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Current Treatment Recommendations in Antiarrhythmic Therapy

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Summary

Over the past decade, various studies have demonstrated that class I antiarrhythmic drugs should be avoided in patients with heart failure, cardiac ischaemia or a previous myocardial infarction. In contrast, class II drugs (β-blockers) reduce morbidity and may even lower mortality in patients suffering from moderate to severe heart failure. In these patients, careful titration of the drug dosage, frequently during hospital admission, may be necessary.

If in the setting of heart failure ventricular arrhythmias are symptomatic and/or sustained, patients can be treated effectively, after appropriate treatment of the underlying disease, with the class III drug amiodarone. Unfortunately, this drug does not lower overall mortality, implying that prophylactic institution of amiodarone is not indicated. Pure class III antiarrhythmic drugs like *d*-sotalol, ibutilide and dofetilide show a high rate of torsade de pointes. Currently, only ibutilide has been approved for clinically monitored intravenous administration. Class IV drugs, the calcium channel blockers, are still very useful for rate control of atrial fibrillation and conversion or prevention of atrioventricular nodal re-entrant tachycardias and circus movement tachycardias using a (concealed) bypass tract.

Finally, an implantable cardioverter defibrillator seems to improve overall survival in patients with life-threatening ventricular arrhythmias. This may imply that an increasing number of patients will be candidates for such a device. However, it will be necessary to await publication of data involving these devices from current ongoing studies.

Antiarrhythmic drug (AAD) therapy has always been the cornerstone of treatment for cardiac rhythm disturbances. Limited efficacy and the potential to aggravate arrhythmias and to induce conduction disturbances and/or heart failure (HF), together with the success of radiofrequency ablation and new devices for the management of arrhythmias, have reduced the previous enthusiasm for prescribing these drugs. The present review deals with new data on AAD therapy.

1. Antiarrhythmic Drug Classification

Over the past 2 decades, the Vaughan Williams classification has guided clinicians in their choice of AADs.[1-4] In this classification system, AADs were divided into 4 classes primarily on the basis of their effects on transmembrane action potentials (table I). The classification typically originated in an era when only a few antiarrhythmic agents were available and there was little knowledge of electrophysiological mechanisms and the role of receptors and ion channels. Since then, its limitations have become increasingly evident. For example, a single class effect can be produced by a number of mechanisms (prolongation of the action potential duration, a class III effect, can result from blockade of one of the K^+ channels or modification of the Na^+ or Ca^{++} channels). In addition, some drugs have more than one class effect (amiodarone, a class III AAD, also possesses class I, II and IV effects). Finally, the classification is incomplete, e.g. adenosine and digitalis do not fit within it.

Since that classification system was defined, cardiac electrophysiology and molecular biology have increased our knowledge of the underlying mechanisms of arrhythmias and a more sophisticated classification of AADs was proposed which was called the Sicilian Gambit (table II).[5] If the clinician wants to use this system for treatment of an arrhythmia, 4 steps must be followed:

- The underlying mechanism (re-entry, automaticity or triggered activity) first must be identified (or hypothesised).
- Secondly, the parameter which is susceptible to modification, e.g. action potential duration or conduction velocity, must be determined (or hypothesised).
- Next, the ionic current, receptor or pump which can modify this parameter, e.g. prolongation of

Table I. Antiarrhythmic drugs classified according to the Vaughan Williams classification[1-3]

Class	Mechanism of action	Representative drugs
IA	Na^+ channel blockade (moderate block) decrease of conduction velocity (QRS widening) prolonged repolarisation (QT prolongation)	Quinidine, disopyramide, procainamide
IB	Mild block of Na^+ channels decrease of conduction velocity shortened repolarisation	Lidocaine (lignocaine), mexiletine, phenytoin
IC	Marked block of Na^+ channels decrease of conduction velocity no change in repolarisation	Flecainide, propafenone, encainide
II	β-Adrenoceptor antagonists lowering of sinus rate	Metoprolol, atenolol and others
III	Marked prolongation of repolarisation	Sotalol, ibutilide, amiodarone, new class III drugs
IV	Calcium channel blockers	Verapamil, diltiazem

Table II. Classification of arrhythmogenic mechanisms at the cellular level in terms of vulnerable parameters (modified after the Sicilian Gambit)[5]

Mechanism	Arrhythmia	Vulnerable parameter	Ionic current	Antiarrhythmic drug
Automaticity				
enhanced normal	Inappropriate sinus tachycardia	Phase 4 depolarisation (decrease)	I_f; I_{ca-t} (block) $I_{K(ACh)}$ (activate)	β-Adrenoceptor antagonists
abnormal	Ectopic focal atrial tachycardia	Hyperpolarisation of diastolic potential or phase 4 depolarisation (decrease)	I_K; $I_{K(ACh)}$ (activate) I_{Ca-L}; I_{Na} (block)	M_2 agonists *or* calcium or sodium channel blocking agents
Triggered activity				
early after depolarisations	Torsade de pointes	Shortening of action potential duration or suppression of EAD	I_K (activate) I_{Ca-L}; I_{Na} (block)	β-adrenoceptor agonists [e.g. isoprenaline (isoproterenol)]; calcium channel blockers; Mg^{++}, β-adrenoceptor antagonists
late after depolarisations	Digitalis-induced arrhythmias	Unload of calcium overload or DAD suppression	I_{Ca-L} (block) I_{Ca-L}; I_{Na} (block)	Calcium channel blockers; sodium channel blockers
Re-entry				
long excitable gap	Common atrial flutter	Depress conduction and excitability	I_{Na} (block)	Sodium channel blockers
short excitable gap	Atrial fibrillation	Prolong refractory period	I_K (block)	Potassium channel blockers
calcium channel–dependent	AV nodal re-entrant tachycardia	Depress conduction and excitability	I_{Ca-L} (block)	Calcium channel blockers

