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A Benefit-Risk Assessment of Class III Antiarrhythmic Agents

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Abstract

With β-blockers as the exception, increasing doubt is emerging on the value of antiarrhythmic drug therapy following a series of trials that have either shown no mortality benefit or even an excess mortality. Vaughan Williams class I drugs are generally avoided in patients with structural heart disease, and class IV drugs are avoided in heart failure. Unfortunately, arrhythmias are a growing problem due to an increase in the incidence of atrial fibrillation and sudden death. The population is becoming older and more patients survive for a longer time period with congestive heart failure, which again increases the frequency of both supraventricular as well as ventricular arrhythmias.

Class III antiarrhythmic drugs act by blocking repolarising currents and thereby prolong the effective refractory period of the myocardium. This is believed to facilitate termination of re-entry tachyarrhythmias. This class of drugs is developed for treatment of both supraventricular and ventricular arrhythmias. Amiodarone, sotalol, dofetilide, and ibutilide are examples of class III drugs that

are currently available. Amiodarone and sotalol have other antiarrhythmic properties in addition to pure class III action, which differentiates them from the others. However, all have potential serious adverse events. Proarrhythmia, especially torsade de pointes, is a common problem making the benefit-risk ratio of these drugs a key question.

Class III drugs have been evaluated in different settings: primary and secondary prevention of ventricular arrhythmias and in treatment of atrial fibrillation or flutter. Based on existing evidence there is no routine indication for antiarrhythmic drug therapy other than β-blockers in patients at high risk of sudden death. Subgroup analyses of trials with amiodarone and dofetilide suggest that patients with atrial fibrillation may have a mortality reduction with these drugs. However, this needs to be tested in a prospective trial. Similarly, subgroups that will benefit from prophylactic treatment with class III antiarrhythmic drugs may be found based on QT-intervals or – in the future – from genetic testing.

Class III drugs are effective in converting atrial fibrillation to sinus rhythm and for the maintenance of sinus rhythm after conversion. This is currently by far the most important indication for this class of drugs. As defined by recent guidelines, amiodarone and dofetilide have their place as second-line therapy except for patients with heart failure where they are first line therapy being the only drugs where the safety has been documented for this group of high risk patients.

Antiarrhythmic drugs have long been used to convert and prevent both ventricular and supraventricular arrhythmias. Over the last decade, there has been a major change in treatment strategy from the use of antiarrhythmic drugs affecting mainly the sodium channels of the myocardium (Vaughan Williams class I agents) to agents affecting mainly the potassium channels (class III agents).

Several factors have played an influence on this decision. First, post-myocardial infarction (MI) patients enrolled in the first large placebo-controlled Cardiac Arrhythmia Suppression Trial (CAST)[1] showed an increase in mortality compared with placebo when treated with one of the class I agents encainide or flecainide, in spite of a reduction in ventricular arrhythmias on Holter recordings. This was consistent with the second placebo-controlled CAST II trial,[2] which was stopped early due to a trend towards increased mortality associated with another class I agent, moricizine, in a similar population. Secondly, patients with symptomatic ventricular tachycardia and survivors of cardiac arrest included in the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial[3] had a better prognosis with respect to both total mortality, cardiac death, and ventricular tachycardia recurrence with the class III agent sotalol than with six class I agents. Lastly, the Cardiac Arrest in Seattle: Conventional versus Amiodarone Drug Evaluation (CASCADE) study,[4] which compared amiodarone therapy to therapy with nine class I agents administered by guidance from Holter monitoring or programmed electrical stimulation (PES) in survivors of cardiac arrest, found amiodarone to be superior to class I agents in terms of the combined endpoint cardiac mortality, resuscitated ventricular fibrillation, or defibrillator shock delivered during a syncope.

As a consequence of the results from these trials, development of class III agents has progressed. Several trials have tested and are continuing to test newer compounds, and, with the results of the two CAST trials in mind, the focus is equally on efficacy and safety. Both factors are important, as survival benefit must outweigh any drug-related death (often caused by proarrhythmia) for the agent to be potentially acceptable.

The point of safety is especially important since recent trials have shown some newer class III

agents to have a beneficial effect on conversion of atrial fibrillation and maintenance of sinus rhythm.[5] Atrial fibrillation is a common arrhythmia but it is associated with a low mortality compared with many ventricular arrhythmias, and treatment with a potentially harmful agent without proper precautions may result in an increased mortality.

Thus, as with other antiarrhythmic agents, treatment with class III antiarrhythmic drugs is a balance between benefit – survival and/or symptom relief – and risk. Also, as we have entered the era of implantable cardioverter-defibrillators (ICDs), treatment with antiarrhythmic drugs will have to find its role as adjunctive, shock-reducing therapy to these devices.

A number of recent reviews have dealt with class III antiarrhythmic agents in general[6-13] or specifically with the agents dofetilide,[14-21] ibutilide,[22] azimilide,[16] D-sotalol[23] and amiodarone.[24] The recent transatlantic guidelines for the treatment of atrial fibrillation also summarises available knowledge of class III drugs and prioritises their use.[25] The purpose of this current review is to provide an update of the current knowledge with specific attention to the balance between benefit and risk in a variety of clinical circumstances.

1. Basic Electrophysiology of Class III Agents on the Action Potential

Depolarisation of the myocardial cells is principally caused by a rapid and a slow activated inward flow of Na^+ and Ca^{2+} ions, respectively. Repolarisation is based on the balance between inactivation of the slow inward current and the activation of outward currents. These outward currents are dominated by K^+ currents, with the transient outward current (I_{TO}) causing early repolarisation, and the delayed rectifier repolarising current (I_K) causing terminal repolarisation.[26]

Cell membrane channels responsible for the I_K are confusingly labelled 'delayed inward rectifiers' in spite of the outward direction of the current; this is because of the direction of the current at trans-membrane values negative to –98 mV (below resting membrane values).[27] Pharmacologically, I_K can be divided into a rapidly activating component (I_{Kr}) and a slowly activating component (I_{Ks}). Different ion channel proteins are responsible for the two components of I_K, with the human ether-a-go-go-related gene (HERG) encoding the I_{Kr} channel protein, and the KvLTQ1 (a voltage-gated K channel gene causing one of the autosomal dominant forms of long QT syndrome) encoding part of the I_{Ks} channel protein.[28]

I_K blockade is the target of many of the newer class III antiarrhythmic drugs, resulting in a prolongation of the repolarisation phase alone and thus of the action potential duration (APD). Because of their single target of action these drugs are called 'pure' class III antiarrhythmic agents. Prolongation of the repolarisation phase of the ventricular myocardium can be read as a corrected QT (QTc) interval prolongation on the surface electrocardiogram.

