Clinical Aspects and Socio-economic Implications of Implantable Cardioverter Defibrillator Treatment

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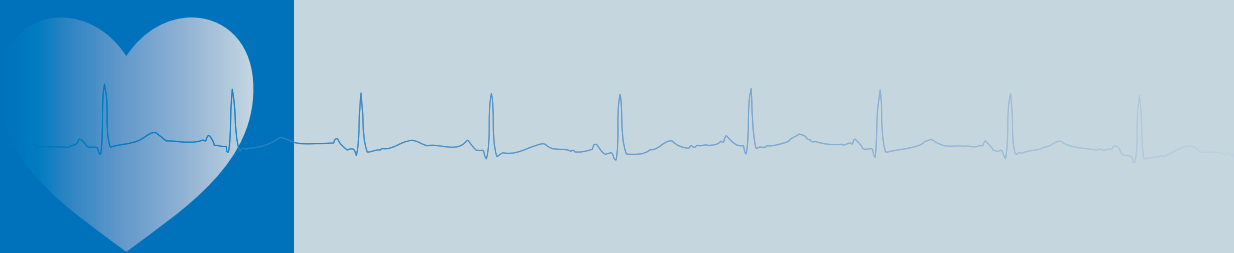
Based on:
Improvements in 25 Years of Implantable Cardioverter Defibrillator Therapy



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INTRODUCTION

Sudden cardiac death

Sudden cardiac death (SCD) is defined as an unexpected circulatory arrest, mostly due to a cardiac arrhythmia, resulting into death.[1-3] Especially patients with coronary heart disease are at risk for SCD, whereof approximately 50% dies unexpectedly shortly after symptoms. Previous studies demonstrated that the incidence of SCD is strongly correlated with the prevalence of coronary heart disease.[4, 5] Consequently, the high number of patients with coronary heart disease in the United States of America, results in massive numbers of patients who die of SCD each year, with estimates ranging from 300 000 to 350 000.[4, 6-9] As numbers are comparable in Europe, more then 700 000 patients die yearly of SCD in the Western world.[5] Of concern is that the majority of patient who died following sudden cardiac arrest, were unidentified to be affected by ischemic heart disease.[2, 3, 8, 10] Although prodromal symptoms are often non-specific, they include chest pain (ischemia), palpitations (tachyarrhythmia), or dyspnea (congestive heart failure) and if present can be related to SCD. Major risk factors, increasing the risk of SCD include (risk factors for) coronary heart disease, prior coronary events, prior ventricular arrhythmia, poor left ventricular systolic function and symptoms of advanced heart failure.[2] Unfortunately, an inverse relationship exists between the risk and total number of SCD in sub-groups of patients at increased risk (Figure 1).[10]

It is reported that 75-80% of SCD cases originate from ventricular fibrillation (VF) whereas in the remaining a bradyarrhythmia, including asystole and complete atrioventricular block is recorded.[11] However, one should note that both causes of sudden death can intertwine: in other words, although the initial rhythm disorder can be VF, after some time VF extinguishes and asystole becomes the presenting rhythm when a first ECG is documented. Conversely,

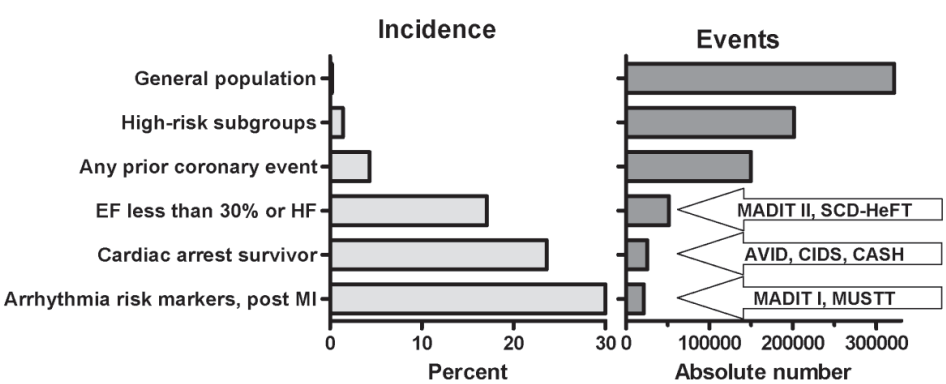

Figure 1. Absolute numbers of events rates of sudden cardiac death in the general population and in specific subpopulations over 1 year. Clinical trials that included specific subpopulations of patients are shown in the right side of the Figure.
AVID = Antiarrhythmics Versus Implantable Defibrillator; CASH = Cardiac Arrest Study Hamburg; CIDS = Canadian Implantable Defibrillator Study; EF = ejection fraction; HF = heart failure; MADIT = Multicenter Automatic Implantation Trial; MI = myocardial infarction; MUSTT = Multicenter UnSustained Tachycardia Trial; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.

bradycardia or atrioventricular conduction delay can trigger VF, which makes a correct estimation of incidences difficult.[6] Further research on the initial rhythm, causing SCD, conducted in 157 patients experiencing SCD during ambulatory Holter monitoring demonstrated VF in 62.4% of patients, a bradyarrhythmia in 16.5% of patients, an episode of *torsades de pointes* in 12.7% of patients, and a ventricular tachycardia (VT) in 8.3% of patients.[12]

Implantable cardioverter defibrillators

Since 40% of all cases of SCD are not witnessed, immediate and adequate treatment is difficult, resulting in high mortality rates.[13] However, if witnessed, cardiac defibrillation can be life-saving. This experience dates back to 1947 when Dr. Claude Beck was correcting a pectus excavatum in a 14-year old boy. When during surgery VF occurred, Dr Beck initiated direct cardiac massage through the opened chest and, after more than a half hour of cardiac massage, used an animal cardiac defibrillator which he had developed while working in an animal laboratory many years earlier. The electrical defibrillation was successful and the rhythm restored to sinus rhythm.[14]

Although this success immediately led to the general acceptance of electrical defibrillation for life-threatening arrhythmias, the development of an implantable cardioverter defibrillator (ICD) took some time. It was Dr. Michel Mirowski, whose friend died due to several bouts of a ventricular tachycardia in 1967, influencing him to pursue the implantable defibrillator. In 1980, he and his team implanted the first implantable cardioverter defibrillator (ICD) in patients and successfully defibrillated VF.[15]

Secondary prevention

The invention of the ICD raised the question if patients would benefit from ICD therapy and how to properly select them. Based on epidemiological studies, patients with life-threatening ventricular arrhythmias were found to have a two-year recurrence rate of 30-50%.[16, 17] Accordingly, this population was the first in which the effect of ICD treatment was evaluated and eligibility for ICD treatment was based on the survival of at least one-life-threatening ventricular arrhythmia such as VF or sustained VT (secondary prevention).[15, 18-24] Wever et al. ,working in Utrecht the Netherlands, performed the first study in which fifty patients who survived a cardiac arrest were randomized to be treated with antiarrhythmic drugs or an ICD.[24] After a median follow-up of 24 months, it was demonstrated that the ICD treated group had lower rates of major outcome events such as death, recurrent cardiac arrest or cardiac transplantation, underwent fewer invasive procedures, and were hospitalized less frequently.[24] Thereafter, the effectiveness of ICD therapy was further assessed in three larger trials: the Antiarrhytmics Versus Implantable Defibrillator (AVID), the Canadian Implantable Defibrillator Study (CIDS), and the Cardiac Arrest Study Hamburg (CASH).[18-20] Patients included in these trials survived an episode of cardiac arrest or had a documented episode of sustained VT and were randomized to optimal pharmacological antiarrhythmic therapy or ICD treatment (Table 1). Although only AVID demonstrated a significant reduction in mortality, a meta-analysis of these three trials, demonstrated a significant 28% reduction in all-cause mortality in favor of ICD treatment and, with these results, the survival benefit of the ICD was proven and ICD therapy for secondary prevention was generally accepted.[25]

Table 1. Major secondary prevention implantable cardioverter defibrillator (ICD) Trials.

	AVID[18]	CIDS[19]	CASH[20]
Sample size	1016	659	288
Design	ICD vs. antiarrhythmic drugs	ICD vs. amiodarone	ICD vs. amiodarone vs. metoprolol
Patients	Resuscitated VF or postcardioversion from sustained VT	Resuscitated VF or VT with unmonitored syncope	Survivors of cardiac arrest secondary to documented ventricular arrhythmias
Follow-up, months	18	36	57
Risk reduction with ICD	28% (p = 0.02)	20% (p = 0.14)	23% (p = 0.08)

ICD = implantable cardioverter defibrillator; VF = ventricular fibrillation; VT = ventricular tachycardia.

Primary prevention

Although secondary prevention ICD therapy was proven to be beneficial, the most important limitation is that only 6% of patients survive an episode of cardiac arrest and therewith becomes eligible for ICD therapy.[13] Accordingly, focus shifted to the identification of patients at high risk for life-threatening ventricular arrhythmias (primary prevention). Previous trials demonstrated that a left ventricular ejection fraction (LVEF) below 40% and frequent (runs of) premature ventricular beats were risk factors for SCD.[26, 27]

Accordingly, patients included in the first small primary prevention trials were selected based on a reduced LVEF due to prior myocardial infarction and the presence of non sustained VT on 24-hour Holter monitoring in patients or inducible non-suppressible (by pharmacological treatment) sustained VT/VF on electrophysiological study.[28, 29] Later on, multiple large randomized control trials were performed to assess if primary prevention ICD therapy was beneficial in selected populations (Table 2).[30-37] [30-32, 34-37] One of these was the Multicenter Automatic Defibrillator Implantation Trial (MADIT) which enrolled patients with a prior myocardial infarction, LVEF less than 35%, documented non sustained VT, and inducible/non-suppressible VT/VF during electrophysiological study.[35] Subsequently, patients were randomized to either ICD treatment or optimal medical therapy. During a follow-up of 27 months and with the inclusion of only 196 patients, the study demonstrated a 54% mortality reduction in the ICD group. Important limitations of this trial were the relatively small cohort of patients and the significantly higher use of beta blockers in the ICD treatment group when compared with the optimal medical therapy group. Additional subgroup analysis of survival benefit demonstrated that the highest benefit was reached in patients with a LVEF less than 26%.[38]

Accordingly, this observation led to a simplified design, the MADIT II trial, randomizing patients post infarction with a LVEF less than 30% to either an ICD or no ICD without additional electrophysiological testing. The study required premature closure since the efficacy boundary had been reached. During an average follow-up of 20 months, a mortality reduction of 28% was observed in patients treated with an ICD.[36]

With publication of the results of the MADIT trials, it became clear that patients with a poor left ventricular systolic function are at risk for sudden cardiac death due to a

Table 2. Major primary prevention implantable cardioverter defibrillator (ICD) trials.

	MADIT[35]	MUSTT[32]	MADIT II[36]
Sample size	196	704	1232
Design	ICD vs AAD	EPS-guided: ICD vs AAD vs no AAD	ICD vs AAD
Patients	Prior MI, EF ≤0.35, nsVT, EPS+	Prior MI, EF ≤0.40, EPS+	Prior MI, EF ≤0.30
Follow-up, months	27	39	20
Risk reduction with ICD vs AAD	54% (p = 0.01)	58% (p < 0.001)	31% (p = 0.02)

AAD = antiarrhythmic drugs; CRT-D = cardiac resynchronization therapy-defibrillator; EF = ejection fraction; EPS = electrophysiological study; HR = heart rate; ICD = implantable cardioverter defibrillator; I = ischemic; MI = myocardial infarction; NICM = non-ischemic cardiomyopathy; nsVT = non sustained ventricular tachycardia.

ventricular arrhythmia, which risk is high enough to warrant ICD treatment. And with this proven reduction in mortality, additional trials were designed in populations at high risk for life-threatening ventricular arrhythmias. Earlier studies and daily clinical practice had shown that patients are at very high risk for hemodynamically compromising ventricular arrhythmias in the period following acute myocardial infarction.[10, 28, 39-41] Therefore, Hohnloser and coworkers started the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), including patients with a reduced left ventricular ejection fraction 6 to 40 days after acute myocardial infarction and randomizing between ICD treatment and optimal medical therapy alone.[33] During a mean follow-up period of 30 months, no over-all mortality difference was observed between the two treatment groups. Further classification by cause of death showed that ICD treated patients were 58% less likely to experience arrhythmic death but had a 75% higher risk for non-arrhythmic death. These results imply that ICD treatment following recent myocardial infarction does not improve patient outcome, but merely changes the mode of death in this vulnerable population. More recently, a similar trial (Immediate Risk Stratification Improves Survival (IRIS)) was conducted randomizing 898 patients 5 to 31 days after myocardial infarction.[37] Additional inclusion criteria were a left ventricular ejection fraction ≤40% and a heart rate of 90 or more beats per minute or nonsustained ventricular tachycardia. During a mean follow-up of 37 months, overall mortality was not reduced in the ICD treated group. However, risk of sudden cardiac death was 45% lower in the ICD group, but the risk of nonsudden cardiac death was 92% higher. These results confirmed the conclusions stated by DINAMIT that following recent myocardial infarction, patients do not benefit from ICD treatment.

Based on all previously described primary prevention trials, Nanthakumar and co-workers conducted a meta-analysis, which demonstrated a 25% mortality reduction in favor of ICD patients and, consequently, these findings led to the inclusion of primary prevention ICD treatment in the current guidelines.[42, 43]

COMPANION[31]	DEFINITE[34]	SCD-HeFT[30]	DINAMIT[33]	IRIS[37]
1520	458	2521	674	898
CRT-D vs CRT vs AAD	ICD vs AAD	ICD vs AAD vs AAD + amiodarone	ICD vs AAD	ICD vs AAD
I & NICM, EF ≤0.35, QRS >120ms	NICM, EF ≤0.35	I & NICM, EF ≤0.35	Prior MI, EF ≤0.35, HR ≥80	Prior MI, EF ≤0.40, HR ≥90
14	29	46	30	37
40% (p < 0.001)	35% (p = 0.08)	23% (p = 0.007)	-8% (p = 0.66)	-4% (p = 0.78)

Cardiac resynchronization therapy

Following the inclusion of primary prevention in the guidelines, a shift occurred in the population receiving an ICD device. Firstly, in 1996 only patients with a survived cardiac arrest received an ICD (secondary prevention), however in 2008 already 80% of ICD recipients had a primary prevention indication.[44] As a result, an increasing part of ICD recipients suffered from a more advanced stage of heart disease with a reduced LVEF.[45] Importantly, left ventricular failure is associated with conduction disturbances causing mechanical dyssynchrony which further contributes to a reduction in the LVEF.

Consequently, cardiac resynchronization therapy (CRT) devices were designed to improve LV performance by restoring the atrio-ventricular, interventricular en intraventricular synchronicity and therewith increase LV filling time, reduce MR, and correct septal dyskinesis.[46] In numerous randomized and multicenter trials, CRT has shown to improve the systolic LV function and clinical prognosis of patients with end-stage, drug refractory heart failure (Table 3).[31, 47-61] For instance, in the CARE-HF trial, patients with severe NYHA functional class ≥III heart failure due to a reduced LVEF (≤35%) and cardiac dyssynchrony (QRS ≥120msec) were randomly assigned to receive medical therapy alone or in combination with CRT.[53] During follow up, CRT demonstrated to be beneficial with a hazard ratio of 0.63 (95% CI 0.51 – 0.77) for the primary endpoint (a composite of death from any cause or an unplanned hospitalization for a major cardiovascular event) in patients treated with CRT as compared with patients treated with medical therapy only. Almost simultaneously, the COMPANION trial reported results of advanced heart failure patients (NYHA III or IV) with a depressed LVEF (≤35%) and a wide QRS complex (≥120ms) who were randomly assigned to receive optimal medical therapy alone or in combination with CRT with either a pacemaker or a pacemaker defibrillator (CRT-D).[31]Again, the risk of the combined endpoint of death from or hospitalization for heart failure was significantly reduced by 34% and 40% in the CRT and CRT-D respectively if compared with the conventionally treated group. In addition, CRT-D therapy also significantly reduced mortality with 36% when compared with the pharmacologic-therapy group.

Table 3. Overview of inclusion criteria and main findings of randomized clinical trials evaluating cardiac resynchronization therapy in heart failure patients.

	Sample size	NYHA class	LVEF (%)	QRS (ms)	ICD	Main findings
MUSTIC-SR[52]	58	III	≤35	≥150	No	· Reduction in hospitalization · Improvement in 6 MWT, NYHA class, QoL, and Peak VO_2 · Reduction in LV volumes and MR
MIRACLE[47]	453	III, IV	≤35	≥130	No	· Improvement in 6 MWT, NYHA class, and QoL · Reduction in LVEDD, MR, increase in LVEF
PATH-CHF[49]	41	III, IV	≤35	≥120	No	· Reduction in hospitalization · Improvement in 6 MWT, NYHA class, and QoL
MUSTIC-AF[57]	59	III	≤35	≥200	No	· Reduction in hospitalization · Improvement in 6 MWT, NYHA class, QoL, and Peak VO_2
MIRACLE-ICD[61]	369	III, IV	≤35	≥130	Yes	· Improvement in NYHA class, QoL, and Peak VO_2
CONTAK-CD[56]	490	II-IV	≤35	≥120	Yes	· Improvement in 6 MWT, NYHA class, and QoL · Reduction in LV volume, increase in LVEF
PATH-CHF II[50]	86	III, IV	≤35	≥120	Yes/No	· Improvement in 6 MWT, QoL, and Peak VO_2
COMPANION[31]	1520	III, IV	≤35	≥120	Yes/No	· Reduction in all-cause mortality or hospitalization
MIRACLE-ICD II[48]	186	II	≤35	≥130	Yes	· Improvement in NYHA class · Reduction in LV volumes, increase in LVEF
CARE-HF[53, 54]	813	III, IV	≤35	≥120	No	· Reduction in all-cause mortality or hospitalization · Improvement in NYHA class, QoL
RETHINQ[51]	172	III	≤35	<130	Yes	· Improvement in NYHA class
REVERSE[55, 58]	610	I, II	≤40	≥120	Yes/No	· Reduction in hospitalization · Reduction in LVESV
MADIT-CRT[59]	1820	I, II	≤30	≥130	Yes	· Reduction in all-cause mortality or heart failure event · Reduction in LVESV
RAFT[60]	1798	II, III	≤30	≥130	Yes	· Reduction in all-cause mortality or heart failure hospitalization

6 MWT = 6 minutes walk test; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVESV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; QoL = quality of life

Accordingly, these findings resulted in the American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines to consider CRT a class I indication in patients with end-stage heart failure (NYHA III-IV) with an LVEF ≤35% and a QRS complex duration of ≥120ms.[62] Similar recommendations were provided by the European Society of Cardiology in 2007.[63]

Despite the widely proven beneficial effects of CRT therapy, 20-30% of CRT recipients do not show any clinical or echocardiographic improvement and are considered CRT non responder.[46] Already several factors such as LV dyssynchrony, extent and location of scarred

tissue and position of the LV pacing lead have demonstrated to determine the response to CRT.[64-70] However, it is of interest if patients who respond to CRT, and therewith have a decreased myocardial wall tension, have less ventricular arrhythmias if compared to CRT non-responders.

Complication of device treatment

With expending indications for ICD treatment, worldwide implantation rates increased to an estimated 275.000 units in 2008.[62, 71] Although the beneficial effect on mortality has been thoroughly proven in a selected population, some serious drawbacks of ICD therapy should not be overseen.

Firstly, device implantation is associated with a number of complications, such as pneumothorax and endovascular lead related complications such as right ventricular perforation and coronary vein dissection (Table 4).[72-79] The first days following implantation can be accompanied by pocket hematoma and lead dislodgement.

Secondly, during longer follow-up, other complications can occur, such as defibrillation lead failure,[72-77, 80] pocket infections,[79, 81-83] and inappropriate device discharge[18, 30, 32-34, 36, 84]. An important difficulty is the limited service life of the pulse generator, resulting in device replacement approximately every 4-5 years.[85, 86] With increased survival of patients it is estimated that over 70% of implanted patients require an ICD replacement due to end-of-life of the device and 40% even require a second replacement.[86] These figures imply that the number of replacements can be expected to outnumber first implantations in the

Table 4. Implantation related complications of implantable cardioverter defibrillators and cardiac resynchronization therapy-defibrillators in major randomized clinical trials.

	Number of Patients implanted	Duration in Months	Pneumo-thorax, n (%)	In-Hospital Mortality, n (%)	Hematoma or bleeding, n (%)	Lead dis-lodgement, n (%)	Coronary vein Com-plications, n (%)
AVID[18, 76]	539	27	6 (1.1)	NR	8 (1.5)	8 (1.5)	NA
MADIT II[36]	742	20	NR	0 (0.0)	NR	NR	NA
DINAMIT[33]	312	30	NR	0 (0.0)	NR	NR	NA
DEFINITE[34]	229	29	2 (0.9)	0 (0.0)	NR	6 (2.6)	NA
SCD-HeFT[30]	829	46	NR	NR	NR	NR	NA
IRIS[37]	445	37	NR	5 (0.8)	NR	NR	NA
MADIT-CRT[59]	1829	29	24 (1.3)	1 (0.1)	54 (3.0)	44 (4.4)	5 (0.5)
MIRACLE[47, 79]	571	6	1 (0.2)	2 (0.4)	NR	31 (5.9)	35 (6.2)
MIRACLE ICD[61, 79]	429	6	3 (0.7)	0 (0.0)	NR	11 (2.9)	19 (4.5)
COMPANION[31]	1212	16	NR	8 (0.6)	NR	NR	22 (1.8)
CARE-HF[53, 78]	409	29	2 (0.5)	0 (0.0)	NR	11 (2.8)	6 (1.5)
RethinQ[51]	250	6	2 (1.1)	0 (0.0)	2 (1.2)	13 (7.6)	1 (0.6)
REVERSE[58]	684	12	4 (0.6)	NR	5 (0.8)	66 (10.6)	3 (0.5)

near future.[87] Previous studies have demonstrated that surgical re-interventions, such as device replacements, are correlated to an increased occurrence of device infections.[82, 83] Additionally, Gould and Krahn reported that the consequences of an early re-intervention for a non-infectious cause can be considered more harmful than the underlying complication itself.[88] However, the effect of replacement on non-infectious pocket related complications and the effect of additional replacements has not yet been assessed.