Abbreviations: AV = atrioventricular; DAD = delayed afterdepolarisations; EAD = early afterdepolarisations; I_{Ca-L} = calcium current through L-type calcium channel; I_{Ca-T} = calcium current through T-type calcium channel; I_f = inward current carried by Na^+ generating phase 4 depolarisation (sinus and AV nodal cells and His-Purkinje cells) and contributing to pacemaker function; I_K = potassium channel, 'delayed rectifier'; $I_{K(ACh)}$ = acetylcholine-dependent potassium channel, activated by muscarinic (M_2) receptor; I_{Na} = sodium channel; M_2: muscarinic receptor.

the action potential duration in case of re-entry as underlying mechanism, must be identified (or hypothesised).

- Finally, the AAD which may act in the desired manner can be chosen.

In the example of re-entry with a short excitable gap the delayed rectifier, I_K, is the ionic current which needs to be modified. Although a very interesting approach for electrophysiologists, it has several limitations for a clinician. First and most importantly, identification of the mechanism underlying a particular arrhythmia is not always possible in clinical practice, which makes the Sicilian Gambit approach rather difficult to use. Secondly, the knowledge of a clinician on ion channels and receptors is usually rather limited. Therefore, in this article, AADs are discussed according to the Vaughan Williams classification, which is still quite useful for routine clinical practice. A listing of the indications, adverse effects and contraindications of antiarrhythmic drugs is listed in table III.

2. Class I Antiarrhythmic Drugs

2.1 Ventricular Arrhythmias

Although believed to be benign in the absence of structural heart disease, premature ventricular complexes are a risk factor for sudden cardiac death in the post-myocardial infarction (MI) condition.[6] The Cardiac Arrhythmia Suppression Trial (CAST) was designed to test whether suppression of premature ventricular complexes with either of the AADs encainide or flecainide could prevent mortality in patients with asymptomatic or mildly symptomatic ventricular arrhythmias after MI.[7] Compared with placebo, the mortality rate in the patients treated with flecainide or encainide was 2 to 3 times higher. In CAST II, mortality was significantly higher in the patients treated with moricizine, another class IC AAD, compared with placebo.[8,9] Thus, CAST I and II clearly showed that in post-MI patients, suppression of premature ventricular beats by means of class IC AADs does

Table III. Indications, dose, adverse events and contraindications of antiarrhythmic drugs

Drug	Dose		Indication	Adverse events		Contraindications
	oral (mg)	intravenous		cardiac	noncardiac	
Class I						
Quinidine sulphate	200-400 tid-qid	NA	Prevention of SVT, VT, VF[a]	Torsade de pointes, heart failure, AV block	Gastrointestinal complaints	Heart failure
Lidocaine (lignocaine)	NA	2-4g/24h	Prevention of VT/VF during ischaemia	AV block	Dizziness, speech disturbances	AV conduction disturbances
Flecainide	150-300	150mg in 15 min	Conversion/prevention of SVT/VT/VF	Ventricular tachycardia, AV block, bundle branch block, heart failure	Blurred vision	QRS duration >120 msec, heart failure, ischaemia, old MI
Propafenone	400-900	1-2 mg/kg in 10 min	Conversion/prevention of SVT/VT/VF	Ventricular tachycardia, AV block, heart failure	Dry mouth, obstipation	QRS duration >120 msec, HF, ischaemia
Classes II, III and IV						
Metoprolol	50-200	5mg	Prevention of sympathetic induced SVT/VT/VF, prevention of SCD in post-MI and HF patients, prevention of AVNRT, CMT[b], rate control in AF	Hypotension, heart failure, AV block, sinus bradycardia	Impotence, fatigue, bronchospasm	Severe COPD, careful administration in patients with HF and AV conduction disturbances
Sotalol	160-320	100mg in 15 min	Prevention of SVT/VT/VF	Torsade de pointes, AV block, hypotension, HF	Impotence, fatigue, bronchospasm	Severe COPD, careful administration in patients with HF
Ibutilide	NA	0.01 mg/kg in 10 min (if necessary repeated after 10 min)	Conversion of AFL/AF	Torsade de pointes	No data available	NA
Amiodarone	200-300[c]	800-1200mg/24h	Prevention of SVT/VT/VF[d]	Torsade de pointes, AV block, hypotension, sinus bradycardia, HF	Photosensitivity, hypo-/hyperthyroidism, pulmonary toxicity, liver toxicity	Thyroid disease
Verapamil	120-240	5-10mg in 5-10 min	Termination and prevention of AVNRT, CMT[b], rate control in AF	AV block, hypotension, bradycardia, heart failure	Ankle oedema, dizziness, fatigue	Careful administration in patients with AV conduction disturbances

a No first choice therapy.

b Prevention only in case of concealed CMT.

c After loading 600-800mg over 4wk for SVT and 800-1200mg for VT.

d No first-choice therapy except for patients suffering from HF.

