Role of antiarrhythmic drugs in patients with implantable cardioverter defibrillators

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The transvenous implantable cardioverter defibrillator (ICD) has emerged as the primary therapy for patients at high risk of life-threatening ventricular arrhythmias. A high number of ICD recipients will require subsequent adjunctive treatment with antiarrhythmic drugs (AADs). This review provides an overview of potential reasons for AAD initiation, candidates for treatment, current medical options, and possible drug-device interactions.

Introduction

Randomized clinical trials have clearly established the superiority of the transvenous implantable cardioverter defibrillator (ICD) over antiarrhythmic drugs (AADs) as primary therapy in the treatment of patients at high risk of life-threatening ventricular arrhythmias, both in primary as well as secondary prevention.1–4 The ICD has therefore become the treatment of choice for patients at risk of these arrhythmias.

However, patients with an ICD may still require adjunctive therapy with AADs at some point during follow-up. Various studies have reported that 16–70% of patients who received an ICD were ultimately treated with AADs.5–7 In the Multicenter Automatic Defibrillator Implantation trial-II (MADIT-II) 16% of patients in the ICD arm received treatment with AADs at last follow-up (average 20 months).6 In the Antiarrhythmics vs. Implantable Defibrillators (AVID) trial 18% of patients, randomized to the ICD arm, required AADs after a median follow-up of 135 days.7 Because it was a controlled clinical trial, the addition of AADs to ICD therapy was strongly discouraged. This percentage therefore probably approximates the absolute minimum requirement of adjunctive treatment with AADs in ICD patients in secondary prevention.

The addition of AADs in patients with ICDs might entail beneficial as well as adverse effects. Concomitant therapy with AADs is intended to reduce the number of ICD interventions, but also exposes the patient to potential drug-related side effects and adverse drug–device interactions. There are unfortunately few randomized trials to guide therapy with AAD in ICD patients.

Reasons for treatment with antiarrhythmic drugs

The main goal of AAD therapy in ICD recipients should be the avoidance of shocks by the device, both appropriate for ventricular arrhythmias and inappropriate for supraventricular arrhythmias (SVT; Figure 1).

Virtually all studies that evaluated the psychological impact of living with an ICD have described a statistically significant decrease in the quality of life of ICD patients receiving shocks (both appropriate and inappropriate) compared with those who did not.8–10 In the MADIT-II trial, patients who experienced appropriate ICD-shocks also reported significant changes in their physical health compared with those who did not have an appropriate shock.11 Both decrease in self-reported mental health and physical health were significantly associated with non-sudden death but not with sudden death.

In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) the occurrence of shocks (both appropriate and inappropriate) was associated with a markedly increased risk of death, mainly due to progressive heart failure.12 It is unknown if prevention of shocks with AADs would change this relationship; however, shocks should lead to a review of the overall medical treatment

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of the ICD patient to ensure it is optimized. Particularly in post-infarction patients and patients with congestive heart failure (CHF), the role of beta-adrenergic agents at appropriate doses cannot be overemphasized.

Increasing frequency of device treated arrhythmias results in increased hospital admissions. Multiple ICD shocks may also cause premature device battery depletion. A reduction in the burden of ICD shocks can therefore have a significant impact on the consumption of health care resources.

AADs can prevent or decrease the frequency of ventricular tachycardia (VT) resulting in a reduced number of appropriate shocks. They can also prevent or decrease SVT burden resulting in a reduced number of inappropriate ICD shocks. Treatment for SVT can potentially also decrease the number of appropriate shocks since it has been reported that persistent atrial fibrillation (AF) is a strong independent predictor of the occurrence of ventricular tachyarrhythmias among ICD recipients when compared with patients with persistent sinus rhythm. Furthermore, retrospective studies found that VT or ventricular fibrillation (VF) is triggered by a paroxysm of SVT in up to 10% of cases, suggesting that SVT may increase the risk of ventricular tachyarrhythmias.

If AADs are unable to successfully prevent recurrence of VT they may increase the tachycardia cycle length if VT occurs. This may render the arrhythmia haemodynamically better tolerated, make the VT more amenable to antitachycardia pacing therapy (ATP) and avoid uncomfortable shock therapy.