Socio-economic implications

As already discussed, ICDs have shown to be an effective treatment modality in the prevention of sudden cardiac death in selected patients.[18-20, 30, 32, 35, 36] However, it has been recognized that ICD recipients have an ongoing risk of sudden cardiac incapacitation that might cause harm to others when driving a car. Although numerous recommendations exist, thus far evidence is scarce to justify them and large variation exist between different countries concerning the legislation of driving restriction after ICD implantation (Table 5).[89, 90] Keeping in mind that driving restrictions are often being perceived as difficult for patients and their families, clear evidence on the necessity of these restrictions is vital.

Furthermore, with increased implantation rates, clinicians have expressed concern that the number-needed-to-treat with a primary prevention ICD might be too high and that the population eligible for primary prevention ICD treatment is of such magnitude that ICD therapy will strain financial resources and the pool of trained personnel.[91, 92] Concomitantly, it is essential to assess the cost-effectiveness of ICD therapy in different subgroups in order to specify which patients would have a reasonable cost to benefit ratio if treated with an ICD. It is therewith important to realize that the accepted cost-effectiveness ratio per gained quality-adjusted life year vary widely per country. In the Netherlands a cost-effectiveness ratio below €40,000 per gained quality-adjusted life year is accepted whereas in the United States of America a threshold of $60.000 is accepted.[93, 94]

Previously, several studies have assessed the cost-effectiveness of the prophylactic use of ICDs and showed a wide diversity in the cost and benefit ratio if the current guidelines are followed (Table 6).[95-100] However, these dissimilarities in the beneficial effect of ICD therapy,

Table 5. Overview of the recommendations by the American Heart Association (AHA) and the European Heart Rhythm Association (EHRA) for ICD patients with private driving habits.

	AHA[89]	EHRA[90]
ICD for secondary prevention	6 months	3 months
ICD for primary prevention	1 week	4 weeks
Following appropriate ICD therapy	6 months	3 months
Following inappropriate ICD therapy	None	Until measures are taken
Following ICD replacement	None	1 week
Following lead replacement	None	4 weeks

ICD = implantable cardioverter defibrillator.

Table 6. Results of increased costs, increased life years, increased quality-adjusted life years, and incremental cost-effectiveness ratios for implantable cardioverter defibrillators compared with control therapy in different primary prevention ICD trials.

	Increase in Cost ($)	Increase in LY	Increase in QALY	ICER ($/LY)	ICER ($/QALY)
MADIT I[35, 98]	92,100	3.64	2.64	25,300	34,900
CABG Patch[98, 101]	55,700	(0.40)	(0.29)	Dominated	Dominated
MUSTT[32, 98]	101,500	4.14	2.99	24,500	34,000
MADIT II[36, 98, 100]	79,400	2.03	1.47	39,000	54,100
DEFINITE[34, 98]	100,500	2.73	1.96	36,800	51,300
DINAMITE[33, 98]	58,800	(0.48)	(0.34)	Dominated	Dominated
COMPANION[31, 98]	68,300	1.87	1.36	36,500	50,300
SCD-HeFT[30, 98]	71,000	1.40	1.01	50,700	70,200

ICER = incremental cost-effectiveness ratio; LY = life years; QALY = quality-adjusted life year

based on results from clinical trials, are difficult to extrapolate to routine clinical practice since these studies mainly used experts' opinions for complication rates, device longevity, and costs. Furthermore, differences in study population and patient characteristics in previous analysis presumably had a large effect on the final cost-effectiveness of ICD therapy. Consequently, it is important to determine the cost-effectiveness of ICD therapy, based on clinical data and detailed costs derived from routine clinical practice.

Furthermore, the effect on the cost-effectiveness of ICD therapy should be calculated for various clinical circumstances as for instance an older age at implantation, higher rate of complications, and the obtained quality of life. Hence, based on these results one is able to allocate the limited financial resources and trained personnel in the most efficient manner for the health care system.

AIM AND OUTLINE OF THE THESIS

In large clinical trials, ICD therapy and CRT-D have been proven to be an effective treatment in selected patients. However, the population assessed in these trials does not reflect the population receiving an ICD or CRT-D in the "real world". Therefore the aim of the current thesis was to evaluate the clinical aspects and socio-economic implications of ICD and CRT-D treatment in the population presently receiving device therapy.

In **Part I**, the clinical characteristics and outcomes of the population indicated for defibrillator treatment in routine clinical practice were studied. Chapter 2 describes the mode of death and prognosis for different subgroups of device recipients outside the setting of a clinical trial. The increasing risk for pocket-related complications with recurrent device replacements is evaluated in chapter 3. Chapter 4 studied the effect of CRT on the occurrence of ventricular arrhythmias in patients who underwent upgrade from ICD to CRT-D. Finally, in chapter 5, the suitability and predictors of the unsuitability for an entirely subcutaneous ICD system were established.

In **Part II**, the social and economic implications of ICD and CRT-D therapy are examined. In chapter 6, lifetime cost and gained quality-adjusted life years were estimated for primary prevention ICD recipients. Device longevity and reasons for defibrillator replacement were studied in chapter 7. In chapter 8, an evidence based approach for driving restrictions in defibrillator patients was based on real-world incidences of appropriate and inappropriate device shocks. Finally, in chapter 9, strategies to identify those patients most likely to benefit from primary prevention ICD therapy are discussed.

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I

Part I

Clinical Aspects of Implantable Cardioverter Defibrillator Treatment

2

Chapter 2

The Mode of Death in Implantable Cardioverter Defibrillator and Cardiac Resynchronization Therapy – Defibrillator Patients: Results from Routine Clinical Practice

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ABSTRACT

Background

Although data on the mode of death of implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy- defibrillator (CRT-D) patients have been examined in randomized clinical trials, in routine clinical practice data is scarce. To provide reasonable expectations and prognosis for patients and physicians, this study assessed the mode of death in routine clinical practice.

Objective

To assess the mode of death in ICD/CRT-D recipients in routine clinical practice.

Methods

All patients who underwent an ICD or CRT-D implantation at the Leiden University Medical Center, the Netherlands between 1996 and 2010 were included. Patients were divided into primary prevention ICD, secondary prevention ICD, and CRT-D patients. For patients who died during follow-up, the mode of death was retrieved from hospital and general practitioner records and categorized according to a predetermined classification: heart failure death, other cardiac death, sudden death, non-cardiac death, and unknown death.

Results

A total of 2859 patients were included in the analysis. During a median follow-up of 3.4 years (interquartile range, 1.7-5.7 years), 107 (14%) primary prevention ICD, 253 (28%) secondary prevention ICD, and 302 (25%) CRT-D recipients died. The 8-year cumulative incidence of all-cause mortality was 39.9% (95% CI 37.0–42.9%). Heart failure death and non-cardiac death were the most common modes of death for all groups. Sudden death accounted for approximately 7-8% of all deaths.

Conclusion

For all patients, heart failure and non-cardiac death are the most common modes of death. The proportion of patients who died suddenly was low and comparable for primary and secondary ICD and CRT-D patients.

INTRODUCTION

Sudden cardiac death (SCD), mainly caused by life-threatening ventricular arrhythmias, is responsible for 50% of all cardiac mortality worldwide.[1] As demonstrated by large randomized clinical trials, implantable cardioverter defibrillators (ICDs) are able to reduce the risk of SCD in survivors of life-threatening arrhythmias (i.e. secondary prevention), as well as in selected patients with ischemic and non-ischemic heart disease at high risk of sudden arrhythmic death (i.e. primary prevention).[2-8] Nowadays, most defibrillators are implanted in combination with cardiac resynchronization therapy (CRT-D), which has a beneficial effect on mortality in heart failure patients with ventricular dyssynchrony (i.e.mechanical delay between septum and lateral wall contraction).[9, 10]

As a result of the prevention of sudden death, it was hypothesized that most patients will ultimately die of causes other than sudden death and that this will lead to a shift in the mode of death in patients with an implanted defibrillator device. Interestingly, subgroup analyses of randomised controlled ICD trials failed to demonstrate such a shift.[7, 11]

In routine clinical practice, data regarding the mode of death are rarely examined and extrapolating data from randomised controlled trials to routine clinical practice is difficult given the strict inclusion criteria of the trials. To provide reasonable expectations and prognosis for patients and physicians, it is necessary to assess the mode of death in a population with ICDs or CRT-Ds outside the setting of a clinical trial.

Since 1996, all ICD and CRT-D recipients in the Leiden University Medical Center have been assessed and followed up. This cohort offers a unique opportunity to assess the mode of death in routine clinical practice.

METHODS

Patients

Since 1996, all patients who received an ICD or CRT-D at the Leiden University Medical Center, the Netherlands are registered in the departmental Cardiology Information System (EPD-vision®, Leiden University Medical Center) and prospectively recorded. For the current study, all patients who underwent ICD/CRT-D implantation for primary or secondary prevention of SCD between January 1996 and December 2010 were included. Patients with a congenital structural or monogenetic heart disease (e.g. tetralogy of Fallot, hypertrophic cardiomyopathy, long QT syndrome) were excluded. At baseline, patient characteristics and implantation data were collected and during follow-up, all visits were noted.

Patients received a single-chamber or dual-chamber ICD after surviving life-threatening ventricular arrhythmias or in the presence of a depressed left ventricular function (left ventricular ejection fraction [LVEF] ≤35%) with or without non sustained ventricular tachycardia. CRT-D implantation occurred in patients with advanced heart failure (New York Hart Association [NYHA] class III or IV), depressed LVEF (i.e. ≤35%) and a wide QRS complex (>120ms). Eligibility for ICD implantation in this population was based on international guidelines which, due to evolving guidelines, might have changed over time.[9, 12-17]

Device implantation

All defibrillator systems used were implanted transvenously without thoracotomy. Testing of sensing, pacing thresholds and defibrillator thresholds was performed during the implant procedure. Implanted systems were manufactured by Biotronik (Berlin, Germany), Boston Scientific (Natick, MA, United States, formerly CPI, Guidant [St. Paul, MN, United States]), Medtronic (Minneapolis, MN, United States), and St. Jude Medical/ Ventritex (St. Paul, MN, United States).

All devices were programmed with three consecutive zones with limits slightly varying per manufacturer: a monitor zone (lower limit between 150-155 beats per minute (b.p.m.); upper limit between 185-190 b.p.m.), an antitachycardia pacing (ATP) shock zone (lower limit between 185-190 b.p.m.; upper limit between 205-210 b.p.m.) and an initial shock zone (≥205-210 b.p.m.). In the monitor zone, no therapy was programmed unless ventricular arrhythmia 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 ventricular arrhythmia faster than the ATP shock zone, device shocks were the initial therapy. Furthermore, atrial arrhythmia detection was set to >170 b.p.m. with supraventricular tachycardia discriminators enabled. Therapy settings were adapted, only when clinically indicated.

Follow-up

All patients were evaluated regularly at 3-6 month intervals for follow-up or more frequently when clinically indicated. Printouts of device interrogations were checked for delivered therapy, which was classified as appropriate when occurring in response to ventricular tachycardia or ventricular fibrillation and included ATP and shocks. The survival status of patients was retrieved from municipal civil registries, which are updated regularly. Subsequently, the cause of death was assessed in all deceased ICD/CRT-D patients. Only in a few cases the cause of death was assessed by a pathologist. In all other cases, the cause of death was either based on letters and follow-up reports from patients who died in the hospital without autopsy or by the expertise of the contacted general practitioners.

Event subclassification and definitions

Causes of death were categorized according to a modified Hinkle Taler classification and categorized into 3 groups: cardiac, non-cardiac and sudden death.[18] The cardiac group was further categorized in tachyarrhythmic, bradyarrhythmic, heart failure, non-arrhythmic non heart failure, and in cardiac but unable to classify further. The non-cardiac death group was further divided into a vascular and a non-vascular mode of death. Patients who died in their sleep or died unexpectedly without worsening of their clinical situation were categorized as sudden death. Patients who died suddenly but with a clear alternative mode of death were categorized as non-sudden (e.g. someone who died suddenly of acute myocardial infarction was categorized as "cardiac, non-arrhythmic non-heart failure" and not as sudden death). Heart failure was diagnosed when patients died of terminal heart failure, progressive failure of cardiac pump function, or cardiac asthma under maximum inotropic drug support. All other causes were categorized as cardiac but unable to classify further. In all cases, the mechanism underlying the immediate demise was selected as the mode of death.

Statistical analysis

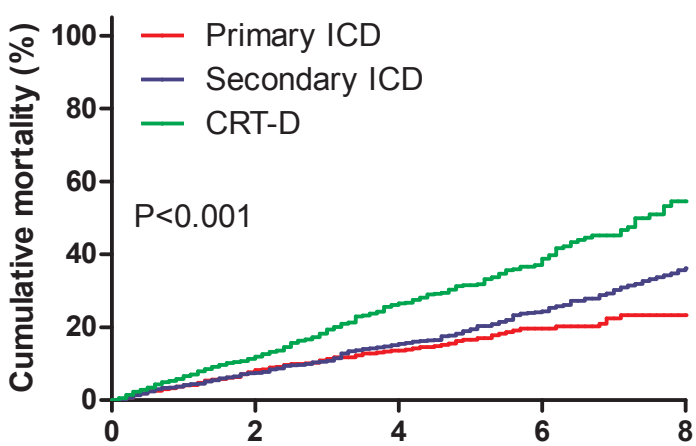
Continuous data are expressed as mean ± standard deviation; dichotomous data are presented as numbers and percentages. Device recipients were divided into 3 groups: primary prevention ICD patients, secondary prevention ICD patients and CRT-D patients.

One-way analysis of variance test was used to assess differences in continuous variables across different groups of patients; if the result of the analysis was significant, Bonferroni post hoc test was applied. Differences in categorical variables were analyzed using chi-square tests or Fischer's exact tests, as appropriate. Event rates over time were analyzed by method of Kaplan-Meier with corresponding log-rank test for differences in distribution between the curves. A competing-risk model was used to analyze the cause-specific mortality.[19] The statistical software program SPSS 17.0 (Chicago, Illinois, United States) was used for statistical analysis. A p-value of < 0.05 was considered significant.

RESULTS

Patients

Since January 1996, 756 (26%) patients received an ICD for primary prevention of SCD, 914 (32%) patients received an ICD for secondary prevention, and 1189 (42%) patients received a CRT-D. Median follow-up was 3.4 years (interquartile range, 1.7-5.7 years). Baseline characteristics are summarized in Table 1.



Patients at risk					
Primary ICD	756	545	298	149	59
Secondary ICD	914	715	543	378	227
CRT-D	1189	794	386	143	29

Figure 1. Kaplan Meier curve for all-cause mortality in primary prevention ICD recipients (bold line), in secondary prevention ICD recipients (dashed line) and in CRT-D recipients (dotted line).

Table 1. Baseline characteristics.

	Primary ICD patients (n = 756)	Secondary ICD patients (n = 914)	CRT-D patients (n =1189)	p-value
Clinical characteristics				
Age, mean (SD), years	60 ± 12	62 ± 14*	65 ± 10*†	<0.001
Male (%)	627 (83%)	733 (80%)	911 (77%)*	<0.001
Left ventricular ejection fraction (%)	32 ± 13	40 ± 15*	26 ± 9*†	<0.001
QRS, mean (SD), ms	109 ± 25	115 ± 29*	146 ± 33*†	<0.001
Renal clearance. mean (SD), mL/min	85 ± 36	82 ± 40	74 ± 40*†	<0.001
Ischemic heart disease (%)	584 (77%)	654 (72%)*	734 (62%)*†	<0.001
History of atrial fibrillation/flutter (%)	160 (21%)	197 (21%)	370 (31%)*†	<0.001
Medication				
ACE-inhibitors/AT II antagonist (%)	626 (83%)	614 (67%)*	1038 (87%)*†	<0.001
Diuretics (%)	454 (60%)	412 (45%)*	1013 (85%)*†	<0.001
Statins (%)	540 (71%)	479 (52%)*	741 (62%)*†	<0.001
Anti-arrhythmic medication				
Beta-blocker (%)	476 (63%)	385 (42%)*	769 (65%)†	<0.001
Amiodarone* (%)	78 (10%)	217 (24%)*	205 (17%)*†	<0.001
Sotalol* (%)	101 (13%)	177 (19%)*	106 (9%)*†	<0.001
Antiarrhytmic medication combined* (%)	617 (82%)	696 (76%)*	986 (83%)†	<0.001

*ACE = angiotensin-converting enzyme; AT = angiotensin;CRT-D = cardiac resynchronization therapy defibrillator; ICD = implantable cardioverter defibrillator; SD = standard deviation. * Patients could be taking >1 antiarrhythmic drug. * p<0.05 versus primary ICD patients; † p<0.05 versus secondary ICD patients.*

Mode of death

At the end of follow-up, 662 (23%) patients had died. For 548 (83%) patients the mode of death was obtained (Table 2). The cumulative incidence of all-cause mortality was 10.0% (95% CI 8.8-11.1%) after 2 years, 19.6% (95% CI 17.9-21.3%) after 4 years and 39.9% (95% CI 37.0–42.9%) after 8 years.

All-cause mortality was significantly different between the 3 groups and was highest for patients who received a CRT-D (Figure 1).

A total of 107 (14%) primary prevention ICD patients died during follow-up. In 85 (79%) of these patients, the mode of death was obtained. In absolute terms, most patients died from heart failure (n=37, 35%), followed by a non-cardiac cause (n=35, 33%). Seven patients (7%) died suddenly (Table 2, Figure 2). In the group with secondary prevention ICD recipients, 253 (28%) patients died during follow-up and for 197 (78%) patients the mode of death was obtained. Further sub classification revealed that most patients died from a non-cardiac cause (n=95, 38%), but still a significant part died from heart failure (n=71, 28%). Twenty patients (8%) died suddenly. In the CRT-D group, 302 (25%) patients died during follow-up. The mode of death was obtained in 266 (88%) of these patients. Not unexpectedly,

most patients died from heart failure (n=131, 43%), but still 30% (n=92) died from a non-cardiac cause.

MORTALITY RATES PER MODE OF DEATH

Categorization by mode of death showed heart failure death and non-cardiac death as the main causes of death, which consequently had the highest 8-year cumulative incidence. For heart failure death, the 8-year cumulative incidence was 8.6% (95% CI 5.3-12.0%) in primary prevention ICD recipients, 9.6% (95% CI 7.1-12.0%) in secondary prevention ICD recipients, and 22.6% (95% CI 17.8-27.5%) in CRT-D recipients (log rank p<0.001). The 8-year cumulative incidence for non-cardiac death was 7.0% (95% CI 4.4-9.5%) in primary prevention ICD recipients, 13.8% (95% CI 10.9-16.7%) in secondary prevention ICD recipients, and 18.7% (95% CI 13.7-23.7%) in CRT-D recipients (log rank p<0.001). In Figure 3, cumulative incidences for heart failure death, sudden death, non-cardiac death, and other cardiac death are displayed according to the 3 device groups.

Sudden death

Sudden death was the mode of death in 49 (7%) patients, of whom 17 (3%) patients died from a recorded sustained tachyarrhythmia (Table 2). ICD function was switched off in only 2 cases by patient request; one in the tachyarrhythmic and one in the sudden death group. The 8-year cumulative incidence was 2.1% (95% CI 0.3 – 4.0 %) in primary prevention ICD patients, 3.2% (95% CI 1.6 – 4.8%) in secondary prevention ICD patients, and 3.6% (95% CI 1.8 – 5.3%) in CRT-D recipients (log rank p=0.026).

DISCUSSION

The main findings of the present study can be summarized as follows: (1) large differences in the annual mortality rates between ICD and CRT-D patients were found during the first 8 years of follow-up with CRT-D patients having the highest annual mortality; (2) heart failure and non-cardiac death were the most common causes of death in device recipients; (3) sudden death rates were low and comparable between primary and secondary prevention ICD patients and CRT-D patients.

All-cause mortality in routine clinical practice

In the current study, the annual mortality rate for the total cohort was 5.0% during the first 8 year of follow-up. However, when subcategorized according to device type, large differences were found with an annual mortality of 2.9% in the primary prevention ICD patients, 4.5% in secondary prevention ICD patients, and 6.9% in the CRT-D patients. It is evident that these dissimilar mortality rates are due to the completely different composition of the groups, which is demonstrated by the significant differences in patient characteristics between those groups at baseline (Table 1).

In comparison, in the ICD treated arms of major randomized trials, higher annual mortality rates were observed ranging from 5.8%-8.4% in primary prevention patients and from 6.0%-8.2% in secondary prevention patients.[2-4, 6, 8, 20-22] The differences could

Table 2. Causes of death of ICD patients.

	Primary ICD patients (n = 756)	Secondary ICD patients (n =914)	CRT-D patients (n = 1189)
Cardiac	**44**	**91**	**159**
Tachyarrhythmic	1	9	7
Bradyarrhythmic	0	0	0
Heart failure	37	71	131
Nonarrhythmic, non-heart failure	3	9	17
Cardiac but unable to classify further	3	2	4
Non-cardiac	**35**	**95**	**92**
Stroke and other cerebrovascular disease	3	5	7
Other vascular disease	2	4	10
Vascular but unable to classify further	0	1	0
Malignant neoplasm	15	35	32
Infectious	8	28	29
COPD	2	3	2
Alzheimer and other dementias	0	2	1
Other nonvascular disease	4	16	11
Non-vascular but unable to classify further	1	1	0
Sudden death: unable to classify further	**6**	**11**	**15**
Unknown	**22**	**56**	**36**
Total death	**107**	**253**	**302**

COPD = chronic obstructive pulmonary disease, ICD = implantable cardioverter defibrillator.

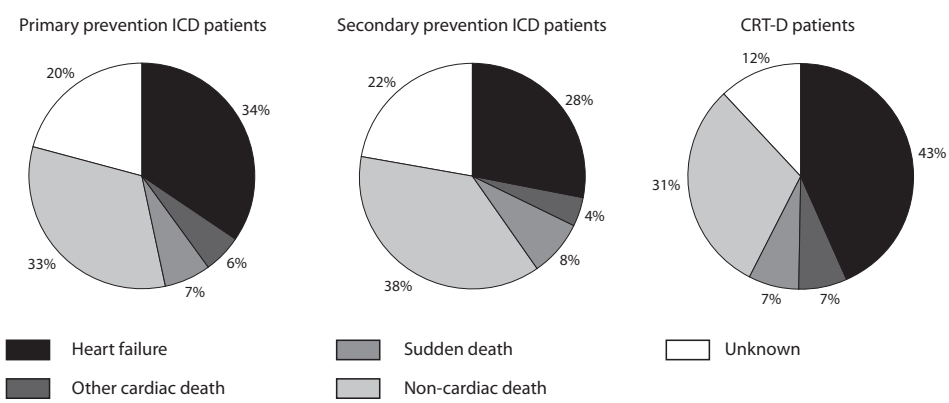


Figure 2. Distribution of the mode of death.