Abbreviations: AF = atrial fibrillation; AFL = atrial flutter; AV = atrioventricular; AVNRT = atrioventricular nodal re-entrant tachycardia; concealed CMT = circle movement tachycardia in patients with a (concealed) bypass tract; COPD = chronic obstructive pulmonary disease; HF = heart failure; MI = myocardial infarction; NA = not available; qid = 4 times daily; SCD = sudden cardiac death; SVT = supraventricular tachycardia; tid = 3 times daily; VF = ventricular fibrillation; VT = ventricular tachycardia.

not reduce post-MI sudden death mortality. To the contrary, these drugs may even promote the incidence of lethal ventricular arrhythmias. Since then, it has been recommended that class IC AADs should not be given to patients with cardiac ischaemia, a previous myocardial infarction or impaired left ventricular (LV) function and non–life-threatening arrhythmias. However, class IC AADs can safely be prescribed in patients without underlying heart disease.[10-12]

2.2 Supraventricular Arrhythmias

In acute haemodynamically stable atrial fibrillation (AF), pharmacological therapy by means of a class IC AAD results in conversion to sinus rhythm in about 60 to 90% of the patients.[13-15] During infusion of a class IC AAD (propafenone or flecainide), close monitoring of the QRS duration should be secured because these drugs induce broadening of the QRS complex due to a decrease in the conduction velocity. If the QRS duration rises by more than 50% of the baseline value, administration should be terminated because proarrhythmias in the form of a sustained ventricular tachycardia may result. Conditions in which class IC AADs should not be administered for this indication include HF, acute ischaemia (chest pain), known sick sinus syndrome or in cases where the baseline QRS duration exceeds 120 msec. In these patients, proarrhythmic effects or conduction disturbances may occur.

For prophylaxis of both paroxysmal and chronic AF, class IC AADs are moderately effective.[16,17] Although class IC AADs are well known for their proarrhythmic adverse events, in patients without underlying heart disease, and with the precautions kept in mind stated above, the chance of proarrhythmia is low.[10-12] Additionally, in the case of a relapse on a class IC drug, AF may regularise to a slow atrial flutter. During exercise this slow atrial flutter may lead to high ventricular rates, due to 1 : 1 atrioventricular conduction inducing HF.[18] Therefore, it seems advisable to use β-adrenoceptor blockers, calcium channel blockers or digitalis concomitantly with class IC drugs to prevent rapid ventricular rates at the moment of a relapse of the atrial arrhythmia.

Quinidine, a class IA AAD, has been studied frequently for the prevention of AF. In a meta-analysis of 6 controlled trials it was shown that by using quinidine compared with no treatment, 50 versus 25% of the patients, respectively, remained in sinus rhythm during the course of 1 year. However, the total mortality was significantly higher in the quinidine group [12 of 413 patients (2.9%) versus 3 of 387 patients (0.8%), respectively, $p < 0.05$].[19] Another recent study also demonstrated about 10% sudden death in patients treated with quinidine.[20] These findings make it somewhat questionable whether there is still a role for quinidine in the prophylaxis of a relapse of AF.

The poor safety of class I drugs in the presence of HF was also demonstrated by a subgroup analysis of the Stroke Prevention in Atrial Fibrillation Trial (SPAF). Mortality was 5-fold higher in patients treated with an AAD and suffering from HF, compared with those not in this condition.[12] However, patients without a history of HF had no increased risk of cardiac mortality while being treated with an AAD.

Additional information on the efficacy and safety of AADs in the prevention of recurrent AF came from a meta-analysis of 11 placebo-controlled studies by Nattel and Talajic.[21] In addition to a higher mortality in quinidine-treated patients, they found 2.5% mortality in patients treated with disopyramide (another class IA drug) and 1.6% mortality in flecainide-treated patients, compared with no mortality in the placebo arm. Mortality on sotalol was 2.0% compared with 0.2% on placebo. No increased mortality was observed in patients treated with amiodarone.

Apart from the harmful effects of class I drugs in general, a second conclusion may be drawn from these studies: that patients suffering from HF carry a greater risk for AAD-related mortality. This opinion is also supported by Middelkauff et al.[22] and Stevenson et al.[23] who demonstrated that during the past few years, when fewer patients received a class I AAD, mortality was lower for those with AF and HF. Thus, in patients with AF and HF, treatment of the underlying disease is of greater importance than prevention of the arrhythmia. Whereas proarrhythmia induced by class IC drugs is, as mentioned above, almost exclusively observed in patients with structural heart disease, torsade de pointes induced by class IA and also class III drugs may occur in patients without structural heart disease.[10-12]

3. Class II Antiarrhythmic Drugs

3.1 Ventricular Arrhythmias

β-Blocker therapy has been demonstrated to reduce sudden cardiac death, presumably due to arrhythmias, after MI.[24-26] In the β-Blocker Heart Attack (BHAT) study, patients with HF treated with propranolol experienced a similar decrease in total mortality (most likely through prevention of sudden death), compared with those without HF.[24] Other classical trials of β-blockers in HF are the Metoprolol in Dilated Cardiomyopathy (MDC) trial[27] and the Cardiac Insufficiency Bisoprolol Study (CIBIS).[28] These have illustrated improvement in clinical parameters of morbidity and, although statistical significance or trends were borderline, in mortality, if β_1-selective agents were added on top of current therapy.[27-29]

Recently, newly developed β-blockers with α_1-blocking, antioxidant and possibly other unidentified properties have been proven to lower morbidity and even mortality in patients with HF.[30] These data indicate that β-blockers improve survival, both in post-MI patients and in those with moderate to severe HF. Those patients with nonischaemic HF seem to benefit more than those with HF on the basis of coronary artery disease. Since β-blockers have negative inotropic properties, they may aggravate HF if administered in too high an (initial) dosage or in unstable HF. Therefore, there is often some reluctance to prescribe these drugs.

In 211 patients with coronary artery disease or cardiomyopathy resulting in HF and complicated by sustained monomorphic ventricular tachycardias, β-blockers have been evaluated among other drugs.[31] First, a class I AAD was administered; in the case of a recurrence of the arrhythmia, amiodarone and/or a β-blocker was given. If this therapy was ineffective, rhythm surgery was attempted. In patients with a left ventricular ejection fraction (LVEF) of <30%, among those who received a β-blocker alone or in combination with a class I AAD, survival was significantly higher than in those not on a β-blocker.