**Which patients should be treated?**

The risk of ICD shocks should be estimated for the individual patient and AAD therapy should be tailored to this estimate (Table 1). Patients who undergo ICD-implantation in primary prevention are at considerably lower risk of ICD shocks than secondary prevention patients. In the SCD-HeFT trial, the average annual rate of appropriate ICD shocks was 5.1%. In the MADIT-II trial, 35% of the patients received at least one appropriate therapy (ATP and shock) at 3 years after implantation. The higher incidence of appropriate ICD-therapy in MADIT-II is probably due to the higher arrhythmia detection rates and shock-only strategy in SCD-HeFT. In the MADIT-II trial the risk for appropriate therapy (ATP and shock) increased significantly with worsening clinical condition as measured by hospitalization for CHF or coronary events during follow-up. In this patient population with a poor left ventricular ejection fraction (LVEF) (<30%) further stratification of LVEF was not associated with an increased risk of ICD-therapy.

Secondary prevention ICD recipients who have VT as their index arrhythmia are more likely to have appropriate therapy (ATP and shock) than those who underwent ICD-implantation after an episode of VF (75.5% vs. 47.4% during 3 years of follow-up in AVID). In a prospective cohort study the relative risk for first ICD therapy (ATP and shock) in patients presenting with VT vs. VF was 2.57 (range, 1.32–5.01). In that study patients were also more at risk for a first ICD therapy (ATP and shock) if LVEF was <25%; if AAD therapy was not changed 80% of patients received additional therapy after a first appropriate ICD-therapy within 1 year. Subsequent device therapy (ATP and shock) was found to occur sooner (66 ± 93 days for second therapy

**Table 1 Risk factors for ICD-shock therapy**

<table>
<thead>
<tr>
<th>Secondary prevention</th>
<th>VT as index arrhythmia</th>
<th>Recent first appropriate ICD-therapy</th>
<th>Hospitalization for congestive heart failure</th>
<th>Hospitalization for coronary event</th>
<th>LVEF &lt; 25%</th>
<th>SVT with fast ventricular rate</th>
<th>response</th>
</tr>
</thead>
</table>

**Figure 1** Reasons for treatment with AADs in ICD recipients. AAD, antiarrhythmic drug; VT, ventricular tachycardia; VF, ventricular fibrillation; SVT, supra ventricular tachycardia; TCL, tachycardia cycle length; ICD, implantable cardioverter defibrillator; ATP, antitachycardia pacing.
compared with 138 ± 168 days for first therapy) and to be unpredictable in that trial. A sub-analysis of the SHIELD trial confirmed that recurrent VT/VF events were highly clustered in secondary prevention patients, with >50% of inter-event intervals <1 day.21

Little is known about ICD therapy delivery in patients without ischaemic or dilated cardiomyopathy (channelopathy and idiopathic VF) since these patients are poorly represented in both randomized clinical trials and cohort studies. One registry reported outcome results on this subpopulation as a group.22 Delivery of appropriate therapy was half as frequent, whereas life-threatening arrhythmias (VF or VT with a heart rate >240 bpm) were observed as frequently as in the cardiomyopathy patients.

When to initiate antiarrhythmic drug?

On the basis of these data we do not recommend starting AADs at the time of implant in patients who receive an ICD in primary prevention, apart from beta-blockers for the post-infarction or CHF patient. In secondary prevention patients, AAD treatment at implant is reasonable if the ICD is implanted soon after an episode of VT. Since a second appropriate device therapy tends to come earlier and to be less predictable, it is reasonable to consider AAD treatment after the first appropriate therapy for symptomatic arrhythmia, especially if there are several events in a short space of time.

Whether or not AADs should be started should depend on the nature of the event (e.g. presence and severity of symptoms, VT vs VF, multiple episodes, possible reversible causes), the type of delivered device therapy (ATP or shock) and the pattern of recent episodes. As a general rule AAD treatment should be started earlier in patients with multiple episodes of symptomatic VTs not responsive to ATP in the absence of reversible causes (e.g. heart failure, ischaemia, alcohol excess). Changes in ATP therapy should always be considered prior to AAD initiation. Because of the clustered course of VT/VF recurrence, we do not necessarily start treatment in a patient who received appropriate therapy weeks or months prior to the current interrogation and has been stable since.

