ELSEVIER
SAUNDERS

Cardiol Clin 26 (2008) 405–418

CARDIOLOGY
CLINICS

Role of Drug Therapy for Sustained Ventricular Tachyarrhythmias

L. Brent Mitchell, MD, FRCPC

Libin Cardiovascular Institute of Alberta and Department of Cardiac Sciences, Calgary Health Region and University of Calgary Foothills Hospital, 1403 - 29th Street NW Calgary, Alberta T2N 2T9, Canada

Sudden death is responsible for 20% of all deaths in the industrialized world [1]. Most sudden deaths are caused by sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) [2]. Thus, prevention of VT/VF and sudden death has attracted significant attention. Despite the use of implantable cardioverter defibrillators (ICDs), antiarrhythmic drugs still play a dominant role. These therapies, in their broadest sense, include both acute/direct antiarrhythmic drugs (including standard antiarrhythmic agents) and delayed/indirect antiarrhythmic drugs (including agents that modify cardiovascular remodeling processes, thereby reducing the likelihood of future VT/VF and sudden death in patients who have coronary artery disease [CAD], prior myocardial infarction [MI], or congestive heart failure [CHF]). This article examines the current role of pharmacologic therapy for the prevention of VT/VF and sudden death.

Drug therapy for ventricular tachycardia/ventricular fibrillation and sudden death

Randomized, controlled clinical trials (RCTs) show that ICDs are more effective than drugs in preventing sudden death and all-cause mortality. Thus, most patients who have a demonstrated or presumed propensity for VT/VF receive an ICD. Meta-analysis of RCTs of patients who had prior VT/VF (the secondary prevention ICD trials) showed that the use of ICDs reduced all-cause mortality from 27.4% in the control group (most of whom were treated empirically with amiodarone) to 21.4% (hazard ratio [HR], 0.72; 95% confidence interval [CI], 0.60–0.87) over 2.3 years [3]. Meta-analysis of RCTs of patients who did not have VT/VF (the primary prevention ICD trials) showed that the use of ICDs reduced all-cause mortality from 26.4% in the control group (most of whom received usual care) to 18.5% (HR, 0.75; 95% CI, 0.63–0.91) over the course of 1 year [4]. Nevertheless, most patients use drugs to prevent VT/VF and sudden death, either instead of an ICD when the use of an ICD is inadvisable or, more often, in addition to an ICD to decrease further the risk of sudden death, to decrease VT/VF, to render VT more receptive to ICD treatments, and to treat supraventricular tachyarrhythmias that confuse the ICD.

Class I antiarrhythmic drugs

Class I drugs (sodium-channel blockers) are subdivided further into class Ia drugs that have intermediate onset/offset kinetics and delayed rectifier potassium-channel (I_{Kr}) blockade (quinidine, procainamide, disopyramide), class Ib drugs that have fast kinetics (lidocaine, tocainide, phenytoin, mexiletine), and class Ic drugs that have slow kinetics (propafenone, encainide, flecainide, moricizine).

Effects on ventricular arrhythmias

Class I drugs are the prototypical antiarrhythmic agents. Each has been well demonstrated to suppress spontaneous ventricular premature beats (VPBs) and spontaneous and inducible VT/VF in humans by a large data set that is not reviewed further in this article.

E-mail address: brent.mitchell@calgaryhealthregion.ca

0733-8651/08/$ - see front matter
doi:10.1016/j.ccl.2008.03.004

Effects on sudden death/all-cause mortality

In the Cardiac Arrhythmia Suppression Trials, CAST I [5] and CAST II [6], patients who had prior MI and frequent VPBs participated in a placebo-controlled RCT of encainide, flecainide, or moricizine. Encainide or flecainide increased death/cardiac arrest from 3.5% patients in the placebo group to 8.3% in patients in the treatment group (relative risk [RR], 2.38; 95% CI, 1.59–3.57) over 10 months [5]; moricizine increased death/cardiac arrest from 0.5% in patients in the placebo group to 2.6% in patients in the treatment group (RR, 5.6; 95% CI, 1.7–19.1) within 2 weeks [6]. A meta-analysis of 61 RCTs involving 23,486 patients also showed that class I drugs increased all-cause mortality (odds ratio [OR], 1.13; 95% CI, 1.01–1.27) [7].

Safety

The mortality associated with class I drugs is related in part to ventricular proarrhythmia seen in 1% to 5% of patients [8] and in part to worsening CHF. CAST I [5] showed a statistical trend, and CAST II [6] showed a statistical increase in new/worsened CHF with therapy using class I drugs. Finally, each class I agent also has adverse effects specific to that drug; these effects are especially common with class Ia and Ib drugs.

Inferences

Class I drugs treat and prevent VT/VF but increase sudden death and all-cause mortality. Accordingly, this therapy is reserved for its imperative need when other treatments have failed and the advantages of suppressing VT/VF outweigh the increased risk. In practice, the use of class I agents is limited to short-term therapy of an episode of VT/VF, short-term therapy of an electrical storm of VT/VF, or long-term therapy in patients who have not responded to or are not candidates for any other therapies (including an ICD).

Class II antiarrhythmic drugs

Class II antiarrhythmic drugs have, as their dominant effect, blockade of one or more of the beta subtypes of adrenergic receptors (beta-blockers).

Effects on ventricular arrhythmias

The arrhythmogenic effects of sympathetic stimulation and the antiarrhythmic effects of beta-blockers were reviewed recently [9]. Beta-blockers prevent VT/VF with efficacies comparable to those of class I drugs when used empirically [10] or when their effectiveness is predicted by suppression of either frequent/complex VPBs [11] or inducible VT/VF [12,13]. Ethical concerns, however, precluded the use of placebo controls. Recently, patients who have an ICD have been used to test antiarrhythmic drugs using appropriate ICD therapy as a surrogate for sustained VT/VF. One crossover trial in 11 patients who had sustained VT/VF found the rate of appropriate ICD shocks to be lower with a beta-blocker than without a beta-blocker (0.12 ± 0.24 versus 1.09 ± 1.41 shocks per month; $P = .03$) [13]. The combined results of three RCTs of intravenous beta-blockers in acute MI showed a decrease in sustained VT/VF from 3.1% in the control group to 0.8% in the treatment group (RR, 0.42; 95% CI, 0.32–0.55) [14–16].

Beta-blockers are particularly effective for right ventricular outflow tract VT [17], for rapid polymorphic VT/VF precipitated by sympathetic discharge states [18], and as an adjunct to prevent adrenergic stimulation from reversing the benefits of other antiarrhythmic drugs [19].

Effects on sudden death/all-cause mortality

A meta-analysis of 16 RCTs involving 15,819 patients who had prior MI reported that sudden death was reduced from 5.2% in the control group to 3.6% in the treatment group (OR, 0.68; 95% CI, 0.60–0.80), and a meta-analysis of 24 RCTs involving 20,312 patients who had prior MI reported that all-cause mortality was reduced from 10.0% in the control group to 7.9% in the treatment group (OR, 0.77; 95% CI, 0.70–0.85) after 20 months [20]. Meta-analysis of 17 RCTs involving 3039 patients who had CHF reported that all-cause mortality was reduced from 12.1% in the control group to 7.8% in the treatment group (OR, 0.69; 95% CI, 0.54–0.88) after 9 months, that beta-blockers reduced all-cause mortality in patients who had ischemic cardiomyopathy (OR, 0.69; 95% CI, 0.49–0.98) or nonischemic cardiomyopathy (OR, 0.69; 95% CI, 0.47–0.99), and that the reduction in all-cause mortality with carvedilol (OR, 0.44; 95% CI, 0.28–0.69) was greater than

with other beta-blockers (OR, 0.79; 95% CI, 0.56–1.10) [21].

