Antiarrhythmic Drug Therapy to Avoid Implantable Cardioverter Defibrillator Shocks

Jaber Abboud and Joachim R Ehrlich

St. Josefs-Hospital, Wiesbaden, Germany

Abstract

Implantable cardioverter defibrillators (ICDs) are effective in the prevention of arrhythmic sudden cardiac death. Many patients receiving an ICD are affected by heart failure and are at risk of ventricular arrhythmias, which may lead to appropriate shocks. On the other hand, in this population the incidence of atrial fibrillation, giving rise to inappropriate ICD shocks, is high. Accordingly, ICD discharges occur frequently and many patients with an ICD will need concomitant antiarrhythmic drug therapy to avoid or reduce the frequency of shocks. Therapeutic agents such as β -blockers, class I or class III antiarrhythmic drugs effectively suppress arrhythmias, but may have side-effects. Some drugs could eventually influence the function of ICDs by altering defibrillation or pacing threshold. Few prospective randomised trials are available, but current data suggest that amiodarone is most effective for prevention of appropriate or inappropriate ICD shocks. This review article summarises current knowledge regarding the antiarrhythmic management of patients with ICDs.

Keywords

Implantable cardioverter defibrillator, autonomic tone, ventricular fibrillation, atrial fibrillation, pharmacological management, antiarrhythmic drugs, defibrillation threshold, pacing threshold, sudden cardiac death, resuscitation

Disclosure: The authors have no conflicts of interest to declare

Received: 23 December 2015 **Accepted:** 6 July 2016 **Citation:** *Arrhythmia & Electrophysiology Review* 2016;**5**(2):117–21 DOI: 10.15420/AER.2016.10.2

Access at: www.AERjournal.com

Correspondence: Joachim R. Ehrlich, Division of Cardiology, St. Josefs-Hospital, Beethovenstr. 20, 65189 Wiesbaden, Germany. E: joachimehrlich@t-online.de

Implantable cardioverter defibrillators (ICDs) have been used for over 30 years to prevent sudden cardiac death (SCD). The first indications for ICD placement were secondary prevention; later trials demonstrated a primary prevention benefit of ICD therapy in patients at risk of SCD. ICD therapy prolongs life in both patient populations.¹ However, the efficacy of an ICD depends on its ability to correctly detect ventricular arrhythmia and deliver antitachycardia pacing or shocks. In cases of inadequate arrhythmia classification by the device, atrial fibrillation (AF) with rapid conduction to the ventricles can lead to inappropriate shocks. The ability of an ICD to correctly detect this arrhythmia is essential to avoid shock delivery. Furthermore, technical problems such as lead fractures, oversensing of myopotentials or external noise can lead to shock application. ICD shocks can be painful if experienced in the awake state and may reduce quality of life in affected patients.² Shocks, whether appropriate or not, tend to occur frequently after the implantation of an ICD and avoiding shocks is a reasonable therapeutic target.³

Current evidence suggests that ICD shocks increase the risk of mortality.⁴ It remains a matter of debate if this finding depends on the context of a specific cardiac substrate or the shock *per se*.⁵ Of less controversy is the fact that patients who receive ICD shocks experience reduced quality of life. This has been a consistent finding in published studies that was already evident from data in the first available trials, such as the Antiarrhythmics Versus ICDs (AVID) trial.² The occurrence of ICD shocks was associated with reduced physical functioning and decreased mental wellbeing. Another study reported that patients who experienced an ICD shock did not adapt well to

living with an ICD and were generally more anxious than ICD recipients who received no shock.⁶ Accordingly, shock reduction by medical, interventional or technical means is a desirable goal.

General Measures

Most patients receiving ICDs for primary prevention of SCD are affected by heart failure with reduced left ventricular ejection fraction (LVEF <35 %). Should these patients meet the criteria for cardiac resynchronisation therapy (CRT), implantation is indicated to achieve mortality and morbidity benefits.⁷ In addition, CRT responders exhibit fewer ventricular tachycardia/ventricular fibrillation (VT/VF) episodes after implantation than patients not receiving CRT.⁸ In general, care should be taken to keep these patients on optimal medical therapy including high-dose β -blockers, as these drugs lead to a reduction in rates of SCD and overall mortality in patients with ischaemic and non-ischaemic cardiomyopathy. If such treated patients develop arrhythmias despite β -blocker treatment, an additional anti-arrhythmic treatment will be necessary. In clinical practice, an adjunctive antiarrhythmic is administered to more than half of patients who have an ICD.⁹