2. Class III Antiarrhythmic Drugs

Class III antiarrhythmic drugs are by definition antiarrhythmic agents that act by prolonging APD of the myocardial cell by a prolongation of the repolarisation phase and thus of the effective refractory period.[26] This prolongation is believed to facilitate termination and prevention of both ventricular and supraventricular re-entry arrhythmias by producing block within re-entry circuits, and the drugs thus provide both an elevation on atrial and ventricular fibrillation threshold, as well as a reduction on atrial and ventricular defibrillation threshold. This effect is mainly mediated through a blockade of one or more of the potassium channels in the myocardium. In addition, the 'older' class III antiarrhythmic agents amiodarone and sotalol have effects other than prolongation of repolarisation.

2.1 Amiodarone

Not all of the pharmacological effects of the broad-spectrum antiarrhythmic drug amiodarone are known. In addition to a block of both the de-

layed rectifier I_K and the transient outward flow I_{TO}, it also blocks the fast sodium and the slow calcium channels.[24] Blockade of the calcium channel has been speculated to be a main explanation for the lower incidence of proarrhythmic events seen with this drug compared with 'pure' class III antiarrhythmic drugs, in spite of an often pronounced prolongation of the repolarisation phase and thus of the QTc interval. This is based on the observation that initiation of the polymorphic ventricular tachycardia torsade de pointes is in part caused by calcium-dependent early afterdepolarisations (EADs)[29] and amiodarone has been shown to abolish EADs in isolated cardiac tissue.[30]

Also, amiodarone differs from most other class III drugs by not showing reverse rate dependence[31] (see section 3.2). It has a different pharmacological profile when given acutely (intravenously) than with long-term use, both profiles having antiarrhythmic potential.[32-34] It possesses a non-competitive β-blocker effect,[35] mostly seen with long-term use.[36] Although amiodarone has a sodium channel blocking effect, it does not exhibit class I related proarrhythmias (monomorphic ventricular tachycardia).

2.2 Sotalol

Sotalol is a racemic mixture of D- and L-isomers, both of which have a dose-dependent prolonging effect on repolarisation.[37] Both isomers selectively block the I_{Kr} with no effect on the I_{Ks}.[38,39] Only in very high doses are sodium channels affected.[40] The L-isomer also exhibits nonselective competitive β-blocker properties,[41] which may cause bradycardia.

Within the last decade, the D-isomer of sotalol has been under clinical investigation as a potential 'pure' class III antiarrhythmic drug, but development has been discontinued due to the negative mortality results in post-MI patients included in the Survival with Oral D-Sotalol (SWORD) trial.[42] At present ersentilide, a compound resembling sotalol, is under investigation.[43]

2.3 'Pure' Class III Antiarrhythmic Drugs

In general, these drugs are specific blockers of $I_{K,}$ with I_{Kr} being the prime target for the first line of drugs to be developed in this class. Several drugs have been tested, and after discontinuation of many of these (including D-sotalol, MK499, and sematilide), dofetilide[21,44] stands as a prototype of this drug category. Dofetilide exerts no blockade on other ion channels apart from I_{Kr}, and as for other 'pure' drugs of this class, it has no β-blocker effect, little or no affect on atrioventricular conduction, and has no negative inotropic activity.[45] Ibutilide has an additional effect to I_{Kr} blockade, as it augments the slow inactivated sodium current.[46,47] This latter drug is only available for intravenous administration, as first-pass hepatic metabolism is extensive.

Within recent years, a second, and not so selectively 'pure', line of class III drugs has been investigated. These agents exert a block on multiple ion channels. The reason for this has been a desire to develop class III agent with the relatively lower incidence of proarrhythmia of amiodarone, but without the many non-cardiac adverse effects of this agent. The first of these agents was tedisamil,[48,49] which blocks both I_{Kr} and I_{TO}, and modifies the responses of the ATP-dependent potassium channel. Two other drugs, azimilide[50,51] and ambasilide[52,53] block both I_{Ks} and I_{Kr}, and they may prove valuable in terms of diminishing reverse rate dependence (see section 3.2). Dronedarone, which is a de-iodinated derivative of amiodarone, is in its early stage of clinical testing.

Of the above drugs, only dofetilide and ibutilide are beyond clinical testing, and are marketed.

3. Adverse Effects

3.1 Proarrhythmia

The term 'proarrhythmia' is not strictly defined. Various paraclinical markers have been suggested to delimit drug-induced proarrhythmia from other arrhythmias. These include increases in total number of premature ventricular complexes (PVCs), changes in complexity of PVCs, and inducibility

of new, or more easily induced, ventricular arrhythmias with PES.[54-57] In the CAST studies, however, mortality was increased in those patients responding to class I antiarrhythmic drugs with a reduction in PVCs.[1,2] This obliterated the use of PVCs in the definition of proarrhythmias induced by antiarrhythmic drugs. The use of PES is limited by the only moderate reproducibility of repeated PES tests even in a drug-free state.[58,59] In addition, responses in PES may be drug specific.[60]

As a result of the above observations, a clinical approach to defining proarrhythmia was recently suggested,[29] including only patients with an increase in mortality compared with no treatment/placebo, and patients with an increase in symptomatic on-treatment arrhythmias. This seems a reasonable approach, although one could add another category, namely those patients with non-fatal aggravation in symptoms (for example, on-treatment syncope as opposed to no syncope before treatment).