In another study, survivors of sustained ventricular tachycardia or ventricular fibrillation were randomised to metoprolol, without invasive evaluation of drug efficacy (54 patients), or to serial AAD testing guided by invasive testing (61 patients).[32] Serial testing was performed with a class I (always combined with metoprolol) or class III AAD as the first step. The drugs were instituted in a random order, but amiodarone was tested last. During a mean follow-up of 23 months, the arrhythmia recurrence rate was 48% in the patients treated with metoprolol versus 46% in those undergoing serial drug testing. This result suggests that electrophysiologically guided AAD therapy was not superior to metoprolol therapy.

The data of the abovementioned studies, together with a recently published overview of randomised controlled trials of β-blocker therapy in HF,[33] indicate that β-blockers may be used with beneficial effects in patients with HF and/or life-threatening ventricular arrhythmias.

3.2 Supraventricular Arrhythmias

β-Blocker therapy is frequently prescribed for control of the ventricular rate in patients suffering from chronic AF. To date, no long term data are available comparing the efficacy of calcium channel blockers, digitalis or β-blocker therapy on prevention of HF and improvement of exercise tolerance in these patients with chronic AF.

4. Class III Antiarrhythmic Drugs

4.1 Sotalol

4.1.1 Ventricular Arrhythmias

Sotalol is a drug with both class II (β-blocking) and class III (repolarisation lengthening) antiarrhythmic activity. Studies investigating its efficacy in preventing ventricular tachycardias or ventricular fibrillation in patients who had suffered from sustained ventricular tachycardias or aborted sudden cardiac death, showed that sotalol was relatively effective. It prevented induction of ventricular arrhythmias in 30 to 60% of the patients.[34,35] Although long term follow-up studies are scarce, a

recent study demonstrated that sotalol 240 to 640 mg/day prevented arrhythmia recurrences in 89 and 77% of patients after 1 and 3 years of follow-up, respectively.[35]

Sotalol was also effective and relatively well tolerated in patients suffering from life-threatening arrhythmias in the Electrophysiology Study Versus Electrocardiographic Monitoring (ESVEM) study. That study included 486 patients with a history of sustained ventricular tachycardia who had spontaneous or inducible arrhythmias in the electrophysiological laboratory.[36] It showed first, that drug administration guided by programmed electrical stimulation, i.e. serial testing in random order with mexiletine, pirmenol, imipramine, procainamide, propafenone, quinidine and sotalol, proved to be equally as effective as therapy guided by Holter monitoring. Secondly, in this nonrandomised study, sotalol was more effective than the other 6 drugs for the prevention of recurrent arrhythmias and mortality.

Although the reported efficacy rates of sotalol in patients suffering from life-threatening ventricular arrhythmias were generally higher than those with class I AAD, most of the studies were uncontrolled, precluding firm conclusions.[34,36] Also, sotalol may aggravate pre-existing arrhythmias or provoke new arrhythmias. It may induce torsade de pointes (by prolonging the action potential duration), especially in the presence of predisposing factors, such as hypokalaemia, bradycardia or concomitant use of drugs that prolong the repolarisation (e.g. antibiotics such as ampicillin, etc., antimalarial drugs and antidepressant drugs). These proarrhythmic events have been reported in up to 8% of the patients treated with sotalol.[34] Most of these proarrhythmic events occurred within a few days of the initiation of therapy, which implies that therapy with sotalol, and also class IA drugs, should preferably be initiated in hospital. In sharp contrast to most of the β-blocker studies (section 3.1) was the finding that sotalol 320mg once daily was just as effective as placebo in patients who had survived an acute myocardial infarction.[37] Possibly, this may relate to the occurrence of proarrhythmic events.

4.1.2 Supraventricular Arrhythmias

For acute conversion of AF, sotalol must be considered ineffective.[15,34] This has only become apparent after the drug has been used as the 'active' comparator in trials studying new class III agents.[15] On the other hand, sotalol is effective for the prevention of AF.[38-40] This discrepancy may relate to its property of prolonging the refractory period predominantly at lower atrial rates, but not during rapid AF, due to its so-called reverse use-dependence. In contrast, class III AADs, including ibutilide, are more effective than class IC drugs for the conversion of atrial flutter.[41,42] However, the efficacy rate of both sotalol and ibutilide still seems to be rather low.[43]

4.2 Pure Class III Drugs

In the search for more effective and safe AADs, pure class III agents have been developed. These drugs prolong atrial and ventricular action potential duration by extension of the refractory period, without affecting the conduction velocity. Several pure class III AADs have been tested in clinical practice. Although each prolongs refractoriness, they may act by blocking different potassium channels. Most of these drugs, however, seem to act via blockade of the rapid delayed rectifier I_{Kr}.[44,45]

4.2.1 Ventricular Arrhythmias

d-Sotalol has recently been evaluated in the Survival With Oral *d*-sotalol (SWORD) study.[46] This randomised trial was designed to test the hypothesis that *d*-sotalol 200 to 400mg daily, compared with placebo, would reduce mortality in survivors of an MI with an LVEF of <40%.[46,47] It was planned to enrol 6400 patients, but the study was stopped by the safety committee after the inclusion of half that number because of an excessive mortality in the *d*-sotalol group. Among 1549 patients assigned to *d*-sotalol, there were 78 deaths (5%) compared with 48 (3.1%) of the 1572 patients who were treated with placebo (relative risk 1.65, p = 0.006).[47] There were more deaths in patients with

an LVEF of 31 to 40% than in those with an LVEF of <30%. These findings indicate that not only class IC drugs, but also pure class III AADs, may have deleterious effects in patients who have suffered a MI. The increased mortality during treatment with class III drugs predominantly relates to the induction of torsade de pointes.[48] Lengthening of the action potential duration by a class III agent sets the stage for this potentially lethal proarrhythmia. Combination with diuretics, which decrease intracellular potassium and magnesium levels, may trigger torsade de pointes, predominantly if the heart rate is low, due to the reverse use-dependence of class III drugs.