Serum Potassium Levels

Besides pharmacological interventions, simple methods aiming to normalise serum electrolyte levels could be of clinical value. Electrolyte imbalance is an important reversible cause for ventricular arrhythmias and often encountered clinically. In particular, hypokalaemia enhances cardiac electrical vulnerability.¹⁰ Conversely, where serum electrolyte levels are normalised, a stabilising effect in terms of arrhythmia

Table 1: Summary of Antiarrhythmic Drug Dosages Applied in Clinical Trials

Antiarrhythmic Drug	References	Dosage	Notes
Amiodarone	15,17–19	200 mg once daily	Saturation dose 10–12 g
Sotalol	17–21	160 mg twice daily	Care should be taken to monitor for renal dysfunction
Ranolazine	32–35	375 mg twice daily	Applied in addition to sotalol or amiodarone
Dofetilide	23–25	500 µg once daily	Care should be taken to monitor for renal dysfunction
Azimilide	15,22	175 mg once daily	Not clinically available
Dronedarone	26,27	400 mg twice daily	Contraindicated in patients with heart failure
Mexilitine	28–29	100 mg twice daily	Applied in addition to amiodarone

incidence has been reported. For instance, a database study including >38,000 patients with acute MI showed the lowest risk of VF, cardiac arrest or death with potassium concentrations of 3.5–4.5 mmol/l.¹¹ In contrast, hyperkalaemia may lead to intermittent or permanent loss of capture or T-wave oversensing. While the former may lead to arrhythmia induction, the latter could lead to double counting and inappropriate shock delivery.¹² Accordingly, care should be taken to keep potassium levels within the normal range. While a high-to-normal range may be preferred, this certainly needs to be adjusted to account for the clinical characteristics of individual patients. Understanding the role of electrolyte imbalance for arrhythmia incidence is of particular importance as mineralocorticoid receptor-blocker treatment is a guideline-recommended aspect of heart failure therapy.¹³ Care should be taken if patients receive such treatment as an increase in hyperkalaemia-associated deaths became evident after the publication of the Randomized Aldactone Evaluation Study (RALES).¹⁴

Adjunctive Antiarrhythmic Therapy to Reduce Shocks

Although modern ICDs incorporate antitachycardia pacing to treat ventricular arrhythmias prior to shock application, the efficacy of such pacing therapy is sometimes limited. Furthermore, inaccurate classification of non-life-threatening tachyarrhythmia, such as supraventricular tachycardia (particularly AF) as ventricular in origin, increases the rate of inappropriate ICD shocks. These drawbacks associated with the use of ICDs raise questions of how and when to administer adjunctive anti-arrhythmic drug therapy in order to reduce the rate of ICD shocks and improve quality of life.¹⁵

Class III Antiarrhythmic Drugs

Vaughan–Williams class III drugs that prolong cardiac action potential duration and thus refractoriness are indicated for suppressing atrial and ventricular arrhythmias. In general, antiarrhythmic drug treatment needs to be weighed against risks and potential side-effects. To date, there has been no study demonstrating a positive effect of antiarrhythmic drug therapy on mortality in patients with an ICD. In addition, in the light of reduced systolic left ventricle (LV) function one has to consider that antiarrhythmic drugs in general further suppress contractility. Only one study has demonstrated an increase in systolic LV function in patients with heart failure treated with amiodarone.¹⁶ This finding has not been replicated by other trials.

Amiodarone and Sotalol

The Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) study represents the largest randomised trial (n=412) comparing the antiarrhythmic drugs amiodarone, *d,l*-sotalol and β -blockers for ICD shock reduction.¹⁷ The OPTIC study included patients with a secondary prevention ICD indication and found

that amiodarone in conjunction with a β -blocker greatly reduced the risk of both appropriate (HR 0.30, 95 % CI 0.14–0.68, $p<0.05$ versus β -blocker alone) and inappropriate (HR 0.22, 95 % CI 0.07–0.64, $p<0.05$ versus β -blocker alone) shocks. In addition to its direct antiarrhythmic effects on supraventricular and ventricular arrhythmias, amiodarone affects the atrioventricular node by slowing conduction and reducing heart rate, which also may help prevent inappropriate shocks due to supraventricular tachycardia.¹⁷ In the same study, *d,l*-sotalol when compared with β -blockers did not significantly reduce the frequency of ICD shocks; however, a numerical trend towards fewer shocks was evident (HR 0.61, 95 % CI 0.37–1.01, $p=0.055$ versus β -blocker alone).¹⁷

