Improvements in implantable cardioverter defibrillator patient stratification

Welsenes, G.H. van

Chapter 3

Primary prevention ICD recipients: the need for defibrillator back-up after an event-free first battery service-life

Guido H. van Welsenes, MS, Johannes B. van Rees, MD, Joep Thijssen, MD, Serge A. Trines, MD, PhD, Lieselot van Erven, MD, PhD, Martin J. Schalij, MD, PhD, C. Jan Willem Borleffs, MD, PhD

From the Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

J Cardiov Electrophysiol 2011; in press

Abstract

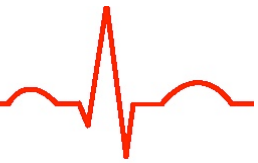
Background: In primary prevention implantable cardioverter defibrillator (ICD) patients, the relatively low incidence of ventricular arrhythmias (VA), combined with the limited battery service-life potentially results in a large group of patients who have had no benefit of the ICD during first service-life. Data on the occurrence of VA after device replacement remain scarce.

Objective: The purpose of this study was to give clinicians better insight in the dilemma whether or not to replace an ICD after an event-free first battery service-life.

Methods: All patients treated with an ICD for primary prevention who had a replacement because of battery depletion and who did not receive appropriate therapy before device replacement were included in the current analysis.

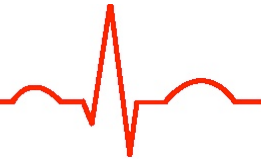
Results: Out of 154 primary prevention ICD patient needing replacement because of battery depletion, 114 (74%) patients (mean age 61 ± 11 years, 80% male) had not received appropriate ICD therapy for VA. Follow-up was 71 ± 24 months after the initial implantation and 25 ± 21 months after device replacement. Following replacement, three year cumulative incidence of appropriate therapy in response to ventricular tachycardia or ventricular fibrillation was 14% (95% CI 5-22%).

Conclusion: The majority of primary prevention ICD patients do not experience VA during first battery service-life. However, a substantial part of these patients does experience appropriate ICD therapy after replacement.



Introduction

Sudden cardiac death mainly caused by ventricular arrhythmias (VA) is a major cause of mortality in the western world.[1-4] Initially, patients were treated with implantable cardioverter defibrillator (ICD) therapy after survival of a life threatening VA (secondary prevention), but because of the low survival rate after experiencing a VA, focus shifted to the identification of patients at high risk for developing an arrhythmic event (primary prevention). Large randomized trials demonstrated a reduction in all-cause mortality in patients treated with ICD therapy, initially in patients treated for secondary prevention,[5-7] but later also in patients who are at risk for arrhythmic death, the primary prevention.[8-11] Findings of these trials led to the inclusion of primary prevention ICD treatment in the current guidelines. Not only did the implementation of these results change the ICD-treated population from VA survivors to patients, characterized by a low LVEF and symptomatic or asymptomatic heart failure, it also increased the number of implantations dramatically.[12] Hauser demonstrated that current ICD service-life is approximately 4.7 years for single-chamber devices and 4.0 years for dual-chamber devices and therefore, a large number of (mainly primary prevention) ICD replacements can be expected.[13] Although these primary prevention patients are at high risk for developing an arrhythmia, data from randomized studies showed that only 35% receives appropriate therapy for ventricular tachycardia (VT) or ventricular fibrillation (VF).[14] Data from observational clinical studies even showed a lower number of patients receiving appropriate therapy.[15] Therefore, a significant number of patients treated for primary prevention who are eligible for ICD replacement, have not developed a VA during the first ICD service-life, posing a dilemma whether or not the patient will receive potentially life saving ICD therapy after this replacement. In other words: do patients not experiencing a VA during the first ICD service life need a replacement?



Since 1996, all primary prevention ICD recipients in the Leiden University Medical Center have been assessed and followed-up. This large cohort offers possibilities for the evaluation of patient follow-up after a long event-free period.