The proarrhythmia most likely to be induced by class III agents is a polymorphic ventricular tachycardia with a characteristic twisting round the isoelectric line. For this reason, it has been labelled torsade de pointes. It is often self-limiting, may result in presyncope or syncope, and occasionally it deteriorates into ventricular fibrillation and death.[61,62]

Data accumulating suggest that inducement of torsade de pointes is caused by a combination of two factors: (i) generation of EADs if repolarisation prolongs excessively, leading to EAD-induced triggered activity;[63-66] and (ii) existing or induced uneven distribution of repolarisation length throughout the myocardium.[67-69]

EADs have been shown *in vitro* to arise primary in the Purkinje fibres and in the subendocardial/middle cell layer of the ventricle (the M-layer as opposed to the endocardial or the epicardial layers). Bradycardia, hypokalaemia, hypomagnesemia, ventricular hypertrophy, female gender, and prolongation of repolarisation enhance the risk of EADs.

Prolongation of repolarisation is affected differently throughout the myocardial layers. Animal[67,68,70] and human[71] *in vitro* experiments have shown a more pronounced bradycardia-induced prolongation of APD in the Purkinje fibres and in the M-cells than in other layers, with an even more striking prolongation in these cells when exposed to hypokalaemia and drugs prolonging repolarisation. Thus, the combination of EAD-triggered activity in a substrate of cells in different states of repolarisation seems to increase the risk of inducing a re-entry based arrhythmia.[72]

Not all drugs blocking the I_K have the same proarrhythmic propensity[73] (table I), and dose-response to a particular drug may also be individual.[74] Although not fully elucidated, the reason for this latter observation may be that some individuals have a genetically or acquired reduced repolarisation reserve, which will be unmasked by the prescription of potassium channel blockers,

Table I. Incidence of torsade de pointes (TdP) for class III antiarrhythmic drugs

Antiarrhythmic agent	Incidence of TdP (%)	Comments
Amiodarone	<1	
Sotalol	1-5	Dose-dependent
Ibutilide	3.6-8.3	Highest incidence for patients with atrial flutter than atrial fibrillation. May be lower for patients concomitantly treated with long-term amiodarone
Dofetilide	0.8-3.3[a]	Highest incidence for patients with congestive heart failure
Azimilide	<1	Tested in one trial for patients with atrial fibrillation and in one large trial for postmyocardial infarction patients with left ventricular dysfunction

a A recent trial[78] randomising patients with implantable cardioverter-defibrillators due to clinical ventricular tachycardia (VT)/ventricular fibrillation to dofetilide or placebo found an incidence of TdP in 17% of dofetilide-treated patients as opposed to 6% of placebo-treated patients ($p < 0.5$), but total VT incidence was similar in both treatment groups.

especially in the presence of other risk factors (table II).[75-77] Thus, it is difficult to compare the incidence of torsade de pointes proarrhythmia between the different class III agents as the difference may reflect differences in the populations tested instead of a genuine difference in incidence. Studies including more elderly and frail patients may come out with a higher incidence of proarrhythmias than trials with younger patients. For some of the drugs renal function seems to be very important. Secondly, trials reporting the incidence of torsade de pointes may also yield different results depending on whether patients were monitored or treated as out-patients. Head-to-head comparisons between different class III drugs are limited.

To minimise the risk of proarrhythmia one has to be attentive to the predisposing factors for torsade de pointes (table II). Hypokalaemia[79] has to be corrected before initiation of treatment. Renal function must be known for drugs with active metabolites excreted this way (for example sotalol[37] and dofetilide[21]), and doses adjusted in case of affected renal function. Many drugs are metabolised by liver enzymes, for class III agents in particular the cytochrome P450 (CYP) isoenzyme CYP3A4, and coadministration of other drugs metabolised by the same enzymes may lead to elevated plasma levels.[73] Also, concomitant treatment with other drugs may interfere with absorption or excretion of the antiarrhythmic agent. Bradycardia may be considered a contraindication, as prolongation of repolarisation can be excessive in case of a low heart rate[80] (leading to EADs), and as some of the drugs themselves exert a negative chronotropic effect. Likewise, prescription of class III agents to patients with a pre-treatment QTc interval above a certain limit and on-treatment excessive prolongation of the QTc interval should be avoided, as further prolongation could induce arrhythmia.[29] The upper normal limit is usually set at 440ms, although several survival trials are employing higher upper acceptable values.[81-84] It has recently been proposed that multiple leads be used when measuring QTc interval,[73] and this may alter the upper normal value of 440ms, which has been based mainly on single lead measurements (preferably in lead II). Measurements of the QTc interval is an unresolved issue for patients with atrial fibrillation because of the lack of data on reproducibility and on the relation to survival, but in spite of this, larger studies are using QTc interval prolongation as an exclusion criteria for these patients.[85]

Table II. Risk factors associated with torsade de pointes induced by class III agents

Congenital repolarisation disorders (including long QT syndrome and reduced reserve)
Female gender
History of sustained ventricular tachycardia or ventricular fibrillation
Hypertrophy and heart failure
Use of diuretics
Recent conversion from atrial fibrillation
Sympathetic activity and calcium loading
Hypokalaemia
Hypomagnesemia
High drug doses
Metabolic factors (affected metabolism or excretion, e.g. renal failure)
Electrocardiogram-related factors: bradycardia; short-long-short coupling interval; long baseline QTc interval; excessive on-treatment QTc interval prolongation; T-wave lability (T-wave alternans and other T-wave morphology changes)

QTc = corrected QT interval.

QT dispersion measurements from a standard 12-lead electrocardiogram (ECG) probably has no place in clinical monitoring of proarrhythmic risk. Firstly, it appears that QT dispersion is merely a very incomplete measure of variation of the T loop morphology,[86] but it is important to note that two large prognostic studies of QT-dispersion in patients with MI[87] and patients with heart failure[88] have failed to demonstrate any importance.