An earlier trial prospectively compared *d,l*-sotalol with placebo treatment and documented a significant benefit with sotalol in terms of shock reduction.¹⁸ Patients were included if they had a secondary prevention indication for an ICD and were stratified according to LVEF function below or above 30 %. In 302 patients with an ICD, *d,l*-sotalol was titrated up to 160 mg twice daily in addition to concomitant β -blocker therapy. In case of renal dysfunction (30–60 ml/min), one of the daily sotalol doses was skipped. In that trial, *d,l*-sotalol led to a 48 % relative risk reduction for any shock or death from any cause (HR 0.52, 95 % CI 0.37–0.74, $p<0.05$) compared with placebo. The incidence of inappropriate shocks for supraventricular arrhythmias was also significantly reduced (relative risk reduction by 64 %, $p<0.05$).¹⁸ The effectiveness of sotalol did not differ significantly in patients with a systolic LV function ≤ 30 % versus >30 %.

AF with rapidly conducted ventricular activation is a common cause of inappropriate ICD shocks. Current AF guidelines recommend the use of amiodarone for AF relapse prevention in patients with relevant structural heart disease such as heart failure.¹⁹ In contrast, sotalol is not recommended for relapse prevention in the setting of heart failure as there is concern about the safety of sotalol in patients with AF.²⁰ While heart failure patients may be particularly prone to sotalol-induced ventricular proarrhythmia, no increased mortality rate was observed in the specific population of patients with an ICD.¹⁸ It can be speculated that the ICD may protect patients from potential proarrhythmic events and, accordingly, sotalol could represent a therapeutic alternative in selected patients with an ICD, particularly those with normal renal function. The effectiveness of amiodarone to reduce the risk of inappropriate shocks is already evident even from small studies. In an observational study of 55 patients evaluating the incidence of inappropriate shocks after ICD implantation, amiodarone was most effective in reducing the rate of inappropriate shocks and was superior to β -blockers.²¹

The finding of amiodarone being the most potent antiarrhythmic drug for overall shock reduction is supported by a meta-analysis of 1889

patients in several trials.¹⁵ This report pooled data from the above-mentioned prospective trials with several retrospective observational studies, and found that the risk of overall ICD shocks was reduced when comparing amiodarone plus β -blocker with β -blocker alone (HR 0.27, 95 % CI 0.14–0.52). Similarly, in that meta-analysis, sotalol was found to be superior to placebo (HR 0.55, 95 % CI 0.40–0.78), but not to other β -blockers (HR 0.61, 95 % CI 0.37–1.00).¹⁵ This meta-analysis was largely supported by the results of the OPTIC study. Given the tendency towards a greater effect of sotalol over β -blockers in the OPTIC study and a statistically significant effect of sotalol in the trial by Pacifico et al., it appears reasonable to keep both substances in mind for shock prevention, realising that amiodarone is most effective (see Figure 1).

Azimilide and Dofetilide

Azimilide is an experimental class III agent that is not clinically available. The meta-analysis by Ferreira-Gonzalez et al. looked at trials of patients treated with class III substances azimilide or dofetilide for shock reduction.¹⁵ It failed to document a relevant effect of these two drugs on shock reduction in comparison with placebo (azimilide: HR 0.78, 95 % CI 0.58–1.04, and dofetilide: HR 0.67, 95 % CI 0.43–1.04). In one prospective randomised study involving 633 patients with an ICD, two doses of azimilide were compared with placebo.²² This study documented a dose-dependent suppression of the incidence of ICD shocks by azimilide. However, after addition of data from several smaller dose-ranging studies these effects could no longer be observed.¹⁵

In contrast to azimilide, dofetilide is available in several countries. The Danish Investigations of Arrhythmia and Mortality on Dofetilide with Congestive Heart Failure (DIAMOND-CHF) trial suggested a mortality benefit for patients with heart failure with an LVEF <35 % who converted from AF to sinus rhythm on dofetilide.²³ The trial was designed to study safety and efficacy of this class III antiarrhythmic drug in patients with heart failure and AF. In that study, ICD placement was an exclusion criterion, thus no data regarding incidence of shocks were available. One recent report suggests effectiveness of dofetilide in reducing the frequency of ventricular tachyarrhythmias in patients with an ICD even after failure of amiodarone. In that observational series 30 patients with symptomatic VT/VF episodes were treated with dofetilide and followed for over 2 years.²⁴ In contrast, oral dofetilide was not effective for shock reduction (HR 0.67, 95 % CI 0.43–1.04, p =NS) in another small study.²⁵ Accordingly, this substance holds some minor potential with an apparent safety profile. It needs to be studied in larger randomised trials.