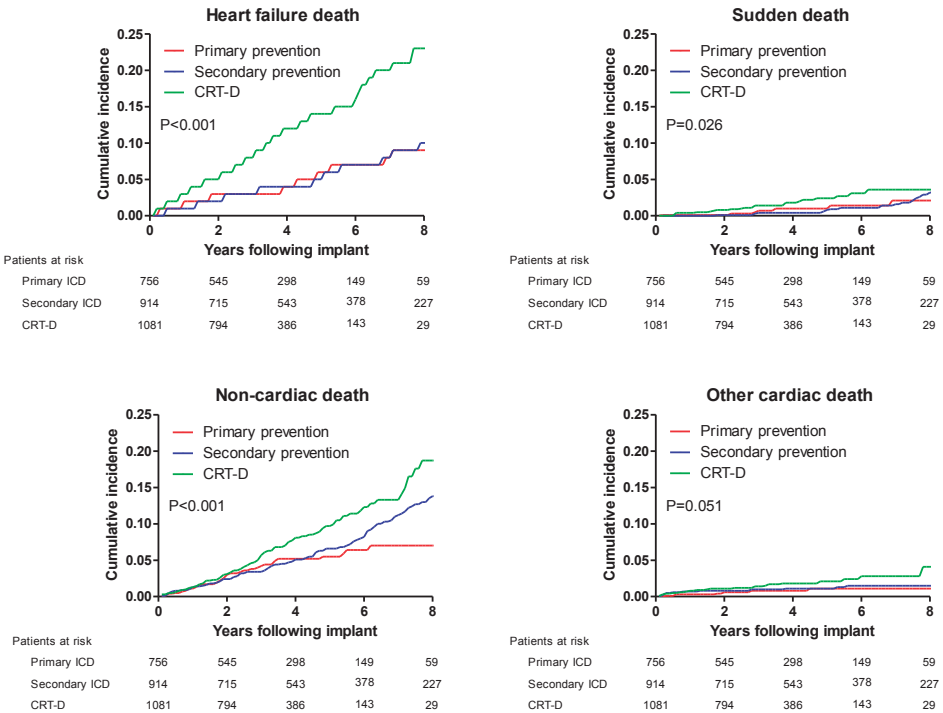


Figure 3. Kaplan Meier curve categorized in heart failure death, sudden cardiac death, non cardiac death, and other cardiac death. Cumulative mortality is presented for primary prevention ICD recipients (red line), secondary prevention ICD recipients (blue line) and CRT-D recipients (green line) separately. Modes of death other than the one described were censored.

be explained by either a healthier population at baseline, better (pharmacotherapeutic) treatment during follow-up, or a combination of both. Baseline mean left ventricular systolic function, for example, was higher in primary prevention patients in the current study (LVEF 32%) than in the major primary prevention ICD trials (LVEF 21%-30%).[5, 8, 23, 23, 24] Furthermore, inclusion of patients in the three major secondary prevention trials occurred between 1987 and 1998, while in the current study, patients received an ICD between 1996 and 2010.[4, 6, 20]

Also for CRT-D patients, the annual mortality rate was lower in the current analysis when compared with the outcomes of large clinical trials. For instance, in the CARE-HF and COMPANION, annual mortality rates of respectively 9% and 12% were reported.[25, 26] Again, these differences are mainly due to differences in the selection and composition of the patient population. The effect hereof is clearly illustrated in the MADIT-CRT Trial, were selection of patients with mild cardiac symptoms resulted in an annual mortality rate of only 3%.[27]

HEART FAILURE MORTALITY

As one of the major causes of death, the high rate of heart failure death in ICD recipients is confirmed in the current study. For primary prevention ICD patients, one might expect an increased risk of heart failure mortality when compared with secondary prevention ICD patients because having a low LVEF is one of the main criteria to be selected for primary prevention ICD implantation.[9] Interestingly, primary and secondary ICD patients have a similar annual heart failure mortality of approximately 1.1-1.2% within the first 8 years of follow-up (Figure 3A). There are several explanations for this similarity. First of all, the difference in baseline LVEF, albeit statistically significant, was only 8% between primary prevention ICD patients and secondary prevention ICD patients (mean LVEF 32% vs 40% respectively). Secondly, Poole et al demonstrated that in ICD patients, the occurrence of an appropriate ICD shock was associated with a markedly increased risk of death.[28] Furthermore, they demonstrated that the most common mode of death among patients who received an ICD shock was progressive heart failure. Since secondary prevention ICD patients receive more appropriate ICD shocks than primary prevention ICD patients, secondary prevention ICD patients exhibit in theory an increased risk of heart failure mortality.[29]

Finally, it has been demonstrated that in patients with heart failure, prolongation of QRS is associated with worse prognosis and higher cardiac mortality. [30] As can be seen in Table 1, secondary prevention ICD patients had a significantly longer QRS duration than primary prevention ICD patients putting them at increased risk of heart failure mortality.

Interestingly, in the major ICD trials, higher rates of heart failure mortality were observed: in MADIT-2, Greenberg et al reported annual rates for non-sudden cardiac death of 2.5% and in the SCD-HeFT, the cumulative incidence of heart failure mortality after 5-years of follow-up was approximately 13% (value estimated from graph) resulting in an annual rate of approximately 2.6%.[31] Even higher incidences were observed in the AVID trial: after 4 years of follow-up, cumulative incidence was approximately 13% (value estimated from graph), resulting in an annual incidence of 3.3%.[7] Comparing the results of the current study with major randomized trials is difficult given the different time periods during which the studies were conducted as well as differences in patients' characteristics.

A remarkable outcome of the present analysis is the absence of any bradyarrhythmic death in all three subgroups of defibrillator recipients. Though, in other studies, were this mode of death was specified, bradyarrhythmic death also occurred in less than 1% of all deceased patients.[11, 32, 33] A possible clarification for this finding could be the programmed backup pacing of defibrillator devices, avoiding serious deteriorating bradyarrhythmias and therewith bradyarrhythmic death. This explanation is supported by the results of Packer et al., in which only 1 out of 829 (1%) ICD treated heart failure patients deceases due to a bradyarrhythmic death versus 8 out of 1692 (5%) conventional treated heart failure patients.[11]

SUDDEN CARDIAC DEATH

In the current study, sudden death accounted for 7% of cases in all ICD recipients. These results are strikingly different when compared with the results presented in the randomized

clinical trials concerning ICD treatment. For instance, sudden death rates ranged from 30 to 36% (AVID trial 30%, CIDS trial 36% and CASH trial 36%) in the secondary prevention trials and from 15 to 34% (MADIT I 20%, MADIT II 27%, SCD-Heft 20%, CABG patch 15% and MUSTT 34%) in the primary prevention trials regarding ICD therapy.[2, 6, 7, 11, 21, 23, 31, 34] Although the study populations included in the clinical trials were different than the one discussed currently, it could not clarify these significant differences in the proportion of patients who died suddenly. A more plausible explanation is the unknown cause of death in 17% of the patients in the present analysis, which probably contains a relatively high number of patients who died suddenly. In addition, variation in the definition for sudden death between the previously described trials and the current study could be the reason for these large dissimilarities.

Interestingly, comparable sudden death rates were found in primary prevention ICD recipients (7%), secondary prevention ICD recipients (8%), and CRT-D recipients (7%). This is remarkable since – by definition – all secondary prevention ICD recipients survived an episode of ventricular arrhythmia and consequently have an increased risk of ventricular arrhythmias during follow-up.[29] In theory, this should lead to an increased risk of sudden death. However, this was not observed in the current study. Probably, the rate of persistent, shock refractory and thereby fatal ventricular arrhythmias between the three groups similar despite having different baseline characteristics. These results should be interpreted with caution since the low rates of sudden death lead to wide confidence intervals making accurate comparison difficult between the three groups. Further studies are needed to confirm these low sudden death rates.

LIMITATIONS

There are limitations to this study. First of all, in 17% of all patients, the cause of death could not be identified and post-mortem reports were unavailable. Secondly, since only a part of patients died in our hospital (i.e. cause of death identified), cooperation of the general practitioners for retrieving the cause of death was crucial. Furthermore, in the Netherlands, ICD/CRT-D implantations are performed in academic medical centers (n=7) and large community hospitals (n=18) and patients are referred to our hospital from smaller, regional hospitals. Consequently, the study population does represent routine clinical practice in the Netherlands. However, current study population could differ from routine clinical practice in other countries.

CONCLUSION

In routine clinical practice, the annual mortality rate of ICD and CRT-D patients is approximately 5%. However, large differences in the annual mortality rates between primary prevention ICD patients, secondary prevention ICD patients, and CRT-D patients were found during the first 8 years of follow-up. The most common modes of death are heart failure death and non-cardiac death. Remarkably, sudden death rates were comparable between primary prevention ICD patients, secondary prevention ICD patients, and CRT-D patients.

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3

Chapter 3

Recurrent Implantable Cardioverter-Defibrillator Replacement is Associated with an Increasing Risk of Pocket-related Complications

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ABSTRACT

Background

Despite the positive effect on mortality of ICD therapy in selected patients, limited service life of the ICD results in a necessity of replacement in the majority of patients. Data on the effect of replacement procedures on the occurrence of pocket related adverse events are scarce.

Methods and Results

Since 1992, a total of 3161 ICDs were implanted in 2415 consecutive patients (80% men, mean age 62 (SD 13) years) ICDs were grouped by the consecutive number in which they were implanted, resulting into a group of first implanted ICDs and multiple groups of consecutive replacement ICDs. All pocket related complications requiring surgical re-intervention following ICD implantation or replacement were noted. In total, 145 surgical re-interventions were required in 122 (3.9%) patients, with a median time to first re-intervention of 75 days. The three years cumulative incidence of first re-intervention was 4.7% (95% CI 3.9-5.5%) and the incidence of re-intervention was 1.9 (95% CI 1.6-2.2) per 100 ICD-years. Event rate comparison of replacement ICDs versus first implanted ICDs showed a more than doubled need for re-interventions in replacement ICDs (rate ratio 2.2 [95% CI 1.5-3.0]). Further sub-division by the consecutive number of ICD replacements, shows an increase in the annual need for surgical re-intervention, ranging from 1.5% (95% CI 1.2-1.9%) in the first implanted ICD, to 8.1% (95% CI 1.7-18.3%) in the fourth implanted ICD.

Conclusion

ICD replacement is associated with a doubled risk for pocket related surgical re-interventions. Furthermore, the occurrence of the need for re-intervention increases with every consecutive replacement.

INTRODUCTION

Implantable cardioverter-defibrillators (ICDs) have shown to be an effective treatment modality in the primary and secondary prevention of sudden cardiac death in selected patients.[1-7] With expending indications for ICD therapy, worldwide implantation rates have increased to an estimated 275.000 units in 2008.[8, 9] Although these major advances have a positive effect on mortality, some serious drawbacks of ICD therapy should not be overseen. The most important being the limited service life of the pulse generator, resulting in device replacement approximately every 4-5 years.[10, 11] With increased survival of patients it is estimated that over 70% of implanted patients require an ICD replacement due to end-of-life of the device and 40% even require a second replacement.[11] These figures imply that the number of can be expected to outnumber first implantations in the near future.[12] Previous studies have demonstrated that surgical re-interventions, such as device replacements, are correlated to an increased occurrence of device infections.[13, 14] Additionally, Gould and Krahn reported that the consequences of an early re-intervention for a non-infectious cause can be considered more harmful than the underlying complication itself.[15] However, the effect of replacement on non-infectious, pocket related complications and the effect of additional replacements has not yet been assessed.

This current increase in ICD replacements warrants clear mapping of the associated risks for complications, such as hematoma or infection. In this analysis a comparison is made to determine the requirement for pocket related surgical re-intervention in first implanted ICDs and replacement ICDs in a large number of implanted ICDs (n= 3161).

METHODS

Patients

The study population consisted of consecutive patients who received an ICD system in the Leiden University Medical Center. Since 1992 all implant procedures were registered in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center). Data of the implant procedure and all follow-up visits were recorded prospectively. The data collected for the current registry ranged up to August 2008. Abdominal implanted ICDs were excluded from the current analysis.

Indications for ICD treatment were made according to international guidelines at that time. Due to evolution of these guidelines, indications will have changed over time. [8, 16] Majority of patients were indicated for ICD treatment in the presence of prior life-threatening ventricular arrhythmia or poor left ventricular ejection fraction [LVEF].

Device implantation and discharge

At implantation, patients were clinically assessed, as described previously.[17-19] During the implant procedure testing of sensing and pacing thresholds and defibrillation threshold testing was performed. Before discharge all patients underwent pocket inspection to exclude hematoma or early signs of infection. If no abnormalities were found and temperature was normal, patients were discharged.

End-point and follow-up

The primary end-point was the occurrence of a surgical re-intervention of the ICD pocket (not because of an elective device replacement, lead failure or device malfunction). Since the aim of the current study was to evaluate the differences in event-rates between first implanted ICDs and replacement ICDs, only pocket related causes were considered. If other causes, such as lead related complications or pulse generator malfunction were taken in account, comparison would be difficult, given the fact that commonly, leads are only implanted at the initial ICD implantation and can therefore not be compared to lead related complications at replacement.

In the Dutch health care system, all patients are followed by the implanting center and periodical follow-up was performed every three to six months. This study included follow-ups performed up to September 2008. During periodical follow-up the pocket was inspected for abnormalities and ICDs were checked at their functionality and battery status.

Since periodical follow-up was performed every three to six months, patients with more than six months of missing data were considered as lost to follow-up.

Statistical analysis

Continuous data are expressed as mean and standard deviation or range, median and first and third quartile where appropriate; nominal data are presented as numbers and percentages. ICDs were grouped by the consecutive number in which they were implanted in the patient. This classification divides the implanted ICDs into a group of first implanted ICDs and multiple groups of replacement ICDs. The number of required re-interventions and the sum of years the ICDs were followed-up (ICD-years) were calculated for each group. Event rates were calculated by dividing the number of surgical re-interventions by the number of ICD-years, expressed with a two-sided 95% confidence interval (95% CI). In the calculation of the 95% CI for event rates, a Poisson distribution of the observed number of events was presumed. Rate ratios were used to assess the differences in event rates between groups. Cumulative incidences were analyzed with the method of Kaplan-Meier. For all tests, a p-value <0.05 was considered significant.

RESULTS

Defibrillator implantations

A total of 3328 ICDs were implanted in 2521 patients between 1992 and August 2008. For the current analysis, all abdominal (n= 102, 3%) placed ICDs were excluded. Sixty-five (2.0%) ICDs were lost to follow-up. The remaining 3161 devices, implanted in 2415 patients were included in the analysis. These consisted of 2415 (76%) first implanted and 746 (24%) replacement ICDs. Figure 1 shows the annual proportion of replacements out of all device implantations.

Patients and ICD characteristics

The majority of patients (80% men, mean age 62 (SD 13) years) had ischemic heart disease (62%) and a poor LVEF (33±15%) (Table 1). At implantation, QRS duration (124±37 ms) and renal clearance (79±38 ml/min) were measured. At discharge, patients were using beta-

blockers (54%), ACE inhibitors/AT II antagonists (75%), diuretics (62%), aspirin (40%) and oral anticoagulants (50%). Implanted first ICDs were single chamber devices (n=335, 14%), dual chamber devices (n=1171, 48%) or cardiac resynchronization therapy-defibrillators (CRT-Ds) (909, 38%).

Incidence and causes of surgical re-intervention

During 7632.3 ICD-years of follow-up, 145 surgical re-interventions were required in 122 (3.9%) patients. Median time to first re-intervention was 75 days (interquartile range, 14 to 258 days).

Cumulative incidence of first surgical re-intervention after the most recent ICD implantation was 3.5% (95% CI 2.9-4.1%) after one year, 4.3% (95% CI 3.5-5.1%) after two years and 4.7% (95% CI 3.9-5.5%) after three years. Over-all the event-rate of a surgical re-intervention was 1.9 (95% CI 1.6-2.2) per 100 ICD-years.

Table 1. Patient characteristics at first ICD implantation.

	Patients (n=2415)
Clinical characteristics	
Age, mean (SD), years	62 (13)
Male sex (%)	1921 (80)
Primary indication (%)	1504 (62)
Ejection fraction (%)	33 (15)
QRS, mean (SD), ms	124 (37)
Renal clearance, mean (SD), ml/min	79 (38)
Device type	
Single chamber (%)	335 (14)
Dual chamber (%)	1171 (48)
CRT-D (%)	909 (38)
Medication	
Beta-blocker (%)	1291 (54)
Sotalol (%)	333 (14)
ACE inhibitors/AT II antagonist (%)	1806 (75)
Calcium antagonist (%)	220 (9)
Diuretics (%)	1506 (62)
Statins (%)	1395 (58)
Nitrates (%)	430 (18)
Amiodarone (%)	454 (19)
Aspirin (%)	961 (40)
Oral anticoagulants (%)	1217 (50)

CRT-D = cardiac resynchronization device-defibrillator

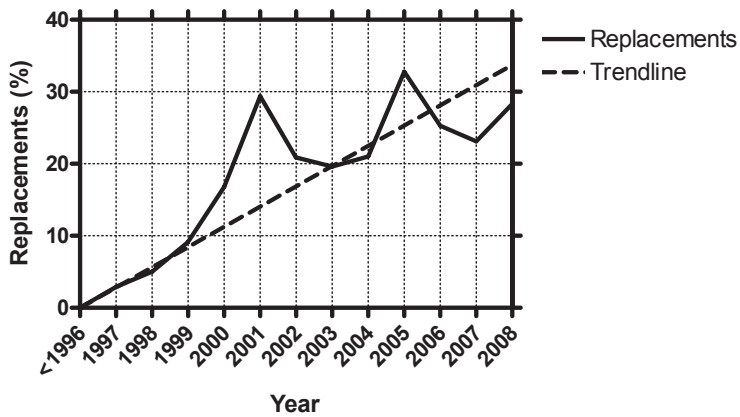


Figure 1. Annual percentage of replacements out of all implanted ICDs (bald line) and trend line (dashed line).

Ninety-five (66%) re-interventions were due to an infectious cause and the remaining 50 (34%) were due to a non-infectious cause (Table 2). Infectious causes were pocket infections (57, 60%%) and decubic ulcers, requiring explantation (11, 12%) or relocation (27, 28%). Hematoma, requiring evacuation was the most common (31, 21%) non-infectious cause for surgical re-intervention. Calculated event rate for the occurrence of surgical re-intervention was 1.2 (95% CI 1.0-1.5) per 100 ICD-years for infectious cause and 0.7 (95% CI 0.5-0.9) per 100 ICD-years for non-infectious cause.

Table 2. Causes for surgical re-intervention.

	All ICDs (n=3161)	First ICD (n=2415)	Replacement ICD (n=746)
Infectious cause			
Pocket infection leading to explantation	57/57	38/38	19/19
Decubic ulcer leading to explantation	11/11	7/7	4/4
Decubic ulcer leading to relocation	27/22	11/9	16/13
Non-infectious			
Hematoma requiring evacuation	31/29	24/24	7/5
Device migration leading to relocation	10/10	3/3	7/7
Pain complaints of the patient leading to relocation	9/7	7/6	2/1
Total infectious causes	95/81*	56/47*	39/34*
Total non-infectious causes	50/45*	34/32*	16/13*
Total	145/122*	90/77*	55/45*

**Since multiple re-interventions could have been required in a single ICD treatment, the number of different ICDs does not add up to the total.*

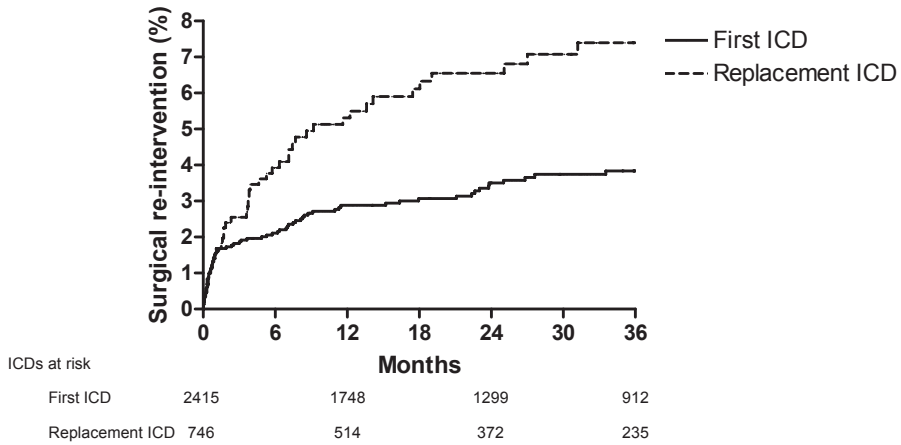


Figure 2. Kaplan-Meier curve for first surgical re-intervention, first implanted ICD vs. replacement ICD.

First implanted ICD vs. replacement ICD

In the first implanted ICD group (2415, 76%), 90 surgical re-interventions were required in 77 different ICDs during a summed follow-up of 5949 ICD-years. The 746 (34%) replacement ICDs required 55 surgical re-interventions in 45 patients during a summed follow-up of 1683 ICD-years.

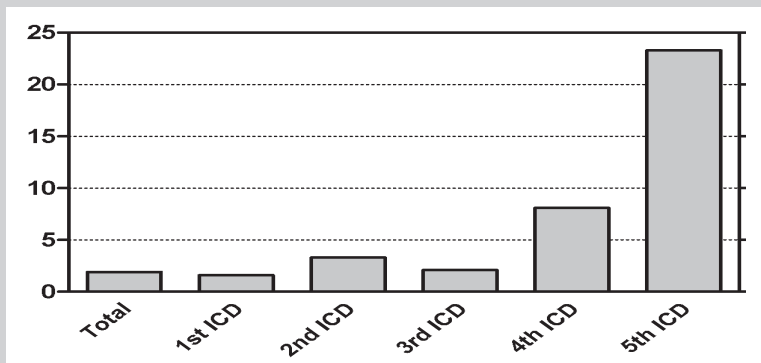
As shown in Figure 2, three years cumulative incidence of first surgical re-intervention was 3.9% (95% CI 3.1-4.7%) for first implanted ICDs and 7.5% (95% CI 5.3-9.7%) for replacement ICDs. The calculated event-rate per 100 ICD-years was 1.5 (95% CI 1.2-1.9) for the first implanted ICDs and 3.3 (95% CI 2.5-4.3) for replacement ICDs, corresponding to a more than doubled (rate ratio 2.2 [95% CI 1.5-3.0, p<0.001]) requirement for surgical re-intervention in replacement ICDs.