Because SVT may lead to inappropriate device therapy or may induce VT and lead to subsequent appropriate device therapy, AAD treatment can be considered in this context if device reprogramming or a rate control approach proves insufficient.

Antiarrhythmic drugs that reduce the frequency of implantable cardioverter defibrillator therapy

For the purpose of this review we will refer to the Vaughan Williams classification which classifies AADs based upon the site of channel blockade and effect of the drugs on conduction velocity and action potential duration.23,24 Although several of the discussed studies were performed in the ‘pre ICD’ era, they were included in the review because the results contribute to the overall approach of AAD treatment in ICD patients.

Class I activity

The Cardiac Arrhythmia Suppression Trial (CAST) compared class IC drugs to placebo in post-infarction patients with impaired LVEF (ejection fraction of 40% or less (55% or less if within 90 days post-infarction]) to suppress ventricular premature depolarizations.25 There was an excess mortality in patients treated with class IC drugs compared with placebo, due to arrhythmic and non-arrhythmic cardiac death. Early studies comparing other class I drugs with, respectively, amiodarone26 and sotalol27 in secondary prevention after VT/VF in the pre ICD era have shown superiority of both amiodarone and sotalol to class I drugs.

Monotherapy with class I drugs for the prevention of ventricular arrhythmia therefore does not appear to be safe or effective.

Class II activity

Both in post-infarction patients and in patients with CHF beta-blockers should be a cornerstone of therapy. Although there are no placebo controlled studies of beta-blockers in ICD-recipients, beta-blockade has been shown to reduce arrhythmia and sudden cardiac death in these populations. The meta-analysis of beta-blocker studies in post-infarction patients suggest that there is a greater relative benefit in preventing sudden cardiac death than all-cause mortality.28 In the Cardiac Insufficiency Bisoprolol Study II, bisoprolol reduced all-cause mortality by 34% (P < 0.0001) and sudden cardiac death by 44% in patients with CHF (P = 0.0011).29

Beta-blockers are the medical treatment of choice for certain channelopathies (e.g. congenital long QT-syndrome type 1 and catecholaminergic polymorphic VT).

Class III activity

Sotalol has a beta-blocking effect (class II effect) at lower dosages and a class III antiarrhythmic effect at higher dosages.30 A double blind placebo controlled trial randomized 302 patients with an ICD in secondary prevention to either racemic (D, L-) sotalol (160–320 mg) or placebo.31 Thirty-four per cent of patients in the sotalol group and 54% of patients in the placebo group met the primary endpoint of death from any cause or delivery of a first shock for any reason during 1 year of follow-up (relative risk reduction 48%; P < 0.001). In that trial treatment with conventional beta-blockers was suboptimal (37% of patients in the placebo group and 23% in the sotalol group).

Amiodarone combines antiarrhythmic effects of Vaughan Williams class I, II, III, and IV.32 The efficacy of amiodarone in the prevention of sudden cardiac death had already been well established in the ‘pre ICD’ era. A meta-analysis of all randomized trials showed that amiodarone reduced total mortality by 10–19%. The risk reduction was similar in patients after myocardial infarction, with CHF, or prior cardiac arrest.33 The amiodarone maintenance dose varied from 200 to 400 mg/day. In a pooled database from two similar randomized clinical trials, the European Amiodarone Myocardial Infarction Trial and the Canadian Amiodarone Myocardial Infarction Trial that evaluated use of amiodarone in patients recovering from myocardial infarction, cardiac death and arrhythmic death, or resuscitated cardiac arrest were significantly lower (P = 0.05 and 0.03, respectively) in patients receiving beta-blockers and amiodarone than in those without beta-blockers, with or without amiodarone.34

The Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) study was a randomized trial that compared amiodarone (200 mg) plus beta-blocker with sotalol alone (240 mg, adjusted for renal function) or beta-blocker alone...
(bisoprolol 10 mg or equivalent) in 412 patients who had received a dual-chamber ICD for inducible or spontaneous VT or VF and LVEF ≤ 40% or syncope. All ICDs were optimally programmed to avoid shocks (ATP up to a rate of 222 beats/min; SVT discriminators enabled). During 1 year of follow-up shocks (appropriate and inappropriate) occurred in 41 patients (38.5%) assigned to beta-blocker alone, 26 (24.3%) assigned to sotalol alone, and 12 (10.3%) assigned to amiodarone plus beta-blocker. Amiodarone plus beta-blocker significantly reduced the risk of any shock compared with beta-blocker alone (HR, 0.27; 95% CI, 0.14–0.52; P < 0.001) and sotalol (HR, 0.43; 95% CI, 0.22–0.85; P = 0.02). There was a trend for sotalol to reduce shocks compared with beta-blocker alone (HR, 0.61; 95% CI, 0.37–1.01; P = 0.055). The rates of study drug discontinuation at 1 year were 18.2% for amiodarone, 23.5% for sotalol, and 5.3% for beta-blocker alone.

Dofetilide is a selective blocker of the Kv component of the potassium current. The drug is currently only available in North America. Although no studies have been performed in ICD recipients, one double blind randomized crossover trial in patients with ischaemic heart disease and sustained VT in the 'pre ICD' era showed equal efficacy in preventing recurrence of arrhythmia and arrhythmic death during 1 year of follow-up for dofetilide and sotalol. Dofetilide was better tolerated during the acute phase than sotalol.

Azimilide is currently still an investigational AAD which blocks potassium currents I_{Kr} and I_{Ks}. In the Shock Inhibition Evaluation with Azimilide (SHIELD) trial azimilide significantly reduced the recurrence of VT/VF terminated by shocks or ATP in ICD patients compared with placebo, with relative risk reductions of 57% (P = 0.0006) and 47% (P = 0.0053) at 75 and 125 mg doses, respectively, during 1 year of follow-up (38% of 214 patients on azimilide 75 mg, and 737 events in 50% of 199 patients treated with azimilide 125 mg).

New alternatives

Dronedarone is a derivative of amiodarone with a similar electropharmacologic profile, but without iodine to eliminate the iodine-related adverse reactions. The ATHENA study showed fewer cardiovascular hospitalizations or death in patients with AF, treated with dronedarone, compared with placebo. However, the Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Mortality Decrease (ANDROMEDA) had to be halted early because of increased mortality in the dronedarone group. In that trial patients who were hospitalized with symptomatic heart failure and severe left ventricular systolic dysfunction were randomized to receive 400 mg of dronedarone twice a day or placebo. Dronedarone has not been specifically tested for VT.

Celivare is a drug with similar electrophysiological effects to dronedarone. A randomized trial will be started shortly to evaluate the efficacy of this novel drug for the prevention of ICD interventions or death in ICD recipients with LVEF ≤ 40% and at least one appropriate ICD intervention or ICD-implant in secondary prevention in the last month.

Combination therapy

Theoretically the combination of a class I drug (with the exception of a class IC) and dofetilide might have comparable effects to amiodarone if added to beta-blocker therapy. No randomized trial has compared these drug regimes however. Some studies have suggested a beneficial effect from the combination of mexiletine and amiodarone and procainamide or quinidine with d,L-sotalol. If mexiletine, procainamide, or quinidine are combined with amiodarone their doses should be reduced in order to avoid side effects.

What antiarrhythmic drug to select?

On the basis of the current evidence we recommend treating all patients with structural heart disease with beta-blockers at the time of ICD-implant (Figure 2). If the patient develops recurrence of VT or VF with symptoms or shocks, addition of amiodarone, with a maintenance dose of 200 mg once daily to beta-blockers should be considered. If the arrhythmia stabilizes during low dose amiodarone treatment, discontinuation of amiodarone can be considered after 1 year. If the patient has significant recurrence of arrhythmia under a low dose of amiodarone, we raise the maintenance dose to 300 or 400 mg once daily. If the arrhythmia stabilizes under a high dose of amiodarone we lower the dose again to 200 mg once daily after 6 months. If the patient experiences only infrequent recurrence of VT with moderate symptoms and without shocks during high dose amiodarone treatment we still lower the dose to 200 mg once daily after 6 months and add a class I AAD. In case of insufficient arrhythmia control with a beta-blocker and a high dose of amiodarone, ablation has to be considered. In case of side effects of amiodarone we switch to therapy with dofetilide, with or without a class I AAD. At this point sotalol may be a reasonable alternative although it requires a relatively high dose to achieve the class III drug effect. At higher doses, patients often develop side effects, particularly fatigue. The use of sotalol may also complicate the co-administration of beta-blockers which have a clearly established benefit in patients with structural heart disease.