Methods

Patient population

Since 1996, all patients who received an ICD in Leiden University Medical Center were registered in the departmental Cardiology Information System. Characteristics at baseline and data of all follow-up visits were recorded. Eligibility for ICD implantation was based on the international guidelines which, due to evolving guidelines, might have changed over time.[4, 12] For the current study, all ICD treated patients up to august 2008 with a primary indication for implantation, who had a replacement because of battery depletion and who did not receive appropriate therapy before device replacement were included. Prevention was considered primary in case of poor LVEF without prior sustained VA.[8, 9, 11, 12] Patients with a congenital structural or monogenetic heart disease (associated with increased risk of ventricular arrhythmias) were excluded.

Device implantation and programming

All implantations were carried out in the catheterization laboratory and all devices were implanted transvenously and without thoracotomy. During implantation, sensing and pacing thresholds were tested and defibrillation threshold testing was performed. Implanted devices included single-chamber, dual-chamber and cardiac resynchronization therapy-defibrillator (CRT-D) devices and were manufactured by Biotronik (Berlin, Germany), Medtronic (Minneapolis, MN, United States), Boston Scientific (Natick, MA, United States, formerly CPI,

Guidant [St. Paul, MN, United States]) and St. Jude Medical/Ventritex (St. Paul, MN, United States).

All devices were programmed with three consecutive zones: a monitor zone (150-188 bpm), an antitachycardia pacing (ATP) shock zone (188-210 bpm) and an initial shock zone (≥210 bpm). In the monitor zone, no therapy was programmed unless VA was detected during follow-up. In the ATP-shock zone, arrhythmias were initially attempted to be terminated by two bursts of ATP and, if arrhythmia continued, defibrillator shocks were used. In case of VA faster than 210 bpm, device shocks were the initial therapy. Furthermore, atrial arrhythmia detection was set to >170 bpm with supraventricular tachycardia discriminators enabled. In replaced devices, therapy settings were adopted from the initially implanted devices.

Follow-up and device interrogation

ICD treated patients were periodically followed-up every 3-6 months, which included device interrogation. Printouts were checked for appropriate and inappropriate therapy (ATP and shocks). Unscheduled device interrogations were performed in case of symptomatic episodes of arrhythmia and during unplanned hospitalization. Last follow-up data were acquired in August 2008.

Since periodical follow-up is performed every 3-6 months, patients with more than six months of missing data were considered lost to follow-up.

Statistical analysis

Continuous data are expressed as mean ± standard deviation; categorical data are presented as numbers and percentages. Baseline characteristics for patients who received appropriate therapy versus those who did not were compared with the independent-sample t-test for continuous variables and Chi-square test for categorical variables. For all tests a p-value <0.05 was

considered significant. VT or VF, triggering appropriate ICD therapy was considered the primary endpoint. Cumulative incidences were analyzed by method of Kaplan-Meier. Mortality was considered a censoring event.

Results

Baseline characteristics

A total of 2437 patients were treated with an ICD during the study period. Of these, 184 (8%) were diagnosed with a congenital structural or monogenetic cardiac disease and therefore excluded from the study. Of the remaining 2253 patients, 1367 (61%) patients had a primary indication for ICD implantation of whom 154 (11%) had a replacement because of battery depletion. Of these patients, 114 (74%) did not receive appropriate therapy before device replacement and were therefore considered the study population. Mean follow-up was 71 ± 24 months after the initial implantation and 25 ± 21 months after device replacement. At baseline, the majority of patients (mean age 61 ± 11 years, 80% male) had a depressed LVEF (26 ± 9%, range 7-39%), wide QRS complex (136 ± 36 ms) and poor renal function (renal clearance 76 ± 31 ml/min). Sixty-seven (59%) patients had ischemic heart disease, 28 (25%) patients had a history of atrial fibrillation and the majority of patients were in New York Heart Association functional class 3 (n=60, 53%). Medication included beta blockers in 54%, ACE inhibitors in 80% and diuretics for heart failure in 71%. Baseline characteristics are summarized in Table 1.

Table 1. Baseline characteristics.