Further stratification demonstrated an event-rate of surgical re-intervention for an infectious cause of 0.9 (95% CI 0.7-1.2) per 100 ICD-years in first implanted ICDs and 2.3 (95% CI 1.6-3.2) per 100 ICD-years in replacement ICDs. Per 100 ICD-years, the need for surgical re-intervention for non-infectious causes was 0.6 (95% CI 0.4-0.8) in first implanted ICDs and 1.0 (95% CI 0.5-1.5) in replacement ICDs. When comparing replacement ICDs with first implanted ICDs, the calculated rate ratios are 2.5 (95% CI 1.6-3.7, p<0.001) for infectious causes and 1.7 (95% CI 0.9-3.0, p=0.09) for non-infectious causes.

As is shown in Table 3, further sub-division in the consecutive number of ICD replacements, shows an increase in the need for surgical re-intervention with every consecutive ICD replacement. Event-rates per 100 ICD-years range from 1.5 (95% CI 1.2-1.9) in the first implanted ICD, to 8.1 (95% CI 1.7-18.3) in the fourth implanted ICD.

Table 3. Requirement for re-intervention per consecutive implanted ICD.

	Total	1st ICD	2nd ICD	3rd ICD	4th ICD	5th ICD
Number of ICDs	3161	2415	609	107	24	6
Events	145	90	46	5	3	1
Total years implanted	7632.3	5949	1406	236	37	4.3
Events per 100 ICD-years (95% CI)	1.9 (1.6 – 2.2)	1.5 (1.2 – 1.9)	3.3 (2.4 – 4.4)	2.1 (0.7 – 4.9)	8.1 (1.7 – 18.3)	23.3 (0.6 – 129.6)



DISCUSSION

In this assessment of the requirement of pocket related surgical re-interventions after ICD treatment, the findings can be summarized as follows: 1) The three years cumulative incidence of first surgical re-intervention in all implanted ICDs was 4.7% (95% CI 3.9-5.5%) with an event-rate of 1.9 (95% CI 1.6-2.2) per 100 ICD-years; 2) Replacement ICDs demonstrate a doubled occurrence of surgical re-interventions (rate ratio 2.2 [95% CI 1.5-3.0]); 3) Infectious causes (rate ratio 2.5, 95% CI 1.6-3.7), as well as non-infectious causes (rate ratio 1.7 [95% CI 0.9-3.0, p=0.09) seem to be more frequent in replacement ICDs; 4) The occurrence of surgical re-interventions seem to increase with every consecutive replacement.

Replacements

Since large randomized trials have proven ICD treatment to improve survival in the primary and secondary prevention of sudden cardiac death, worldwide implantation rates have amplified substantially.[8, 9, 20] With increased survival of patients and limited service life of the devices, Hauser estimated that over 70% of the currently implanted patients outlive their ICD and therefore requires replacement.[11] which is in line with the results of this study. Due to the significant increase of ICD implantations the number of replacements is increasing rapidly. However, with the limited service life of the current devices, it can be expected that replacements will increase drastically and potentially even outnumber first implanted ICDs.[12] Previous studies have described the increasing risk for complications, associated with device replacements.[11, 13, 21-24] The current study adds to prior literature in that it compares the

event rates in a large population and differentiates in the cause of intervention (infectious or non-infectious) and in the consecutive number of ICD replacements.

Re-interventions

The present study reports differences in the risk of surgical re-interventions between first implanted ICDs and replacement ICDs. In the comparison with previous trials, differences in defining end points should be taken into account. For a decent comparison between first implantation and replacement, the current analysis did not take causes in account that would distort comparison. Therefore, since leads are commonly only implanted at first implantation, lead related complications were not used in the analysis and only pocket related complications were noted.

The most frequent infectious cause for device explantation is cardiac device infection (CDI), a serious and potentially life threatening condition which is associated with significant morbidity and mortality. Additionally, CDI is associated with additional medical costs which have been estimated at an average of $50.000 per patient.

With the expansion of evidence based indications for cardiac devices the number of device related procedures has rapidly increased over the past decade which also resulted in an increased number of CDI. Furthermore it has been reported that the increase in CDI has outpaced the increase in implantation rate.[25] Recent reported rates of CDI vary between approximately 0.5% and approximately 5%.[13, 14, 24, 26]

It has been hypothesized that local perioperative wound contamination is a major mechanism predisposing to local or systemic pacemaker infection.[27] Da Costa et al. evaluated the role of local bacterial flora on pacemaker-related infection and skin erosion and concluded that their results strongly support this hypothesis.[26] Furthermore, it has been reported that device revision procedures (generator exchange / lead related procedure) are associated with CDI. Gould and Krahn reported that ICD generator replacement in patients with advisory devices is associated with a substantial rate of infectious complications (1.9% after a mean follow up of 2.7 months). Furthermore it should be taken in account that the consequences of an early re-intervention for a non-infectious cause can be considered more harmful than the underlying complication itself.[15] In their recent paper Lekkerkerker et al. reported that device revisions are an important risk factor for CDI with an odds ratio of 3.67 (95% CI 1.51 to 8.96, $p<0.01$) for any device related revision procedure, or an odds ratio of 2.47 (95% CI 1.25 to 4.87, $p<0.01$) for a generator exchange and an odds ratio of 6.67 (95% CI .33 to 33.49, $p=0.02$) for a lead related intervention.[14] Furthermore Klug and co-workers also described an odds ratio of 2.2 for generator replacements, after 12 months follow-up in 6319 implanted devices, of which 1854 being replacement devices.[13] In the current study, during 7623.3 ICD-years of follow-up, per 100 ICD-years, the need for surgical intervention for infectious causes was 0.6 (95% CI 0.4-0.8) in first implanted ICDs and 1.0 (95% CI 0.5-1.5) in replacement ICDs. When comparing replacement ICDs with first implanted ICDs, the corresponding rate ratio was 2.5 (95% CI 1.6-3.7, $p<0.001$).

Considering the above, the need for device replacement should be reduced to a minimum and all effort should be made to improve device longevity.

CONCLUSION

Replacement ICDs demonstrated a doubled occurrence of pocket related surgical re-interventions when compared to first implanted ICDs. Furthermore, both the requirement for surgical re-intervention due to infectious cause and non-infectious cause seemed to be increased in replacement ICDs and the requirement for re-intervention increased with every consecutive replacement. Therefore, every effort should be addressed to improve ICD

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Chapter 4

Implantable Cardioverter Defibrillator Patients who are Upgraded and Respond to Cardiac Resynchronization Therapy have Less Ventricular Arrhythmias Compared to Non-responders

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ABSTRACT

Objective

To evaluate the impact of upgrading implantable cardioverter defibrillator (ICD) therapy to cardiac resynchronization therapy (CRT) combined with defibrillator (CRT-D) on the occurrence of ventricular arrhythmias (VAs) and appropriate ICD therapies.

Background

CRT has shown to improve left ventricular (LV) systolic function and induce reverse LV remodeling. In addition, it has been hypothesized that CRT may reduce the incidence of VAs.

Methods

Heart failure patients receiving an upgrade from ICD to CRT-D were evaluated. Patients were considered responders to CRT if LV end-systolic volume reduced ≥15% at 6 months follow-up. Episodes of VA, triggering device therapy (anti-tachycardia pacing and shocks) were recorded before and after upgrade for the overall population. In addition, these outcomes were compared between CRT responders and non-responders during the follow-up period after CRT response was assessed.

Results

One-hundred-fifteen patients (93 (81%) male, 65±12 years) were evaluated during a mean follow-up of 54±34 months before and 37±27 months after CRT-D upgrade. In CRT responders (n=70), the frequency of VAs requiring appropriate device therapy demonstrated a trend toward a decrease from 0.51±0.79 to 0.30±0.59 per patient per year after CRT-D upgrade (p=0.052). In CRT non-responders (45), the frequency of VAs requiring appropriate device therapy significantly increased from 0.40±0.69 to 1.21±2.53 per patient per year after CRT-D upgrade (p=0.014).

Conclusion

After upgrade from ICD to CRT-D, non-responders to CRT showed a significant increase in VAs burden requiring appropriate device therapy.

INTRODUCTION

Cardiac resynchronization therapy (CRT) has demonstrated to be an effective treatment in patients with advanced heart failure. CRT improves clinical symptoms, reduces heart failure related hospitalization rates and improves long-term survival.[1-4] These beneficial effects have been related to left ventricular (LV) reverse remodelling following CRT implantation. In addition, heart failure patients with a low ejection fraction (EF) are at risk of sudden arrhythmic death and prophylactic implantable cardioverter defibrillator (ICD) implant is indicated in many of these patients [5, 6]. However, the effects after upgrade from ICD to CRT-defibrillator (CRT-D) on the occurrence of ventricular arrhythmias (VAs) are controversial so far [7-10]. While some studies have demonstrated a significant decrease in the burden of VA along with significant LV reverse remodelling [7, 9], other studies have shown no reduction or even an increase in the frequency of VAs or appropriate ICD therapies [8, 10]. In addition, the association between LV reverse remodeling after CRT upgrade and changes in VA burden and frequency of appropriate ICD therapies is unclear.

Patients who received an ICD may develop heart failure symptoms at follow-up. Upgrading these patients to CRT has shown to improve clinical symptoms and LV function [11]. Importantly, this subgroup of patients provides a unique opportunity to evaluate the effects of CRT upgrade on the burden of VAs. Accordingly, the present evaluation assessed the impact of CRT-D upgrade on the occurrence of VAs and appropriate therapies. In addition, the association between LV reverse remodeling and VA burden was evaluated.

METHODS

Patient population and data collection

Since 1996, data from all patients who received an ICD device at the Leiden University Medical Center were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands). Characteristics at baseline, data of the implant procedure and of follow-up visits were recorded. For the current analysis, ICD patients who underwent an upgrade to CRT-D were selected.

The patient population included consecutive patients who underwent upgrade from single- or dual- chamber ICD to CRT-D due to progressive symptoms of heart failure. Before upgrading to CRT-D, all patients underwent complete clinical history, physical examination, 12-lead electrocardiogram and transthoracic echocardiography. Clinical parameters included cardiovascular risk factors, renal function, New York Heart Association (NYHA) functional class, quality of life score as assessed with the Minnesota Living with Heart Failure questionnaire and the 6-minute walk distance [12, 13]. Echocardiographic parameters included LV dimensions and LVEF. At 6 months follow-up after CRT-D upgrade, according to the current clinical protocol, clinical status was reassessed and a repeat transthoracic echocardiogram was performed to evaluate LV dimensions and systolic function. Patients were considered responder if a reduction in LV end-systolic volume (LVESV) ≥15% was documented.[14]

All patients were followed-up from the ICD implantation date until September 2010 for the occurrence of all-cause mortality and appropriate therapies due to ventricular tachycardia

or ventricular fibrillation. Arrhythmia burden was calculated from the total number of episodes divided by the total number of years of ICD or CRT-D and presented in patient per year basis. These end points were prospectively recorded during two correlative follow-up periods:

1. from the ICD implantation date to the CRT-D upgrade date and from the CRT-D upgrade date until the latest device interrogation follow-up. Changes in number of appropriate therapies and shocks after CRT-D upgrade were evaluated for the overall population. Therefore, each patient served as his or her own control for comparison of frequency of appropriate therapies and shocks prior and following CRT-D upgrade.
2. from the evaluation of response to CRT-D (at 6 months follow-up) until the last device interrogation follow-up. The incidence of appropriate therapies and shocks and arrhythmia burden after CRT-D upgrade were then compared between responders and non-responders to CRT-D.

Device implantation and settings

Eligibility for ICD implantation in this population was based on international guidelines for primary and secondary prevention [5, 6]. Upgrade to CRT-D was performed according to current guidelines: advanced symptoms of heart failure despite optimized medical therapy, LVEF ≤35%, and a wide QRS complex (>120ms).[15]

Implantation of defibrillator systems were performed transvenously, with conventional right atrial and ventricular leads positioning. During CRT-D implantation, the LV lead was inserted via the subclavian vein followed by cannulation of the coronary sinus. Subsequently, the LV pacing lead was inserted through the coronary sinus with the help of an 8 Fr guiding catheter and positioned as far as possible in the venous system, preferably in a (postero-) lateral vein. Implanted systems were manufactured by Biotronik (Berlin, Germany), Boston Scientific [Natick, MA, USA, formerly CPI, Guidant (St Paul, MN, USA)], Medtronic (Minneapolis, MN, USA), and St Jude Medical/Ventritex (St Paul, MN, USA).

Defibrillators were programmed as follows: a ventricular arrhythmia monitor zone was programmed in all patients (150-188 beats/min). No therapy was programmed in this zone until arrhythmias were detected during follow-up. VAs faster than 188 bpm were initially attempted to be terminated with two bursts of antitachycardia pacing and, after continuation of the arrhythmia, device shocks were the indicated therapy. VAs >210 beats/min were directly attempted to be terminated by device shocks. Furthermore, atrial arrhythmia detection was set to >170 beats/min with supraventricular arrhythmia discriminators enabled. Settings were adapted, only if clinically indicated (e.g. hemodynamic well-tolerated ventricular tachycardia at high rate; ventricular tachycardia in the monitor zone).

Echocardiography

Transthoracic echocardiography was performed with the patients in left lateral decubitus position before CRT-D upgrade and at 6 months follow-up with commercially available ultrasound transducer and equipment (M4S probe, Vivid 7, GE-Vingmed, Horten, Norway). All images were digitally stored on hard disks for offline analysis (EchoPAC version 108.1.5, GE-Vingmed, Horten, Norway). LVESV, LV end-diastolic volume (LVEDV), and LVEF were measured from the apical 2- and 4-chamber views using the modified biplane Simpson's

method [16]. As previously described, response to CRT was defined by ≥15% reduction in LVESV at 6 months follow-up as compared with baseline echocardiogram (prior to CRT-D upgrade) [14].

Follow-up and definition of end points

Patients who were lost at follow-up or died before the 6-month echocardiography after CRT-D upgrade were excluded from the analyses. All remaining patients were followed in the ICD clinic at 3-6 monthly intervals. Occurrences of appropriate, successful ICD therapies were recorded as events. During device interrogation, episodes were assessed for appropriate ICD therapy (anti-tachycardia therapies or shocks) and verified by an electrophysiologist. Shocks were classified as appropriate when they occurred in response to ventricular tachycarrhythmia or ventricular fibrillation. Electrical storm was defined as three or more therapies for ventricular tachyarrhythmias within 24 hours [17].

The burden of VAs requiring ICD therapy or shock was determined by calculating the number of episodes per patient per year. ICD therapies delivered within 24 hours following the previous therapy were not included for the analysis of the burden of VAs. Separate analyses for appropriate shocks only and for appropriate therapies (including appropriate shock and anti-tachycardia pacing) were performed.

Statistical analysis

For reasons of uniformity, summary statistics for all continuous variables are expressed as mean and standard deviation. Dichotomous data are presented as numbers and percentages. Kolmogorov-Smirnov test was used to evaluate the distribution of continuous data. Student-t test was used to compare continuous data normally distributed whereas Mann-Whitney U-test was used to compare continuous data non-normally distributed. Categorical variables were compared with chi-squared test (when no cells had an expected frequency <5) and Fisher's exact test (when 1 or more cells had an expected frequency <5). Comparisons of continuous data at baseline and at 6 months follow-up were performed with paired Student-t test (when data distribution was normal) or Wilcoxon Signed Rank test (for continuous data non-normally distributed). Specifically, changes in NYHA functional class between baseline and 6 months follow-up were evaluated with Wilcoxon Signed Rank test since this parameter followed a non-normal distribution whereas changes in other clinical parameters (quality of life and 6-minute walk test) and echocardiographic parameters of LV function and volumes were compared with paired Student-t test. Variables related to VAs burden and appropriate ICD therapies and shocks were not normally distributed and therefore, changes between baseline and 6 months were evaluated with Wilcoxon Signed Rank test.

Cumulative event rates from the date of CRT-D upgrade until the last follow-up were calculated using the Kaplan-Meier method. The log-rank tests for time-to-event data with respect to the end points (appropriate shocks and appropriate therapies) were used for statistical comparison between the 2 patients groups dichotomized based on response to CRT at 6 months follow-up. Univariate and multivariate Cox proportional-hazards models were constructed to identify independent determinants of the end points (appropriate therapies and appropriate shocks) after CRT-D upgrade. All independent variables with a

p-value<0.25 were retained in the multivariate model. In addition, VT-ablation was entered as a time-dependent covariate. A p-value of <0.05 was considered significant. All statistical analyses were performed with SPSS software (version 18.0, SPSS Inc., Chicago, Illinois).

RESULTS

Patient population

A total of 123 patients underwent a successful CRT-D upgrade because of worsening symptoms of heart failure. Eight patients who were lost at follow-up (n=2, 2%) or died (n=6, 5%) before the 6-month echocardiography following CRT-D upgrade were excluded from the analysis. Consequently, 115 patients were included in the analysis with a mean follow-up of 54±34 months after ICD implantation and an additional mean follow-up of 37±27 months following CRT-D upgrade. Demographic, clinical and echocardiographic characteristics before CRT-D upgrade are summarized in Table 1. Mean age was 65±12 years and 92 (80%) were male. Ischemic heart failure etiology was recorded in the majority of the patients (75%). Most patients had NYHA functional class III heart failure symptoms (93%) and a severely depressed LV function, with a mean LVEF of 26±8%. Mean QRS duration was 167±35 ms. Finally, medical therapy included angiotensin-converting enzyme inhibitors (90%), diuretics (85%), beta-blockers (77%) and amiodarone (40%). During the entire follow-up of the study (from ICD implantation to last follow-up after CRT-D upgrade), 21 (18%) patients underwent successful VT ablation and 11 (10%) patients underwent successful atrioventricular junctional ablation. Seventeen (81%) and 4 (19%) patients underwent VT ablation before and after CRT-D, respectively.

Six months follow-up after CRT-D upgrade: clinical and echocardiographic parameters.

At 6 months follow-up after CRT-D upgrade, a significant improvement in clinical status and LV volumes and LVEF was observed in the overall population. NYHA functional class improved from 3.1±0.3 to 2.3±0.7 (p<0.001) and quality-of-life score decreased from 36±18 to 29±17 (p<0.001). In addition, the 6-minute walk distance increased from 320±129 m to 372±138 m (p<0.001). In the overall population, the LVESV and LVEDV reduced significantly (from 168±66 mL to 143±61 mL; p<0.001 and from 223±76 mL to 204±72 mL; p<0.001, respectively) with a significant increase in LVEF (from 26±8% to 31±9%, p<0.001).

Appropriate device therapy burden before and after CRT-D upgrade in the overall population

During the time elapsed between ICD implantation and CRT-D upgrade (54±34 months), 59 (51%) patients received appropriate therapies. The total number of appropriate therapies was 11±50 per patient and the burden of VAs was 0.46±0.75 per patient per year. The appropriate ICD shock burden was 0.36±0.77 per patient per year. A total of 8 (7%) patients experienced an electrical storm before CRT-D upgrade. Of the 59 patients receiving appropriate device therapy before CRT-D upgrade, 9 (15%) patients underwent VT-ablation. Cumulative incidence of device therapy was 29% (95% CI 21-37%) after one year, 36% (95% CI 27-45%) after two years, and 56% (95% CI 45-66%) after 5 years. After CRT-D upgrade,

Table 1. Patient characteristics at CRT-D upgrade.

Variable	N= 115
Age, years	65 ± 12
Male sex, n (%)	93 (81%)
Primary indication (%)	35 (30%)
QRS duration, ms	167 ± 35
History of Atrial fibrillation (%)	24 (21%)
Renal clearance, mL/min	63 ± 34
Ischemic heart disease, n (%)	86 (75%)
NYHA functional class, n (%)	
III	107 (93%)
IV	8 (7%)
6-Minute walk test, m	312 ± 130
Quality-of-life score	37 ± 18
Left ventricular end-diastolic volume, mL	225 ± 79
Left ventricular end-systolic volume, mL	169 ± 67
Left ventricular ejection fraction, %	26 ± 8
Device type	
Single-chamber (%)	36 (31%)
Dual-chamber (%)	79 (69%)
Medication	
Amiodarone, n (%)	46 (40%)
Anticoagulants, n (%)	100 (87%)
Diuretics, n (%)	98 (85%)
Ace-inhibitors/AT II antagonist, n (%)	104 (90%)
Beta-blocker, n (%)	89 (77%)
Spironolactone, n (%)	54 (47%)

Continuous variables are expressed as mean ± SD. ACE = angiotensin-converting enzyme; AT = angiotensin; NYHA = New York Heart Association.

49 (43%) patients experienced appropriate therapies during an additional mean follow-up of 37±27 months. The total number of appropriate therapies reduced to 5±17 per patient, although this change was not statistically significant (p=0.119). In addition, the frequency of VAs (0.66±1.70 per patient per year; p=0.775) and appropriate ICD shocks (0.52±3.01 per patient per year, p=0.218) remained unchanged. A total of 8 (7%) patients experienced an electrical storm after CRT-D upgrade. Of the 49 patients receiving appropriate device therapy after CRT-D upgrade, 11 (22%) patients underwent VT-ablation. Cumulative incidence of device therapy was 25% (95% CI 17-34%) after one year, 34% (95% CI 25-44%) after two years, and 62% (95% CI 49-75%) after 5 years. Finally, a total of 34 (30%) patients died after CRT-D upgrade.

Changes in appropriate device therapy burden after CRT-D upgrade according to the echocardiographic response

Based on a reduction of LV end-systolic volume ≥15% at 6 months follow-up after CRT-D upgrade, 70 (61%) patients were responders. Table 2 summarizes the changes in clinical status and echocardiographic parameters at 6 months follow-up after CRT-D upgrade for both groups of patients, responders and non-responders.