Dronedarone

Dronedarone was developed to circumvent the untoward side-effect profile of amiodarone, but it is contraindicated in patients with heart failure or permanent AF. The Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) was initially designed to study a potential beneficial effect of dronedarone on the prognosis of patients with heart failure.²⁶ The trial was stopped early as increased mortality rates were observed with the drug. There are no systematic studies of this substance for ICD shock reduction, but case reports suggest potential benefit in individual patients treated with the substance despite the presence of heart failure.²⁷ The substance should not be used routinely, but may remain a 'last-resort' alternative in selected individual cases.

Figure 1: Recommendations for Treating Inappropriate and Appropriate Implantable Cardioverter Defibrillator Shocks

AAD = antiarrhythmic drug; AF = atrial fibrillation; ICD = implantable cardioverter defibrillator; PVI = pulmonary vein isolation; SVT = supraventricular tachycardia.

Sodium Channel Blockers

Although the sodium channel blockers are sometimes used as a last-resort therapy in patients with refractory ventricular tachyarrhythmias who fail or do not tolerate amiodarone, there are very limited clinical trial data available.²⁸ In some patients with repetitive ventricular tachyarrhythmias a combination of class I and class III antiarrhythmic drugs – mostly amiodarone – is applied.²⁹ Mexiletine is a Vaughan–Williams class Ib sodium channel blocker. In general, class I drugs should be avoided in patients with heart failure, but in an observational single-centre study, mexiletine given at a dose of 100 mg twice daily in addition to amiodarone 200 mg once daily was effective in reducing the rate of recurrent VT/VF episodes. A combination of mexiletine with sotalol did not have the same effect. However, this effect was only present at short-term follow-up (3 months). At 12 months no such effect remained. This drug may accordingly represent a short-term option for patients with refractory VT/VF episodes.²⁸

Application of mexiletine in patients with long QT syndrome type 3 demonstrates a pathophysiological rationale for use. In this subtype of long QT syndrome a sodium channel gain-of-function mutation underlies QT prolongation and mexiletine shortens the QT interval in this context. It may accordingly reduce ventricular arrhythmias in these patients.³⁰ The class Ic antiarrhythmic drug quinidine has a potential for treatment of arrhythmias in patients with Brugada syndrome.³¹ These substances may be used to prevent ICD shocks in specific patient populations.

Ranolazine

Ranolazine inhibits the late sodium current that is increased in heart failure and leads to arrhythmia occurrence.³² Late sodium current is also a target for AF therapy.³³ However, ranolazine displayed only moderate efficacy in a prospective randomised trial of AF relapse prevention.³⁴ In a multicentre observational series of 12 patients, ranolazine was added to sotalol, amiodarone or amiodarone/mexiletine and effectively reduced the rate of ICD shock recurrence.³⁵ Beyond its observational nature, the trial was limited by the small sample size. Prospective randomised trial data are needed for a valid judgement regarding the use of ranolazine as adjunct therapy to reduce ICD shocks. Currently, this substance cannot be generally recommended for ICD shock reduction.

Potential Influences on Pacing and Defibrillation Thresholds

Patients may die from arrhythmogenic causes despite the use of an ICD.³⁶ Reasons for such ICD-unresponsive SCD may be patient or device related, including refractory electrical storm, asystole, pulseless electrical activity or technical defects of the implanted device and leads or potentially elevated defibrillation thresholds (DFTs).³⁷ While there are several reports on changes of DFT by antiarrhythmic drugs in the literature (mostly historical studies and case reports from the 1980s and 1990s), there are few recent data regarding pacing threshold.

Pacing Threshold

Chronic pacing threshold elevation with contemporary steroid-eluting electrode tips is much less of a problem than it was decades ago. However, chronic elevation of pacing thresholds may still occur with longer time since implantation, increasing age of the patient and disease progression.