	All patients (n=114)
Clinical parameters	
Male gender	91 (80%)
Age (yrs)	61 ± 11
Ischemic heart disease	67 (59%)
NYHA functional class	
I	24 (21%)
II	27 (24%)
III	60 (52%)
IV	3 (3%)
QRS-duration (ms)	136 ± 36
Renal clearance (ml/min)*	76 ± 31
LVEF (%)	26 ± 9
Range (%)	7-39
History of atrial fibrillation	28 (25%)
Medication	
Diuretics	81 (71%)
ACE inhibitors	91 (80%)
Beta blocker	62 (54%)

** Renal clearance was determined with the formula of Cockcroft-Gault. ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.*

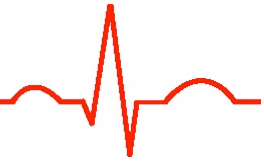
Device replacement

By definition, all patients in the study population had a device replacement because of battery depletion. Over-all device longevity was 47 ± 12 months and differences were observed between different types of ICDs. The longevity was 54 ± 10 months for single-chamber devices, 55 ± 15 months for dual-chamber devices and 42 ± 8 months for CRT-D devices (Table 2).

Table 2. Device longevity per type of ICD.

	All (n=115)	Single-chamber ICD (n=17)	Dual-chamber ICD (n=30)	CRT-D (n=67)
Longevity (months)	47 ± 12	54 ± 10	55 ± 15	42 ± 8

ICD = implantable cardioverter defibrillator; CRT-D = cardiac resynchronization therapy – defibrillator



Occurrence of ventricular arrhythmia

In the study population, 14 (12%) patients received appropriate therapy in response to VT or VF, on average 65 ± 21 months after the first implantation and 20 ± 15 months after device replacement. The cumulative event rate for appropriate therapy *after replacement* was 7% (95% CI 2-13%) at one year, 9% (95% CI 5-15%) at 2 years and 14% (95% CI 5-22%) at 3 years (Figure 1). In Table 3, baseline clinical characteristics between patients who received appropriate therapy versus patients who did not receive appropriate therapy are demonstrated. As can be seen, the only significant difference was observed in the number of patients who used beta blockers: 29% of patients who received appropriate therapy used beta blockers versus 58% of patients who did not receive appropriate therapy ($p<0.05$) (Table 3).

Table 3. Baseline characteristics for patients who received ICD therapy after replacement versus patients who did not receive ICD therapy after replacement.

	Patients who received therapy (n=14)	Patients who did not receive therapy (n=100)	p-value
Clinical parameters			
Male gender	11 (79%)	80 (80%)	0.569
Age (yrs)	60 ± 11	62 ± 11	0.798
Ischemic heart disease	11 (79%)	56 (56%)	0.108
NYHA functional class			0.467
I	4 (29%)	20 (20%)	
II	4 (29%)	23 (23%)	
III	5 (36%)	55 (55%)	
IV	1 (6%)	2 (2%)	
QRS-duration (ms)	125 ± 29	139 ± 35	0.263
Renal clearance (ml/min)*	83 ± 31	77 ± 30	0.678
LVEF (%)	23 ± 10	27 ± 9	0.211
Range (%)	7-39	10-39	
History of atrial fibrillation	5 (36%)	23 (23%)	0.301
Medication			
Diuretics	10 (71%)	71 (71%)	0.974
ACE inhibitors	10 (71%)	81 (81%)	0.403
Beta blocker	4 (29%)	58 (58%)	0.038

** Renal clearance was determined with the formula of Cockcroft-Gault. ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.*