In patients with channelopathies and absence of structural heart disease AAD treatment should be tailored to the specific underlying syndrome.

Non-pharmacological treatment options

No well conducted randomized clinical trials have been published that compare VT ablation with AADs for the reduction of device therapy in ICD recipients. Two randomized trials have compared ICD implant and prophylactic ablation to ICD implant alone in secondary prevention in patients with a history of myocardial infarction. The SMASH-VT trial enrolled patients with a history of VT or VF, not treated with AADs. In that trial, prophylactic substrate-based catheter ablation reduced ICD shocks from 31 to 9% over a mean follow-up of 22.5 ± 5 months (P = 0.003), and reduced VT from 33 to 12% (P = 0.007). Substantial ablation-related complications (pericardial effusion, exacerbation of CHF, and deep venous thrombosis) occurred in 5% of patients. The 30-day mortality rate was zero after ablation. The VTACH trial enrolled patients with a history of stable VT. In that trial the number of appropriate events of ICD therapy per-patient and per-year was also lower in the ablation group than in the control group (median 0.2 vs. 3.0; P = 0.013). 3.8% of patients from the ablation group developed substantial ablation-related complications.
complications (two ablation procedures had to be terminated prematurely because of transient ischaemic ST-segment elevation in one patient and a transient cerebral ischaemic event in another patient). Again no deaths occurred within 30 days after ablation. Although the results of these trials are promising it is not clear whether outcomes of ablation would be similar for non-ischaemic patients or in less experienced centres. At this point ablation is therefore not recommended as a first line treatment. In cases of electrical storm (ES), resistant to AAD, VT ablation should also be considered.

Electrical storm

Electrical storm is defined as recurrent VT or fibrillation resulting in three or more separate device interventions during a single 24-h period. Ten to 30% of patients who undergo ICD-implantation for secondary prevention experience ES at some point during follow-up. The majority of ES are due to VT. In general ES occurs at least several months after ICD-implantation and leads to an important increase in hospitalizations, compared with isolated VT/VF. Data regarding the impact of ES on mortality are conflicting.

Both prevention and acute treatment can be achieved by AADs. In the SHIELD trial azimilide (125 mg/day) reduced the risk of recurrent ES by 55% (HR, 0.45, 95% CI, 0.23–0.87, $P = 0.018$), compared with placebo. If the arrhythmia cluster occurs it can be terminated by a combined therapy with intravenous beta-blocker and amiodarone (bolus of 150–300 mg/1 h and 1–1.2 g/24 h). Both therapies can be effective even in patients who are taking beta-blockers or amiodarone chronically. The aetiology of ES is not completely understood, but correctable causes such as ischaemia, worsening heart failure, electrolyte disturbance, increased sympathetic tone, and drug induced proarrhythmia are all potential precipitating factors. If identified, correction of reversible causes should be attempted. If no apparent causes are found, ES should lead to initiation or optimization of chronic AAD therapy.

Table 2 Potential drug and device interactions

<table>
<thead>
<tr>
<th>Potential drug and device interactions</th>
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<tbody>
<tr>
<td>Increase of ventricular tachycardia cycle length, leading to VT-undersensing</td>
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<tr>
<td>Increase in ventricular pacing threshold, especially at fast pacing rates</td>
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<tr>
<td>Increase in defibrillation threshold (DFT)</td>
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<tr>
<td>Increased bradycardia pacing due to changes in sinus rate/atrio-ventricular conduction</td>
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<tr>
<td>Increased device therapy due to proarrhythmia and rhythm misclassification</td>
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</table>

Drug and device interactions

Prior to the initiation of AADs in ICD recipients it is important to recognize potential drug and device interactions. AADs may enhance device use, but also may interfere with the detection and treatment of ventricular arrhythmia (Table 2). Most AADs will increase the VT cycle length. If the VT rate slows down more than anticipated it may fall below the lower rate cut off of the ICD detection and escape device therapy. Slowing of conduction is caused by Na-channel blockade. Therefore, a large increase in VT cycle length will be primarily seen with Vaughan Williams class I AADs. Typically VT cycle length will not change significantly for class III drugs with the exception of...
amiodarone, due to its class I action. Amiodarone may prolong the VT cycle length up to 20%.54 Slowing of the VT rate may on the other hand make it haemodynamically better tolerated and a longer VT cycle length also makes the arrhythmia generally more amendable to ATP.55