Antiarrhythmic drugs may alter the excitability of cardiac tissue. While loss of atrial capture has been reported after the application of flecainide and propafenone,^{38,39} data on ventricular pacing thresholds are highly controversial.^{40,41} Similarly, loss of atrial capture has been reported with amiodarone,⁴² whereas no such effect was seen on ventricular pacing thresholds.⁴³ All of these studies were observational in nature. Loss of capture may develop over time in any implantable device. Whether this is truly related to drug administration in these observational patient series is difficult to judge owing to the lack of a control group.

In summary, there is no evidence that any antiarrhythmic drug will consistently alter pacing thresholds in patients. Rather, a specific cardiac substrate may alter pacing thresholds by itself over time.

Defibrillation Threshold

DFT is defined as the lowest amount of energy required to successfully defibrillate the heart and restore normal sinus rhythm. Optimal determination of DFT theoretically includes construction of a continuous dose–response curve between the energy delivered and the success of the defibrillation shock.⁴⁴

Experimental data and early clinical studies indicate that antiarrhythmic drugs may alter defibrillation energy requirements, usually measured as the DFT.⁴⁵ Routine ICD testing is no longer recommended as randomised trials evaluating DFT testing versus a non-testing strategy were neutral in terms of predicting effectiveness of ICD therapy.⁴⁶ The Shockless Implant Evaluation (SIMPLE) study prospectively included patients with a left-sided ICD implant and a no-testing strategy was non-inferior to a testing strategy with respect to the endpoint of failed appropriate shock or death. Data from the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) trial indicated no difference in survival if DFT was >20 J in comparison with ≤20 J.⁴⁷

In a large retrospective analysis, Shukla et al. evaluated data from 968 patients who were enrolled in two separate clinical studies evaluating biphasic shock generators.⁴⁸ In these uncontrolled studies, 11 % of patients had high DFTs defined as energy requirement ≥18 J. Several indices of advanced structural heart disease, such as NYHA functional class III/IV or low LVEF and the preoperative use of amiodarone, were predictive of higher DFTs.⁴⁸

The prospective randomised OPTIC trial provided an opportunity to obtain properly controlled data regarding effects of amiodarone, sotalol and β -blockers on DFT with contemporary ICDs. In patients exposed to 6–8 weeks of amiodarone therapy, a minor increase in defibrillation energy requirement of ~1.3 J was observed, which was statistically significant when compared with a small decrease in DFT in the two other groups. However, a mean 1 J increase in DFT is unlikely to have any effect on outcomes, particularly in light of the potentially high energy delivery with modern ICD systems. Large increases in DFT with amiodarone were rare. In the sole case with a >10 J increase in DFT, an adequate safety margin of 10 J was maintained because of low DFT at baseline (2.5 J). This increase may be due in part to regression to the mean rather than only an effect of amiodarone. In the study, no significant delay in detection of VF on repeat DFT assessment was reported.⁴⁹ The OPTIC study was the first randomised evaluation to demonstrate that effects of sotalol on DFT are similar to those of conventional β -blockers without class III antiarrhythmic properties.⁴⁹ Accordingly, it appears generally safe to treat ICD patients with amiodarone and not necessary to perform DFT testing after drug application. Another study suggested that while oral therapy with amiodarone increased DFT during acute ischaemia in a closed-chest animal model, dronedarone in the same model had no effect on DFT either under basal state or after acute myocardial ischaemia.⁵⁰

While DFT testing should not routinely be performed (neither at implant nor after administration of amiodarone), special situations – for instance if right-sided implants combined with amiodarone therapy or lead replacements – may still warrant such tests.

Summary and Future Direction

Recent trials of ICD programming have shown a significant reduction of ICD shocks. The management of appropriate shocks is still challenging and may be optimised by assessment and treatment of the underlying ventricular arrhythmias and structural correlate in terms of revascularisation or ablation therapy.

For current clinical practice, *d,l*-sotalol can be considered to reduce ICD shocks (appropriate or inappropriate) in patients without severe renal dysfunction. If sotalol is ineffective, amiodarone has a greater potential to reduce arrhythmia burden and subsequent shock delivery for a larger amount of potential side-effects. One has to keep in mind that both substances may suppress intrinsic sinus rate and accordingly atrial pacing may become necessary. Further clinical trials are needed to assess the long-term benefit of amiodarone to prevent ICD shocks in the context of potential side-effects. Whether other substances, such as ranolazine or dronedarone, will obtain a role in the management of arrhythmias in patients with an ICD is subject to future investigation. Patients with refractory VT/VF episodes despite amiodarone treatment may experience short-term benefit from the addition of mexiletine.