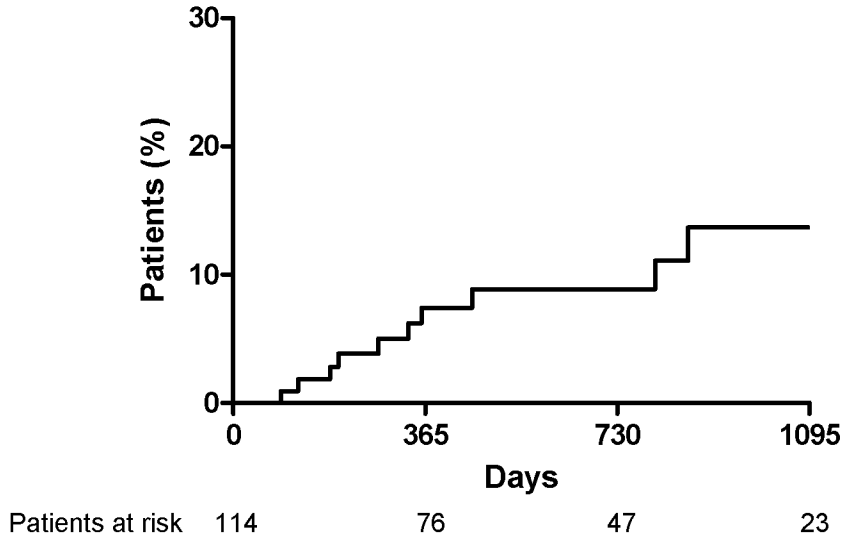


Figure 1: Appropriate therapy after a long event-free period. Kaplan-Meier curve for cumulative incidence of appropriate ICD therapy after device replacement.

Discussion

The main findings of the current study on the occurrence of ventricular arrhythmia after an event-free first ICD service-life can be summarized as follows: 1) 74% of patients did not receive appropriate therapy, prior to the first battery depletion; 2) Following device replacement after a therapy-free first ICD service-life, 14% of the patients received appropriate ICD therapy after 3 years of follow-up.

The current study is of additive value to current literature since it is the first to assess the need for ICD back-up after an event-free first battery service-life. These data could give clinicians better insight in the dilemma whether or not to replace an ICD.

The inclusion of primary prevention ICD treatment in the current guidelines increased the number of implantations dramatically. Because of reported device longevities of 4 - 4.7 years and an increased number of implantations,[13] a large number of ICD replacements because of battery

depletion can be expected.[16] Since primary prevention ICD recipients show a relatively low occurrence of appropriate therapy, battery depletion will occur prior to the need for ICD back-up in a large number of patients.[14, 17] This hypothesis is supported by the findings in the current study that in 74% of cases of battery depletion, the ICD has not been required to give its potentially life-saving therapy. Since the patients have not needed ICD back-up during this first battery life, clinicians involved in the follow-up of ICD patients will be posed with questions about the usefulness of device replacement.

The present study is the first to assess the occurrence of VA, requiring ICD back-up after an event-free first battery-life, making direct comparison to previous studies difficult. However, other studies have assessed the occurrence of first appropriate device therapy after long term follow-up and demonstrate a substantial rate of first VA, long after implantation. Alsheikh-Ali and co-workers have evaluated the occurrence and time-dependence of first appropriate therapy, standardized by patient-years in primary prevention ICD patients. The results demonstrated an increased rate of first appropriate therapy in the first two years following implantation. Annual rates of first appropriate therapy were similar in year three, four, five, six and seven after implantation. These results support the current findings that first VA can occur long after the initial implantation and thereby after ICD replacement because of battery depletion.[18] In the Leiden out-of-hospital cardiac arrest study, 456 secondary prevention ICD patients with ischemic heart disease were followed for a mean of 54 months. During this follow-up, Borleffs et al. described a 9% increase in first appropriate ICD therapy from the fifth to the eighth year following implantation. Additionally, the authors state that during this long period of follow-up, 12% of patients experiencing a life threatening VA had their first occurrence more than five years after implantation.[19] Finally, in a study by Tandri and co-workers, incidences of appropriate therapy after 5 event-free years were assessed in primary and secondary prevention ICD

recipients. In the total study population, probability of appropriate therapy was 8% over the following year, 20% over the next five years, and 24% over the next 10 years.[20]

Although the higher incidence of appropriate therapy in secondary prevention ICD patients might make comparison to findings in the currently studied (primary prevention) population difficult,[17] results from previous studies are consistent in the finding of a steady rate of first VA, even after a long event-free period. These findings, combined with the results of the present study indicate that, although the majority of patients do not receive appropriate therapy during first battery service-life, a substantial number of these patients will still receive potentially life-saving appropriate therapy after replacement, warranting device replacement.