In the group of responders, the percentage of patients who received appropriate device therapies decreased from 54% to 33% after CRT-D upgrade. In addition, the total number of appropriate device therapies also decreased from 12±62 to 2±4 per patient after CRT-D upgrade. Furthermore, the frequency of VAs requiring appropriate device therapy demonstrated a trend toward a decrease from 0.51±0.79 to 0.30±0.59 per patient per year after CRT-D upgrade (p=0.052) (Figure 1). Interestingly, the frequency of appropriate device shocks reduced significantly from 0.21±0.32 to 0.11±0.33 per patient per year (p=0.009) (Figure 1). Furthermore, in the group of responder patients to CRT, 3 (4%) patients experienced an electrical storm and 12 (17%) patients underwent VT-ablation. In the group of patients who did not show response to CRT, the percentage of patients who received appropriate device therapies was 47% before CRT-D upgrade and 58% after CRT-D upgrade. In these patients, the total number of appropriate device therapies per patient was 8±22 prior to CRT-D upgrade and 10±25 after CRT-D upgrade. In addition, the frequency of appropriate device shocks remained unchanged after CRT-D upgrade (from 0.24±0.52 to 0.46±1.23 per patient per year, p=0.333) (Figure 1). In contrast, the frequency of VAs significantly increased from 0.40±0.69 per patient per year before CRT-D upgrade to 1.21±2.53 per patient per year after CRT-D upgrade (p=0.014) (Figure 1). In the non-

Table 2. Clinical and echocardiographic parameters at 6 months follow-up in responders and non-responders to CRT-D.

	Responder			Non-responder		
	Baseline	6 month	P-value	Baseline	6 month	P-value
NYHA functional class, n (%)			<0.001*			0.211*
I	0	10 (13)		0	4 (9)	
II	0	39 (52)		0	22 (49)	
III	71 (95)	25 (33)		41 (91)	17 (38)	
IV	4 (5)	1 (1)		4 (9)	2 (4)	
6 MWT, m	339±137	382±146	0.009	291±113	357±124	0.001
QoL score	36±18	29±17	0.001	36±17	27±17	0.005
LVEDV, mL	227±72	190±65	<0.001	216±82	223±77	0.113
LVESV, mL	172±62	128±51	<0.001	163±72	164±67	0.879
LVEF, %	25±9	33±9	<0.001	26±7	27±8	0.140

Continuous variables are expressed as mean ± SD. 6 MWT = 6 min walk test; QoL = Quality-of-life; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association.

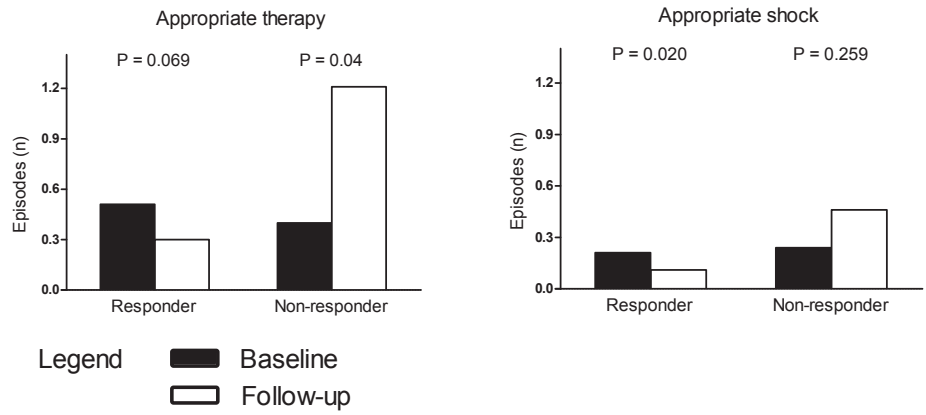

Figure 1. Changes in the number of episodes of appropriate ICD therapy and appropriate ICD shocks per patient per year in responders and non-responders to CRT.

responder patients group, 5 (11%) patients experienced an electrical storm and 9 (20%) patients underwent VT-ablation.

Predictors of combined end point after CRT-D upgrade

Figure 2 shows the Kaplan-Meier estimates of the combined end point (appropriate ICD therapies) for responder and non-responder patients after CRT-D upgrade. The cumulative incidence for appropriate ICD therapy in the group of responder patients was 19% (95%

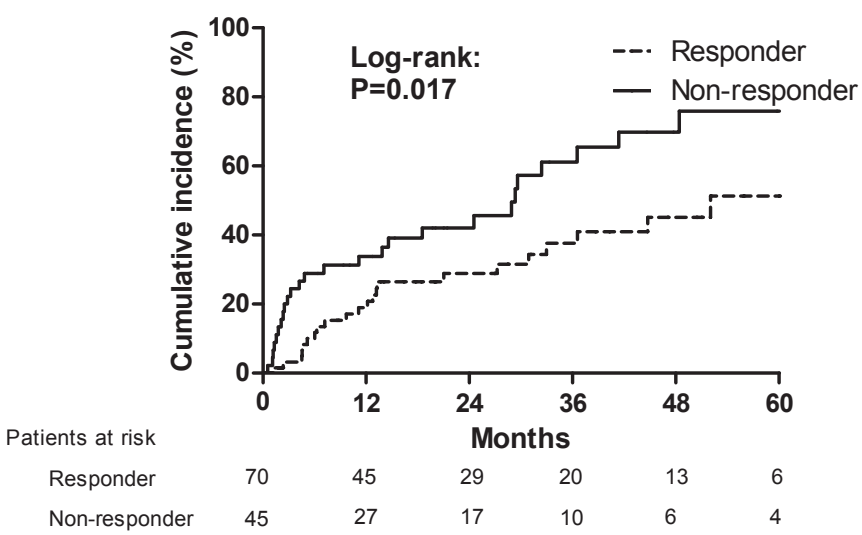

Figure 2. Kaplan-Meier curve for appropriate ICD therapy in responders and non-responders following CRT up-grade.

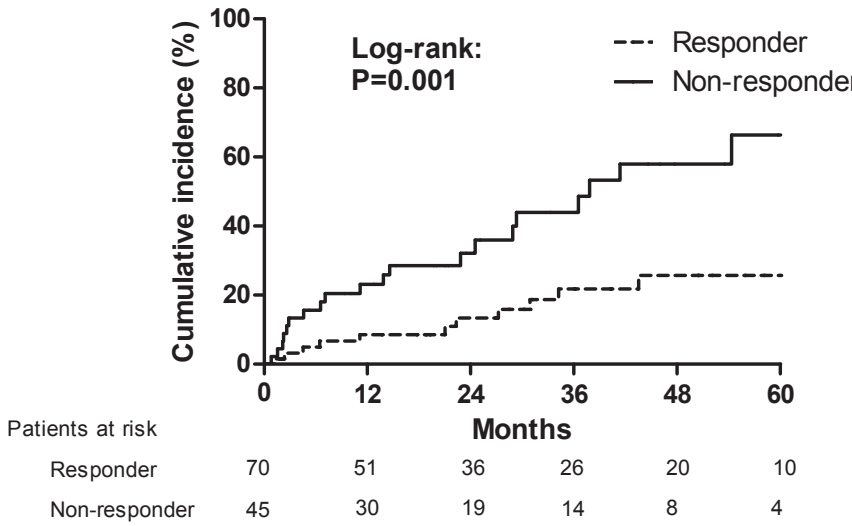

Figure 3. Kaplan-Meier curve for appropriate ICD shock in responders and non-responders following CRT up-grade.

CI 9-29%) after one year, 29% (95% CI 17-41%) after two years, and 51% (95% CI 33-69%) after 5 years. In contrast, in the group of non-responders a significantly higher cumulative incidence of 34% (95% CI 20-48%) after one year, 42% (95% CI 27-57%) after two years, and 76% (95% CI 59-93%) after 5 years was observed (log rank p=0.017).

Regarding appropriate ICD shocks, cumulative incidences in responder patients at one, two and 5 years of follow up were 9% (95% CI 1-16%), 13% (95% CI 4-23%), and 26% (95% CI 12-40%), respectively. In contrast, the group of non-responders showed significantly higher cumulative incidences of ICD shocks: 23% (95% CI 11-36%) after one year, 32% (95% CI 17-47%) after 2 years, and 66% (95% CI 45-88%) after 5 years (log rank p=0.001) (Figure 3).

On multivariate Cox regression analysis, response to CRT defined as reduction in LVESV≥15% was independently associated with lower risk of appropriate ICD therapies (hazard ratio: 0.439 [95% CI: 0.245-0.786], p<0.001) (Table 3) and ICD shocks (hazard ratio: 0.354 [95% CI: 0.167-0.750], p=0.007) (Table 4).

DISCUSSION

The findings of the present study can be summarized as follows: 1) "upgrade" of ICD to CRT-D did not result in a significant change in the frequency of appropriate ICD therapies and shocks in the overall population; 2) responder patients to CRT-D (with a significant reduction in LVESV at 6 months follow-up) demonstrated a trend towards a reduction in the frequency of appropriate device therapies and a significant reduction in the frequency of appropriate device shocks; 3) in contrast, patients who did not show response to CRT had a significant increase in the frequency of VAs requiring device therapy.

Table 3. Cox proportional hazard ratio model to predict appropriate ICD therapies.

	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Gender, male	1.011	0.472-2.163	0.978			
NYHA functional class	1.451	0.443-4.757	0.539			
Ischemic cardiomyopathy	0.675	0.362-1.257	0.215*	0.522	0.273-0.999	0.049
Creatinine clearance (mL/min)	1.001	0.993-1.010	0.740			
Amiodarone	0.632	0.347-1.153	0.135*	0.598	0.323-1.110	0.107
Response to CRT	0.509	0.290-0.893	0.019*	0.439	0.245-0.786	<0.001
Interim successful VT ablation	1.375	0.487-3.885	0.548			

*CI = confidence interval; CRT = cardiac resynchronization therapy; HR = hazard ratio; NYHA = New York Heart Association; VT = ventricular tachycardia. *variable was included in multivariate analysis.*

Table 4. Cox proportional hazard ratio model to predict appropriate ICD shocks.

	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Gender, male	1.066	0.437-2.599	0.889			
NYHA functional class	2.004	0.604-6.651	0.256			
Ischemic cardiomyopathy	0.977	0.437-2.188	0.956			
Creatinine clearance (mL/min)	0.991	0.977-1.004	0.174*	0.993	0.980-1.007	0.326
Amiodarone	0.874	0.424-1.803	0.715			
Response to CRT	0.319	0.153-0.668	0.002*	0.354	0.167-0.750	0.007
Interim successful VT ablation	2.038	0.702-5.915	0.190*	1.987	0.683-5.783	0.208

*CI = confidence interval; CRT = cardiac resynchronization therapy; HR = hazard ratio; NYHA = New York Heart Association; VT = ventricular tachycardia. *variable was included in multivariate analysis*

Effect of CRT upgrading on the occurrence of VAs

In the present study, the overall population showed significant clinical and echocardiographic improvements at 6 months follow-up after CRT. These findings are in line with previous studies in which CRT is associated with an improved clinical and echocardiographic outcome in heart failure patients (12). Interestingly, these improvements in clinical status and LV systolic performance was not accompanied by a significant change in the number of appropriate ICD therapies or the burden of ICD shocks.

The effects of CRT upgrade on VAs have remained controversial, so far. In a study by Ermis et al., in which 18 consecutive ICD patients underwent an "upgrade" to CRT-D, the frequency of arrhythmias and number of appropriate device therapies were reduced following CRT-D implantation (8). The appropriate shock burden in these 18 patients was 0.58±1.02 per patient per year prior to CRT and declined significantly (p=0.05) to

0.04±0.19 per patient per year following CRT. Similar results were found in the study by Kiès et al., in which 17 consecutive ICD patients underwent an "upgrade" to CRT-D (9). In that study, the number of VAs was significantly ($P < 0.01$) reduced from 0.92±2.2 episodes per patient per month to 0.12±0.2 episodes per patient per month after CRT-D upgrading. Permanent biventricular pacing has been proposed as one of the mechanisms to reduce the frequency of VAs requiring ICD therapy. During permanent biventricular pacing, the ventricular conduction delay is reduced leading to a decrease in the occurrence of re-entry, avoidance of pause-dependent tachyarrhythmias and reduction in the circulating levels of norepinephrine, all known mechanisms that may trigger VAs [18, 19]. However, on the other hand, both basic science and clinical studies have shown a proarrhythmic effect of biventricular pacing due to a reversed direction of activation of the left ventricular wall. This reversal of the normal activation sequence may prolong the QT interval and increase the existing transmural dispersion of repolarization, creating the substrate and trigger for re-entrant arrhythmias [20].

Interestingly, in the Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD) trial, the occurrence of appropriate ICD therapies or shocks in the group of patients who received CRT-D did not show a significant reduction [21]. In this trial, a total of 369 patients with moderate to severe heart failure symptoms and wide QRS complex were randomized to biventricular ICD (CRT on group) or to ICD only (CRT off group). There were no significant differences between both groups with respect to the occurrence of appropriate therapies and/or appropriate shocks, despite improved quality of life, functional status and exercise capacity in the CRT group [21]. In addition, in the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study, in which 508 mild heart failure patients were randomized to activated CRT (CRT ON) and activated ICD (CRT OFF), the estimated event rate for a first treated VA episode was not significantly different between the two groups after 2 years follow-up period (18.7% in the CRT ON group vs. 21.9% in the CRT OFF group, $p=0.84$) [22]. The event rates observed in the REVERSE study are significantly lower as compared to the results of the present study. However, it must be noted that in the REVERSE study only subjects with mild heart failure were included and therefore the reported outcomes may not necessarily apply to patients with more severe symptoms of heart failure as those included in the current analysis. The presence of more advanced heart failure status with dilated LVs may be associated with an increased likelihood of VAs requiring device therapy [10]. Based on this assumption, it can be hypothesized that patients with LV reverse remodeling following CRT may show a significant reduction in the incidence of VAs when compared with the patients who do not show LV reverse remodeling following CRT.

Device therapy in responders and non-responders

Gold et al., showed that the antiarrhythmic effect of CRT could be explained by induction of a favourable LV reverse remodelling and decreased myocardial wall tension and electrical stabilization of the myocyte membranes [22]. In the present study, the group of responders to CRT showed a trend toward a reduction in the number of appropriate device shocks after CRT upgrading. In the REVERSE study, in which the patients from the CRT ON group who showed LV reverse remodelling had a decrease in the incidence of VAs compared with

those without such a favourable reverse remodelling (5.6% vs 16.3%, Hazard Ratio=0.31, p=0.001) [22]. These findings may confirm the hypothesis of Gold and co-workers in that the improvement in LV dimensions and function, accompanied by a reduction in wall tension, results in a decreased arrhythmogenicity of the myocardium and reducing ICD therapy in responders to CRT-D (after upgrade). Additional studies are warranted in order to elucidate how much LV reverse remodelling is needed to minimize the number of appropriate ICD therapies in patients who were upgraded to CRT.

Study limitations

A number of limitations should be acknowledged. This was a retrospective observational analysis of prospectively assessed data evaluating the occurrence of VAs requiring appropriate device therapy in a cohort of patients before and after CRT-D upgrade. Since patients received ICDs in a single center over a long period of time, evolving guidelines may resulted in a heterogeneous population. Furthermore, few patients had multiple device therapies within 24 hours following the previous therapy. These episodes were not counted for analysis of the burden of ventricular arrhythmias. In addition, since all CRT-D devices had antitachycardia treatment function and the oldest implanted ICD devices did not have this function, the number of appropriate shocks in the ICD group might be overestimated when compared with the CRT-D group. To date, definition of response to CRT is still a debated issue. In the present evaluation, a cut-off value of 15% reduction in LVESV was used to divide the patient population in responders and non-responders to CRT. Using the median value of LVESV reduction at 6 months follow-up would be a valuable option to dichotomize the population. However, in the present evaluation this value was 17% and the analysis based on the median reduction in LVESV yielded similar results. In addition, further studies are needed in order to evaluate if LV reverse remodeling occurs beyond 6 months follow-up after CRT-D upgrade and if this may result or not in further reduction in VA burden.

CONCLUSION

In this large single-centre study, the frequency of VAs requiring appropriate device therapy did not significantly change in the overall population following "upgrade" of ICD to CRT-D. Most important however, in the subgroup of patients who showed echocardiographic response to CRT at 6 months follow-up (reduction in LV end-systolic volume ≥15%), a trend toward a reduction in the frequency of appropriate device therapies and a significant reduction in the frequency of appropriate device shocks was observed. Moreover, echocardiographic non-responders following CRT-D had a significant increase in the frequency of VAs requiring device therapy when compared to the period prior to CRT.

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5

Chapter 5

Suitability for Subcutaneous Defibrillator Implantation: Results Based on Data from Routine Clinical Practice

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ABSTRACT

Aims

Currently, Implantable Cardioverter Defibrillators (ICDs) rely on transvenously implanted leads for cardiac sensing, pacing, and defibrillation. Recently, an ICD with a subcutaneous lead (S-ICD) was developed which may be easier to implant and has fewer device related-complications. Since the S-ICD is incapable of cardiac pacing, it is of interest what proportion of ICD recipients is suitable for an S-ICD and what the characteristics of these patients are.

Methods and Results

The study cohort consisted of all patients who received a single or dual-chamber ICD in our center between 1996 and 2011. Patients without a preexistent indication for pacing were defined suitable for an S-ICD if they did not reach one of the following endpoints during follow-up: 1) an atrial and/or right ventricular pacing indication, 2) successful antitachycardia pacing without a subsequent shock, 3) an upgrade to a CRT-D device. A total of 1,742 patients were included in the analysis. During a median follow-up of 3.3 years (interquartile range, 1.8 – 5.6 years), 627 (36%) patients reached an endpoint. The cumulative incidence of ICD recipients, suitable for an initial S-ICD implantation was 60.2% (95% CI 57.4%-62.9%) after 5 years. Significant predictors for the unsuitability of an S-ICD were: older age, secondary prevention, severe heart failure, atrial fibrillation, and a wide QRS.

Conclusion

After 5 years of follow-up, approximately 60% of the patients would have been suitable for an S-ICD implantation. Several baseline clinical characteristics were demonstrated to be useful in the selection of patients suitable for an S-ICD implantation.

INTRODUCTION

In the past decades implantable cardioverter-defibrillators (ICDs) have become an established therapy for the prevention of sudden cardiac death.[1-4] Since the first implantation in 1980, ICDs have undergone many improvements and have evolved from large abdominally placed devices into substantially smaller devices placed pectorally.[5] Currently, ICDs rely on transvenously implanted leads for cardiac sensing, defibrillation, and if necessary also for cardiac pacing. Recently however, a new, entirely subcutaneous, ICD system avoiding the need for the placement of sensing and therapy electrodes within or on the heart has been developed. Initial results demonstrated that this device adequately detected and treated episodes of sustained ventricular tachyarrhythmia.[6] It is suggested that the subcutaneous ICD might be easier to implant and will result in a lower proportion of device related complications when compared with a transvenously implanted ICD.[6] However, despite the supposed advantages, an important drawback of the subcutaneous ICD is the incapability of cardiac pacing.[7] Therefore, patients that have a cardiac (atrial and or ventricular) pacing indication at implantation are unsuitable for such a device. Moreover patients that develop such an indication during follow-up would preferably also not receive a subcutaneous ICD. Furthermore, the latter device is also not capable of antitachycardia pacing (ATP), resulting in a diminished suitability for the subcutaneous ICD in patients receiving successful ATP for ventricular arrhythmias. Finally, for patients requiring an upgrade to a cardiac resynchronization therapy defibrillator (CRT-D) due to worsening heart failure, an initial transvenously implanted ICD is preferred over a subcutaneous implanted ICD.

The objective of this study was to establish, in a large clinical cohort of ICD recipients, the suitability for an entirely subcutaneous ICD system. Furthermore, among baseline clinical parameters, predictors of the unsuitability for a subcutaneously implanted ICD were established.

METHODS

Patients

This retrospective analysis comprised all consecutive patients who received an ICD system at Leiden University Medical Center. Implant procedures were registered in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center). Characteristics at baseline, data of the implant procedure and all follow-up visits were recorded. The data for the current registry were collected between January 1996 and April 2011.

Eligibility for ICD implantation in this population was based on international guidelines for primary and secondary prevention. Due to evolving guidelines, indications will have changed over time.[8, 9]

Device implantation and programming

All defibrillator system implantations were performed transvenously, without thoracotomy. During the implant procedure, sensing and pacing thresholds were determined and a

defibrillation test was performed. Used systems were manufactured by Biotronik (Berlin, Germany), Boston Scientific [Natick, MA, USA, formerly CPI, Guidant (St Paul, MN, USA)], Medtronic (Minneapolis, MN, USA), and St Jude Medical/Ventritex (St Paul, MN, USA).

Devices were programmed according to a strict protocol to guarantee uniformity. In single-chamber ICD recipients, cardiac stimulation parameters were set to VVI 40. In dual-chamber ICDs, a non-tracking backup mode of DDI 40 was programmed with sufficiently long AV delay to secure intrinsic conduction at the lower rate. If applicable, algorithms such as managed ventricular pacing (MVP) or remote mode switching (RMS) were also used to avoid unnecessary right ventricular pacing.[10]

The antitachycardia modes in all devices were programmed with three consecutive zones with limits slightly varying per manufacturer: a monitor zone (lower limit between 150-155 bpm; upper limit between 185-190 bpm), an antitachycardia pacing (ATP) shock zone (lower limit between 185-190 bpm; upper limit between 205-210 bpm), and an initial shock zone (≥205-210 bpm). In the monitor zone, no therapy was programmed unless a ventricular arrhythmia was detected during follow-up. In the ATP-shock zone, arrhythmias were initially attempted to be terminated by two bursts of ATP and, if the arrhythmia persisted, defibrillator shocks were used. In case of a ventricular arrhythmia faster than the ATP shock zone, device shocks were the initial therapy. Detection times or number of intervals for ATP treatment were programmed as follows: 26 intervals for Biotronik, 1.5 seconds for Boston Scientific/Guidant, 18 out of 24 intervals for Medtronic and 12 intervals for St Jude Medical/Ventritex devices. Furthermore, atrial arrhythmia detection was set to >170 bpm with supraventricular tachycardia discriminators enabled. Therapy settings were adapted, only when clinically indicated.

Device interrogation was scheduled every 3-6 months after implantation. Delivered therapies were then adjudicated by a trained electrophysiologist. Data of these ICDs were included until the last date of ICD check-up.