That carvedilol may reduce all-cause mortality more than other beta-blockers was supported by a meta-analysis of 32 RCTs involving 26,580 patients who had prior MI and 28 RCTs involving 15,905 patients who had CHF [22]. Beta-blockers with additional $beta_2$ and/or $alpha_1$ blockade (carvedilol, timolol, propranolol) reduced all-cause mortality (post-MI: OR, 0.69; 95% CI, 0.61–0.79; CHF: OR, 0.58; 95% CI, 0.48–0.71) more than selective $beta_1$-blockers (metoprolol, bisoprolol, atenolol); (post-MI: OR, 0.79; 95% CI, 0.66–0.95); (HF: OR, 0.67; 95% CI, 0.58–0.77) which in turn reduced all-cause mortality, more than beta-blockers with intrinsic sympathomimetic activity (oxprenolol, bucindolol, xamoterol, practolol, alprenolol, acebutolol, pindolol) (post-MI: OR, 0.85; 95% CI, 0.74–0.99; CHF: OR, 0.90; 95% CI, 0.77–1.06). In the Carvedilol or Metoprolol European Trial, 3029 patients who had CHF were assigned randomly to carvedilol or metoprolol [23]. Carvedilol reduced the rate of sudden death from 17% in patients treated with metoprolol to 14% (OR, 0.81; 95% CI, 0.68–0.97) and reduced all-cause mortality from 40% in patients treated with metoprolol to 34% (OR, 0.83; 95% CI, 0.74–0.93) over 58 months [24].

Carvedilol is a $beta_1$-, $beta_2$-, and $alpha_1$-blocker; does not cause $beta_1$-receptor up-regulation; blocks the rapidly activating component of the I_{Kr}; and, at higher dosages, blocks L-type calcium channels ($I_{Ca,L}$), the transient outward potassium current (I_{to}), and the slowly activating component of the delayed rectifier (I_{Ks}) [22,25]. Thus, there is biologic rationale for the contention that carvedilol has greater antiarrhythmic activity than other beta-blockers.

The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) and Carvedilol Post-infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trials tested carvedilol against VT/VF [26,27]. In COPERNICUS, in 2289 patients who had class III-IV CHF and a left ventricular ejection fraction (LVEF) below 0.25, VT decreased from 2.3% in the placebo group to 1.0% in the carvedilol group (RR, 0.62; 95% CI, 0.15–0.55), and VF decreased from 2.0% in the placebo group to 1.0% in the carvedilol group (RR, 0.68; 95% CI, 0.48–0.94; $P < .05$) over 10.4 months. In the CAPRICORN trial in 1959 patients who had a prior MI and an LVEF of 0.40 or lower, VT/VF decreased from 3.9% in the placebo group to 0.9% in the carvedilol group (HR, 0.24; 95% CI, 0.11–0.49) over 1.3 years.

Safety

The antiarrhythmic benefits of beta-blockers are achieved at very low risk. The only expressions of proarrhythmia with beta-blockers are sinus bradycardia and atrioventricular (AV) block. The latter has been estimated to occur in less than 1% of patients [20].

Inferences

Beta-blockers treat and prevent VT/VF and reduce sudden death and all-cause mortality. Given the safety of beta-blockers, nearly all patients who have a propensity to VT/VF should receive this therapy. Exceptions include patients unable to tolerate beta-blockers and patients who do not have structural heart disease who have an idiopathic VT that responds to other therapy. In this regard, it is possible that carvedilol has advantages over other beta-blockers.

Class III antiarrhythmic drugs

Class III drugs (potassium-channel blockers) include d,l-sotalol, d-sotalol, dofetilide, azimilide, and amiodarone.

Effects on ventricular arrhythmias

Reviews documenting the antiarrhythmic efficacy of d,l-sotalol [28], d-sotalol [29], dofetilide [30], azimilide [31], and amiodarone [32] have been published.

D,l-sotalol was superior to placebo [33] and beta-blockers [34] for suppression of VPBs, was comparable to class Ia drugs for suppression of VPBs [35], and was effective for prevention of VT/VF [36]. The Electrophysiologic Study Versus Electrocardiographic Monitoring trial tested seven randomized antiarrhythmic drugs in 486 patients who had VT/VF [37]. D,l-sotalol, compared with imipramine, mexiletine, pirmenol, procainamide, propafenone, and quinidine, suppressed inducible VT/VF more than class I drugs (25% versus 16%; $P < .001$), had fewer adverse events than class I drugs (23% versus 47%; $P < .001$), and had a lower 1-year probability of VT/VF recurrence on predicted effective therapy (0.20 ± 0.04) than class I drugs (range, 0.38–0.60) [36].

Empiric d,l-sotalol was evaluated in a placebo-controlled RCT involving 302 patients who had

prior VT/VF and an ICD [38]. D,l-sotalol reduced the probability of death or appropriate ICD therapy from 0.42 in the placebo group (most of whom were not treated with beta-blockers) to 0.27 in the d,l-sotalol group (RR, 0.56; 95% CI, 0.36–0.85) after 1 year. D,l-sotalol was compared with standard beta-blockers in three RCTs. In one trial, d,l-sotalol increased the 1-year probability of both VT and fast VT/VF (0.43 and 0.46, respectively) compared with metoprolol (0.17 and 0.12, respectively; $P = .02$) [39]; in the other two trials there was no difference in VT/VF between the patients treated with d,l-sotalol and those treated with standard beta-blockers [40,41].

D-sotalol, a relatively pure I_{Kr} blocker, was superior to placebo for suppression of VPBs [42], was superior to class Ia drugs for suppression of inducible sustained VT/VF [43], and was effective for long-term prevention of VT/VF [44].

Dofetilide, another relatively pure I_{Kr} blocker, was superior to placebo for suppression of inducible VT/VF [45] and for time to first appropriate ICD therapy in patients who had prior sustained VT/VF [46]. Dofetilide was equivalent to d,l-sotalol for suppression of inducible VT [47,48].

Azimilide blocks both components of delayed rectifier (I_{Kr} and I_{Ks}), is a weak blocker of the $I_{Ca,L}$, and has weak alpha- and beta-blocking effects [31,49]. These actions should increase antiarrhythmic potency by lessening reverse use dependence and should reduce the probability of torsade de pointes. In an animal model of torsade de pointes, azimilide was less proarrhythmic than dofetilide or d,l-sotalol [50]. Azimilide is effective for suppression of both VPBs and inducible VT/VF [49]. Two RCTs tested azimilide for prevention of VT/VF in patients who had spontaneous or inducible VT/VF and who had an ICD. In a dose-ranging study in 172 patients, Singer and colleagues [51] reported the annual incidence of appropriate ICD therapy was reduced from 36% in patients who received placebo to 10%, 12%, and 9%, respectively, in patients who received 35 mg, 75 mg, and 125 mg azimilide daily (all comparisons, $P < .0001$). In the Shock Inhibition Evaluation with Azimilide trial, 633 patients who had prior VT/VF and an ICD were assigned randomly to placebo, to azimilide, 75 mg/d, or to azimilide, 125 mg/d [52]. The annual number of appropriate ICD therapies decreased from 25.1 in the placebo group to 17.1 in patients who received azimilide, 75 mg/d ($P = .02$) and to 9.6 in patients who received azimilide, 125 mg/d (all comparisons, $P < .05$).