Because many (but not all) proarrhythmic events are likely to occur upon initiation of treatment, patients should be continuously ECG-monitored during initiation (the duration of this monitoring should be determined by the drug profile).[7]

3.2 Reverse Rate Dependence

In contrast to class I agents that produce an increasing block on sodium channels as heart rate increases, class III agents' prolonging effect on repolarisation diminishes as heart rate increases. This is seen particularly with agents selectively blocking the I_{Kr} and has been termed 'reverse rate dependence'.[80,89] For dofetilide, which only blocks I_{Kr}, experiments have shown that even though I_{Kr}-block itself was unaffected by heart rate, the rate-induced enhancement in I_{Ks} attenuated the repolarisation prolonging effect of dofetilide at high rates.[90] Also, tachycardia results in an accumulation of extracellular potassium, which is known to reduce the effect of dofetilide.[79,91]

Class III agents with multiple channel action (azimilide), including some agents that have β-blocker effect (amiodarone), have been shown to have very little or no reverse rate dependence.[31,92] The reason for this may be the combination of multiple channel blocks, and in particular the additional block on I_{Ks}.[93,94] Also, β-adrenergic stimulation has been shown to increase I_{Ks} activity with no effect on I_{Kr},[53] and therefore agents with β-blocking properties should theoretically provide a further suppression on β-adrenergic enhancement on I_{Ks}.[95] In contrast with this theory, sotalol shows reverse rate dependence,[29] but becomes rate independent if combined with quinidine or procainamide.[96]

The clinical aspect of reverse rate dependence is the risk of proarrhythmia with lower heart rates and the loss of beneficial effect at higher heart rates. As described, prolongation of the repolarisation phase beyond a certain point, especially in the case of bradycardia, leads to EADs in part of the myocardium, presumably facilitating torsade de pointes. The loss of beneficial effect at higher heart rates deprives the agents of beneficial potential in a setting where it is particularly needed (with high sympathetic drive, and in the case of a high-rate atrial or ventricular tachycardia). Therefore, future clinical application of class III drugs may be as multichannel blockers or in combination with other antiarrhythmic agents providing additional blockade.[10] The phenomena described above may explain the clinical observation that the risk of torsade de pointes is particularly high at the time of conversion of atrial fibrillation.

3.3 Amiodarone-Related Non-Cardiac Adverse Effects

The use of amiodarone is somewhat limited by its many non-cardiac adverse effects including pneumonitis or lung fibrosis, hypo- or hyperthyroidism, corneal deposition, gastrointestinal (including hepatic) disorders, neuropathy, and skin discolouration upon exposure to the sun. In three large placebo-controlled, randomised trials allocating a total of 1685 patients to amiodarone therapy,[81,82,97] study drug discontinuation ranged between 26.2 and 38.5%, mostly for non-cardiac adverse effects. In comparison, study drug discontinuation for placebo-treated patients in the same trials ranged from 13.7 to 23%. Pulmonary fibrosis may be irreversible and occasionally result in death.[97] In a meta-analysis of 13 randomised trials including 6500 patients[98] with congestive heart failure or MI treated with amiodarone or placebo, treatment was discontinued in 1.6% of amiodarone-treated patients as opposed to 0.5% of placebo-treated patients due to lung infiltrates (p-value for odds ratio 0.0003). This emphasises the need for close monitoring of patients treated with amiodarone. As a consequence, patients treated with amiodarone should be informed about signs of potential adverse events and followed closely by a specialist.

4. Benefit-Risk in Primary Prevention of Ventricular Arrhythmias by Class III Drugs

Primary prevention is defined as treatment in patients without previous life threatening ventricular arrhythmias. All trials performed have included patients with structural heart disease and used other criteria in order to select patients at high risk of experiencing sudden death. Reduced left ventricular ejection fraction (LVEF),[83,84] multiple PVCs seen during monitoring or non-sus-

tained ventricular tachycardia[81] in addition to congestive heart failure or coronary artery disease are criteria that have frequently been used.

Class I drugs were empirically used for many years for suppression of asymptomatic ventricular ectopy, but following CAST[1,2] this approach has been abandoned. A meta-analysis of nearly 100 000 patients indicated that class I agents increased mortality by approximately 20% in patients following MI.[99] This was followed by series of studies testing class III antiarrhythmic drugs. Characteristics and outcome of primary prevention trials are listed in table III. The first trial with racemic D,L-sotalol was published as early as 1982 and included 1456 patients following an MI.[100] Of note, the dose of sotalol was 320 mg/day, which was very high. There was a trend towards a reduction in all cause mortality, but this did not reach statistical significance. The survival curves were still separating when the study closed and sotalol might have improved survival with longer treatment time. However, there was an almost significant reduction of reinfarction of 41% ($p = 0.08$), which probably can be related to the β-blocking properties of the drug. The SWORD trial[42] published in 1996 tested whether D-sotalol could reduce mortality in patients with reduced ejection fraction (≤ 0.40) and an MI within 6 to 42 days. Patients could be included later than day 42 if they had heart failure corresponding to New York heart Association (NYHA) class II-III. The trial was stopped prematurely due to an excess mortality rate in the D-sotalol arm. This was primarily due to an excess of presumed arrhythmic death. It was an unexpected finding, because D-sotalol has been demonstrated to have antifibrillatory action in an animal model.[101] However, D-sotalol was unable to prevent ventricular fibrillation in dogs during increased sympathetic activity and ischaemia.[102] The lack of the protective effect of D-sotalol in this setting may be explained by the observation that its effect on action potential prolongation is largely lost when sympathetic activity increases.[103] D-sotalol blocks only the rapid component of the delayed-rectifier current, I_{Kr}, and not the slow component I_{Ks}, which is activated by fast heart rates and by catecholamines. Thus, patients like those in the SWORD trial in which the risk of arrhythmias is provoked by ischaemia and/or sympathetic stimulation, might not benefit from treatment. Subgroup analysis of the SWORD trial, showed that D-sotalol increased risk of death in most subgroups, but two emerged with a much higher risk. Both female gender and LVEF of 30 to 40% were associated with a relative risk of total mortality of approximately 4.0.

Since the SWORD trial, two trials have tested class III drugs in post-MI patients with reduced LVEF without increasing mortality, but also without reducing it. In the first trial, dofetilide, which is very is similar to D-sotalol in that it blocks only I_{Kr}, was tested in the Danish Investigators of Arrhythmia and Mortality on Dofetilide in Myocardial Infarction (DIAMOND-MI) trial.[84] It is not entirely clear what caused the difference in outcome between the SWORD trial and DIAMOND-MI trial. However, there were some methodological differences between these trials. Most patients in SWORD had a remote MI (>40 days), whereas DIAMOND-MI included patients with a recent (<7 days) MI. Patients included in the DIAMOND-MI trial had more advanced heart failure. In SWORD, treatment was initiated out of hospital, whereas in the DIAMOND-MI trial treatment was initiated in hospital and patients were kept on telemetry for 3 days. In the DIAMOND-MI trial, the dosage of the drug was adjusted for creatinine clearance and QT prolongation during follow-up, in the SWORD trial dosage was only adjusted according to QT prolongation. The second study was the Azimilide Post-Infarct Survival Evaluation (ALIVE) trial[84] which has been completed but the results of the trial have not been published to date. Azimilide is different from both dofetilide and D-sotalol, because it blocks both I_{Kr} and I_{Ks}. In most patients, treatment was initiated out of hospital. We await publication of this trial in order to identify further differences.