4.2.2 Supraventricular Arrhythmias

Ibutilide has recently been approved by the US FDA for monitored intravenous administration. The disadvantage of all new pure class III AADs is that the frequency of proarrhythmia, i.e. torsade de pointes, does not seem to be lower than during sotalol therapy. Of 180 patients who received ibutilide 1.0mg, followed by another bolus of 0.5 or 1.0mg after 10 minutes, 15 (8.3%) developed torsade de pointes during or immediately after its infusion. 11 of these 15 patients did so during or after the first bolus of 1.0mg.[41] Given the high rate of adverse events, it was logical to restrict the use of ibutilide to in-hospital situations.

The exact mode of action of ibutilide is still a matter of discussion. Suggested mechanisms are activation of the slow sodium inward current,[49] blockade of I_{Kr},[50,51] additional effects, or a combination[51] of these. Ibutilide can be used in one or two 10-minute infusions of 1.0mg, each separated by 10 minutes for termination of AF or flutter. In this dosage, however, it is less effective than class IC drugs for the conversion of AF, but it is more effective than class IC drugs for the conversion of atrial flutter.[41] It has been suggested that ibutilide may convert AF of a longer duration, but firm proof has yet to be given. Preliminary data of a comparison between ibutilide and *d,l*-sotalol indicate that ibutilide is more effective than *d,l*-sotalol for the conversion of atrial flutter.[52] However, proarrhythmic events (torsade de pointes) were more common in the ibutilide-treated patients (7.3 versus 3.7%). Thus, for an attempt to convert atrial flutter to sinus rhythm, ibutilide may be preferable to sotalol. However, definite data have to be awaited, especially on its proarrhythmic effects.[41,42,52]

Since the SWORD trial data were published, further research with *d*-sotalol has been cancelled. The same holds true for the pure class III AAD almokalant, whose use was also associated with a high rate of torsade de pointes. Dofetilide, sematilide and other class III AADs are still under investigation, but these may also induce torsade de pointes.

4.3 Amiodarone

4.3.1 Ventricular Arrhythmias

In patients with HF, often as a result of several MIs, ventricular arrhythmias are an important cause of death. Amiodarone, a class III AAD with additional class I, II and IV properties,[53-55] has been evaluated in these patients as well as in patients with nonischaemic cardiomyopathy. These trials are summarised in table IV. Some of the larger trials are discussed briefly.

The European Myocardial Infarct Amiodarone Trial (EMIAT) was a large scale trial in which 1486 post-MI patients with an LVEF of <40% were randomised to low dose amiodarone or placebo.[59] The occurrence of ventricular arrhythmias was not an inclusion criterion. After 2 years of follow-up neither total nor cardiac mortality was significantly different between both groups. However, there was a trend for a reduction of arrhythmic death and the combined end-point of arrhythmic death and resuscitated cardiac arrest in patients treated with amiodarone. In a retrospective analysis, it was found that those who received amiodarone and a β-blocker were significantly less likely to die.

The Canadian Amiodarone Infarction Arrhythmia Trial (CAMIAT) included post-MI patients with frequent or repetitive ventricular premature beats during 24-hour Holter monitoring.[60] Patients were treated with low dose amiodarone (n = 606) or placebo (n = 596) and followed for 24

months. The risk of arrhythmic death or resuscitated ventricular fibrillation was significantly smaller (risk reduction 48.5%) with amiodarone (3.3%) compared with placebo (6%). As in EMIAT, all-cause mortality was not significantly reduced by amiodarone. It must be mentioned that the largest reduction in absolute risk was observed in patients with more severe HF. As was observed above, amiodarone-treated patients appeared to derive additional benefit from adjunctive β-blocker therapy. Proarrhythmia due to amiodarone was rarely observed.

In the Gruppo de Esdo de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA)[62] and Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (CHF-STAT)[63] study, the safety and efficacy of amiodarone were analysed in patients with moderate to severe HF, due to ischaemic or nonischaemic cardiomyopathy. Coronary artery disease was the underlying disease in 40 and 70% of the GESICA and CHF-STAT patients, respectively. New York Heart Association (NYHA) class of HF was III or IV in 80 and 40% of the GESICA and CHF-STAT participants, respectively. GESICA showed a significant reduction in total mortality in those who were treated for 1 year with amiodarone (33.5%) compared with placebo (41%). Unaffected was the occurrence of sudden death and the rate of progression of CHF. In contrast, in CHF-STAT only a trend to lower mortality was found in patients with nonischaemic cardiomyopathy who were treated with amiodarone.

Patients who had survived an out-of-hospital episode of sustained ventricular tachycardia or ventricular fibrillation, unassociated with an MI, were randomised to amiodarone or conventional (class I) AAD therapy in a study with the acronym CASCADE.[65] Since 1988, some of the patients had received a ventricular defibrillator, equally divided in both limbs. These were patients primarily enrolled during the last half of the study because of a relatively high observed mortality rate. Clearly, implantable cardioverter-defibrillator (ICD) treatment was at that time generally accepted, whereas it was still experimental at the start of the study.[65] After a follow-up of 2 to 6 years, mortality due to cardiac death, resuscitated ventricular fibrillation or syncopal defibrillator shock was significantly lower in those treated with amiodarone.[64]