Amiodarone expresses class I, II, III, and IV antiarrhythmic effects, is the most potent antiarrhythmic drug, has a low risk of torsade de pointes (<1%), has very slow pharmacokinetics, and has frequent and unusual long-term adverse effects [32]. In the Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation trial, 228 patients resuscitated from VT/VF were assigned randomly to empiric amiodarone or to a class I drug predicted to be effective by its suppression of frequent and complex VPBs or inducible VT/VF [53]. Amiodarone reduced the 2-year probability of cardiac death or sustained VT/VF from approximately 0.48 in patients taking the class I drug to approximately 0.23 ($P < .001$). In the Optimal Pharmacologic Therapy in Cardioverter Defibrillator Patients trial, standard beta-blockers, d,l-sotalol, and amiodarone plus a standard beta-blocker were compared for the prevention of appropriate ICD therapy in patients who had spontaneous or inducible VT/VF [41]. The use of amiodarone plus a standard beta-blocker reduced the annual VT/VF rate from 0.45 in patients receiving standard beta-blockers and from 0.39 in patients receiving d,l-sotalol to 0.19 ($P < .001$).

Effects on sudden death/all-cause mortality

Julian and colleagues [54] randomly assigned 1456 patients who had prior MI to d,l-sotalol or placebo. They found no difference in sudden death between the patients receiving placebo and patients receiving d,l-sotalol (2.4% versus 2.9%; RR, 1.07; 95% CI, 0.82–1.39). They similarly found no difference in all-cause mortality between patients receiving placebo and patients receiving d,l-sotalol (8.9% versus 7.3%; RR, 0.81; 95% CI, 0.55–1.19) after 1 year.

The Survival with Oral D-sotalol (SWORD) investigators randomly assigned 3121 patients who had prior MI and who had an LVEF of 0.40 or lower to d-sotalol or placebo [55]. After 5 months, d-sotalol increased the rate of death from presumed arrhythmic causes from 2.0% in patients receiving placebo to 3.6% (RR, 1.77; 95% CI, 1.15–2.74) and increased all-cause mortality from 3.1% in patients receiving placebo to 5.1% (RR, 01.65; 95% CI, 1.15–2.36).

The Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) group randomly assigned 1518 patients who had CHF to dofetilide or placebo with mandated drug initiation in hospital (DIAMOND-CHF) [56].

After 18 months, there were no differences between the patients receiving dofetilide or placebo in death ascribed to arrhythmia (20% and 20%, respectively) or in all-cause mortality (41% and 42%, respectively). These investigators also randomly assigned 1510 patients who had prior MI with an LVEF of 0.35 or lower to dofetilide or placebo with mandated drug initiation in hospital (DIAMOND-MI) [57]. After 15 months, there were no differences between patients treated with dofetilide or placebo in death assumed to be caused by arrhythmia (17% and 18%, respectively) or in all-cause mortality (31% and 32%, respectively).

In the Azimilide Post-infarct Survival Evaluation (ALIVE) trial, 3381 patients who had prior MI and an LVEF of 0.15 to 0.35 were assigned randomly to azimilide or placebo [58]. After 1 year, there were no significant differences between the patients treated with azimilide and patients who received placebo in death attributed to arrhythmia (6.7% and 5.4%, respectively) or in all-cause mortality (12% and 12%, respectively).

Meta-analysis of eight RCTs involving 5101 patients who had prior MI and of five RCTs involving 1452 patients who had CHF reported that amiodarone reduced the rate of sudden death from 5.7% in patients in the control group to 4.0% (HR, 0.71; 95% CI, 0.59–0.85) and reduced all-cause mortality from 12.3% in patients in the control group to 10.9% (HR, 0.87; 95% CI, 0.78–0.99) without affecting New York Heart Association (NYHA) status [59]. In the Sudden Cardiac Death in Heart Failure Trial, 2521 patients who had CHF with an LVEF of 0.35 (stratified by NYHA class) were assigned randomly to placebo, amiodarone, or an ICD [60]. There was no difference in all-cause mortality between patients treated with amiodarone and patients receiving placebo (HR, 1.06; 97.5% CI, 0.86–1.30), although there was an increase in all-cause mortality in patients who had NYHA class III disease taking amiodarone (HR, 1.44; 95% CI, 1.05–1.97).

Safety

The use of a class III drug carries a risk of torsade de pointes: 1% to 5% with d,l-sotalol, 1% to 2% with d-sotalol, 1%to 3% with dofetilide, less than 1% with azimilide, and less than 1% with amiodarone [29,61].

In RCTs, adverse events (particularly dizziness, depression, and nausea [54]) caused d,l-sotalol to be discontinued more often than placebo (27% versus 12%; RR, 1.54; 95% CI, 1.15–2.04) [38]. In the SWORD trial, there were no differences in serious adverse effects, including recognized torsade de pointes, between d-sotalol and placebo [55]. In the DIAMOND-CHF and DIAMOND-MI trials the dofetilide dosage initially was fixed [56,57]. Later, the dofetilide dosage was individualized based on creatinine clearance and QT interval. In the patients treated with dofetilide, torsade de pointes occurred in 4.8% of patients who had CHF before the dosing change and in 2.9% of these patients after the dosing change and in 3.0% of patients who had prior MI before the dosing change and in 0.6% of these patients after the dosing change. Seventy-six percent of the torsade de points episodes in the DIAMOND-CHF trial and 71% of the torsade de pointes episodes in DIAMOND-MI occurred during the 3-day drug-initiation hospitalization. Other adverse events occurred equally in patients treated with dofetilide and patients receiving placebo. One comparison of dofetilide and d,l-sotalol reported that withdrawals for adverse events were equal (19% and 26%, respectively) and that the risks of ventricular proarrhythmia were equal during acute titration (4.5% and 3.1%, respectively) and during follow-up (4.9% and 7.7%, respectively) [51]. Three RCTs found adverse events to occur equally with azimilide and placebo [51,52,58] except for severe neutropenia (0.9% versus 0.2%, respectively; $P = .01$) [58]. In the ALIVE trial, torsade de pointes occurred in 0.3% of patients treated with azimilide and in 0.1% of patients receiving placebo [58]. The Amiodarone Trials Meta-Analysis investigators found amiodarone to have more adverse events than placebo: hypothyroidism (7.0% and 1.1%, respectively), hyperthyroidism (1.4% and 0.5%, respectively), peripheral neuropathy (0.5% and 0.2%, respectively), lung infiltrates (1.6% and 0.5%, respectively), bradycardia (2.4% and 0.8%, respectively), and liver abnormalities (1.0% and 0.4%, respectively) [59].

Inferences

Class III drugs treat and prevent VT/VF. D,l-sotalol, d-sotalol, and dofetilide have a significant risk of torsade de pointes. Azimilide has a smaller risk of torsade de pointes. In patients who have structural heart disease, d,l-sotalol, dofetilide, and azimilide have no effect on sudden death or

all-cause mortality; d-sotalol increases sudden death and all-cause mortality. Amiodarone has a lesser risk of torsade de pointes, has a greater adverse effect profile, and decreases sudden death and all-cause mortality in patients who have structural heart disease. In general, class III drugs are more effective and better tolerated than class I drugs. Accordingly, class III drugs are used only when other treatments have failed and the advantages of suppressing VT/VF outweigh the risk of torsade de pointes and, with some drugs, the increase in all-cause mortality. In practice, class III agents are used for short-term therapy of an episode of VT/VF, for short-term therapy of an electrical storm of VT/VF, or for long-term therapy in patients who have not responded to or are not candidates for other therapies (excluding class I drugs). In these settings, amiodarone is preferred. Nevertheless, if time permits, amiodarone may be preceded by a trial of other class III agents (traditionally d,l-sotalol, but dofetilide or azimilide also are appropriate).

Class IV antiarrhythmic drugs

Class IV drugs (the nondihydropyridine calcium-channel blockers verapamil and diltiazem) have as their dominant electrophysiologic effect inhibition the $I_{Ca,L}$.

Effects on ventricular arrhythmias

Class IV drugs have minimal effects on reentrant ventricular arrhythmias [62] but are effective for ventricular arrhythmias based on triggered activity. Thus, class IV drugs are useful for Belhassen VT (left septal or verapamil-sensitive VT) [63], for right ventricular outflow tract VT [64], for catecholaminergic polymorphic VT [65], and for some VTs related to acute myocardial ischemia, particularly those associated with coronary artery spasm [66].