Endpoints

Patients who received a CRT-D device were not included in the current analysis. Furthermore, all patients who were pacemaker-dependent or had another clear indications for pacing directly following implantation (i.e. settings other than VVI 40 or DDI 40) were excluded from the study population.[8, 9] (Figure 1) For the remaining patients (i.e. the study population) the combined primary endpoint of this analysis was the unsuitability for an S-ICD, which was defined as the occurrence of one of the following individual endpoints:

1. The development of an atrial and/or right ventricular pacing indication:
   In the event that patients during follow-up required atrial and/or right ventricular pacing, this was considered as the development of a pacing indication.[8, 9] Also, if the pacing settings of the ICD required adaptation by the treating physician (e.g. due to a reduced heart rate on heart rate histogram in combination with fatigue), this was considered as the development of a pacing indication. Furthermore, when the pace burden significantly increased between 2 routine follow-up visits (pace burden became >20%), it was also considered as an indication for pacing. The date at which the development of a pacing indication became apparent was considered the date of the endpoint.

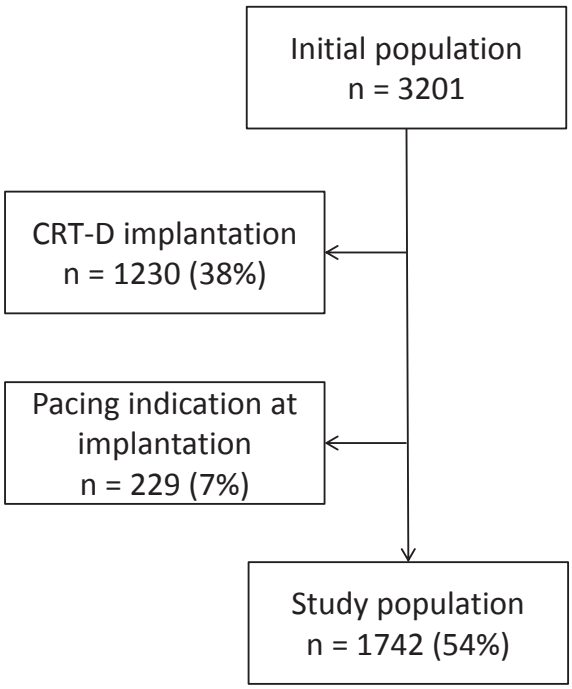


Figure 1. Flowchart describing the selection of the study population.

2. ATP delivery: the first date of successful appropriate ATP (i.e. without subsequent appropriate shock) was considered the endpoint.
3. Device upgrade: if a patient required upgrade to a CRT-D device (NYHA III/IV despite optimal medical therapy, LVEF ≤35% and QRS ≥120ms or NYHA II despite optimal medical therapy, LVEF ≤35%, QRS ≥150ms, and sinusrhythm), the date of the upgrade was considered as the endpoint.[11, 12]

For all patients, the first date at which a patient reached one of the above endpoints was considered the date for reaching the primary endpoint. If the patient did not develop one of the above mentioned endpoints, the patient was censored at the date of last ICD follow-up.

If a patient deceased during follow-up, censoring at the date of death occurred.

Statistical analysis

Continuous data are expressed as mean and standard deviation (SD) or median with 25th and 75th percentile where appropriate; dichotomous data are presented as numbers and percentages.

Event-free rates from all three individual endpoints, indicating the suitability for an S-ICD (i.e. patients without pacing dependence, ATP delivery or device upgrade during

follow-up), were analyzed separately using the method of Kaplan-Meier and the log-rank test. Consequently, also the combined endpoint was analyzed using the same statistical tests. In patients with more than one endpoint, the date of the first endpoint was used for analysis with the method of Kaplan-Meier and the log-rank test. In order to correct for competing risk of the S-ICD unsuitability (i.e. death), a competing-risk model was used.[13, 14] Univariate and multivariate Fine-Gray regression models were constructed to identify independent determinants of the combined endpoint.[15] All variables with a p-value<0.20 in univariate analysis were retained in the multivariate model. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS software (version 18.0, SPSS Inc., Chicago, Illinois) and R software (version 2.15.1, R Foundation, Vienna, Austria).

RESULTS

Patients

During the study period, a total of 3,201 patients received a ventricular antitachycardia device. Of these, 38% (n=1230) received a CRT-D and 7% (n=229)were pacing dependent directly following implantation . Consequently, these patients were excluded from the current analysis. (Figure 1) The remaining 1,742 (54%) patients were considered the study population and had a median follow-up of 3.3 years (interquartile range, 1.8 – 5.6 years). Of these patients (80% men, average age 59 ± 14 years), 47% received an ICD for primary prevention. (Table 1)

Follow-up

In primary prevention patients, the 5 year cumulative incidence for an appropriate shock was 15.2% (95% CI 11.9 – 18.5%) and the 5-year cumulative incidence for an inappropriate shock was 24.3% (95% CI 20.4 – 28.2%). At the end of follow-up, 94 (12%) patients were deceased, which resulted in a cumulative incidence for all-cause mortality of 14.0% (95% CI 10.9% – 17.1%) at 5 years following device implantation.

In secondary prevention patients, 5-year cumulative incidences for appropriate and inappropriate shock were 35.2% (95% CI 31.5 – 38.9%) and 24.3% (95% CI 21.0 – 27.6%) respectively. A total of 241 (26%) of these patients died, resulting in a 5-year cumulative incidence for all-cause mortality of 18.6% (95% CI 15.7% – 21.5%) following ICD implantation.

Incidence of the individual endpoints:

During follow-up, 215 (12%) patients developed an indication for atrial and/or ventricular pacing. The cumulative incidence for the necessity of cardiac pacing was 4.2% (95% CI 3.2% to 5.3%) at 1 year follow-up and increased to 13.0% (95% CI 11.1% to 15.0%) at 5 years follow-up. (Figure 2a)

With respect to ATP, a total of 472 patients (27%) experienced at least one successful appropriate ATP delivery during follow-up. Consequently, the cumulative event rate for a first successful appropriate ATP was 11.3% (95% CI 9.8% to 12.9%) at 1 year follow-up and increased to 27.9% (95% CI 25.5% to 30.4%) at 5 years follow-up. (Figure 2b)

Table 1. Baseline clinical characteristics.

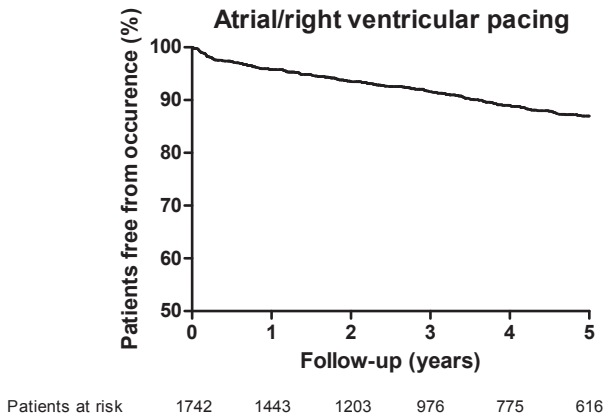
	Total (n = 1742)	Primary prevention (n = 817)	Secondary prevention (n = 925)
Clinical characteristics			
Age, mean (SD), years	59 ± 14	58 ± 13	60 ± 15
Male (%)	1394 (80)	656 (80)	738 (80)
Ischemic heart disease (%)	1170 (67)	553 (68)	617 (67)
Monogenetic congenital heart disease (%)	136 (8)	84 (10)	52 (6)
Structural congenital heart disease (%)	30 (2)	13 (2)	17 (2)
LVEF (%)	39 ± 16	36 ± 15†	41 ± 16
QRS duration, mean (SD), ms	111 ± 27	108 ± 24	114 ± 29
NYHA functional class III/IV (%)	207 (12)	114 (14)	93 (10)
Renal clearance, mean (SD), mL/min	86 ± 40	89 ± 36	85 ± 42
History of atrial fibrillation (%)	318 (18)	141 (17)	177 (19)
Device type			
Single-chamber (%)	388 (22)	92 (11)	296 (32)
Dual-chamber (%)	1354 (78)	725 (89)	629 (68)
Medication			
Statins (%)	977 (56)	529 (65)	448 (48)
Diuretics (%)	830 (48)	436 (53)	394 (43)
ACE inhibitors/AT II antagonist (%)	1195 (69)	624 (76)	571 (62)
Calcium antagonist (%)	177 (10)	89 (11)	88 (10)
Antiarrhythmic medication			
Beta-blockers* (%)	863 (50)	491 (60)	372 (40)
Sotalol* (%)	301 (17)	107 (13)	194 (21)
Amiodarone* (%)	275 (16)	68 (8)	207 (22)
Antiarrhythmic medication combined* (%)	1329 (76)	631 (77)	698 (75)

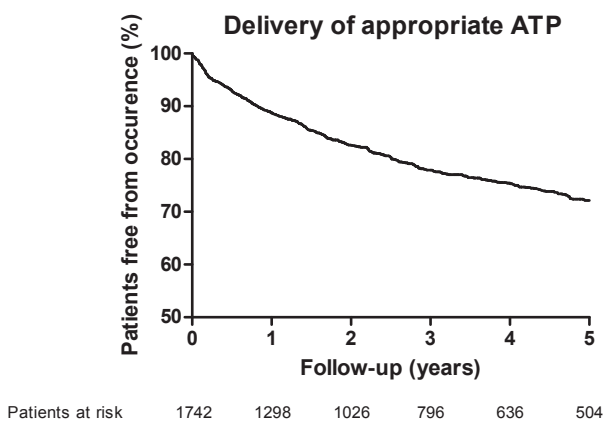
*ACE = angiotensin-converting enzyme; AT = angiotensin; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SD = standard deviation. * Patients could be taking >1 antiarrhythmic drug. † The mean is above 35% due to substantial proportion of patients with a congenital heart disease (e.g. hypertrophic cardiomyopathy).*

CRT-D upgrades were performed, according to the then current guidelines, in 121 (7%) of the patients. Consequently, the cumulative incidence for the requirement of a CRT-D upgrade was 0.3 (95% CI 0.1% to 0.7%) at 1 year follow-up and increased to 5.9% (95% CI 4.6% to 7.3%) at 5 years follow-up. (Figure 2c)

Incidence of the combined endpoint:

The combined endpoint (the necessity for cardiac pacing, appropriate ATP without subsequent shock or device upgrade) was reached in 627 patients (36%). At 1 year follow-up the cumulative incidence of the combined endpoint was 14.8% (95% CI 13.1% to 16.6%) (i.e. S-ICD suitability 85.1%) which increased to 39.8% (95% CI 37.1% to 42.6%) (S-ICD





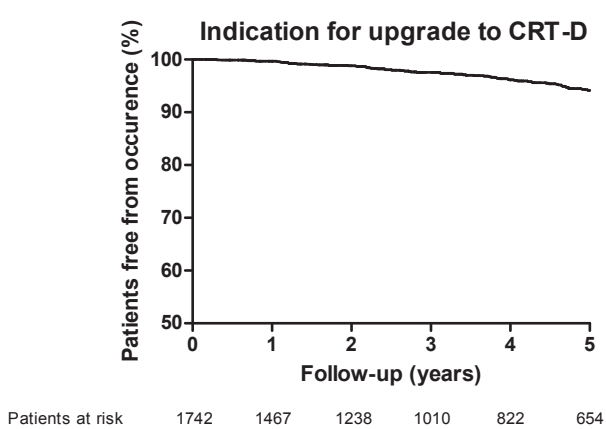


Figure 2. Kaplan-Meier curve showing the cumulative event-free survival of A) the occurrence of atrial and/or right ventricular pacing; B) delivery of ATP; C) indication for upgrade to CRT-D.

suitability 60.2%) at 5 years follow-up. (Figure 3) Appropriate ATP and the necessity of cardiac pacing resulted in the unsuitability for an S-ICD in approximately 90% of the cases, whereas device upgrade was responsible for the unsuitability in approximately 10% of the cases.

Monogenetic congenital heart disease

A monogenetic congenital heart disease (e.g. Brugada syndrome, hypertrophic cardiomyopathy) was present in 136 (8%) of the patients included in the current study. (Table 1) Eighty-four patients had a primary prevention indication and of these, 16 (19%) patients received appropriate ATP, 2 (2%) patients underwent a CRT-D upgrade, and 8 (10%) patients developed the necessity for cardiac pacing. This resulted in a cumulative incidence for the combined endpoint of 9.9% (95% CI 2.6% to 15.2%) at 1 year follow-up and 24.6% (95% CI 14.2% to 35.0%) at 5 year follow-up. For secondary prevention patients with a monogenetic heart disease (n = 52), ATP occurred in 14 (27%) patients, a CRT-D upgrade was performed in 1 (2%) patient, and 12 (23%) patients required cardiac pacing. This resulted in a cumulative incidence for the combined endpoint of 18.8% (95% CI 7.6% to 30.0%) at 1 year follow-up and 47.4% (95% CI 31.9% to 62.9%) at 5 year follow-up for secondary prevention patients with a monogenetic congenital heart disease.

Predictors of the unsuitability for an S-ICD

A Fine-Gray regression analysis was performed in order to establish determinants of the unsuitability for an S-ICD. Multivariate analysis controlling for factors with a univariate p value < 0.2 indicated that secondary prevention (HR 1.54; 95% CI 1.29 - 1.85, p <0.01), NYHA class III/IV (HR 1.68; 95% CI 1.36 - 2.07, p<0.01), history of atrial fibrillation (HR 1.31; 95% CI 1.04 1.65, p<0.05), and QRS duration (HR 1.24 per 30ms increase; 95% CI 1.13 - 1.36, p<0.01) were independent determinants of the unsuitability for an S-ICD. (Table 2)

Figure 3. Kaplan-Meier curve showing the cumulative suitability for an S-ICD.

DISCUSSION

In the assessment of the suitability for an S-ICD, findings can be summarized as follows: 1) a considerable proportion (60.2%) of the patients, currently having a transvenously implanted ICD without a preexistent indication for pacing, could have been considered suitable for an S-ICD implantation, retrospectively, after 5 years of follow-up; 2) a sub-analysis in patients with a structural or monogenetic congenital heart disease demonstrated that after 5 years of follow-up, approximately 75% of primary prevention ICD recipients with a monogenetic heart disease would have been suitable for an S-ICD implantation; 3) important predictors for the unsuitability of an S-ICD are: secondary prevention, severe heart failure, atrial fibrillation, and prolonged QRS duration.

Unsuitability for the S-ICD

In the current analysis, 3 variables excluding the suitability for an S-ICD implantation were defined and merged as a combined endpoint. Firstly, those who developed an indication for atrial and/or right ventricular pacing during follow-up were considered unsuitable for an S-ICD.[8, 9] It is conceivable that these patients would be better off with a transvenously implanted device system, which would only require changes in device settings, when the patient develops a pacing indication. Based on the results of the current study, atrial and/or right ventricular pacing during follow-up was indicated approximately in 12% of the patients. The significant proportion of patients who developed an indication for atrial and/or right ventricular pacing during follow-up, underlines the importance of an adequate selection of patients suitable for an S-ICD implantation. Hence, implantation of an S-ICD in these patients would otherwise result in unnecessary additional procedures (i.e. pacemaker implantation or conventional ICD implantation).

The second distinguishing difference between the subcutaneous and conventional ICD is the ability for the delivery of ATP. ATP has proven to effectively and safely terminate life threatening ventricular tachycardias and thereby avoiding the consequences of painful shocks.[16, 17] Therefore, ATP is currently programmed as the initial therapy for life threatening ventricular tachyarrhythmias in conventional devices followed by device shocks if conversion to a normal rhythm is unsuccessful. Although S-ICDs have the ability to successfully terminate life threatening ventricular arrhythmias (i.e. ventricular tachyarrhythmias and ventricular fibrillation) with shocks, they are unable to deliver ATP. This might be considered an important drawback since it has been reported that ICD patients who receive shocks might exhibit a decline in the quality of life.[18] Therefore, for this study, the first date of successful appropriate ATP (i.e. without subsequent appropriate shock) was registered as an endpoint. According to the results of the present study, 27% of the patients implanted with a conventional ICD would be considered unsuitable for an S-ICD implantation because of the delivery of successful appropriate ATP.

It is however important to realize that due to a short detection time or low number of intervals, a number of these appropriate ATPs are treating potentially self-limiting VTs and therewith overestimate the proportion of patients unsuitable for an S-ICD implantation.[19, 20]

The third and last variable included in the combined endpoint is the upgrade to a CRT-D device. During follow-up, ICD patients may require an upgrade to a CRT-D system due to a deterioration of heart failure.[11, 12] In these patients, conventional ICD upgrade would require pulse generator replacement and implantation of a left ventricular pacing lead. However, if those patients were implanted with an S-ICD, upgrading to a CRT-D device would often require total explantation of the S-ICD and corresponding lead, followed by the implantation of the CRT-D in the pectoral region with corresponding transvenous leads. This strategy would most likely be more cumbersome and inefficient for the health care system. Therefore, upgrading from a conventional ICD is preferable and makes patients in whom during follow-up an upgrade becomes necessary unsuitable for an S-ICD implantation. Based on the results of the current study, approximately 7% of the patients underwent CRT upgrade and would consequently be considered unsuitable for an S-ICD implantation. However, with expanding indications for CRT-D, a higher proportion of patients will be eligible for initial CRT-D implantation or CRT-D upgrade and becomes unsuitable for an S-ICD implantation.[21, 22]

ICD or S-ICD

Conventional ICDs are associated with specific complications that might be overcome with an S-ICD. For instance, several complications associated with transvenous leads, such as not reaching vascular access, pneumothorax, and lead dislodgement can be avoided with the implantation of an S-ICD . Although it should be noted that these complications do not occur frequently and that S-ICDs might have their own unrevealed implantation related complications.[23] Another suggested advantage of S-ICDs over conventional ICDs is the preservation of venous access for other uses (i.e. central line, etc.). It has been reported that transvenous system implantation is frequently associated with venous lesions and accordingly with total venous obstruction in approximately 3.6% of the patients.[24] Finally, it is suggested that the removal of failed leads is more difficult and dangerous in patients with a transvenous system. On the other hand, recent reports indicate that transvenous leads can be removed with high success rates and low concomitant adverse events.[25] It should however be noted that the risk for adverse events during the removal of an S-ICD lead compared with the removal of conventional ICD leads is currently lacking.

Even though there might be certain advantages for an S-ICD compared to a conventional ICD in patients that can be considered suitable for such a device, it should be kept in mind that current data regarding S-ICDs are scarce and true comparisons regarding efficacy, safety and cost-effectiveness with conventional ICDs cannot (yet) be made. Consequently, conclusions regarding the potential benefits of an S-ICD would currently be preliminary and therefore should be carefully drawn.

Who are suitable for an S-ICD

Patients who remain free from the combined endpoint of ATP, development of an atrial and/or right ventricular pacing indication or the necessity for an upgrade to a CRT device, are patients who are most likely to benefit of the suggested advantages of an S-ICD. Based on the results of this study, it can be concluded that the patients most likely to benefit from an

S-ICD are in sinus rhythm, have a primary prevention indication, and have a relative good condition and no evidence of electrical dyssynchrony. Moreover, it should be noted that also primary prevention ICD recipients with a monogenetic congenital heart disease are likely to benefit from an S-ICD implantation.

Study limitations

There are several limitations to this analysis assessing the suitability for an entirely subcutaneous ICD system. Since this is a retrospective single center study, ascertainment bias could have influenced the results. Also, ICD tachycardia therapy programming was not homogeneous, since in the minority of the patients, ICD settings were adapted when clinically indicated. Moreover, it should be emphasized that a pace burden > 20%, in the current study considered as the development of a pacing indication, is an arbitrarily chosen cut-off value which may influence the results. Furthermore, besides the combined endpoint (i.e. pacing indication, appropriate ATP without subsequent shock and/or device upgrade) other parameters such as posture or vascular anatomy potentially influencing the feasibility of a device implantation were not assessed. Another limitation of this study is that all patients were considered suitable for defibrillation with an S-ICD. Although current data does not indicate that there is a proportion of patients not suitable for defibrillation using this new device, it should be acknowledged that this issue should be explored in more detail in future studies.[6, 26] Furthermore, in the current study, CRT-D implantation was done according to the then existing guidelines, therefore changes in these guidelines could not be accounted for.[11, 12] Finally, the preference of the patient for the implantation of a conventional ICD or an S-ICD system, an important factor in decision making, was also not included in the present analysis.

CONCLUSION

At 5 years after ICD implantation, approximately 60% of the patients do not reach the combined endpoint of ATP, development of an atrial or right ventricular pacing indication or the necessity to undergo an upgrade to CRT-D. Based on those results, these patients would have been suitable for implantation of an S-ICD instead of a conventional ICD that depends on transvenous leads. Additionally, baseline clinical factors have been identified for the selection of patients suitable for an S-ICD implantation.

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II

Part II

Socio-economic Implications of Implantable Defibrillator Treatment

6

Chapter 6

Cost-Effectiveness of Primary Prevention Implantable Cardioverter Defibrillator Treatment: Data from a Large Clinical Registry

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ABSTRACT

Background

Although randomized trials have shown the beneficial effect on survival of an implantable cardioverter defibrillator (ICD) as primary prevention therapy in selected patients, data concerning the cost-effectiveness in routine clinical practice remain scarce. Accordingly, the purpose of the current study was to assess the cost-effectiveness of primary prevention ICD implantation in the real world.

Methods

Patients receiving primary prevention single-chamber or dual-chamber ICD implantation at the Leiden University Medical Center were included in the study. Using a Markov model, lifetime cost, life years (LY), and gained quality-adjusted life years (QALY) were estimated for device recipients and control patients. Data on mortality, complication rates, and device longevity were retrieved from our center and entered into the Markov model. To account for model assumptions, one-way deterministic and probabilistic sensitivity analyses were performed.

Results

Primary prevention ICD implantation adds an estimated mean of 2.07 LYs and 1.73 QALYs. Increased lifetime cost for single-chamber and dual-chamber ICD recipients were estimated at €60,788 and €64,216 respectively. This resulted for single-chamber ICD recipients, in an estimated incremental cost-effectiveness rate (ICER) of €35,154 per QALY gained. In dual-chamber ICD recipients, an estimated ICER of €37,111 per QALY gained was calculated. According to the probabilistic sensitivity analysis, estimated cost per QALY gained are €35,837 (95% CI: €28,368 - €44,460) for single-chamber and €37,756 (95% CI: €29,055-€46,050) for dual-chamber ICDs.

Conclusion

Based on data and detailed costs, derived from routine clinical practice, ICD therapy in selected patients with a reduced LVEF appears to be cost-effective.