No straightforward conclusions can be drawn from these studies, since patients differed in characteristics like underlying disease, NYHA classification of HF, incidence and severity of ventricular arrhythmias and, finally, dosage of amiodarone. However, some lessons may be learned: (a) in contrast to class I and pure class III drugs, amiodarone may reduce arrhythmic events in patients with HF post-MI; (b) as overall mortality was unaffected, prophylactic use of amiodarone in patients suffering from nonsustained ventricular arrhythmias cannot be supported; (c) amiodarone seems to be effective predominantly in patients with nonischaemic and more severe HF; (d) amiodarone treatment fares well with adjunctive β-blocker therapy; and finally, (e) in cases of symptomatic, or sustained, ventricular arrhythmias, in the setting of HF, amiodarone is the drug of choice. Although proarrhythmia seldomly occurs during long term amiodarone treatment,[66] noncardiac adverse effects do, even if low dose amiodarone therapy has been instituted.[67,68]

In a meta-analysis of 4 randomised, placebo-controlled studies including 738 patients who received amiodarone and 727 patients given placebo, the mean amiodarone dose ranged from 152 to 330mg daily.[67] Amiodarone was given for at least one year. No higher incidence in hepatic and gastrointestinal adverse effects was observed in the amiodarone group. However, thyroid, neurological, ocular and bradycardic adverse effects occurred more frequently in the amiodarone group. Patients on amiodarone discontinued the drug 1.5 times more frequently than patients treated with placebo.[67] Data on adverse effects reported in CAMIAT and EMIAT confirm the abovementioned impression.[68] Nonetheless, the annual rate of difficult-to-treat or irreversible serious adverse effects was low.

Table IV. Summary of amiodarone (A) studies

Study	Randomisation	LVEF (%)	Post-MI (%)[a]	Degree of VA at inclusion	Follow-up (y)	Reduction with A			
						VA	SCD	CHF death	total death
BASIS[56]	A 200 mg/day (n = 98) Control (n = 114) Individualised (n = 100)	43 ± 16	100	Asymptomatic complex VA (no VT/VF)	1	A *vs* control, p = 0.024	NS	NA	A *vs* control, p = 0.048
Polish[57]	A 400 mg/day (n = 305) Placebo (n = 302)	60% of pts. >40	100	ND	1	A *vs* placebo, p = 0.048	A *vs* placebo, p = 0.048	NA	NS
SSSD[58]	A 200 mg/day (n = 115) Metoprolol (n = 130) Antiarrhythmics (n = 123)	20-45	100	≥3 VPC/h	2.8	A *vs* groups 2 and 3, p = 0.001	NS	NS	A *vs* group 2, p = 0.02
EMIAT[59]	A 200 mg/day (n = 743) Placebo (n = 743)	<40	100	40% >10 VPC/h	1.7	NA	A *vs* placebo, p = 0.05	NS	NS
CAMIAT[60]	A 200 mg/day (n = 606) Placebo (n = 596)	NA	100	VPC ≥ 10/h or ≥1 run VT	1.8	NA	A *vs* placebo, p = 0.016	NA	NS
EPAMSA[61]	A 400 mg/day (n = 66) No treatment (n = 61)	<35	40 CAD	Asymptomatic Lown II-IV	1	NA	A *vs* no drug, p = 0.04	NA	A *vs* no drug, p = 0.02
GESICA[62]	A 300 mg/day (n = 260) Standard (n = 256)	≤35	40 CAD	70% >10 VPC/h	2	NA	A *vs* standard, p = 0.16	A *vs* standard, p = 0.16	A *vs* standard, p = 0.024
CHF-STAT[63]	A 300 mg/day (n = 336) Placebo (n = 338)	≤40	70 CAD	≥10 VPC/h	3.8	A *vs* placebo, p < 0.001	NS	NS	NS
CASCADE[64]	A 100-400 mg/day (n = 113) Conventional (n = 115)	35 ± 14	80	VT/VF	2-6	A *vs* group 2, p < 0.05	A *vs* group 2, p < 0.01	NA	NA

a Percentage of patients who had suffered a previous myocardial infarction.

Abbreviations: CAD = coronary artery disease; CHF = congestive heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NA = not available; ND = not defined; NS = not statistically significant; SCD = sudden cardiac death; VA = ventricular arrhythmias; VF = ventricular fibrillation; VPC = ventricular premature complex; VT = sustained ventricular tachycardia.

As newer class III AADs have failed to fulfil hopes that they may share the efficacy of amiodarone without its toxicity,[47] there is still a place for (low dose) amiodarone. However, the risk of adverse effects, the perceived benefit and the available alternative treatments should be weighed up on an individual basis. When amiodarone is prescribed, adverse liver, thyroid or pulmonary effects should be monitored by checking transaminases and thyroid function, and regularly performing a chest x-ray. The loading dose depends on clinical parameters. In stable patients, loading may be performed by prescribing amiodarone 600 to 800mg daily for 4 weeks. If patients suffer from frequent episodes of ventricular tachycardia or ventricular fibrillation requiring defibrillator treatment, the loading dose may be increased to 1200 to 1800mg daily for 1 to 2 weeks. Preferably, the maintenance dosage amounts to 200mg daily. Target plasma concentrations of 1.0 mg/ml for both amiodarone and its active metabolite desethyl-amiodarone[69,70] are recommended.[71]

4.3.2 Supraventricular Arrhythmias

Minimal prospective comparative data of amiodarone for the prevention of chronic AF are available, but favourable outcomes have been reported when amiodarone has been instituted as a last-resort agent.[72] The drug is particularly useful in AF complicated by HF. Unfortunately, its use is limited by potentially severe noncardiac adverse effects, as mentioned above. Gosselink et al.[72] included 89 patients with chronic AF who had failed previous treatment aimed at maintenance of sinus rhythm. These patients were treated with a mean dose of amiodarone of 204 ± 66mg. Actuarially, 53% of these patients were still in sinus rhythm after a follow-up of 3 years.