Effects on sudden death/all-cause mortality

A meta-analysis of RCTs of class IV drugs included 26 trials of 21,644 patients who had prior MI and reported that class IV drugs had no effect on all-cause mortality (OR, 1.03; 95% CI, 0.94–1.13) [7].

Safety

Class IV drugs have an excellent safety profile in patients without structural heart disease. Withdrawal for adverse effects is uncommon and is comparable to placebo (4%–8%). Serious adverse effects, such AV block or rash, occur in less than 2% of patients [67]. Nevertheless, in patients who have depressed left ventricular function, class IV drugs may hasten the progression of CHF [68].

Inferences

The use of class IV drugs for VT/VF is limited to niche indications. They are first-line therapies for Belhassen VT and for VT/VF related to coronary artery spasm. They also are used for right ventricular outflow tract VT or catecholaminergic polymorphic VT for patients who cannot take or who have not responded to beta-blocker therapy. Most such patients are not at risk for progression of CHF.

Statins

Hydroxymethylglutaryl coenzyme-A reductase inhibitors (statins) have many effects other than cholesterol lowering. These pleiotropic effects include those on signaling pathways for inflammation, endothelial nitric oxide synthesis, plasminogen, endothelin-1, platelet activation, angiotensin II receptor regulation, sympathetic nerve activity, oxidative stress, left ventricular mass regression, left ventricular reverse remodeling, and antiarrhythmic effects [69]. The last includes changes in properties of the sarcolemmal membrane with resultant alterations in ion-channel function.

Effects on ventricular arrhythmias

A meta-analysis of three nonrandomized studies in patients who had CAD with prior VT/VF and an ICD reported that lipid-lowering drugs reduced appropriate ICD therapy from 58% in 457 patients not taking taking lipid-lowering drugs to 38% in 264 patients taking lipid-lowering drugs (89% of which were statins) (RR, 0.60; 95% CI, 0.49–0.73) after 16 months [70–72]. The Cholesterol Lowering and Arrhythmia Recurrences after Internal Defibrillator Implantation trial randomly assigned 106 patients who had CAD and prior VT/VF and an ICD to atorvastatin or placebo [73]. By intention-to-treat, atorvastatin had a nonsignificant effect, reducing appropriate ICD therapy from 36% in the placebo group to 21% in the atorvastatin group (HR, 0.58; $P = .07$). By treatment received, atorvastatin significantly reduced appropriate ICD therapy from 40% in the placebo group to 16% in the atorvastatin group (HR, 0.39; $P = .02$).

A nonrandomized substudy of the Multicenter Automatic Defibrillator Implantation II Trial reported that patients who had CAD, depressed LVEF, and a primary-prevention ICD who took a statin had a lower 2-year probability of first appropriate ICD therapy than patients who did not take a statin (0.26 versus 0.35; HR, 0.72; 95% CI, 0.52–0.99) after 17 months [74]. The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation reported that patients who had nonischemic cardiomyopathy who had a primary-prevention ICD and who took a statin had a nonsignificant reduction in first appropriate ICD shock compared with patients who did not take a statin (12.5% versus 15.6%; HR, 0.80; 95% CI, 0.35–1.84) after 29 months [75].

Effects on sudden death/all-cause mortality

Meta-analysis of 10 RCTs involving 22,275 patients who had CAD reported that statins reduced the rate of sudden death from 3.8% in the control group to 3.0% in patients treated with statin (HR, 0.81; 95% CI, 0.71–0.93) after 4.4 years [76]. Another meta-analysis of 14 RCTs involving 90,056 patients who had CAD reported that statins reduced all-cause mortality from 9.7% in the control group to 8.5% in patients treated with statin (HR, 0.87; 95% CI, 0.84–0.91) after 5 years [77]. Patients who had CHF were excluded from most statin RCTs because of safety concerns [78]. Recently, the Controlled Rosuvastatin Multinational heart failure trial randomly assigned 5011 patients aged 60 years and older who had CHF and a depressed LVEF to rosuvastatin or placebo and reported equivalent risks of all-cause mortality (29.0% and 30.4%, respectively; HR, 0.95; 95% CI, 0.86–1.05) after 33 months [79].

Safety

The Cholesterol Treatment Trialists' collaborators meta-analysis of statin trials reported a nonsignificant 5-year excess risk of rhabdomyolysis with statins of 0.01% ($P = .4$) [77].

Inferences

Statins prevent VT/VF, sudden cardiac death, and all-cause mortality in patients who have CAD (and perhaps in patients who have idiopathic dilated cardiomyopathy or advanced CHF) with a very low risk of therapy. Statins should be used in patients who have CAD and may be considered in patients who have idiopathic congestive cardiomyopathy or advanced CHF if VT/VF management is problematic.

Renin-angiotensin-aldosterone system inhibitors

Activation of the renin-angiotensin-aldosterone system (RAAS) results in dysregulation of many cardiovascular processes causing vascular and myocardial inflammation, vascular smooth muscle proliferation, myocyte hypertrophy, endothelial dysfunction, myocardial fibrosis, thrombotic cascade activation, platelet activation, oxidative pathway activation, interstitial matrix remodeling, coronary plaque destabilization, hypokalemia, and hypomagnesemia [80,81]. The RAAS may be suppressed by inhibiting angiotensin-converting enzyme (ACE) hydrolysis of inactive angiotensin I to active angiotensin II with an ACE inhibitor, by blocking the AT_1 receptor through which many deleterious effects of angiotensin II are mediated with an angiotensin receptor blocker (ARB), or by blocking the effects of aldosterone with an aldosterone blocker.

Effects on ventricular arrhythmias

Other than by correction of hypokalemia or hypomagnesemia, suppression of the RAAS would not be expected to be acutely antiarrhythmic. Some studies report that ACE inhibitors decrease VPB frequency and complexity; others do not. In general, the positive studies were longer-term trials in patients who had CHF associated with increases in serum potassium or decreases in autonomic sympathetic tone [82–84]. In one trial in patients who had inducible VT, captopril treatment had no significant effect on the inducibility of VT [85]. Few studies have examined the antiarrhythmic effects of ARBs in humans. One study found that losartan had no significant effects on the frequency or complexity of spontaneous VPBs in hypertensive men who had preserved left ventricular systolic function [86]. Three RCTs of spironolactone in patients who had CHF reported a decrease in the frequency and complexity of VPBs [87–89]. Again, these were longer-term trials, and efficacy was correlated inversely with plasma or erythrocyte magnesium levels.

Effects on sudden death/all-cause mortality

Meta-analyses of ACE inhibitor RCTs consider patients in three groups: patients who have CHF of any cause (mostly CAD), patients who

have had a recent MI (often with CHF or depressed LVEF), and patients who have demonstrated or possible CAD without CHF or left ventricular dysfunction. In patients who have CHF, a meta-analysis of 32 RCTs involving 7105 patients reported that treatment with an ACE inhibitor reduced the rate of sudden death nonsignificantly from 5.6% in the control group to 4.7% (OR, 0.91; 95% CI, 0.73–1.12) while reducing all-cause mortality from 21.9% in the control group to 15.8% (OR, 0.77; 95% CI, 0.67–0.88) [90]. A meta-analysis of 15 RCTs involving 15,104 patients who had a recent MI reported that treatment with ACE inhibitors reduced the rate of sudden death from 6.6% in the control group to 5.3% (OR, 0.80; 95% CI, 0.70–0.92) and reduced all-cause mortality from 16.8% in the control group to 14.4% (OR, 0.83; 95% CI, 0.71–0.97) [91]. In patients who had documented or possible CAD and preserved left ventricular function, meta-analysis of six RCTs involving 33,500 patients reported that treatment with ACE inhibitors reduced all-cause mortality from 8.3% in the control group to 7.2% (OR, 0.87; 95% CI, 0.81–0.94) over 4.4 years [92]. A substudy in the Heart Outcome Prevention Evaluation trial in patients who had or were at high risk of developing CAD without overt CHF reported that treatment with ramipril reduced the rate of sudden death/documented arrhythmic death/resuscitated cardiac arrest from 4.2% in the control group to 3.3% (OR, 0.79; 95% CI, 0.64–0.98) over 4.5 years [93].