The studies conducted with amiodarone following an MI have given variable results (table III)

Table III. Trials of class III antiarrhythmic drugs used in the primary prevention of ventricular arrhythmias.

Population	Trial	Agent tested	Population requirements	No. of patients	Mean follow-up (mo)	Outcome
Post-MI	BASIS[104]	Amiodarone *vs* placebo or class I agents	Asymptomatic ventricular ectopy	312	72	Total mortality[a]: amiodarone 5%; class I 10%; placebo 13%
	The Polish Pilot Study[105]	Amiodarone *vs* placebo	β-blockers excluded	613	12	Total mortality: amiodarone 6.9%; placebo 10.7% Cardiac mortality[a]: amiodarone 6.2%; placebo 10.7%
	Sotalol post-MI study[100]	Sotalol *vs* placebo		1456	12	Total mortality: sotalol 7.3%; placebo 8.9%
	SWORD[42]	D-sotalol *vs* placebo	LVEF ≤0.40; NYHA: class II-III	3121	18	Total mortality[a]: sotalol 5.0%; placebo 3.1%
	EMIAT[97]	Amiodarone *vs* placebo	LVEF ≤0.40	1486	21	Total mortality: amiodarone 13.9%; placebo 13.7% Cardiac mortality: amiodarone 11.4%; placebo 12.0%
	CAMIAT[81]	Amiodarone *vs* placebo	≥10 PVCs/hour or non-sustained VT	1202	21	Total mortality: amiodarone 6.1%; placebo 8.4%
	DIAMOND-MI[84]	Dofetilide *vs* placebo	LVEF ≤0.35	1510	15	Total mortality: dofetilide 30.7%; placebo 31.9%
	ALIVE[106]	Azimilide *vs* placebo	15% ≤LVEF ≤35% plus low heart rate variability	3717	12	Total mortality: azimilide 11.6%; placebo 11.6%
CHF	GESICA[107]	Amiodarone *vs* control (not placebo)	LVEF ≤0.35; NYHA class II-IV	516	24	Total mortality: amiodarone 33.5%; controls 41.4%
	CHF-STAT[82]	Amiodarone *vs* placebo	LVEF ≤0.40; NYHA class I-IV	674	45	Total mortality: amiodarone 30.6%; placebo 29.2%
	DIAMOND-CHF[83]	Dofetilide *vs* placebo	LVEF ≤0.35; NYHA class III-IV within 1 month	1518	18	Total mortality: dofetilide 41%; placebo 42%

a $p \leq 0.05$.

ALIVE = Azimilide Post-Infarct Survival Evaluation; **BASIS** = Basel Antiarrhythmic Study of Infarct Survival; **CAMIAT** = Canadian Amiodarone Myocardial Infarction Arrhythmia Trial; **CHF** = congestive heart failure; **CHF-STAT** = Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy; **DIAMOND-CHF** = Danish Investigators of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure; **DIAMOND-MI** = Danish Investigators of Arrhythmia and Mortality on Dofetilide in Myocardial Infarction; **EMIAT** = European Myocardial Infarct Amiodarone Trial; **GESICA** = Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina; **LVEF** = left ventricular ejection fraction; **MI** = myocardial infarction; **NYHA** = New York Heart Association class; **PVCs** = premature ventricular complexes; **SWORD** = Survival with Oral D-Sotalol; **VT** = ventricular tachycardia.

with respect to all cause mortality. The Polish post-MI trial[105] showed a significant reduction in total mortality, but patients receiving β-blockers were excluded. Also for the 1202 patients included in the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT)[81] there was an insignificant trend for a reduction in mortality ($p = 0.12$) compared with placebo. The larger European Myocardial Infarct Amiodarone Trial (EMIAT),[97] which included nearly 1500 patients, did not even show a trend for a reduction in mortality. There was a uniform tendency towards a reduction in arrhythmic death, but the price was an increased in non-cardiac mortality rate due to adverse events. A merged *post hoc* database analysis on the EMIAT and CAMIAT[95] studies found a non-significant

beneficial effect on all-cause mortality of combined treatment with both amiodarone and β-blockers compared with amiodarone alone (with significant effect on cardiac death, and arrhythmic death or resuscitated cardiac arrest), pointing towards a potential benefit on survival of concomitant treatment with β-blockers and amiodarone. Overall mortality for placebo- and amiodarone-treated patients was similar. A meta-analysis of all randomised trials showed a borderline reduction in total mortality,[98] but included a very heterogeneous population. Uniformly, amiodarone has been shown to reduce atrial fibrillation, and in retrospective analyses amiodarone had a beneficial effect in patients obtaining sinus rhythm with respect to survival in comparison with patients remaining in atrial fibrillation.[108]

Patients with congestive heart failure have a high risk of sudden death but only amiodarone and dofetilide have been tested for an influence on survival. The Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) trial[107] showed that the addition of amiodarone to standard therapy resulted in a significant reduction in total mortality. However, the trial was not placebo-controlled and potential biases exist. Patients with non-ischaemic aetiology seemed to benefit more (subgroup analyses) than patients with coronary artery disease. In the Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy (CHF-STAT),[82] for patients with reduced LVEF fraction (≤0.40) and NYHA class I-IV there was no effect on total mortality. Interestingly, a post hoc subgroup analysis indicated a significant effect on the combined endpoint of hospitalisation and cardiac death in non-ischaemic patients in keeping with the GESICA trial.[109] However, development of atrial fibrillation was significantly reduced with amiodarone treatment. The Danish Investigators of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure (DIAMOND-CHF) trial[83] tested dofetilide in 1510 patients with heart failure and reduced left ventricular systolic function (≤0.35). Patients were hospitalised with or for heart failure and had to be in NYHA class III-IV at least once within the last month. Thus, the study included patients with NYHA class I-IV at time of randomisation. There was no effect on total mortality, but a significant reduction in development of congestive heart failure was observed. Also, dofetilide reduced the development of atrial fibrillation and significantly reduced the recurrence of atrial fibrillation after cardioversion to sinus rhythm. The reduction in development of congestive heart failure appeared to be more pronounced in patients with atrial fibrillation at baseline, but was also observed in patients with sinus rhythm.