5. Class IV Antiarrhythmic Drugs

5.1 Ventricular Arrhythmias

The nondihydropyridine calcium antagonists verapamil and, to a lesser extent, diltiazem, are approved for the treatment of hypertension and angina pectoris. Verapamil has been documented to effectively terminate and suppress certain forms of idiopathic ventricular tachycardias.[73] These LV tachycardias predominantly start during adolescence. Patients usually present with haemodynamically stable episodes of sustained ventricular tachycardia. Almost all cases of this so-called verapamil-responsive LV tachycardia have a morphology on the electrocardiogram (ECG) of a right bundle branch block with a left-axis deviation (thus originating from the inferoapical area of the LV). On rare occasions the ECG shows a right bundle branch morphology and right-axis deviation, indicating an origin at the anterior-superior site of the LV. Verapamil 5 to 10mg administered intravenously results in progressive slowing of the ventricular tachycardia, eventually leading to termination of the arrhythmia. In addition, oral verapamil is effective for preventing spontaneous episodes of this arrhythmia.[73]

5.2 Supraventricular Arrhythmias

Intravenous or oral verapamil is effective for the termination of atrioventricular nodal re-entrant tachycardias and circus movement tachycardias associated with a (concealed) bypass tract. Although radiofrequency ablation is currently considered the therapy of choice for these arrhythmias, verapamil also may prevent new episodes. Verapamil, and also digitalis and β-blockers, however, should never be prescribed prophylactically in the Wolf-Parkinson-White syndrome, as at the moment of AF these drugs may cause very high ventricular rates due to preferential conduction through the bypass tract (due to slowing of the atrioventricular conduction), which may eventually lead to ventricular fibrillation. In addition, these class IV AADs slow the conduction rate of the AV node and in this manner decrease the ventricular response in AF.[74]

Experimental data suggest a new role for the calcium channel blocker verapamil, i.e. reduction of atrial electrophysiological remodelling. It is known that AF has the tendency to become chronic over time. Also, cardioversion to sinus rhythm and its subsequent maintenance becomes more difficult the longer the arrhythmia exists.[75] Progres-

sion of the underlying disease is one explanation for the relation between duration and intractability of AF.

Recently, Wijffels et al.[76] described another possible explanation. They found that, in healthy goats, repetitive induction of AF by a pacemaker led to significant shortening of the atrial refractory period and a reversion of the physiological rate–related shortening of the atrial refractory period without major effects on the conduction velocity.[76] These electrophysiological alterations were called atrial electrophysiological remodelling. The inducibility and duration of induced AF increased in these goats, until AF eventually became chronic. Whereas atrial electrophysiological remodelling was complete within 24 to 48 hours of repeated induction of AF, the arrhythmia became chronic after 1 to 2 weeks. The mechanism responsible for atrial electrophysiological remodelling is still under investigation but intracellular calcium overload in the atrial myocytes is likely to play a role. This hypothesis is supported by the observation that verapamil administered during rapid atrial pacing in goats[77] or artificially induced AF in dogs[78] significantly reduced the electrophysiological remodelling of the atrium, although AF promotion was not prevented.[77] Clearly, whether verapamil (instituted precardioversion) may indeed increase the conversion rates of AF, and improve maintenance rates of sinus rhythm in patients suffering from AF, remains to be investigated.

6. Current Perspectives: Drugs or Devices for the Treatment of Arrhythmias?

6.1 Ventricular Defibrillator

The concept of the implantable ventricular defibrillator was developed by Mirowski et al. in 1966 and introduced into clinical practice in 1980.[79] Since then, several studies have substantiated its efficacy for the termination of life-threatening arrhythmias.[80,81] Transthoracic implantation of epicardial patches, however, was associated with morbidity and mortality. Fortunately, technological advances have revolutionised ICD therapy. Complications decreased after the introduction of a nonthoracotomy transvenous single lead system. The size and weight of an ICD was significantly reduced. Moreover, in addition to its defibrillation capability, antitachycardia pacing and back-up pacing also became available. However, randomised controlled studies comparing ICD therapy with conventional drug treatment are still lacking.[82] Only recently have data of 2 large randomised studies become available, and these are discussed briefly.

In the Multicenter Automatic Defibrillator Implantation Trial (MADIT), 196 highly selected patients at high risk for severe cardiac arrhythmias but without a previous cardiac arrest were randomised to an ICD (n = 95) or AADs (n = 95, 74% amiodarone).[83] These patients were post-MI complicated by nonsustained ventricular tachycardias and an ejection fraction of ≤35%. In all patients, sustained ventricular tachycardia was induced during programmed electrophysiological stimulation and not suppressed by procainamide, indicating a poorer arrhythmia prognosis. After a mean follow-up of 27 months, the trial was stopped because of excessive mortality in the AAD group: 39 deaths (27 from cardiac causes) in the AAD group versus 15 (11 from cardiac causes) in the ICD group ($p = 0.009$). Amiodarone, β-blockers and other antiarrhythmic therapy did not influence this outcome.

The Antiarrhythmic Versus Implantable Defibrillator (AVID) study compared amiodarone therapy against ICD therapy in patients who had survived a cardiac arrest due to ventricular tachycardia or fibrillation.[84] Patients were randomised to amiodarone or sotalol, or ICD therapy. The investigators aimed to include 1200 patients. However, in April 1997 the study was interrupted because of a higher mortality in the AAD group. The patients who were treated with an ICD experienced a 25% lower mortality rate compared with AAD group during a follow-up lasting 2 to 3 years.