A meta-analysis of nine RCTs involving 4623 patients who had CHF who were not receiving ACE inhibitors reported that treatment with ARBs decreased all-cause mortality from 17.7% in the control group to 10.6% (OR, 0.83; 95% CI, 0.60–1.00) after 18 months [94]. In eight RCTs evaluating ARBs against ACE inhibitors in 5201 patients who had CHF, all-cause mortality in patients receiving ARBs was no different from that in patients receiving an ACE inhibitor (11.5% versus 12.8%; OR, 1.06; 95% CI, 0.90–1.13) over 14 months. In seven RCTs evaluating ARBs added to ACE inhibitors in 8260 patients who had CHF, all-cause mortality in patients receiving an ARB plus an ACE inhibitor was no different from that in patients receiving only an ACE inhibitor (21.2% versus 22.6%; OR, 0.97; 95% CI, 0.87–1.08) over 27 months. Two RCTs found no difference in all-cause mortality between patients who had high-risk acute MI and depressed LVEF treated with an ARB and an ACE inhibitor and those treated with an ACE inhibitor alone [95,96].

The Randomized Aldactone Evaluation Study (RALES) randomly assigned 1663 patients who had class III-IV CHF treated with ACE inhibitors to receive spironolactone or placebo [97]. Treatment with spironolactone reduced the rate of sudden death from 13.1% in the control group to 10.0% (RR, 0.71; 95% CI, 0.54–0.95) and reduced all-cause mortality from 46% in the control group to 35% (RR, 0.70; 95% CI, 0.60–0.82) after 24 months. Similarly, the Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) randomly assigned 6642 patients who had recent MI and an LVEF of 0.40 or less and (except for patients who had diabetes) symptomatic CHF on optimal CHF therapy to eplerenone or placebo [98]. Treatment with eplerenone reduced the rate of sudden death from 6.1% in the control group to 4.9% (RR, 0.79; 95% CI, 0.64–0.97) and reduced all-cause mortality from 16.7% in the control group to 14.4% (RR, 0.85; 95% CI, 0.75–0.96) after 16 months.

Safety

A meta-analysis of 36 RCTs involving 18,234 patients reported that therapy was withdrawn more often from patients receiving an ACE inhibitor than from control patients because of cough (2.0% versus 1.1%; RR, 3.19; 95% CI, 2.22–4.57), hypotension (1.6% versus 0.8%; RR, 1.95; 95% CI, 1.39–2.74), renal dysfunction (0.9% versus 0.5%; RR, 1.84; 95% CI, 1.20–2.81), and hyperkalemia (0.4% versus 0.03%; RR, 7.11; 95% CI, 2.11–3.94) [99].

In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity–Alternative study, the ARB was withdrawn more frequently than placebo for hypotension (3.7% versus 0.9%; RR, 1.63; 95% CI, 1.22–2.19), renal dysfunction (6.1% versus 2.7%; RR, 1.42; 95% CI, 1.15–1.76), and hyperkalemia (1.9% versus 0.3%; RR, 1.74; 95% CI, 1.14–2.66) [100]. Meta-analysis of RCTs involving 17,337 patients who had CHF or high-risk patients who had prior MI reported that the combination of ARB and ACE inhibitor was withdrawn more often than the ACE inhibitor alone because of adverse effects (11.5% versus 9.0%; RR, 1.28; 95% CI, 1.17–1.40) [101]. The most common reasons for withdrawal were hypotension (11.1% versus 7.5%; RR, 1.48; 95% CI, 1.34–1.62), renal dysfunction

(4.1% versus 2.4%; RR, 1.76; 95% CI, 1.49–2.09), and hyperkalemia (1.6% versus 0.8%; RR, 2.46; 95% CI, 0.68–8.87) [101].

In the RALES trial, therapy was discontinued for adverse events more often in patients receiving spironolactone (8%) than in patients receiving placebo (5%) [97]. The most common adverse effect was gynecomastia or breast pain in men (10% versus 1%). In EPHESUS, this adverse effect was rare. The major adverse effect was serious hyperkalemia in 5.5% of patients taking eplerenone, compared with 3.9% of patients taking placebo ($P = .002$) [98]. This finding was offset by serious hypokalemia in 8.4% of patients taking eplerenone compared with 13.1% of patients taking placebo ($P < .001$).

Inferences

ACE inhibitors, ARBs, and aldosterone blockers have antiarrhythmic effects by increasing potassium and magnesium concentrations and by decreasing sympathetic tone in patients who have CHF. In long-term use they also prevent the development of VT/VF and sudden death in patients who have significant structural heart disease. Thus, an ACE inhibitor or, when an ACE inhibitor is poorly tolerated, an ARB should be used in patients who have structural heart disease. Aldosterone blockers should be used in patients who have class III-IV CHF and for other patients with demonstrated or presumed VT/VF propensity when potassium and/or magnesium conservation is desired.

Digoxin

The dominant actions of digoxin are an inhibition of sodium-potassium ATPase, thereby augmenting transmembrane sodium–calcium exchange resulting in increased intracellular calcium, a reduction of sympathetic tone, and an augmentation of parasympathetic tone [102]. Digoxin also may inhibit the RAAS. In therapeutic concentrations, digoxin has no direct ventricular electrophysiologic effects [103]. In toxic concentrations, myocyte calcium loading causes delayed afterdepolarizations and VT [104]. Unfortunately, the window between therapeutic and toxic dosages of digoxin is small.

Effects on ventricular arrhythmias

Two placebo-controlled RCTs in patients who had CHF found digoxin to have no effect on the frequency or complexity of VPBs [105,106]. A crossover trial suggested that 0.375 mg/d of digoxin reduced the frequency but not the complexity of VPB, perhaps through its sympathiolytic effects [107].

Effects on sudden death/all-cause mortality

The Digitalis Investigator Group (DIG) trial randomly assigned 6800 patients who had class II-IV CHF in sinus rhythm with an LVEF of 0.45 or less to digoxin or placebo [108]. After a follow-up of 37 months, there was no significant difference between the digoxin and the placebo groups in all-cause mortality (34.8% and 35.1%, respectively; RR, 0.99; 95% CI, 0.91–1.07) or in cardiac mortality (29.9% and 29.5%, respectively; RR, 1.01; 95% CI, 0.93–1.10). Treatment with digoxin, however, trended to reduce CHF deaths, from 13.2% in the placebo group to 11.6% (RR, 0.88; 95% CI, 0.77–1.01; $P = .06$). Although the incidence of sudden death was not reported, if cardiac mortality was unaffected and CHF mortality was reduced, sudden death must have increased. In this regard, the incidence of VT/VF was higher in the digoxin group than in the placebo group (1.1% versus 0.8%; RR, 1.40; 95% CI, 0.84–2.3; $P = .20$).