Antiarrhythmic drugs should only be applied after an arrhythmia has occurred (see *Table 1*). This does not necessarily imply that ICD shocks need to have occurred. All prospective trials looking at shock reduction conducted to date included patients who had already experienced ICD shocks. Whether an *a priori* preventive therapy with antiarrhythmic agents might be beneficial remains to be studied. Such an approach could represent an additional option to sustain quality of life in ICD patients. In particular, documented AF in a patient with an ICD should be managed with specific programming and potentially antiarrhythmic drug therapy. ■

1. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPCC). *Eur Heart J* 2015;**36**:2793–867. DOI: 10.1093/eurheartj/ehv316; PMID: 26320108
2. Schron EB, Exner DV, Yao Q, et al. Quality of life in the antiarrhythmics versus implantable defibrillators trial: impact of therapy and influence of adverse symptoms and defibrillator shocks. *Circulation* 2002;**105**:589–94. PMID: 11827924
3. Steinberg JS, Martins J, Sadanandan S, et al. Antiarrhythmic drug use in the implantable defibrillator arm of the Antiarrhythmics Versus Implantable Defibrillators (AVID) Study. *Am Heart J* 2001;**142**:520–9. DOI: 10.1067/mhj.2001.117129; PMID: 11526368
4. Poole JE, Johnson GW, Heikamp AS, et al. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med* 2008;**359**:1009–17. DOI: 10.1056/NEJMoa071098; PMID: 18768944
5. Sood N, Ruwald AH, Solomon S, et al. Association between myocardial substrate, implantable cardioverter defibrillator shocks and mortality in MADIT-CRT. *Eur Heart J* 2014;**35**:106–15. DOI: 10.1093/eurheartj/ehu451; PMID: 24179073
6. Kamphuis HC, de Leeuw JR, Derksen R, et al. Implantable cardioverter defibrillator recipients: quality of life in recipients with and without ICD shock delivery: a prospective study. *Europace* 2003;**5**:381–9. PMID: 14753636
7. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J* 2013;**34**:2281–329. DOI: 10.1093/eurheartj/ehu150; PMID: 23801822
8. van Boven N, Bogaard K, Ruiter J, et al. Functional response to cardiac resynchronization therapy is associated with improved clinical outcome and absence of appropriate shocks. *J Cardiovasc Electrophysiol* 2013;**24**:316–22. DOI: 10.1111/jce.12037; PMID: 23210664
9. Horton RP, Canby RC, Román CA, et al. Determinants of nonthoracotomy biphasic defibrillation. *Pacing Clin Electrophysiol* 1997;**20**:60–4. PMID: 9121972
10. Hohnloser SH, Verrier RL, Lown B, et al. Effect of hypokalemia on susceptibility to ventricular fibrillation in the normal and ischemic canine heart. *Am Heart J* 1986;**112**:32–5. PMID: 3728285
11. Goyal A, Spertus JA, Gosch K, et al. Serum potassium levels and mortality in acute myocardial infarction. *JAMA* 2012;**307**:157–64. DOI: 10.1001/jama.2011.1967; PMID: 22235086
12. Barold SS, Herweg B. The effect of hyperkalaemia on cardiac rhythm devices. *Europace* 2014;**16**:467–76. DOI: 10.1093/europace/eut383; PMID: 24465006
13. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**:709–17. DOI: 10.1056/NEJM199909023411001; PMID: 10471456
14. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004;**351**:543–51. DOI: 10.1056/NEJMoa040135; PMID: 15295047
15. Ferreira-González I, Dos-Subirá L, Guyatt GH, et al. Adjunctive antiarrhythmic drug therapy in patients with implantable cardioverter defibrillators: a systematic review. *Eur Heart J* 2007;**28**:469–77. DOI: 10.1093/eurheartj/ehl478; PMID: 17227788
16. Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia: Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. *N Engl J Med* 1995;**333**:77–82. DOI: 10.1056/NEJM199507133330201; PMID: 7539890
17. Connolly SJ, Dorian P, Roberts RS, et al. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. *JAMA* 2006;**295**:165–71. DOI: 10.1001/jama.295.2.165; PMID: 16403928