The Cardiac Arrest Study Hamburg (CASH) is an ongoing randomised study of treatment of survivors of sudden cardiac death due to ventricular

Table V. Conclusions and guidelines

Drug class or nondrug treatment modality	Comments
Class IA and IC AADs	Not to be prescribed in the presence of cardiac ischaemia, a previous MI or impaired left ventricular function for the prevention of supraventricular arrhythmias
Class II – AADs	Decrease mortality post-MI and in patients with HF
Class III – amiodarone	First-choice therapy for prevention of ventricular arrhythmias in HF patients
Class III – pure class III	High rate of torsade de pointes; only ibutilide approved for intravenous administration for AF/atrial flutter termination
Class IV – AADs	Termination/prevention of supraventricular arrhythmias (AV nodal tachycardia, circus movement tachycardia[a]); verapamil for conversion or prevention of idiopathic left ventricular tachycardia (right bundle branch configuration and left-axis deviation)
Radiofrequency ablation	First-choice therapy in patients suffering from
	recurrent episodes of AV nodal re-entrant tachycardia
	recurrent episodes of circus movement tachycardia due to a (concealed) bypass tract
	Wolff-Parkinson-White syndrome with a bypass tract with a refractory period of <270 msec (malign tract)
Ventricular ICD	Prevent arrhythmic mortality in patients with life-threatening ventricular arrhythmias
Atrial ICD	Group of patients who may benefit from such device remains to be established

a Prevention only in patients with circus movement tachycardia using concealed bypass tract.

Abbreviations: AAD = antiarrhythmic drugs; AF = atrial fibrillation; AV = atrioventricular; HF = heart failure; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction.

tachycardia or fibrillation unrelated to an MI.[85] Patients are enrolled within 3 months of cardiac arrest and are randomly assigned to receive treatment with propafenone, amiodarone, metoprolol or an ICD. The propafenone branch of the study has recently been stopped because of excessive mortality. The other arms of the study are ongoing and the results are eagerly awaited.

Although the final results are not yet published and CASH and the Canadian Implantable Defibrillator Study (CIDS) are still ongoing, ICD therapy seems to be the first choice in patients who are resuscitated for ventricular tachyarrhythmias. Another advantage of such a strategy may be a reduction in the length of hospitalisation. Importantly, one study indicated that ICD devices will be associated with an increasing reduction in healthcare costs, at least in selected patients.[86] Obviously, we should never fail to exclude reversible causes for the cardiac arrest, e.g. ischaemia, and always treat the underlying disease optimally. Whether patients at high risk for sudden cardiac death but without a previous episode of ventricular fibrillation or tachycardia, like the highly selected MADIT population (nonsustained ventricular arrhythmias on 24-hour Holter monitoring and ventricular arrhythmias inducible during an electrophysiological study, and not suppressed after intravenous administration of procainamide), may also be candidates for ICD implantation in the future is still unanswered and warrants further investigations.

6.2 Atrial Defibrillator

An atrial defibrillator is a new device which possesses the possibility, like the ventricular defibrillator for ventricular fibrillation, of restoring sinus rhythm in patients suffering from AF. Shocks delivered between 2 atrial leads (one positioned in right atrial appendage and one in the coronary sinus) effectively convert AF to sinus rhythm.[87] Supposedly, shortening the attacks of AF by such a device may exert an antiarrhythmic effect by limiting electrophysiological, structural and neurohumoral remodelling. Patients with recurrent, but not too frequent, paroxysmal AF and those with recurrent chronic AF are thought to be candidates if conventional therapy fails. However, early relapses of AF occur fairly frequently and may limit

the efficacy of this device.[88] In addition, the degree of discomfort related to the shock is still quite high. Current studies must confirm the safety, feasibility and efficacy of this device and look for strategies to lower the early recurrences. Improvement of leads and (at-home administration of) light sedation in a form that is easy to administer may improve patients' acceptance and tolerance of the shock. If these problems are resolved, the atrial defibrillator may become a more widely applicable therapeutic strategy.

7. Conclusions

Taking into account the data presented above, several conclusions may be drawn (table V). First, there is clear evidence that class II AADs (β-blockers) are effective in decreasing mortality in post-MI patients. In addition, evidence is accumulating that a subset of post-MI patients with moderate to severe HF may benefit from classical β_1-selective or new types of β-blockers with additional properties like α_1-blockade. Secondly, there is also clear evidence that class I AADs should be avoided in post-MI patients or those with HF. In these patients, in particular if symptomatic ventricular arrhythmias are present, amiodarone is a fair choice. It should, however, be realised that an overall reduction of mortality has not been proven and that adverse events occur frequently. Obviously, treatment of the underlying disease in these patients still is of major importance.

Thirdly, the new pure class III AADs unfortunately cause a high rate of the proarrhythmia torsade de pointes. Until now, only ibutilide has been approved in the US for intravenous administration. Research with *d*-sotalol has been cancelled. Fourthly, calcium channel blockers like verapamil and diltiazem keep their important role in supraventricular arrhythmias. They convert and prevent AV nodal re-entrant tachycardias and circus movement tachycardias due to a (concealed) bypass tract. In addition, these drugs control the ventricular rate during AF or atrial flutter. Their significance may increase when an antielectrophysiological remodelling mode of action is proven and if patients benefit clinically because relapses of an arrhythmic episode are more easily accessible to therapy. Perhaps some of these patients may be candidates for an atrial defibrillator, but this is currently under investigation.

Finally, ventricular ICD therapy seems to be a breakthrough in the treatment of life-threatening arrhythmias since, in the now available evaluations, survival was improved. It is likely that in forthcoming years an increasing number of patients will be candidates for these devices. Some restriction of this enthusiasm must be exercised because the results of various ongoing studies must be awaited in order to confirm the earlier beneficial results.

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