A post hoc analysis of DIG trial data examined the effects of digoxin on CHF death and all-cause mortality in male participants who survived 1 month as a function of trough serum digoxin concentration at 1 month [109]. Compared with 1171 men in the placebo group who survived 1 month, patients who had digoxin concentrations of 0.5 to 0.8 ng/mL (n = 572) had an absolute 6.3% lower rate of all-cause mortality (95% CI, 2.1%–10.5%), a 3.7% lower rate of cardiovascular mortality (95% CI, 0.4%–7.7%), and a 4.7% lower rate of CHF mortality (95% CI, 2.1%–7.3%). Comparable reductions in cardiac and CHF mortality suggest a similar reduction in sudden death. In men who had digoxin concentrations of 0.9 to 1.1 ng/mL (n = 322), the rates of all-cause mortality, cardiovascular mortality, and heart failure mortality were similar to those in the placebo group. Those who had digoxin concentrations of 1.2 ng/mL or higher (n = 277) had an absolute higher rate of all-cause mortality (11.8%; 95% CI, 5.7%–18.0%) and a higher rate of cardiovascular mortality (11.5%; 95% CI, 5.4%–17.5%) but an equivalent rate of CHF mortality (1.9%; 95% CI, −2.6%–6.3%). The increase in cardiac mortality but not in CHF

mortality suggests an increase in the rate of sudden death.

Safety

In addition to the possible increase in sudden death, other safety issues with digoxin are frequent drug–drug interactions [102] and digoxin intoxication [102,108]. In the DIG trial suspected digoxin intoxication was more common in patients receiving active treatment (11.9%) than in patients receiving placebo (7.9%) and included supraventricular tachyarrhythmias in 2.5% of patients receiving digoxin and 1.2% of patients receiving placebo (RR, 2.10; 95% CI, 1.45–3.07) and second- or third-degree AV block in 1.2% of patients receiving digoxin and 0.4% of patients receiving placebo (RR, 2.87; 95% CI, 1.56–5.28) [108].

Inferences

Digoxin has no role in the treatment of VT/VF and may increase the rate of sudden death. Patients who have difficult-to-control VT/VF who are receiving digoxin therapy may be helped by ensuring that the serum digoxin concentration is less than 0.9 ng/mL.

Summary

Class I, III, and IV drugs have immediate/direct antiarrhythmic effects. Class I drugs treat and prevent VT/VF at the expense of an increase in sudden death and all-cause mortality. Class III drugs treat and prevent VT/VF with a variable effect on sudden death and all-cause mortality. Class IV drugs treat and prevent certain forms of VT with no effect on sudden death or all-cause mortality. Accordingly, class I and III agents are used for short-term therapy of an episode or storm of VT/VF or for long-term therapy in patients who have not responded to or are not candidates for all other therapies (including the ICD). In these settings, class III agents that do not have a detrimental effect on sudden death (d,l-sotalol, amiodarone) are preferred. Class IV drugs are used in niche applications: as first-line treatment for Belhassen VT or coronary artery spasm VT/VF and after beta-blockers for right ventricular outflow tract VT or catecholaminergic polymorphic VT.

Beta-blockers have both immediate/direct and delayed/indirect antiarrhythmic effects. They treat and prevent VT/VF and decrease sudden death and all-cause mortality in patients who have structural heart disease. Most patients who have a propensity to VT/VF should receive a beta-blocker. Carvedilol may have advantages over other beta-blockers in this setting.

Statins, ACE inhibitors, ARBs, and aldosterone blockers have delayed/indirect antiarrhythmic effects that are expressed dominantly by a decrease in the rate of sudden death and all-cause mortality in patients who have structural heart disease. Statins should be used in patients who have CAD and may be considered in patients who have idiopathic congestive cardiomyopathy or advanced CHF if VT/VF management is problematic. An ACE inhibitor or, when an ACE-inhibitor is poorly tolerated, an ARB should be used in patients who have structural heart disease. Aldosterone blockers should be used in patients who have class III-IV CHF and for other patients who have a propensity to VT/VF when potassium and/or magnesium conservation is desired.

Digoxin has no role in the treatment or prevention of VT/VF and may increase the rate of sudden death. Patients who have difficult-to-control VT/VF who are receiving digoxin therapy may be helped by ensuring that the serum digoxin concentration is less than 0.9 ng/mL.

References

[1] Zheng ZJ, Croft JB, Giles WH, et al. Sudden cardiac death in the United States, 1989 to 1998. Circulation 2001;104(18):2158–63.

[2] Bayes de Luna AB, Coumel P, Leclercq JF. Curriculum in cardiology: ambulatory sudden cardiac death; mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. Am Heart J 1989;117(1):151–9.

[3] Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. Eur Heart J 2000;21(24):2071–8.

[4] Nanthakumar K, Epstein AE, Kay GN, et al. Prophylactic implantable cardioverter-defibrillator therapy in patients with left ventricular systolic dysfunction: a pooled analysis of 10 primary prevention trials. J Am Coll Cardiol 2004;44(11):2166–72.

[5] Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. N Engl J Med 1991; 324(12):781–8.

[6] Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. N Engl J Med 1992;327(4):227–33.

[7] McAlister FA, Teo KK. Antiarrhythmic therapies for the prevention of sudden cardiac death. Drugs 1997;54(2):235–52.
[8] Friedman PL, Stevenson WG. Proarrhythmia. Am J Cardiol 1998;82(7 Suppl 1):50N–8N.
[9] Dorian P. Antiarrhythmic action of ß-blockers: potential mechanisms. J Cardiovasc Pharmacol Ther 2005;10(Suppl 1):S15–22.
[10] Steinbeck G, Andresen D, Bach P, et al. A comparison of electrophysiologically guided antiarrhythmic drug therapy with beta-blocker therapy in patients with symptomatic, sustained ventricular tachyarrhythmias. N Engl J Med 1992;327(14): 987–92.
[11] Lown B, Graboys TB. Management of patients with malignant ventricular arrhythmias. Am J Cardiol 1977;39(6):910–8.
[12] Duff HJ, Mitchell LB, Wyse DG. Antiarrhythmic efficacy of propranolol: comparison of low and high serum concentrations. J Am Coll Cardiol 1986;8(4):959–65.
[13] Leclercq JF, Leenhardt A, Coumel P, et al. Efficacy of beta-blocking agents in reducing the number of shocks in patients implanted with first-generation automatic defibrillators. Eur Heart J 1992;13(9): 1180–4.
[14] Yusuf S, Sleight P, Rossi PRF, et al. Reduction in infarct size, arrhythmias, chest pain, and morbidity by early intravenous beta-blockade in suspected acute myocardial infarction. Circulation 1983; 67(6 Pt 2):I32–41.
[15] Rydén L, Arniego R, Arnmar K, et al. A double-blind trial of metoprolol in acute myocardial infarction: effects on ventricular tachycardia. N Engl J Med 1983;308(11):614–8.
[16] Norris RM, Brown MA, Clarke ED, et al. Prevention of ventricular fibrillation during acute myocardial infarction by intravenous propranolol. Lancet 1984;324(8408):883–6.
[17] Lerman BB, Belardinelli L, West GA, et al. Adenosine-sensitive ventricular tachycardia: evidence suggesting cyclic AMP-mediated triggered activity. Circulation 1986;74(2):270–80.
[18] Sung RJ, Shen EN, Morady F, et al. Electrophysiologic mechanisms of exercise-induced sustained ventricular tachycardia. Am J Cardiol 1983;51(3): 525–30.
[19] Reiter MJ, Reiffel JA. Importance of beta blockade in the therapy of serious ventricular arrhythmias. Am J Cardiol 1998;82(4 Suppl 1):9I–19I.
[20] Yusuf S, Peto R, Lewis J, et al. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985;27(5):335–71.
[21] Heidenreich PA, Lee TT, Massie BM. Effect of beta-blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. J Am Coll Cardiol 1997;30(1): 27–34.
[22] Packer M. Do ß-blockers prolong survival in heart failure only by inhibiting the ß1-receptor? A perspective on the results of the COMET trial. J Card Fail 2003;9(6):429–43.
[23] Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol outcomes in patients with chronic heart failure in the Carvedilol or Metoprolol European Trial (COMET): randomized controlled trial. Lancet 2003;362(9377):7–13.
[24] Torp-Pedersen C, Poole-Wilson PA, Swedberg K, et al. Effects of metoprolol and carvedilol on cause-specific mortality and morbidity in patients with chronic heart failure (COMET). Am Heart J 2005;149(2):370–6.
[25] El-Sharif N, Turitto G. Electrophysiologic effects of carvedilol: is carvedilol an antiarrhythmic agent? Pacing Clin Electrophysiol 2005;28(9):985–90.
[26] Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure. Results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. Circulation 2002;106(17): 2194–9.
[27] McMurray J, Køber L, Robertson M, et al. Antiarrhythmic effect of carvedilol after acute myocardial infarction: results of the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial. J Am Coll Cardiol 2005; 45(4):525–30.
[28] Anderson JL, Prystowski EN. Sotalol: an important new antiarrhythmic. Am Heart J 1999;137(3): 388–409.
[29] Advani SV, Singh BN. Pharmacodynamic, pharmacokinetic and antiarrhythmic properties of d-sotalol, the dextro-isomer of sotalol. Drugs 1995;49(5):664–79.
[30] Mounsey JP, DiMarco JP. Dofetilide. Circulation 2000;102(21):2665–70.
[31] Clemett D, Markham A. Azimilide. Drugs 2000; 59(2):271–7.
[32] Vassallo P, Trohman RG. Prescribing amiodarone: an evidence-based review of clinical indications. JAMA 2007;298(11):1312–22.
[33] Anatasiou-Nana MI, Gilbert EM, Miller RH, et al. Usefulness of d,l sotalol for suppression of chronic ventricular arrhythmias. Am J Cardiol 1991;67(6): 511–6.
[34] Deedwania PC. Suppressant effects of conventional beta blockers and sotalol on complex and repetitive ventricular premature beats. Am J Cardiol 1990; 65(2):43A–50A.
[35] Lidell C, Rehnquist N, Sjögren A, et al. Comparative efficacy of oral sotalol and procainamide in patients with chronic ventricular arrhythmias: a multicenter study. Am Heart J 1985;109(5 Pt 1): 970–5.
[36] Mason JW, ESVEM Investigators. A comparison of seven antiarrhythmic drugs in patients with