Overall, class III drugs have not been established for prophylactic use in high-risk populations. However, amiodarone and dofetilide have been shown to be well tolerated when given according to the study treatment protocols and they appear to be effective in treating atrial fibrillation. Studies focusing on patients with atrial fibrillation, heart failure and reduced left ventricular systolic function seem to be warranted.

As the main problem with pure class III antiarrhythmic drugs is proarrhythmia and in particular torsade de pointes, studies performed in patients without additional risk factors for torsade de pointes may increase the chance of success. A substudy from the DIAMOND-CHF study showed that patients with sinus rhythm and in the lowest quartile of heart rate corrected QT-interval had a significant mortality reduction when treated with dofetilide.[110] Conversely, patients with the highest QTc-interval had a significant increase in mortality when treated with dofetilide. Thus, the overall neutral outcome in the DIAMOND-CHF trial seems to originate from some patients having benefit, while others are being harmed. These results are supported by similar results from the DIAMOND-MI study as well as from follow-up of patients after drug discontinuation.[111,112] A study testing a pure class III antiarrhythmic drug may have the potential to reduce total mortality if patients with heart failure and reduced left ventricular function are selected on the basis of low QT interval and/or atrial fibrillation.

5. Benefit-Risk in Secondary Prevention of Ventricular Arrhythmias

Secondary prophylaxis is, in this context, defined as treatment in patients who have already experienced a cardiac arrest or who have documented sustained ventricular tachycardia. These patients have a high risk of recurrent arrhythmic events. Medical treatment has been tested in a number of small studies using results from electrophysiology (EP) testing as guidance to drug selection (table IV). In the Electrophysiologic Study Versus Electrocardiographic Monitoring Trial (ESVEM),[3] 486 patients with previous cardiac arrest, documented sustained ventricular tachycardia, or syncope with inducible ventricular tachycardia and more than 10 PVCs on Holter monitoring were randomised to EP- or Holter monitoring-guided therapy with a large number of antiarrhythmic drugs given in random order (imipramine, mexiletine, pirmenol, procainamide, propafenone, quinidine or sotalol). When comparing the efficacy of the drugs in terms of recurrence of arrhythmia when the agent was the first one given, sotalol was the most effective. In the EP-monitoring arm of the trial if sotalol failed, other drugs given after sotalol were not effective. Patients treated with a class I drug in combination with a β-blocker had similar mortality compared with patients treated with sotalol, but sotalol was superior to other drugs with or without co-treatment with a β-blocker in terms of recurrence of arrhythmias. There are many methodological problems with this study but most importantly it did not include ICD treatment, and there is no control group. Thus, many of the patient groups may actually have been harmed and it is only possible to conclude that sotalol appeared to be the least harmful drug. Nevertheless, sotalol has been demonstrated to be well

Table IV. Trials of class III antiarrhythmic drugs used in secondary prevention of ventricular arrhythmias in patients with implantable cardioverter-defibrillators (ICD)

Trial	Agent tested	Population requirements	No of patients	Follow-up (mo)	Outcome
CASCADE[4]	Empiric amiodarone *vs* EP/Holter guided drug treatment	Cardiac arrest or sustained VT	228	36	Combined endpoint of cardiac mortality, resuscitated VT or syncopal ICD discharge[a]: amiodarone 47%; other drugs 60%
CASH[114]	ICD *vs* empiric drug treatment (propafenone, amiodarone or metoprolol)	Cardiac arrest with documented VT/VF	349	57	Propafenone discontinued early due to increased mortality rate. Total mortality (p = 0.08): ICD 36%; amiodarone or metoprolol 44%
AVID[115]	ICD *vs* amiodarone or EP-guided antiarrhythmic treatment	Cardiac arrest; sustained VT + syncope; sustained VT + LVEF <0.40 + hypotension	1016	18	Total mortality[a]: ICD 16%; drugs 24%
CIDS[116]	ICD *vs* amiodarone	Cardiac arrest; sustained VT + LVEF ≤0.35; syncope + sustained VT/inducible VT	659	NK	Yearly mortality rate: ICD 8.3%; amiodarone 10.2%

a $p < 0.05$.

AVID = Antiarrhythmics Versus Implantable Defibrillators; **CASCADE** = Cardiac Arrest in Seattle: Conventional versus Amiodarone Drug Evaluation; **CASH** = Cardiac Arrest Study Hamburg; **CIDS** = Canadian Implantable Defibrillator Study; **EP** = electrophysiology; **LVEF** = left ventricular ejection fraction; **NK** = not known; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia.

tolerated and reduce shocks in patients who have an ICD implanted.[113]

In the CASCADE[4] trial conventional therapy was tested against amiodarone in patients who had survived cardiac arrest. Conventional therapy consisted mainly of EP- and/or Holter-guided therapy with class I drugs. The 228 patients included had >10 PVCs per hour and were inducible during the EP testing. Patients with MI as cause of cardiac arrest were excluded. The interpretation of the trial is difficult as 46% of the patients in both groups received an ICD. However, amiodarone significantly reduced time to first ICD discharge as well as survival compared to the class I drug-treated patients. As for any documented value of amiodarone the recurrence rate was very high in both arms and β-blockers were used very limited (<10%). Amiodarone has also been tested against ICD treatment (table IV). In patients surviving cardiac arrest treatment with an ICD is superior to antiarrhythmic drug treatment. In the Antiarrhythmics Versus Implantable Defibrillators (AVID) study[115] antiarrhythmic drugs other than amiodarone were allowed but the vast majority of participants received amiodarone. The ICD arm of the trial showed a reduction in mortality compared with medical treatment. Subgroup analyses indicate that the beneficial effect is found in patients with reduced left ventricular systolic function, whereas patients with normal ejection fraction do not seem to benefit from an ICD. Although the Cardiac Arrest Study Hamburg (CASH)[114] did not reach statistical significance the result is supportive of the result found in AVID.[115] In the Canadian Implantable Defibrillator Study (CIDS)[116] the reduction in total mortality was only borderline ($p = 0.07$). Based on existing evidence, amiodarone or other antiarrhythmic treatment can not be recommended routinely to patients from surviving a cardiac arrest. However, recent trials of out-of-hospital cardiac arrest strongly indicate that intravenous amiodarone is of benefit in patients with cardiac arrest due to ventricular arrhythmias. Two trials have both demonstrated a survival effect either in comparison with placebo[117] or lidocaine (lignocaine).[118] Amiodarone was given only after at least three unsuccessful shocks and the duration from the initial collapse of the patient to administration of amiodarone was relatively long.