INTRODUCTION

Multiple randomized studies have demonstrated a survival benefit in selected groups of patients with ischemic and non-ischemic heart disease following implantable cardioverter defibrillator (ICD) implantation.[1-7]

With the recommendation of ICD therapy as prophylaxis for sudden cardiac death in patients with a depressed left ventricular ejection fraction (LVEF), worldwide implantation rates have increased significantly.[8, 9] Concomitantly, the costs associated with ICD treatment increased as well, putting a heavy cost burden on health care systems, making it essential to assess the cost-effectiveness of ICDs.[10, 11] Previously, several studies have assessed the cost-effectiveness of the primary prevention use of ICDs and demonstrated that ICDs may be cost-effective if current guidelines are followed.[12-18] However, it is difficult to extrapolate these results to routine clinical practice since these studies mainly used experts' opinions for complication rates, device longevity, and costs.

Since 1996, all patients receiving an ICD at the Leiden University Medical Center have been assessed and followed-up. This thoroughly screened cohort provided a unique opportunity to assess cost-effectiveness of primary prevention ICD implantation based on clinical data and detailed costs derived from routine clinical practice.

METHODS

Design of the study

The estimated lifetime cost and effects of primary prevention implantable cardioverter defibrillator (ICD) implantation were compared with conventional pharmacological therapy in patients with a reduced left ventricular ejection fraction (LVEF) using a Markov model. For the current analysis, a model initially developed by Sanders et al. and thereafter further adapted by Cowie et al was used.[13, 15] In this model, a hypothetical cohort of patients receiving ICD therapy or conventional pharmacological therapy were tracked using a 1-month cycle length. In each model cycle, patients from both cohorts were at risk for sudden cardiac death (SCD), heart failure death (HFD), other cardiac death (OCD), and non cardiac death (NCD). Also, patients receiving ICD therapy were at risk for ICD treatment related complications such as: operative death, implant associated complications, device associated complications and discontinuation of ICD therapy. Furthermore, associated medical costs were included in the model and therewith provide the opportunity to estimate the lifetime costs and effects of patients receiving ICD therapy or conventional pharmacological therapy.

In the previous model however, trial data were based on expert opinion and manufacturer data, while in the current study these inputs (i.e. complication rates, device longevity, and costs) were based upon actual data of routine clinical practice at the Leiden University Medical Center, the Netherlands.

Cost-effectiveness was calculated for both single-chamber and dual-chamber ICD devices. Data entered in the model was derived from 483 consecutive patients with a reduced LVEF (≤35%) who received a primary prevention single-chamber (n=45, 9%) or dual-chamber (n=438, 91%) ICD in the LUMC between January 1996 and September

2009. Eligibility for ICD implantation was based on international guidelines for primary prevention.[8, 9] Baseline characteristics for the complete group are summarized in Table 1. During a mean follow-up of 31.7±26.9 months, 22 single-chamber and 86 dual-chamber replacement devices were implanted. Eleven (2%) patients without data for the most recent 6 months prior to the end of the study were considered lost to follow-up, however included in the analysis as far as data was acquired.

Life years and quality-adjusted life years (QALY) gained were discounted at 1.5% per annum and costs were discounted at 4% per annum.[19-21]

Death probabilities

The overall mortality rate in patients with reduced LVEF who received primary prevention ICD implantation was founded on data from routine clinical practice. Since specific causes of death were unavailable in our center, modeling into different categories of death was predicated upon the meta-analysis of mortality rates from six primary prevention trials conducted by Cowie et al.[13] The overall mortality rate in ICD recipients from routine clinical practice was distributed over four different categories of death (SCD, HFD, OCD and NCD) in the same proportion as found in the pooled estimate derived from the meta-analysis. Non cardiac mortality was adjusted to age by incorporating the Dutch lifetable (statline.cbs.nl).

Table 1. Baseline patient characteristics.

	Total (n = 483)
Clinical characteristics	
Age (years)	61±11
Male (%)	409 (85)
Left ventricular ejection fraction (%)	27±7
QRS, mean (SD), ms	111±26
Renal clearance, mean (SD), ml/min	85±35
Ischemic heart disease (%)	399 (83)
History of atrial fibrillation/flutter (%)	96 (20)
Medication	
ACE inhibitors/AT II antagonist (%)	423 (88)
Aspirin (%)	239 (49)
Beta-blocker (%)	331 (69)
Diuretics (%)	328 (68)
Statins (%)	359 (74)
Antiarrhythmic medication *	
Amiodarone (%)	45 (9)
Sotalol (%)	57 (12)

*ACE = angiotensin-converting enzyme; AT = angiotensin; SD = standard deviation. * Patients could be treated with >1 antiarrhythmic drug.*

The efficacy of ICD therapy was defined as the relative risk of death for each type of mortality outcome in the ICD therapy group when compared with the control group. Given that mortality data of a reliable control group (i.e. without ICD therapy) from routine clinical practice was not available, the mortality rates of the control group were assessed by using the mortality rates of the ICD therapy group and the relative risks provided by the meta-analysis of Cowie et al.[13]

In our cohort 62 patients died during a mean follow-up of 31.7 months, resulting in a monthly death probability of 0.0043 for ICD patients in the current analysis. In the meta-analysis of Cowie et al., the monthly death probability for ICD patients was 0.0072 and for patients receiving conventional pharmacological therapy was 0.0105.[13] This resulted in an adjusted death probability for the hypothetical cohort of patients receiving conventional pharmacological therapy in the current analysis of 0.0063. According to the pooled estimate derived from the meta-analysis, these overall monthly death probabilities were then proportionally distributed over the four different categories of death (SCD, HFD, OCD and NCD) (Table 2). It was assumed that the benefit of ICD therapy was constant over time.

Complications of ICD therapy

Patients with reduced LVEF who received primary prevention ICD implantation were at risk for device associated complications. The following complications were included in the model: operative death, device infection, lead dislodgement, inappropriate shocks, discontinuing ICD therapy following inappropriate shock, and lead failures requiring replacement. The probability of experiencing such complications was based on data from routine clinical practice in our center and is presented in Table 3. Complication rates were calculated for the complete group of devices (i.e. all single-chamber and dual-chamber devices). The effect of different complication rates was tested in the sensitivity analysis. Mean device longevity was based on data from our center, and was 4.6 years in single-chamber and 4.7 years in dual-chamber ICD devices.

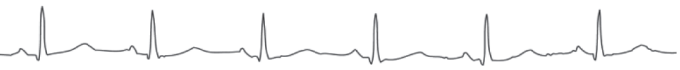
Table 2. Estimated mortality rates for different categories of death based on data from a meta-analysis of 6 primary prevention trials and the all-cause mortality rate of the Leiden ICD population.

	Meta-analysis†		Current study	
One-month death probability	ICD therapy	Conventional therapy	ICD therapy	Conventional therapy
Sudden cardiac death	0.0015	0.0042	0.0009*	0.0025*
Heart failure death	0.0029	0.0029	0.0017*	0.0018*
Other cardiac death	0.0004	0.0002	0.0002*	0.0001*
Non-cardiac death	0.0024	0.0031	0.0014*	0.0019*
All-cause	0.0072	0.0105	0.0043	0.0063*

** Estimated values; †Meta-analysis of mortality rates from the following primary prevention trials: AMIOVIRT, MADIT I, MADIT II, SCD-HeFT, CAT, and DEFINIT.*

Table 3. Base case model inputs.

Model inputs
One month death probability single-chamber ICD cohort
Sudden cardiac death
Heart failure death
Other cardiac death
Non-cardiac death
All cause
Initial implant operative death probability
Mean follow-up (months)
Mean age (years)
Gender (% male)
One-month probability of inappropriate shocks
One-month probability of discontinuing ICD after inappropriate shocks
Monthly probability of a right atrial lead replacement due to failure following initial implant
Monthly probability of a right ventricular lead replacement due to failure following initial implant
Monthly probability of a right atrial lead replacement due to failure following replacement implant
Monthly probability of a right ventricular lead replacement due to failure following replacement implant
Probability of a lead infection at initial implant
Probability of a lead infection at replacement ICD implant
Probability of a lead dislodgement at initial implant
Probability of a lead dislodgement at replacement ICD implant
Initial device + leads cost(€) (2010)
Replacement device cost (€) (2010)
Atrial lead replacement cost per event (lead failure) (€) (2010)
Right ventricular lead replacement cost per event (lead failure) (€) (2010)
Lead infection cost (€) (2010)
Lead dislodgement cost (€) (2010)
Inappropriate shocks cost (€) (2010)
Monthly long term inpatient and outpatient cost (€) (2010)
ICD additional monthly follow-up cost (€) (2010)
Mean device longevity (years)
Duration of ICD benefit
Utility of heart failure patient annual
Utility of ICD complications state (annual)
Discount rate outcomes (%)
Discount rate costs (%)



ICD therapy single-chamber	ICD therapy dual-chamber	Conventional therapy	Data sources
0.000916	0.000916	0.002538	Clinical data /Cowie et al.[13]
0.001743	0.001743	0.001752	Clinical data /Cowie et al.[13]
0.000224	0.000224	0.000102	Clinical data /Cowie et al.[13]
0.001439	0.001439	0.001890	Clinical data /Cowie et al.[13]
0.004322	0.004322	0.006283	Clinical data /Cowie et al.[13]
0.00207	0.00207	Not applicable	Clinical data
31.7	31.7	28	Clinical data/Cowie et al.[13]
60.8	60.8	61.1	Clinical data/Cowie et al.[13]
84.7	84.7	79.5	Clinical data/Cowie et al.[13]
0.00538	0.00538	Not applicable	Clinical data
0.00000	0.00000	Not applicable	Clinical data
Not applicable	0.00017	Not applicable	Clinical data
0.00127	0.00127	Not applicable	Clinical data
Not applicable	0.00083	Not applicable	Clinical data
0.00234	0.00234	Not applicable	Clinical data
0.02277	0.02277	Not applicable	Clinical data
0.03704	0.03704	Not applicable	Clinical data
0.00828	0.00828	Not applicable	Clinical data
0.00000	0.00000	Not applicable	Clinical data
19,600	22,150	Not applicable	Clinical data
17,000	19,000	Not applicable	Clinical data
Not applicable	2,845	Not applicable	Clinical data/Hakkaart et al.[23]
4,895	4,895	Not applicable	Clinical data/ Hakkaart et al.[23]
29,561	32,111	Not applicable	Clinical data/ Hakkaart et al.[23]
4,895	4,895	Not applicable	Clinical data/ Hakkaart et al.[23]
132	132	Not applicable	Clinical data/ Hakkaart et al.[23]
197	197	197	RIVM 2008
43	43	Not applicable	Clinical data/ Hakkaart et al.[23]
4.6	4.7	Not applicable	Clinical data
Lifetime	Lifetime	Not applicable	Assumption
0.85	0.85	0.85	Mark et al.[14]
0.75	0.75	Not applicable	Sanders et al.[15]
1.5	1.5	1.5	CVZ 2006[19]
4.0	4.0	4.0	CVZ 2006[19]

Quality-of-life

Based on the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), an utility score of 0.85 for both the ICD and the conventional therapy group was applied in the current model.[14] Furthermore, it was assumed that ICD implantation had no effect on the quality of life.[14, 22] If patients were exposed to ICD-related complications (e.g. device infection, inappropriate shocks, and lead replacement) a utility score of 0.75 during a period of one month was assumed.[15]

Costs

Cost analyses were performed from the health care perspective. Costs of health care associated with inpatient and outpatient treatment were included. Device and lead costs were based on average contractual price agreements between the Dutch hospitals and manufacturers (expert's opinion). For all routine procedures and ICD treatment related complications requiring hospital admission, the exact average duration of hospital stay, based on the clinical data available, was calculated and then multiplied with the standard cost per hospital day.[23] Procedural costs of device system implantation, device replacement, and lead replacement were derived in a micro cost analysis including personnel costs, diagnostic test, costs of consumables used during the procedure, depreciation of the radiology equipment and catheterization laboratory, and overhead costs.[23] For routine ICD and unexpected ICD check-up (i.e. following an appropriate or inappropriate shock), cost of an outpatient visit were applied.[23] All prices were converted to the price level of 2011 according to the general Dutch consumer price index (statline.cbs.nl, accessed January 2011). Results of other studies, reported in US dollars, were also converted to euros using the purchasing power parity index with a ratio of $1 = €0.8382 (stats.oecd.org, accessed December 2011).

In the current analysis, a cost-effectiveness ratio below €40,000 per gained QALY was assumed to be acceptable according to the current Dutch economic threshold.[24, 25]

Sensitivity analyses

To account for important model assumptions, one-way deterministic sensitivity analyses were performed. Ranges of the variables were established on current literature or on expert's opinion if literature was lacking.

Probabilistic sensitivity analysis (PSA) was performed to evaluate the combined uncertainty of individual input variables on the model's outcome of cost and effects. To achieve this, probability distributions for death and complication rates as well as the utilities scores associated with different states were defined and 10,000 simulations were undertaken.

RESULTS

Base-Case analysis

Following primary prevention ICD implantation, all-cause mortality decreased resulting in an increased life-expectancy of 2.07 years as compared with patients receiving

conventional therapy. With an estimated utility score of 0.85 per life-year saved and 0.75 if patients were exposed to ICD-related complications, incremental QALYs were 1.73 years for ICD recipients.

With respect to single-chamber ICDs, implantation is associated with an average additional lifetime cost of €60,788 per patient when compared with conventional therapy. Consequently, both the lifetime costs and the effectiveness (i.e. life expectancy) were higher in single-chamber ICD recipients as compared with patients receiving conventional therapy. Accordingly, this resulted in an estimated cost-effectiveness of €29,369 per life year gained and €35,154 per QALY gained for patients with a mean age of 61 years receiving single-chamber ICD therapy as compared with patients receiving conventional therapy (Table 4).

Regarding primary prevention dual-chamber ICD implantation, average additional lifetime cost of €64,216 per patient were calculated. With an increased life-expectancy of 2.07 and a incremental QALY of 1.73, estimated cost-effectiveness of €31,025 per life year gained and €37,111 per QALY gained for patients with a mean age of 61 years receiving dual-chamber ICD therapy compared to patients receiving conventional therapy was assessed (Table 4).

Table 4. Costs, life years, quality-adjusted life years, and incremental cost-effectiveness ratios for implantable cardioverter defibrillator compared with control therapy.

	Cost (€)	LY	QALY	ICER (€/LY)	ICER (€/QALY)
Single-chamber					
Discounted					
ICD therapy	79,914	11.62	9.84	29,369	35,154
Control therapy	19,126	9.55	8.11		
Difference	60,788	2.07	1.73		
Undiscounted					
ICD therapy	104,428	13.24	11.21	31,282	37,641
Control therapy	25,299	10.70	9.09		
Difference	79,642	2.55	2.12		
Dual-chamber					
Discounted					
ICD therapy	83,342	11.62	9.84	31,025	37,111
Control therapy	19,126	9.55	8.11		
Difference	64,216	2.07	1.73		
Undiscounted					
ICD therapy	109,132	13.24	11.21	32,928	39,583
Control therapy	25,299	10.70	9.09		
Difference	83,833	2.55	2.12		

ICD = implantable cardioverter defibrillator; ICER = incremental cost-effectiveness ratio; LY = life years; QALY = quality-adjusted life years.

Deterministic sensitivity analysis

With all model variables included in the sensitivity analysis, incremental cost-effectiveness of ICD therapy compared with conventional therapy demonstrated to be most sensitive to variation in the following five factors: device longevity, device and lead costs, quality of life, discount rates, and mortality rates (Figure 1).

Device longevity in the current analyses (i.e. a mean of 4.6 years for single-chamber and 4.7 years for dual-chamber ICDs) was based on data from our own center. However, it is conceivable that device longevity varies according to the device settings and the generation of devices used per center. Accordingly, adaptation of the mean device longevity to 4 years resulted in an incremental cost-effectiveness of €38,123 and €40,746 per QALY for single-chamber and dual-chamber devices respectively. When the mean device longevity was increased to 10 years, incremental cost-effectiveness improves to €23,744 and €25,273 per QALY for single-chamber and dual-chamber devices respectively. As a result, the factor device longevity demonstrated to have the largest effect on the total costs and cost-effectiveness of all factors in the deterministic model.

With respect to device and lead costs, a 25% lowering in prices would affect incremental cost-effectiveness by 19%. Outcomes ranged from €26,392 to €38,817 per QALY for single-chamber devices and from €28,638 to €42,487 per QALY for dual-chamber devices.

Variation in the patients' quality of life to 0.75 in both therapy groups (i.e. ICD and conventional therapy) resulted in an incremental cost-effectiveness of €36,376 per QALY for single-chamber and of €39,675 per QALY for dual-chamber ICD therapy. Consequently, if it was assumed that the patients' quality of life was 0.75 in the conventional therapy group and 0.80 in the ICD therapy group, incremental cost-effectiveness improved to €26,644 per QALY and €29,060 per QALY for single and dual-chamber ICDs respectively.

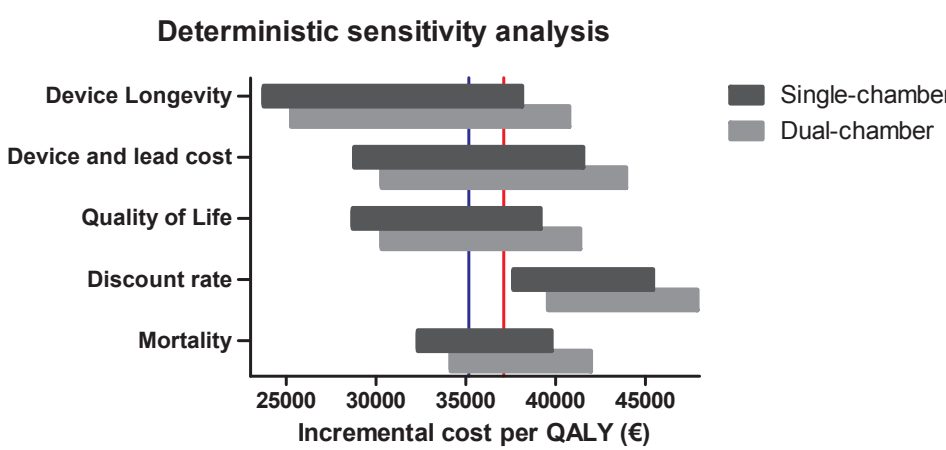


Figure 1. Tornado diagram of the deterministic sensitivity analysis representing the five most sensitive factors with regard to the incremental cost per QALY of ICD therapy compared with conventional therapy. The estimated cost per QALY based on the base case analyses are demonstrated for both single-chamber (blue line) and dual-chamber (red line) ICDs.

A less favorable incremental cost-effectiveness ratio will result if discount rates for both outcomes and cost are assumed to be equal. The effect of the variation of discount rates between 0% (i.e. undiscounted) and the more internationally accepted 3% for both outcomes and costs on the incremental cost-effectiveness of primary prevention ICD therapy is illustrated in Figure 1.

Another important factor determining the incremental cost-effectiveness of ICD therapy is the mortality rate of patients applicable for primary prevention ICD implantation. Based on the outcomes of the deterministic sensitivity analysis, the incremental cost-effectiveness tended to be more favorable in patients with an increased annual mortality. This outcome could be explained by the fact that in the current model a higher mortality is associated with an increased number of sudden cardiac deaths and therewith an improved beneficial effect of ICD therapy. This results in a higher number of incremental life years added for the ICD cohort as compared with the conventional pharmacological therapy cohort.

Probabilistic sensitivity analysis

Based on the PSA, the incremental cost-effectiveness of single-chamber ICDs compared with conventional therapy resulted in a mean estimate of €35,837 per QALY (95% CI: €28,368 - €44,460 per QALY). For dual-chamber ICDs, the PSA resulted in a mean estimate of the incremental cost-effectiveness of €37,756 per QALY (95% CI: €29,055-€46,050 per QALY) when compared with conventional therapy. The cost-effectiveness acceptability curve in Figure 2 shows the probability that single-chamber and dual-chamber ICDs are cost-effective compared with conventional therapy for different values of the willingness to pay. According

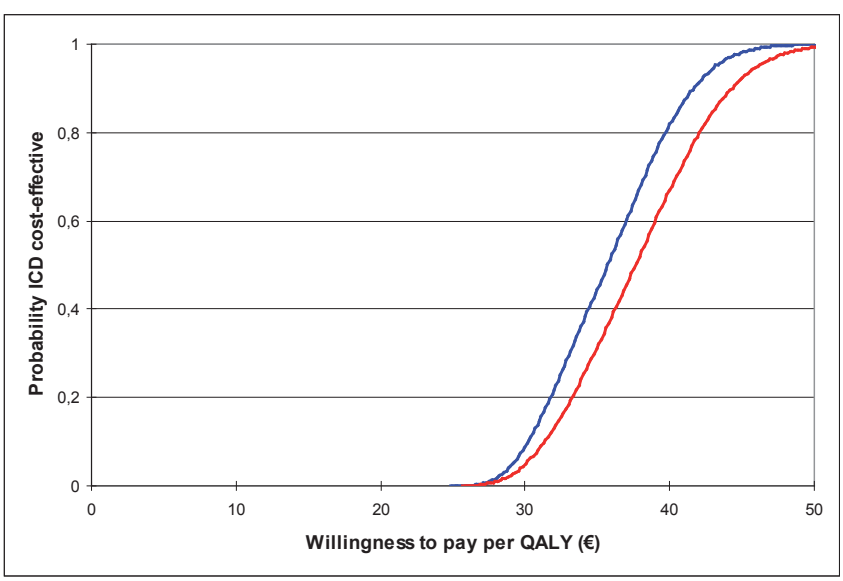


Figure 2. Cost-effectiveness acceptability curve for single chamber (blue line) and dual chamber (red line) ICD therapy compared to conventional therapy.

to the Dutch threshold of €40,000 per QALY, the probability that ICD therapy is cost-effective was estimated at respectively 81% for single-chamber ICDs and 67% for dual-chamber ICDs.

DISCUSSION

In the current analysis, primary prevention ICD implantation in addition to optimal pharmacologic therapy (i.e. conventional therapy) in patients with an increased risk for sudden cardiac death as a result of a reduced LVEF was assessed with the use of a Markov model. Based on the deterministic analysis, both single- and dual-chamber ICD implantation had an incremental cost-effectiveness ratio below the accepted threshold of €40,000 per QALY gained.[24, 25] The probabilistic sensitivity analyses confirms these results, as both single and dual chamber ICD therapy have a high probability of being cost-effective.