ventricular tachyarrhythmias. N Engl J Med 1993; 329(7):452–8.
[37] Mason JW, ESVEM Investigators. A comparison of electrophysiologic testing with Holter monitoring to predict antiarrhythmic-drug efficacy for ventricular tachyarrhythmias. N Engl J Med 1993;329(7):445–51.
[38] Pacifico A, Hohnloser SH, Williams JH, et al. Prevention of implantable-defibrillator shocks by treatment with sotalol. N Engl J Med 1999; 340(24):1855–62.
[39] Seidl K, Hauer B, Schwick NG, et al. Comparison of metoprolol and sotalol in preventing ventricular tachyarrhythmias after the implantation of a cardioverter/defibrillator. Am J Cardiol 1998; 82(6):744–8.
[40] Kettering K, Mewis C, Dörnberger V, et al. Efficacy of metoprolol and sotalol in the prevention of recurrences of sustained ventricular tachyarrhythmias in patients with an implantable cardioverter defibrillator. Pacing Clin Electrophysiol 2002;25(11):1571–6.
[41] Connolly SJ, Dorian P, Roberts RS, et al. Comparison of ß-blockers, amiodarone plus ß-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC study: a randomized trial. JAMA 2006; 295(2):165–71.
[42] Barbey JT, Echt DS, Thompson KA, et al. Effect of d-sotalol on ventricular arrhythmias in man. Circulation 1985;72(4 Pt 2):170–5.
[43] Schwartz J, Crocker K, Wynn J, et al. The antiarrhythmic effects of d-sotalol. Am Heart J 1987; 114(3):539–44.
[44] Brachmann J, Schols W, Beyer T, et al. Acute and chronic antiarrhythmic efficacy of d-sotalol in patients with sustained ventricular tachyarrhythmias. Eur Heart J 1993;14(Suppl H):85–7.
[45] Echt DS, Lee JT, Murray KT, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of dofetilide in patients with inducible sustained ventricular tachyarrhythmias. J Cardiovasc Electrophysiol 1995;6(9):687–99.
[46] O'Toole M, O'Neill G, Kluger J, et al. Efficacy and safety of oral dofetilide in patients with an implanted defibrillator: multicenter study [abstract]. Circulation 1999;100(18):I–794.
[47] Boriani G, Biffi M, De Simone N, et al. Repolarization changes in a double-blind crossover study of dofetilide versus sotalol in the treatment of ventricular tachycardia. Pacing Clin Electrophysiol 2000; 23(11 Pt 2):1935–8.
[48] Boriani G, Lubinski A, Capucci A, et al. A multicentre double-blind randomized crossover comparative study on the efficacy and safety of dofetilide vs sotalol in patients with inducible sustained ventricular tachycardia and ischaemic heart disease. Eur Heart J 2001; 22(23):2180–91.
[49] Karam R, Marcello S, Brooks RR, et al. Azimilide dihydrochloride, a novel antiarrhythmic agent. Am J Cardiol 1998;81(6 Suppl 1):40D–6D.
[50] Brooks RR, Drexler AP, Maynard AE, et al. Proarrhythmia of azimilide and other class III antiarrhythmic agents in the adrenergically stimulated rabbit. Proc Soc Exp Biol Med 2000;223(2):183–9.
[51] Singer I, Al-Khalidi H, Niazi I, et al. Azimilide decreases recurrent ventricular tachyarrhythmias in patients with implantable cardioverter defibrillators. J Am Coll Cardiol 2004;43(1):39–43.
[52] Dorian P, Borggrefe M, Al-Khalidi HR, et al. Placebo-controlled, randomized clinical trial of azimilide for prevention of ventricular tachyarrhythmias in patients with an implantable cardioverter defibrillator. Circulation 2004;110(24): 3646–54.
[53] CASCADE Investigators. Randomized antiarrhythmic drug therapy in survivors of cardiac arrest (the CASCADE study). Am J Cardiol 1993;72(3): 280–7.
[54] Julian DG, Prescott RJ, Jackson FS, et al. Controlled trial of sotalol for one year after myocardial infarction. Lancet 1982;319(8282):1142–7.
[55] Waldo AL, Camm AJ, deRuyter H, et al. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. Lancet 1996;348(9019):7–12.
[56] Torp-Pedersen C, Møller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. N Engl J Med 1999;341(12):857–65.
[57] Køber L, Bloch Thomsen PE, Møller M, et al. Effect of dofetilide in patients with recent myocardial infarction and left-ventricular dysfunction: a randomised trial. Lancet 2000;356(9247):2052–8.
[58] Camm AJ, Pratt CM, Schwartz PJ, et al. Mortality in patients after a recent myocardial infarction: a randomized placebo-controlled trial of azimilide using heart rate variability for risk stratification. Circulation 2004;109(8):990–6.
[59] Amiodarone Trials Meta-Analysis (ATMA) Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomized trials. Lancet 1997;350(9089):1417–24.
[60] Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter defibrillator for congestive heart failure. N Engl J Med 2005;352(3): 225–37.
[61] Brendorp B, Pedersen OD, Torp-Pedersen C, et al. A benefit-risk assessment of class III antiarrhythmic agents. Drug Saf 2002;25(12):847–65.
[62] Mason JW, Swerdlow CD, Mitchell LB. Efficacy of verapamil in chronic, recurrent ventricular tachycardia. Am J Cardiol 1983;51(10):1614–7.
[63] Belhassen B, Shapira I, Pelleg A, et al. Idiopathic recurrent sustained ventricular tachycardia

