (I_{Kr}) and slow (I_{Ks}) components of the delayed rectifier cardiac potassium current. It causes prolongation of the atrial and ventricular

action potential duration and refractory period [36]. As such, azimidide has demonstrated action against both supraventricular and ventricular arrhythmias. In the Shock Inhibition Evaluation with Azimidide (SHIELD) trial, a randomized controlled trial of 633 secondary prevention ICD recipients, the primary endpoint of all-cause shocks plus symptomatic tachyarrhythmias terminated by antitachycardia pacing was significantly reduced in patients receiving azimidide [36]. In addition, the secondary endpoint of appropriate ICD therapies for VT/VF episodes was reduced by 48% and 62%, with the 75 mg and 125 mg doses of azimidide, respectively.

Based on the concerning results from previous antiarrhythmic drug trials in patients with structural heart disease, such as CAST and SWORD, azimidide was studied prospectively in the Azimidide Postinfarct Survival Evaluation (ALIVE) trial, in which 3,717 patients with recent MI and an ejection fraction between 15% and 35% were randomly assigned to receive azimidide, 100 mg daily, vs. placebo. At 1 year of follow-up, there were no significant differences in all-cause, cardiac, or arrhythmic mortality between the azimidide and placebo groups [67].

Overall, azimidide was well tolerated in clinical trials. In the SHIELD trial, its discontinuation rate was similar to the placebo arm. Adverse events with azimidide include neutropenia (seen in 1% of patients) and QT prolongation leading to torsade de pointes (seen in up to 1–2% of patients). It is not currently approved for use in North America or Europe.

Celivarone

Celivarone is a noniodinated benzofuran derivative that is in investigational use for its action against atrial and ventricular arrhythmias [37]. Similar to amiodarone and

dronedaron, it has Class I, II, III and IV antiarrhythmic activity, but with different relative potencies for the various channels and receptors. Also, its structure and kinetics differ from those of amiodarone and lend itself to an improved side effect profile and reduced potential for drug interactions [68]. It was shown in a small phase 2 clinical study of ICD recipients to trend toward fewer VT and VF episodes at the higher dose of celivarone (300 mg daily), although the 46% relative risk reduction at 6 months was not statistically significant [69]. A larger trial of 486 patients with LVEF of 40% or less and at least one VT/VF episode within a month of enrollment, however, did not find that celivarone was any more effective for the prevention of ICD interventions or sudden death than placebo [68]. In both studies, celivarone was well tolerated and had an acceptable safety profile. Nonetheless, in light of the disappointing clinical data to date, it is not currently approved for use in humans.

Future Antiarrhythmic Targets

Novel targets for the treatment of ventricular arrhythmia continue to be explored, and it is likely that pharmacologic agents directed at some of these targets will enter clinical trials in the next few years. The commonly used antiarrhythmic medications for VT/VF primarily target sodium channels (Class I agents) or potassium channels (Class III agents), but are limited by variable efficacy and the potential for ventricular proarrhythmia. Newer therapeutic approaches to cardiac arrhythmias have focused on the roles of intracellular calcium, gap junctions, sodium–calcium exchange, and adenosine triphosphate (ATP)-sensitive potassium channel blockade, and will be reviewed briefly [37].

Intracellular Calcium

Altered intracellular calcium handling has been implicated in ventricular arrhythmogenesis in a number of models [6]. Two important proteins in myocardial calcium homeostasis are the sarcoplasmic reticulum (SR) calcium ATPase (SERCA2a) and the ryanodine receptor (RyR2). The former promotes calcium reuptake into the SR and the latter is a SR calcium release channel that promotes an increase in cytosolic calcium, which in turn activates myocardial contractile proteins. Diastolic calcium leakage via RyR2 is thought to contribute to proarrhythmia, notably by promoting after-depolarizations in the cardiomyocyte. CPVT is one cardiac electrical disorder characterized by leaky RyR2, resulting in delayed after-depolarizations and polymorphic VT triggered by exercise and adrenergic stimulation [6, 41]. The antiarrhythmic agent flecainide targets RyR2, and was shown to prevent arrhythmias in a mouse model of CPVT, by inhibiting RyR2-mediated calcium release. Now this agent has found a role clinically to suppress VT events in patients with CPVT in conjunction with beta-blockers [70].

Pharmacotherapies to normalize intracellular calcium handling by either stabilizing RyR2 activity or modulating associated proteins involved in diastolic SR calcium leakage in order to prevent arrhythmia may prove to be novel antiarrhythmic agents in the future. In a recent report, a pharmacologic RyR2 stabilizer was investigated in both a mouse model and in human nonfailing myocardium, and was found to be effective in reducing SR calcium leak [71]. Another recent report showed that inhibition of calcium/calmodulin-dependent kinase (CaMKII) was able to reduce cardiac arrhythmias and SCD in a proarrhythmic mouse model similar to that seen in CPVT [72].