18. Pacifico A, Hohnloser SH, Williams JH, et al. Prevention of implantable-defibrillator shocks by treatment with sotalol. d.I-Sotalol Implantable Cardioverter-Defibrillator Study Group. *N Engl J Med* 1999;**340**:1855–62. DOI: 10.1056/NEJM199906173402402; PMID: 10369848
19. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;**31**:2369–429. DOI: 10.1093/eurheartj/ehq278; PMID: 20802247
20. Freemantle N, Lafuente-Lafuente C, Mitchell S, et al. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace* 2011;**13**:329–45. DOI: 10.1093/europace/euq450; PMID: 21227948
21. Lee CH, Nam G, Park H, et al. Effects of antiarrhythmic drugs on inappropriate shocks in patients with implantable cardioverter defibrillators. *Circ J* 2008;**72**:102–5. PMID: 18159108
22. Dorian P, Borggreffe M, Al-Khalidi HR, et al. Placebo-controlled, randomized clinical trial of azimilide for prevention of ventricular tachyarrhythmias in patients with an implantable cardioverter defibrillator. *Circulation* 2004;**110**:3646–54. DOI: 10.1161/01.CIR.0000149240.98971.A8; PMID: 15533855
23. Torp-Pedersen C, Möller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. *N Engl J Med* 1999;**341**:857–65. DOI: 10.1056/NEJM199909163411201; PMID: 10486417
24. Baquero GA, Banchs JE, Depalma S, et al. Dofetilide reduces the frequency of ventricular arrhythmias and implantable cardioverter defibrillator therapies. *J Cardiovasc Electrophysiol* 2012;**23**:296–301. DOI: 10.1111/j.1540-8167.2011.02183.x; PMID: 21955243
25. O'Toole M, O'Neill PG, Kluger J, et al. Efficacy and safety of oral dofetilide in patients with an implanted defibrillator: a multicenter study [Abstract]. *Circulation* 1999;**100**(Suppl 2):S794
26. Køber L, Torp-Pedersen C, McMurray JJV, et al. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008;**358**:2678–87. DOI: 10.1056/NEJMoa0800456; PMID: 18565860
27. Fink A, Duray GZ, Hohnloser SH. A patient with recurrent atrial fibrillation and monomorphic ventricular tachycardia treated successfully with dronedarone. *Europace* 2011;**13**:284–5. DOI: 10.1093/europace/euq365; PMID: 20965881
28. Gao D, van Herendael H, Alshengelti L, et al. Mexiletine as an adjunctive therapy to amiodarone reduces the frequency of ventricular tachyarrhythmia events in patients with an implantable defibrillator. *J Cardiovasc Pharmacol* 2013;**62**:199–204. DOI: 10.1097/FJC.0b013e31829651fe; PMID: 23609328
29. Dorian P, Newman D, Berman N, et al. Sotalol and type IA drugs in combination prevent recurrence of sustained ventricular tachycardia. *J Am Coll Cardiol* 1993;**22**:106–13. PMID: 8509529
30. Shimizu W, Aiba T, Antzelevitch C. Specific therapy based on the genotype and cellular mechanism in inherited cardiac arrhythmias. Long QT syndrome and Brugada syndrome. *Curr Pharm Des* 2005;**11**:1561–72. PMID: 15892662
31. Márquez MF, Bonny A, Hernández-Castillo E, et al. Long-term efficacy of low doses of quinidine on malignant arrhythmias in Brugada syndrome with an implantable cardioverter-defibrillator: a case series and literature review. *Heart Rhythm* 2012;**9**:1995–2000. DOI: 10.1016/j.hrthm.2012.08.027; PMID: 23059185
32. Morita N, Lee JH, Xie Y, et al. Suppression of re-entrant and multifocal ventricular fibrillation by the late sodium current blocker ranolazine. *J Am Coll Cardiol* 2011;**57**:366–75. DOI: 10.1016/j.jacc.2010.07.045; PMID: 21232675
33. Verrier RL, Kumar K, Nieminen T, et al. Mechanisms of ranolazine's dual protection against atrial and ventricular fibrillation. *Europace* 2013;**15**:317–24. DOI: 10.1093/europace/eus380; PMID: 23220484
34. Ferrari GM de, Dusi V, Spazzolini C, et al. Clinical management of catecholaminergic polymorphic ventricular tachycardia: the role of left cardiac sympathetic denervation. *Circulation* 2015;**131**:2185–93. DOI: 10.1161/CIRCULATIONAHA.115.015731; PMID: 26019152