responsive to verapamil: an ECG-electrophysiologic entity. Am Heart J 1984;108(4 Pt 1):1034–7.
[64] Iwai S, Cantillon DJ, Kim RJ, et al. Right and left ventricular outflow tract tachycardias: evidence for a common electrophysiologic mechanism. J Cardiovasc Electrophysiol 2006;17(10):1052–8.
[65] Sumitomo N, Harada K, Nagashima M, et al. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death. Heart 2003;89(1):66–70.
[66] Grenadier E, Alpan G, Maor N, et al. Polymorphous ventricular tachycardia in acute myocardial infarction. Am J Cardiol 1984;53(9):1280–3.
[67] Russell RP. Side effects of calcium channel blockers. Hypertension 1988;11(3 Pt 2):II42–4.
[68] Goldstein RE, Boccuzzi SJ, Cruess D, et al. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. Circulation 1991;83(1):52–60.
[69] Shanes JG, Minadeo KN, Moret A, et al. Statin therapy in heart failure: prognostic effects and potential mechanism. Am Heart J 2007;154(4):617–23.
[70] De Sutter J, Tavernier R, De Buyzere M, et al. Lipid-lowering drugs and recurrences of life-threatening ventricular arrhythmias in high-risk patients. J Am Coll Cardiol 2000;36(3):766–72.
[71] Mitchell LB, Powell JL, Gillis AM, et al. Are lipid-lowering drugs also antiarrhythmic drugs? An analysis of the antiarrhythmics versus implantable defibrillators (AVID) trial. J Am Coll Cardiol 2003;42(1):81–7.
[72] Chiu JH, Abdelhadi RH, Chung MK, et al. Effect of statin therapy on risk of ventricular arrhythmia among patients with coronary artery disease and an implantable cardioverter-defibrillator. Am J Cardiol 2005;95(4):490–1.
[73] Cholesterol lowering and arrhythmia recurrences after internal defibrillator implantation: the CLARIDI Trial. Available at: www.clinicalstudyresults.org/documents/company-study_578_0.pdf. Accessed January 8, 2008.
[74] Vyas AK, Guo H, Moss AJ, et al. Reductions in ventricular tachyarrhythmias with statins in the multicenter automatic defibrillator implantation trial (MADIT)-II. J Am Coll Cardiol 2006;47(4):769–73.
[75] Goldberger JJ, Subacius H, Schaechter A, et al. Effects of statin therapy on arrhythmic events and survival in patients with nonischemic dilated cardiomyopathy. J Am Coll Cardiol 2006;48(6):1228–33.
[76] Levantesi G, Scarano M, Marfisi R, et al. Meta-analysis of effects of statin treatment on risk of sudden death. Am J Cardiol 2007;100(11):1644–50.
[77] Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet 2005;366(9493):1267–78.
[78] Rauchhaus M, Clark AL, Doehner W, et al. The relationship between cholesterol and survival in patients with chronic heart failure. J Am Coll Cardiol 2003;42(11):1933–40.
[79] Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357(22):2248–61.
[80] Altas SA. The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic inhibition. J Manag Care Pharm 2007;13(8 Suppl S-b):S9–20.
[81] Maisel WH, Stevenson WG. Sudden death and the electrophysiological effects of angiotensin-converting enzyme inhibitors. J Card Fail 2000;6(2):80–2.
[82] Cleland JG, Dargie HJ, Hodsman GP, et al. Captopril in heart failure: a double-blind controlled trial. Br Heart J 1984;52(5):530–5.
[83] Webster MWI, Fitzpatrick A, Nicholls G, et al. Effect of enalapril on ventricular arrhythmias in congestive heart failure. Am J Cardiol 1985;56(8):566–9.
[84] Hattori Y, Atsushi S, Hiroaki F, et al. Effects of captopril on ventricular arrhythmias in patients with congestive heart failure. Clin Ther 1997;19(3):481–6.
[85] Bashir Y, Sneddon JF, O'Nunain S, et al. Comparative electrophysiological effects of captopril or hydralazine combined with nitrate in patients with left ventricular dysfunction and inducible ventricular tachycardia. Br Heart J 1992;67(5):355–60.
[86] Zakynthinos E, Pierrutsakos Ch, Daniil Z, et al. Losartan controlled blood pressure and reduced left ventricular hypertrophy but did not alter arrhythmias in hypertensive men with preserved systolic function. Angiology 2005;56(4):439–49.
[87] Barr CS, Lang CC, Hanson J, et al. Effects of adding spironolactone to angiotensin-converting enzyme inhibitor in chronic congestive heart failure secondary to coronary artery disease. Am J Cardiol 1995;76(17):1259–65.
[88] Ramires FJ, Mansur A, Coelho O, et al. Effect of spironolactone on ventricular arrhythmias in congestive heart failure secondary to idiopathic or to ischemic cardiomyopathy. Am J Cardiol 2000;85(10):1207–11.
[89] Gao X, Peng L, Adhikari CM, et al. Spironolactone reduced arrhythmias and maintained magnesium homeostasis in patients with congestive heart failure. J Card Fail 2007;13(3):170–7.
[90] Garg R, Yusuf S, Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA 1995;273(18):1450–6.
[91] Domanski MJ, Exner DV, Borkowf CB, et al. Effect of angiotensin converting enzyme inhibition on sudden cardiac death in patients following acute

myocardial infarction: a meta-analysis of randomized clinical trials. J Am Coll Cardiol 1999;33(3): 598–604.

[92] Al-Mallah MH, Tleyjeh IM, Abdel-Latif AA, et al. Angiotensin-converting enzyme inhibitors in coronary artery disease and preserved left ventricular systolic function. J Am Coll Cardiol 2006;47(8): 1576–83.

[93] Teo KK, Mitchell LB, Pogue J, et al. Effect of ramipril in reducing sudden deaths and nonfatal cardiac arrests in high-risk individuals without heart failure or left ventricular dysfunction. Circulation 2004;110(11):1413–7.

[94] Lee VC, Rhew DC, Dylan M, et al. Meta-analysis: angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. Ann Intern Med 2004;141(9):693–704.

[95] Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349(13): 1893–906.

[96] Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomized trial. Optimal trial in myocardial infarction with angiotensin II antagonist losartan. Lancet 2002;360(9335):752–60.

[97] Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341(10):709–17.

[98] Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348(14):1309–21.

[99] Agustí A, Bonet S, Arnau JM, et al. Adverse effects of ACE inhibitors in patients with chronic heart failure and/or ventricular dysfunction. Drug Saf 2003;26(12):895–908.

[100] Granger CB, McMurray JJV, Yusuf A, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003;362(9386):772–6.

[101] Phillips CO, Kashani A, Ko DK, et al. Adverse effects of combination angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors for left ventricular dysfunction: a quantitative review of data from randomized clinical trials. Arch Intern Med 2007;167(18):1930–6.

[102] Eichhorn EJ, Gheorghiade M. Digoxin. Prog Cardiovasc Dis 2002;44(4):251–66.

[103] Ruch SR, Nishio M, Wasserstrom JA. Effect of cardiac glycosides on action potential characteristics and contractility in cat ventricular myocytes: role of calcium overload. J Pharmacol Exp Ther 2003;307(1):419–28.

[104] Rocchetti M, Besana A, Mostacciuolo G, et al. Diverse toxicity associated with cardiac Na+/K+ pump inhibition: evaluation of electrophysiological mechanisms. J Pharmacol Exp Ther 2003;305(2): 765–71.

[105] Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. JAMA 1988;259(4):539–44.

[106] DiBianco R, Shabetai R, Kostuk W, et al. A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. N Engl J Med 1989;320(11): 677–83.

[107] Gradman AH, Cunningham M, Harbison MA, et al. Effects of oral digoxin on ventricular ectopy in relation to left ventricular function. Am J Cardiol 1983;51(5):765–9.

[108] Digitalis Investigator Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336(8):525–33.

[109] Rathore SS, Curtis JP, Wang Y, et al. Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA 2003;289(7): 871–8.