6. Benefit-Risk in Patients with Atrial Fibrillation

Atrial fibrillation is the most common cardiac arrhythmia. It has been estimated that the prevalence is 0.4% in the general population, with a higher prevalence in elderly.[119] It may occur without underlying heart disease, but often underlying heart disease such as hypertension, valvular disease, heart failure or ischaemic heart disease are identified.[120] Atrial fibrillation has been associated with approximately a 2-fold increased risk of death in the general population,[121] is a leading cause of thromboembolism/stroke[122] and adversely affect morbidity and quality of life.[120] The potential benefit of treatment in terms of conversion to and maintenance of sinus rhythm could be expected to improve survival, decrease thromboembolic incidence and improve quality of life.

Despite the fact that this large population of patients is likely to become a main indication for class III antiarrhythmic drugs and already is for a few (sotalol, dofetilide), no appropriately designed trials have prospectively evaluated the benefit-risk of these drugs in this group. This subject has been an area of intensive research in patients groups with sinus rhythm as already mentioned, but it is uncertain whether these results can be applied to patients with atrial fibrillation. Also, concerns about applying these results to patients with atrial fibrillation stems from two retrospective observations. A meta-analysis of randomised placebo-controlled studies in which quinidine,[123] a class I antiarrhythmic drug, was tested as prophylactic treatment after direct current (DC) cardioversion, showed that quinidine use was associated with an increased mortality. Another retrospective analysis from a non-randomised study showed that use of class I antiarrhythmic drugs adversely affected mortality.[124] However, two retrospective studies of class III antiarrhythmic drugs indicate a benefi-

cial effect on mortality and morbidity. A subgroup analysis of patients with atrial fibrillation in the CHF-STAT trial indicated that amiodarone treatment improved survival.[82] This observation was confirmed by a similar subgroup analysis of the DIAMOND studies, which also indicated a benefit of dofetilide on morbidity.[5] While the question of whether class III antiarrhythmic drugs really are safe to use in patients with atrial fibrillation and whether they might reduce morbidity and mortality is still an outstanding issue, there are a number of studies that document their benefit on the maintenance of sinus rhythm and to some extend on quality of life. In addition, one potential benefit of the pure class III antiarrhythmic drugs is that they have no negative inotropic effects and are therefore useful in patients with left ventricular dysfunction.

6.1 Amiodarone

Until recently, the majority of evidence on the efficacy of amiodarone for maintenance of sinus rhythm in patients with atrial fibrillation was based on observations from non-randomised studies. The only older randomised trial, which is poorly known, compared amiodarone with quinidine and demonstrated that amiodarone was effective in maintaining sinus rhythm.[125] After 6 months of treatment, 83% of patients remained in sinus rhythm with amiodarone versus 43% with quinidine.

Two recent studies support this finding. The Canadian Trial of Atrial Fibrillation (CTAF) compared the ability of low-dose amiodarone versus sotalol or propafenone to maintain sinus rhythm in 403 patients with a recent episode of atrial fibrillation or who actually needed cardioversion.[126] In this heterogeneous group, amiodarone was superior to both sotalol and propafenone in maintaining sinus rhythm. After 1 year of treatment, 31% of patients had electrocardiographically documented relapse of atrial fibrillation in the amiodarone group versus 61% in the combined group with sotalol and propafenone. Thirty-six patients assigned to amiodarone (18%) discontinued taking the study drug because of adverse events, as compared with 23 assigned to sotalol or propafenone (11%, $p = 0.06$). No proarrhythmic effect was observed among the patients assigned to amiodarone, and clinically relevant thyroid and pulmonary abnormalities occurred in a small proportion of patients. As the trial only had a minimum 1-year follow-up (mean 450 days) the difference in adverse events could have been reversed had amiodarone been given for a longer period.

The Pharmacological Intervention in Atrial Fibrillation (PIAF) trial was designed to compare the effect of rhythm control (amiodarone treatment and an attempt at cardioversion) versus rate control (diltiazem and no attempt at cardioversion) on symptoms and 6-minute walking test in 252 patients with persistent atrial fibrillation.[127] At 12 months, 60% were in sinus rhythm in the amiodarone group versus 10% in the diltiazem group. Although there were no differences in symptoms between the groups at the end of the trial, the amiodarone group significantly improved in walking distance. However, the amiodarone group also had more hospitalisations. Primarily these hospitalisations were due to the need for DC-cardioversion (67% of all hospital admissions), but in 27% of the patients, hospitalisation was due to amiodarone-related adverse effects. In the diltiazem assigned group, hospitalisation due to drug-related adverse effects occurred in 15% of patients. In the group assigned to diltiazem, treatment was prematurely stopped due to adverse effects in 17 (14%) patients compared with 31 (25%) patients in the group assigned to amiodarone. These results suggest that amiodarone is effective in maintaining sinus rhythm, but still the evidence is limited in patients with persistent atrial fibrillation.

The risks associated with amiodarone treatment are the potential non-cardiac adverse effects, bradycardia and probably a low incidence of torsade de pointes.

6.2 Dofetilide

Dofetilide has been much more extensively studied in patients with atrial fibrillation. The

Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) Study was a randomised comparison of different dosages of dofetilide with placebo in 325 patients.[85] For the patients who successfully cardioverted pharmacologically or electrically, the probability of remaining in sinus rhythm at 1 year was 40, 37, 58 for dofetilide 125, 250, and 500μg twice daily, respectively, and 25% for placebo. Torsade de pointes occurred in 0.8% of dofetilide-treated patients.