35. Bunch TJ, Mahapatra S, Murdock D, et al. Ranolazine reduces ventricular tachycardia burden and ICD shocks in patients with drug-refractory ICD shocks. *Pacing Clin Electrophysiol* 2011;**34**:1600–6. DOI: 10.1111/j.1540-8159.2011.03208.x; PMID: 21895727
36. Duray GZ, Schmitt J, Richter S, et al. Arrhythmic death in implantable cardioverter defibrillator patients: a long-term study over a 10 year implantation period. *Europace* 2009;**11**:1462–8. DOI: 10.1093/europace/eup246; PMID: 19797255
37. Kroll MW, Tchou PJ. Testing of implantable defibrillator functions at implantation. In: Ellenbogen KA, Kay GN, Wilkoff BL (eds). *Clinical Cardiac Pacing and Defibrillation*. Philadelphia: WB Saunders, 2000:540–61
38. Antonelli D, Freedberg NA, Rosenfeld T, et al. Acute loss of capture due to flecainide acetate. *Pacing Clin Electrophysiol* 2001;**24**:1170. PMID: 11475838
39. Montefoschi N, Boccadamo R. Propafenone induced acute variation of chronic atrial pacing threshold: a case report. *Pacing Clin Electrophysiol* 1990;**13**:480–3. PMID: 1692131
40. Stevens SK, Haffajee CI, Naccarelli GV, et al. Effects of oral propafenone on defibrillation and pacing thresholds in patients receiving implantable cardioverter-defibrillators. Propafenone Defibrillation Threshold Investigators. *J Am Coll Cardiol* 1996;**28**:418–22. PMID: 8800119
41. Numata T, Abe H, Nagatomo T, et al. Effect of a single oral dose of pilsicainide on pacing thresholds in pacemaker patients with and without paroxysmal atrial fibrillation. *Jpn Circ J* 2000;**64**:750–4. PMID: 11059614
42. Grande JM, Grande A, Molina M, et al. Atrial selective effect of amiodarone to increase threshold of excitation. *Pacing Clin Electrophysiol* 2013;**36**:e93–6. DOI: 10.1111/j.1540-8159.2011.03272.x; PMID: 22132864
43. Reddy CP, Kuo CS, Jivrajka V, et al. Effect of amiodarone on electric induction, morphology, and rate of ventricular tachycardia and its relation to clinical efficacy. *Pacing Clin Electrophysiol* 1984;**7**:1055–62. PMID: 6209624
44. Dopp AL, Miller JM, Tisdale JE. Effect of drugs on defibrillation capacity. *Drugs* 2008;**68**:607–30. PMID: 18370441
45. Frame LH. The effect of chronic oral and acute intravenous amiodarone administration on ventricular defibrillation threshold using implanted electrodes in dogs. *Pacing Clin Electrophysiol* 1989;**12**:339–46. PMID: 2468144
46. Healey JS, Hohnloser SH, Glikson M, et al. Cardioverter defibrillator implantation without induction of ventricular fibrillation: a single-blind, non-inferiority, randomised controlled trial (SIMPLE). *Lancet* 2015;**385**:785–91. DOI: 10.1016/S0140-6736(14)61903-6; PMID: 25715991
47. Aktas MK, Huang DT, Daubert JP, et al. Effect of defibrillation threshold testing on heart failure hospitalization or death in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Heart Rhythm* 2013;**10**:193–9. DOI: 10.1016/j.hrthm.2012.10.024; PMID: 23085128
48. Shukla HH, Flaker GC, Jayam V, Roberts D. High defibrillation thresholds in transvenous biphasic implantable defibrillators: clinical predictors and prognostic implications. *Pacing Clin Electrophysiol* 2003;**26**:44–8. PMID: 12685138
49. Hohnloser SH, Dorian P, Roberts R, et al. Effect of amiodarone and sotalol on ventricular defibrillation threshold: the optimal pharmacological therapy in cardioverter defibrillator patients (OPTIC) trial. *Circulation* 2006;**114**:104–9. DOI: 10.1161/CIRCULATIONAHA.106.618421; PMID: 16818810
50. Chevalier P, Timour Q, Morel E, Bui-Xuan B. Chronic oral amiodarone but not dronedarone therapy increases ventricular defibrillation threshold during acute myocardial ischemia in a closed-chest animal model. *J Cardiovasc Pharmacol* 2012;**59**:523–8. DOI: 10.1097/FJC.0b013e31824d89fe; PMID: 22330675