AADs can interfere with ventricular pacing thresholds. Flecainide (class IC), propafenone (class IC) and amiodarone have been shown to elevate pacing thresholds.56 The published data for quinidine (class IA), procainamide (class IA), and lidocaine (class IB) are unclear and beta-blockers56 and azimilide28 have no significant effect on pacing thresholds. Regardless of AADs, pacing thresholds will also increase with faster pacing rates.57 This phenomenon can be further enhanced by use-dependency of some drugs (particularly class IC). Thresholds should therefore be closely followed after changes in drug treatment and pacing output values during ATP should be programmed at least four to five times higher than the pacing threshold determined at slow rates.

AADs potentially alter the defibrillation threshold (DFT). The DFT is defined as the minimum amount of energy required to reliably convert VF to a supraventricular rhythm. Data regarding effects of class IA and IC drugs on DFT are inconsistent. Class IB drugs have been consistently found to increase DFT.58 The class III drug dofetilide decreases DFT59 and azimilide does not affect DFT.28 During the OPTIC trial DFTs were measured for the different subpopulations. In both the beta-blocker and sotalol group DFT decreased slightly. In the amiodarone group DFT increased from $8.53 \pm 4.29$ to $9.82 \pm 5.84$ ($P = 0.091$). However, there were highly variable individual changes both with amiodarone and sotalol.60

After initiation of class I drugs a new DFT test might therefore be indicated. On the basis of the results of the OPTIC substudy, this seems not routinely required after initiation of amiodarone.

AADs may suppress sinus rates and alter atrio-ventricular conduction leading to increased bradycardia pacing therapy. This may prematurely drain the battery and may lead to pacemaker syndrome or further impairment of LVEF.61 After initiation of AAD pacemaker parameters should therefore be re-evaluated to minimize the impact of this phenomenon.

Finally, AADs are potentially proarrhythmic and may therefore cause more frequent arrhythmias with subsequent more frequent ICD therapy. Class III AADs can induce QT prolongation and torsade de pointes (tdp). The risk of proarrhythmia differs among class III agents. Amiodarone and azimilide are associated with a much lower risk for tdp than dofetilide and sotalol.62 Several risk factors have been identified for the development of tdp, including female gender, baseline long QT, concomitant therapy with other QT-prolonging agents, hypokalemia and hypomagnesia, bradycardia, structural heart disease (including left ventricular hypertrophy), and renal insufficiency in the case of sotalol and dofetilide.

Class I agents, in addition to amiodarone, slow atrial conduction velocity and may consequently organize AF into atrial flutter with the potential for rapid and potentially 1:1 atrio-ventricular conduction, leading to a regular fast ventricular rhythm. This may confuse the ICD-discriminators and lead to inappropriate device therapy. Because of slowing of intraventricular conduction, class I agents also increase QRS-duration and sensed electrogram duration, especially at higher rates because of use dependent block. During SVT with fast ventricular rate response this may lead to inappropriate therapy. Finally pronounced QT prolongation with class III drugs can cause T-wave oversensing and double counting leading to rhythm misclassification by the device and inappropriate therapy.

Conclusions

Although ICD-implantation should be the primary therapy of choice for patients at risk of life-threatening ventricular arrhythmias, a high number of patients will still need concomitant treatment with AADs during follow-up. The main goal for initiation of AADs should be the avoidance of uncomfortable shocks from the device. Treatment should be started immediately after appropriate device treatment has occurred. On the basis of the current data a combination of beta-blocker and amiodarone should be the AAD therapy of choice. If the patient stabilizes under this treatment dose reduction of amiodarone should be considered after several months since side effects are associated with high cumulative doses of the drug. If side effects occur, a switch to a combination of beta-blocker and dofetilide or sotalol with or without a class I drug can be considered. New AADs may prove to be efficient in the near future with an important decrease in side effects. If AAD therapy is initiated, the potential of drug and device interactions should be recognized and anticipated.

Conflict of interest: none declared.

References


Role of antiarrhythmic drugs