Study limitations

Since patients were collected over a period of time, expanding guidelines for the implantation of defibrillators, treatment of acute myocardial infarction, and pharmacological antiarrhythmic therapy could have created a heterogeneous population. Furthermore, a significant group of patients who received an ICD for primary prevention at the Leiden University Medical Center could not be included in the current study, since their ICDs had not reach end of service life at the time of the study.

Conclusion

The current study demonstrates that the majority of primary prevention ICD patients do not experience VA during first battery service-life. However, a substantial number of these patients do experience appropriate ICD therapy after replacement justifying device replacement even if no VA occurred during the first ICD service life.

Reference List

1. Podrid PJ, Myerburg RJ.: Epidemiology and stratification of risk for sudden cardiac death. Clin Cardiol 2005; 28:I3-11.
2. de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI et al.: Out-of-hospital cardiac arrest in the 1990's: a population-based study in the Maastricht area on incidence, characteristics and survival. J Am Coll Cardiol 1997; 30:1500-5.
3. Zipes DP, Wellens HJ.: Sudden cardiac death. Circulation 1998; 98:2334-51.
4. Zipes DP, Camm AJ, Borggrefe M et al.: ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Europace 2006; 8:746-837.
5. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators.: N Engl J Med 1997; 337:1576-83.
6. Connolly SJ, Gent M, Roberts RS et al.: Canadian implantable defibrillator study (CIDS) : a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 2000; 101:1297-302.
7. Kuck KH, Cappato R, Siebels J et al.: Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest : the Cardiac Arrest Study Hamburg (CASH). Circulation 2000; 102:748-54.
8. Bardy GH, Lee KL, Mark DB et al.: Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005; 352:225-37.
9. Buxton AE, Lee KL, Fisher JD et al.: A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 1999; 341:1882-90.
10. Moss AJ, Hall WJ, Cannom DS et al.: Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996; 335:1933-40.
11. Moss AJ, Zareba W, Hall WJ et al.: Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002; 346:877-83.
12. Epstein AE, Dimarco JP, Ellenbogen KA et al.: ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol 2008; 51:e1-62.
13. Hauser RG.: The growing mismatch between patient longevity and the service life of implantable cardioverter-defibrillators. J Am Coll Cardiol 2005; 45:2022-5.
14. Moss AJ, Greenberg H, Case RB et al.: Long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator. Circulation 2004; 110:3760-5.

15. Borleffs CJ, van Rees JB, van Welsenes GH et al.: Prognostic importance of atrial fibrillation in implantable cardioverter-defibrillator patients. J Am Coll Cardiol 2010; 55:879-85.
16. Borleffs CJ, Wilde AA, Cramer MJ et al.: Clinical implementation of guidelines for cardioverter defibrillator implantation: lost in translation? Neth Heart J 2007; 15:129-32.
17. Germano JJ, Reynolds M, Essebag V et al.: Frequency and causes of implantable cardioverter-defibrillator therapies: is device therapy proarrhythmic? Am J Cardiol 2006; 97:1255-61.
18. Sheikh-Ali AA, Homer M, Maddukuri PV et al.: Time-dependence of appropriate implantable defibrillator therapy in patients with ischemic cardiomyopathy. J Cardiovasc Electrophysiol 2008; 19:784-9.
19. Borleffs CJ, van Erven L, Schotman M et al.: Recurrence of ventricular arrhythmias in ischaemic secondary prevention implantable cardioverter defibrillator recipients: long-term follow-up of the Leiden out-of-hospital cardiac arrest study (LOHCAT). Eur Heart J 2009; 30:1621-6.
20. Tandri H, Griffith LS, Tang T et al.: Clinical course and long-term follow-up of patients receiving implantable cardioverter-defibrillators. Heart Rhythm 2006; 3:762-8