Gap Junctions

Cell–cell coupling in the heart acts to maintain synchronization of depolarization and repolarization between myocytes, and disruption of this coupling is thought to contribute to arrhythmogenesis. It has been proposed that restoration or enhancement of coupling via gap junctions may be an effective antiarrhythmic target [37]. Connexin 43 is the principal gap junction protein responsible for cell–cell coupling in ventricular myocardium, and its function is impaired during acute ischemia and acidosis [73]. Rotigaptide, an antiarrhythmic peptide that improves conduction across gap junctions, has been shown in experimental animal models to suppress ischemia-induced proarrhythmia [73]. The proposed mechanism of action of rotigaptide is prevention of the dephosphorylation of connexin 43 that accompanies acute metabolic stress. By maintaining gap junction conductance, this peptide in turn both prevents conduction slowing in the cardiomyocytes, and synchronizes the action potentials thereby reducing dispersion of refractoriness [74].

While the concept of normalizing gap junction conductance with an antiarrhythmic agent is a promising one, there are multiple mechanisms by which gap junction physiology can be impaired in disease states other than by dephosphorylation. The roles of myocyte fibrosis, connexin protein downregulation and trafficking in the remodeling of gap junctions have all been appreciated and may pose challenges to the development of a single pharmacotherapeutic target or agent [73].

Sodium–Calcium Exchange

The sodium–calcium exchanger (NCX) is the primary pathway for intracellular calcium removal in the cardiomyocyte. It is a cell membrane protein that removes a single

calcium ion in exchange for the import of three sodium ions, while operating in the forward mode. Increased expression or activity of NCX has been associated with impaired cardiac contractility and an increased risk of arrhythmias in the setting of heart failure [75]. NCX also operates in the reverse mode, promoting intracellular calcium loading, during conditions of high cytosolic sodium concentration, or in the setting of digitalis use (which antagonizes the sodium/potassium ATPase). Excessive calcium loading can also be proarrhythmic, as it promotes triggered activity through delayed after-depolarizations [6, 75].

NCX blockade has been considered to be a potential therapeutic strategy for cardiac arrhythmias, in particular with agents that predominantly inhibit the reverse mode over the forward mode. To date, there has been limited progress in the development of clinically useful agents. Two drugs, KBR-7943 and SEA-0400, have been shown to prevent calcium overload in models of ischemia/reperfusion injury, and appear to reduce after-depolarizations in models of vulnerable cardiac tissue [75]. These findings are promising but await further in vivo confirmation in animal models.

ATP-Sensitive Potassium Channel Blockade

Myocardial ischemia is associated with increases in extracellular potassium, which is believed to contribute to ventricular proarrhythmia. The activation of cardiac cell membrane ATP-sensitive potassium channels during myocardial ischemia promotes potassium efflux and reductions in action potential duration; impaired function of the sodium/potassium ATPase may also contribute [76]. In addition, ischemia-induced potassium accumulation is heterogeneous, which leads to dispersion of repolarization and thereby creates a substrate for reentrant arrhythmias.

ATP-sensitive potassium channel activity is inhibited by ATP but activated by adenosine 5'-diphosphate (ADP). Therefore, with a fall in the ATP:ADP ratio during myocardial ischemia, the ATP-sensitive potassium channel opens and potassium leaves the cell. Increases in extracellular potassium are known to promote perturbations in cardiac electrical activity, such as increased excitability of normal ventricular tissues, leading to premature ventricular complexes, and a reduction in action potential duration. Regional dispersion of the refractory period, especially during periods of myocardial ischemia, is a major contributor to the development of VF. Glibenclamide is an ATP-sensitive potassium channel inhibitor that has been shown to attenuate reductions in action potential duration in models of ischemia, and suppress extrasystoles and VF [76].

Glibenclamide is a sulfonylurea that also provokes hypoglycemia due to its effects on noncardiac tissue [76]. For ATP-sensitive potassium channel inhibition to become an attractive therapeutic option, cardioselective pharmaceuticals must be developed and tested. Currently, the agents HMR-1883, HMR-1098 and HMR-1402 have been developed and studied in animals, with favorable results on the reduction of ischemic cardiac arrhythmias [77].

CONCLUSION

In patients with structural heart disease at risk of ventricular arrhythmias, the ICD continues to be the gold standard therapy for the reduction of SCD and improved long-term survival. Antiarrhythmic medication is indicated as add-on therapy in those with VT events to reduce the morbidity associated with recurrent arrhythmic episodes. While amiodarone and sotalol are the principal agents used in this setting, their use is

often limited by suboptimal effectiveness and drug intolerance or toxicity leading to discontinuation.

Newer and emerging antiarrhythmic therapies must meet the challenge of effectively suppressing drug-refractory VT/VF without promoting proarrhythmia or other cardiovascular adverse events. While dofetilide and ranolazine hold promise, and merit further investigation in large prospective studies of ICD patients, dronedarone use in atrial fibrillation has been associated with a disturbing signal of harm in patients with structural heart disease. Therefore its use in patients with VT should be carefully considered or avoided in the absence of prospective data establishing its safety and efficacy in this population. Azimilide and celivarone await more convincing efficacy data in humans before they are approved for clinical use.

A better understanding of the molecular mechanisms of ventricular arrhythmogenesis has provided basic electrophysiologists with new antiarrhythmic targets related to intracellular calcium handling, gap junctions, sodium–calcium exchange, and ATP-sensitive potassium channel activity. Further advances in this field will undoubtedly spur novel drug therapies for patients with refractory ventricular arrhythmias in the future.

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