In a similar study, the European and Australian Multicenter Evaluative Research of Atrial Fibrillation (EMERALD), the effect of dofetilide to maintain sinus rhythm after cardioversion in 671 patients with persistent atrial fibrillation was compared with placebo and sotalol.[128] Again a dose-dependent effect of dofetilide was demonstrated: 51, 57 and 71% of the patients were in sinus rhythm with dofetilide 125, 250 and 500 μg twice daily, compared with approximately 25% assigned to placebo and 60% assigned to sotalol. The dose of sotalol was 80mg twice daily which is lower than the most cost-effective dose of 120mg twice daily found in the study of Benditt et al.[129] The primary risk associated with dofetilide is torsade de pointes and this drug is not associated with serious non-cardiac adverse effect as amiodarone is. Bradycardia is not a problem with dofetilide. In the EMERALD study there were three non-fatal episodes of torsade de pointes and one case of sudden cardiac death, all occurring in the dofetilide 500mg twice daily group.

6.3 Sotalol

Sotalol has been described previously as different from the pure class III antiarrhythmic agents, because it has a β-blocker effect and a class III effect. In a study of three different doses (80, 120 and 160mg twice daily) sotalol was tested against placebo for prevention of recurrence of symptomatic atrial fibrillation. The median times to recurrence were 27, 106, 229, and 175 days for the placebo, 80, 120, and 160mg groups, respectively. The result was not statistically significant for the 80mg twice daily dose and the 120mg twice daily dose appears to be the most cost-effective. Importantly, there were no deaths or cases of torsade de pointes, sustained ventricular tachycardia, or ventricular fibrillation reported. Otherwise, sotalol has mainly been examined in comparison with other antiarrhythmic drugs. In a multicentre study involving 183 patients, sotalol was found to be as effective as quinidine in the prevention of recurrent atrial fibrillation after DC-cardioversion.[130] Fifty-two percent of patients in the sotalol group and 48% of patients in the quinidine group remained in sinus rhythm during the following 6-month treatment period (not significant). Twenty-eight percent of the patients treated with sotalol and 50% of the patients treated with quinidine reported adverse effects. One case of torsade de pointes occurred in the sotalol group. In another trial, sotalol and propafenone were found to be equally effective for the maintenance of sinus rhythm.[131] Potential risks of sotalol are bradycardia and torsade de pointes.

Based on the available evidence, it appears that class III antiarrhythmic are effective in the maintenance of sinus rhythm after cardioversion of atrial fibrillation and are possibly more effective than class I antiarrhythmic drugs. However, studies in patients with persistent atrial fibrillation are still too limited to make firm conclusions. A major benefit of the new pure class III antiarrhythmic agents is that they can be used in patients with heart failure and are devoid of serious non-cardiac adverse effects as compared with amiodarone. However, they carry a potential risk of proarrhythmia. Nearly all of the above mentioned trials excluded patients with QT-intervals above a certain limit to avoid this risk. Which limit of the QT-interval should be used in patients with atrial fibrillation is uncertain and another critical issue is how and when to measure the QT-interval. It may be difficult to measure this interval during atrial fibrillation and it is uncertain whether a reliable interval can be measured after cardioversion.

7. Present and Future Role of Class III Antiarrhythmic Drugs

Amiodarone, sotalol and dofetilide appear to be relatively safe and can be used for long time therapy in patients with atrial fibrillation and structural heart disease. The American Heart Association/American College of Cardiology/European Society of Cardiology atrial fibrillation guidelines recommend the use of dofetilide and amiodarone for maintenance of sinus rhythm in patients with congestive heart failure, as both drugs have been tested in clinical trials and appear to be relatively safe.[25] In patients with stable ischaemic heart disease β-blockers may be recommended, although the documented evidence for efficacy for maintenance of sinus rhythm is sparse in patients with persistent atrial fibrillation. The guidelines recommend the use of sotalol as first-line therapy in these patients with dofetilide as second-line therapy. Patients with hypertension and hypertrophy may be especially prone to torsade de pointes and amiodarone can be considered safe in these patients with respect to proarrhythmia. Ibutilide and amiodarone can be used intravenously for conversion of recent onset atrial fibrillation in monitored patients. All patients with reduced left ventricular systolic function should be started on β-blockers.

In the future, prophylactic therapy with class III agents may become possible, provided relevant subgroups who will benefit from treatment can be identified.

Many other class III agents are under development and there will be minor differences, which may create a substantial difference in the ratio between efficacy and risk of proarrhythmia. Dronedarone may be attractive, provided it is as efficient as amiodarone for treatment of arrhythmias and without the serious non-cardiac adverse events.

In patients with ventricular tachycardia, amiodarone appears to have some effect, but the preferred treatment for patients with documented life-threatening arrhythmias is an ICD. However, as the population with ICDs increase there will be need for antiarrhythmic treatment to reduce the incidence of atrial fibrillation, and potentially also reduce ICD discharges.

The role of antiarrhythmic drug treatment has changed considerably during the last decade. It is apparent that antiarrhythmic drugs have the propensity to suppress arrhythmias, but without a concomitant reduction in mortality. As there is a real risk of harming patients the focus of antiarrhythmic treatment has shifted from prophylactic to symptomatic. Conversely, testing of antiarrhythmic drugs now focus on safety and efficacy for distinct types of arrhythmias. Class III antiarrhythmic drugs have the potential to be first-line therapy for atrial fibrillation provided that a drug and regimen are chosen, that have documented evidence of safety. Amiodarone, sotalol and dofetilide seem to fulfil these objectives. However, many unanswered questions remain. Prophylactic treatment with class III drugs in patients with heart failure, reduced left ventricular systolic function, and short QT-interval or atrial fibrillation needs to be tested in large scale randomised trials. The magnitude of effect of class III drugs also needs to be established in populations where β-blockers are mandatory.

Based on existing evidence patients surviving a cardiac arrest not related to an acute MI should as baseline therapy receive an ICD. Although class III drugs reduce ICD discharges, the combination of class III drugs and β-blockers needs to be explored further.

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