However, variation in specific model factors demonstrated to have major impact on the cost-effectiveness of ICD therapy. For example, an increased device longevity due to improved device batteries would have a considerable beneficial effect on the cost-effectiveness and should therefore be one of the main incentives of device manufacturers in the development of new generation ICDs. Furthermore, significant higher prices for ICD and leads, with respect to base case prices currently used, could easily result in less favorable or even unfavorable cost-effectiveness. Another important model factor with major impact on the cost-effectiveness is the quality of life. In the current study, the quality of life is based on data derived from the SCD-HeFT trial in which all patient received devices unable to deliver ATP.[14] However, nowadays almost all patients receive ICDs capable of ATP and as demonstrated by the PainFREE trial may experience a higher quality of life then reported in the SCD-HeFT trial.[26] Although exact data hereof remains unclear, the deterministic sensitivity analysis demonstrated that an improved quality of life in ICD recipients could have a large, namely beneficial, impact on the actual cost-effectiveness reported in the current study. Although exact data hereof remains unclear, the deterministic sensitivity analysis demonstrated that an improved quality of life in ICD recipients could have a large, namely beneficial, impact on the actual cost-effectiveness reported in the current study. Other factors with noteworthy effects on the cost-effectiveness were discount rates, mortality rates, and ICD efficacy.

Furthermore, worth mentioning is the relatively minor effect that most device related complications had on the cost-effectiveness. Although complications such as lead infections requiring complete replacement of the device and leads are associated with extremely high costs, the relatively low incidence significantly reduces the effect on total cost-effectiveness.

Comparison with different ICD cost-effectiveness analyses

Currently, cost-effectiveness analyses of primary prevention ICD therapy in patients with a reduced LVEF using data from real clinical practice are scarce. However, based on analysis and meta-analysis of the major primary prevention trials of ICD therapy several cost-effectiveness analyses have been published. Results from the SCD-HeFT trial demonstrated a comparable cost-utility ratio (discounted at 3%) of $41,530 (€34,810) per QALY for single-chamber ICDs as compared with medical therapy alone.[14] Of note is that, likewise the current analysis, Mark et al. assumed that the benefits of ICD therapy were constant over time and outcomes became

economically attractive if benefits persist for at least 8 years, which was beyond the empirical 5-year trial data of the SCD-HeFT. Sanders et al. projected the cost-effectiveness of eight randomized trials in which primary prevention ICD implantation among patients who are at risk for sudden cardiac death due to a reduced LVEF was evaluated.[15] In two of those trials, primary prevention ICD implantation did not reduce the risk of death, and thus was both more expensive and less effective than control therapy. Since in these two trials primary prevention ICD implantation occurred in selected patients who are not included in the current analysis, comparison with these outcomes is less appropriate**.** Regarding the six other trials included by Sanders et al., primary prevention single-chamber ICD implantation was projected to add between 1.01 and 2.99 QALYs and the incremental cost-effectiveness (discounted at 3%) ranged from $34,000 (€28,500) to $70,200 (€58,842) per QALY gained. Results of the current study regarding the added life years and incremental costs per QALY are for both single-chamber and dual-chamber ICDs amidst these outcomes of Sanders et al (Table 5).

In the meta-analysis by Cowie et al., consisting out of 6 primary prevention trials with inclusion criteria matching ACC/AHA/ESC Class I or IIa recommendations, direct medical costs were estimated using Belgian national references and complications rates were based on experts opinion.[13] In this analysis, primary prevention single-chamber ICD implantation was projected to add 1.88 LY and the estimated mean lifetime costs per QALY gained were €29,530 and €31,717 according to the deterministic and probabilistic sensitivity analysis respectively. These outcomes are comparable with outcomes of the current analyses, indicating that single-chamber and dual-chamber ICDs are, based on clinical data and detailed costs derived from routine clinical practice, cost-effective as primary prevention therapy in patients with a reduced LVEF (≤35%).

Van Brabandt et al. criticized the fact that Cowie et al. based their results on a meta-analysis of 6 primary prevention trials rather than using data from the SCD-HeFT alone.[27]

Table 5. Results of increased costs, increased life years, increased quality-adjusted life years, and incremental cost-effectiveness ratios for implantable cardioverter defibrillators compared with control therapy in different primary prevention ICD trials and the current analysis for both single-chamber and dual-chamber devices.

	Increase in Cost (€)	Increase in LY	Increase in QALY	ICER (€/LY)	ICER (€/QALY)
MADIT I [6, 15]	77,200	3.64	2.64	21,207	29,254
MUSTT [3, 15]	85,080	4.14	2.99	20,536	28,500
MADIT II [7, 15, 18]	66,555	2.03	1.47	32,690	45,348
DEFINITE [15, 29]	84,241	2.73	1.96	30,847	43,001
COMPANION [15, 30]	57,251	1.87	1.36	30,595	42,163
SCD-HeFT [2, 15]	59,514	1.40	1.01	42,498	58,842
Study single-chamber†	60,788	2.07	1.73	29,369	35,154
Study dual-chamber†	64,216	2.07	1.73	31,025	37,111

† *Converted to euros using the purchasing power parity index with a ratio of $1 = €0.8382 (stats.oecd.org, accessed December 2011).*
ICER = incremental cost-effectiveness ratio; LY = life years; QALY = quality-adjusted life years.

According to the results from the deterministic sensitivity analyses of the current study were ICD effectiveness was based on results from the SCD-HeFT alone, the incremental cost-effectiveness per QALY was €41,837 for single-chamber devices and €44,182 for dual-chamber devices. Consequently, it can be concluded that ICDs would be approximately borderline cost-effective if effectiveness is based on results from the SCD-HeFT trial alone.

Limitations

In the current study, mortality rates of the control group were assessed by using mortality rates of the ICD therapy group and the relative risks provided by the meta-analysis of randomized clinical trials by Cowie et al.[13] This was based on the assumption that the efficacy of ICD therapy in clinical practice is similar to the efficacy of ICD therapy demonstrated in the randomized clinical trials. In addition, the overall mortality rate of the ICD group and control group over the four different categories of death were distributed in a similar proportion as the pooled estimate derived from the meta-analysis. Furthermore, although clinical follow-up data was limited to a mean of 31.7 months, cost and benefits were projected to a lifetime horizon. Also, the current analysis was performed in a relatively small cohort of 483 patients with a low proportion of single chamber ICDs. Finally, the long enrolment time may has resulted in heterogeneity regarding clinical management and device technology within the study cohort. Importantly, all the above study limitations could have resulted in an over- or underestimation of the beneficial effects of ICD therapy, consequently over- or underrating the cost-effectiveness of ICD therapy in clinical practice.

Implications for society

In the current analyses, primary prevention ICD implantation has demonstrated to have a favorable effectiveness versus acceptable costs in patients with a reduced LVEF in the long term. However, despite existing guidelines supporting primary prevention implantation of ICDs in these patients, implementation hereof is currently far from complete as is demonstrated with the widely varying implantation rates across Europe.[9, 28] This might be the result of the high upfront cost of ICD therapy following implantation and the large patient population in which it may be applied.[11] Consequently, wide penetration of ICD therapy in selected patients forms an absolute challenge to health policymakers, since healthcare expenditure for ICDs in Europe could easily exceed several billion Euros per year. On the other hand, a saving effect might be expected due to an increased addition (i.e. work, consumption) to the general economy.

Furthermore it is worth mentioning that the current analysis reflected only the cost-effectiveness of primary prevention ICD therapy without resynchronization therapy in heart failure patients. Since patients, eligible for combined defibrillator and resynchronization therapy, are characterized by a more deteriorated form of heart failure, results of the current analysis do not apply for these patients.

CONCLUSION

Based on data from routine clinical practice, primary prevention single-chamber and dual-chamber ICD therapy in selected patients with a reduced LVEF appears to be cost-effective.

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7

Chapter 7

Implantable Cardioverter-Defibrillator Longevity under Clinical Circumstances: an Analysis According to Device Type, Generation, and Manufacturer

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ABSTRACT

Background

One of the major drawbacks of implantable cardioverter defibrillator (ICD) treatment is the limited device service life. Thus far, data concerning ICD longevity under clinical circumstances are scarce. In this study, the ICD service life was assessed in a large cohort of ICD recipients.

Methods

All patients receiving an ICD in the Leiden University Medical Center were included in the analysis. During prospectively recorded follow-up visits, reasons for ICD replacement were assessed and categorized as battery depletion and non-battery depletion. Device longevity and battery longevity were calculated. The impact of device type, generation, manufacturer, percentage of pacing, pacing output, and the number of shocks on the battery longevity was assessed.

Results

Since 1996, 4,673 ICDs were implanted of which 1,479 ICDs (33%) were replaced. Mean device longevity was 5.0±0.1 years. A total of 1,072 (72%) ICDs were replaced because of battery depletion. Mean battery longevity of an ICD was 5.5±0.1 years. When divided into different types, mean battery longevity was 5.5±0.2 years for single-chamber ICDs, 5.8±0.1 for dual-chamber ICDs and 4.7±0.1 years for cardiac resynchronization therapy-defibrillators (CRT-Ds) ($p<0.001$). Devices implanted after 2002 had a significantly better battery longevity as compared to devices implanted before 2002 (5.6±0.1 vs. 4.9±0.2 years, $p<0.001$). In addition, large differences in battery longevity between manufacturers were noted (overall log rank test $p<0.001$).

Conclusion

The majority of ICDs were replaced because of battery depletion. Large differences in longevity exist between different ICD types and manufacturers. Modern ICD generations demonstrated improved longevity.

INTRODUCTION

Large randomized trials have shown a beneficial effect of implantable cardioverter-defibrillator (ICD) treatment on mortality in selected groups of patients at risk for a life-threatening ventricular arrhythmia.[1-9] With the rapid expansion of indications for ICD therapy, worldwide implantation rates increased greatly in the last decade.[10-12] However, despite the improved survival in selected patients with an ICD, some limitations of ICD therapy should not be overseen. One of these limitations is the finite lifespan of ICD devices and, consequently, 70% of all ICD recipients will need an ICD replacement because of battery depletion at a certain point in time.[10] Since ICD replacement is associated with major drawbacks, such as infectious and non-infectious complications, reduced patient comfort, and reduced cost-effectiveness, assessment of improvement and potential differences in battery longevity is essential for the evaluation of ICD performance.[13-15]

However, most data considering device longevity are provided by manufacturers and are based on intensive testing under standardized and conditioned laboratory measurements. Although this manufacturer provided data might be different from device longevity in clinical practice, data concerning ICD longevity under clinical circumstances are scarce.

The aim of the current study was to assess the longevity of ICDs in routine clinical practice in a large cohort of patients. This assessment was performed over a 15-year period in a large university hospital in the Netherlands. Additionally, the current dataset provides an opportunity to assess potential differences in longevity between different types of ICDs, manufacturers and to evaluate improvements throughout time.

METHODS

Patients

Since 1996, all consecutive patients who received an ICD system in the Leiden University Medical Center were collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center). Baseline characteristics of the patient, data of the implant procedure, and all follow-up visits (until April 2011) were recorded prospectively. Collected data of follow-up visits included the pacing percentage, the pacing threshold, the pacing output, and the number of delivered shocks (appropriate and inappropriate) delivered by each single ICD. Data regarding the implanted defibrillator as manufacturer, device model, and the type of ICD (single-chamber, dual-chamber or cardiac resynchronization therapy-defibrillator (CRT-D)) were noted.

Eligibility for ICD implantation was based on international guidelines and included secondary prevention and primary prevention of sudden cardiac death. Due to the evolution of these guidelines, indications have changed over time.[12, 16]

Device implantation and follow-up

All defibrillator systems used were implanted transvenously and without thoracotomy. During the implant procedure, sensing and pacing thresholds were determined. Used systems were manufactured by Biotronik (Berlin, Germany), Boston Scientific [Natick, MA,

USA, formerly CPI, Guidant (St Paul, MN, USA)], Medtronic (Minneapolis, MN, USA), and St Jude Medical/Ventritex (St Paul, MN, USA).

As a training facility, different physicians were involved with ICD implantation throughout the years and to guarantee uniformity, devices were programmed according to a strict protocol. In general, in single-chamber ICD recipients, cardiac stimulation parameters were set to VVI 40. If patients were dependent on stimulation or rate responsive pacing, a pacing mode of VVIR 40-140 was programmed. To avoid unnecessary right ventricular pacing, dual-chamber ICDs were programmed in the nontracking backup mode DDI in the majority of patients with sufficiently long AV delay to secure intrinsic conduction at the lower rate. For those patients with an indication for stimulation or rate responsive pacing, devices were programmed in a mode of DDDR 40-140 with sufficiently long AV delay to secure intrinsic conduction. CRT-D devices were programmed in a biventricular pacing mode, with the lower rate programmed in favor of the patient's natural sinus rhythm resulting in a minimization of atrial stimulation. During follow-up visits, the pacing output was programmed to a value that was twice as high as the recorded pacing threshold with a minimum pacing output of 2.5 V (e.g., threshold 0.5V, output 2.5V; threshold 2.0V, output 4.0V). The average pacing percentage and pacing outputs recorded during subsequent ICD follow-up visits were used for the current analysis. For dual-chamber and CRT-D devices, the percentage of atrial and (bi)ventricular pacing was added resulting in a maximal pacing percentage of 100% for single-chamber ICDs, 200% for dual-chamber ICDs and 300% for CRT-Ds.

The antitachycardia modes in all devices were programmed with three consecutive zones with limits slightly varying per manufacturer: a monitor zone (lower limit between 150-155 bpm; upper limit between 185-190 bpm), an antitachycardia pacing (ATP) shock zone (lower limit between 185-190 bpm; upper limit between 205-210 bpm), and an initial shock zone (≥205-210 bpm). In the monitor zone, no therapy was programmed unless a ventricular arrhythmia 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 a ventricular arrhythmia faster than the ATP shock zone, device shocks were the initial therapy. Furthermore, atrial arrhythmia detection was set to >170 bpm with supraventricular tachycardia discriminators enabled. Therapy settings were adapted, only when clinically indicated.

Device interrogation was scheduled every 3-6 months after implantation. Data of these ICDs were included until the last date of ICD check-up. ICDs of patients referred to another center were tracked (i.e. last date of ICD check-up in referred center) and if device replacement had occurred, its indication was verified.

Indications for replacement

During follow-up, all ICD replacement procedures were assessed and the indication for device replacement was registered. Replacements were categorized as battery depletion (Elective Replacement Indicator [ERI]) and non-battery related causes resulting in device replacement. Non-battery related causes were further categorized as follows: 1) device upgrade, 2) device infection, 3) device advisory or recall, 4) system malfunction, or 5) heart transplantation. Device upgrade was noted when an initial single-chamber was replaced

for a dual-chamber ICD or CRT-D or when a dual-chamber ICD was replaced for a CRT-D without the necessity for replacement because of battery depletion. Device infection was defined as infective symptoms at the generator pocket site with or without verified invasion of pathogenic microorganisms within the ICD pocket.[13] In addition, patients presenting with fever or recurrent bacteremia without an apparent focus, subsequently causing device replacement, were also classified as device infection. Device advisory or recall consisted of a manufacturer initiated advisory to replace an ICD because of technical problems. System malfunction was defined as malfunction of the device, the leads, the header or insufficient energy capacity for successful defibrillation resulting in device replacement.[17] Finally, analyses were performed for all causes of device replacement (i.e. device longevity) and for device replacements because of battery depletion (i.e. battery longevity).

Statistical analysis

Continuous data are expressed as mean and standard deviation (SD) or median with 25th and 75th percentile where appropriate; dichotomous data are presented as numbers and percentages. Mean longevity was defined in years and was calculated as the time from ICD implantation to the time of replacement and expressed with a two-sided 95% confidence interval (95% CI). As described previously, separate analyses were performed for device longevity, taking into account all causes of device replacement and for battery longevity, taking into account only device replacement because of battery depletion. Additional longevity analyses were performed for the type (i.e. single-chamber, dual-chamber, and CRT-D), time of implant (i.e. implanted before or since 2002) and the manufacturer (i.e. Biotronik, Boston Scientific/Guidant, Medtronic and St Jude Medical/Ventritex). Event-free rates from a device replacement were analyzed with the method of Kaplan-Meier and the log-rank test. A p-value < 0.05 was considered statistically significant. Univariate and multivariate Cox proportional-hazards models were constructed to identify independent determinants of battery longevity. Only variables with a p-value<0.25 in univariate analysis were retained in the multivariate model. All statistical analyses were performed with SPSS software (version 18.0, SPSS Inc., Chicago, Illinois).

RESULTS

Patients and ICD Characteristics

Since 1996, 4,673 consecutive ICDs were implanted in 3,194 patients (78% men, mean age 62 [SD 13] years), which were included in the analysis. The majority of these patients had ischaemic heart disease (64%) and a poor LVEF (mean LVEF 34% [SD 15%]) (Table 1). During mean follow-up of 4.1±3.2 years, 708 (22%) patients died and 128 (4%) patients were lost to follow-up.

Of the 4,673 implanted devices, 3,194 (68%) were initial implantations and 1,479 (32%) were replacement ICDs. The types (single-chamber, dual-chamber, and CRT-D) and manufacturers (Biotronik, Guidant, Medtronic and St Jude Medical/Ventritex) included in the analysis are summarized in Table 2.

Table 1. Patient characteristics at initial ICD implantation.

	Patients (n=3194)
Clinical characteristics	
Age, mean (SD), years	62 (13)
Male sex (%)	2507 (78)
Primary prevention indication (%)	1979 (62)
Ejection fraction (%)	34 (15)
QRS, mean (SD), ms	125 (35)
Renal clearance, mean (SD), ml/min	81 (38)
Ischaemic heart disease (%)	2047 (64)
Medication	
Beta-blocker (%)	1760 (55)
Sotalol (%)	437 (14)
ACE inhibitors/AT II antagonist (%)	2411 (75)
Calcium antagonist (%)	284 (9)
Diuretics (%)	1984 (62)
Statins (%)	1846 (58)
Nitrates (%)	572 (18)
Amiodarone (%)	539 (17)
Aspirin (%)	1295 (41)
Oral anticoagulants (%)	1586 (50)

ACE = angiotensin-converting enzyme; AT = angiotensin; SD = standard deviation.

Table 2. ICDs included for longevity analysis

	Single-chamber	Dual-chamber	CRT-D	Total
Biotronik	23 (3%)	323 (16%)	194 (11%)	540 (12%)
Boston Scientific/Guidant	450 (62%)	835 (40%)	1005 (54%)	2290 (49%)
Medtronic	200 (27%)	717 (34%)	634 (34%)	1551 (33%)
St. Jude Medical/Ventritex	57 (8%)	215 (10%)	20 (1%)	292 (6%)
Total	730	2090	1853	4673

CRT-D = cardiac resynchronization therapy-defibrillator.

As is shown in Figure 1, the implanted number of single-chamber devices, dual-chamber devices, and CRT-D devices is unequally distributed over time. In 1996, all defibrillators implanted were single-chamber devices. In 2002 the distribution was as follows: 21% single-chamber devices, 53% dual chamber devices, 26% CRT-D devices. In 2010, of the implanted devices, 6% were single-chambers, 41% were dual-chambers, and 53% were CRT-Ds.

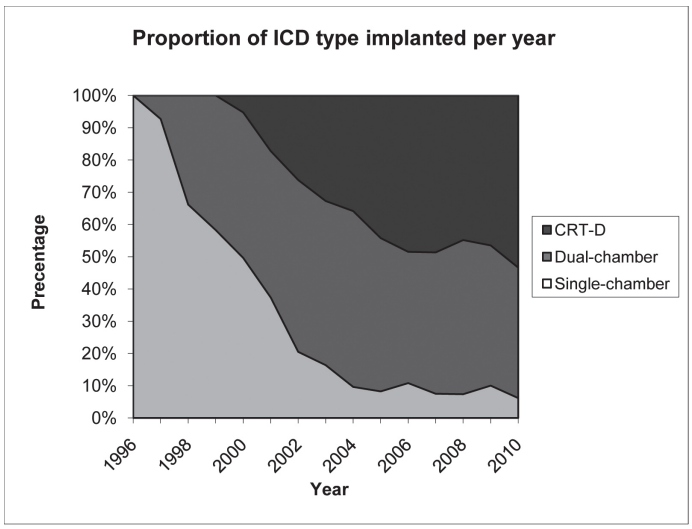


Figure 1. Annual proportion of diverse ICD types out of all implanted ICDs.

Replacement Indications

A total of 1113 (35%) patients experienced device replacement, of whom 229 (21%) patients underwent 2 replacement procedures, 52 (5%) patients underwent 3 replacement procedures and 11 (1%) patients underwent 4 replacement procedures.

The majority of ICD replacements were performed because of an ERI (n = 1072, 72%). Other indications for replacement were device upgrades (n = 145, 10%), device infection (n = 118, 8%), device advisory or recall (n = 49, 3%), system malfunction (n = 83, 6%) and heart transplantation (n = 12, 1%) (Table 3).

Table 3. Indication for replacement

	Total (n=1479)	Single chamber (n=379)	Dual chamber (n=645)	CRT-D (n=455)
End of service, n (%)	1072 (72)	279 (74)	420 (65)	373 (82)
Device upgrade, n (%)	145 (10)	49 (13)	96 (15)	0 (0)
Device infection, n (%)	118 (8)	20 (5)	53 (8)	45 (10)
Device advisory or recall, n (%)	49 (3)	8 (2)	34 (5)	7 (2)
System malfunction, n (%)	83 (6)	23 (6)	38 (6)	22 (5)
Heart transplantation, n (%)	12 (1)	0 (0)	4 (1)	8 (2)

CRT-D = cardiac resynchronization therapy-defibrillator.

Battery and non-battery related longevity

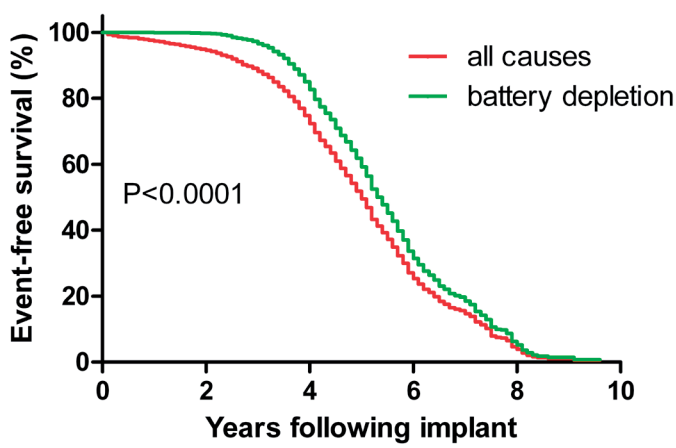
Considering all replacement indications, mean device longevity of ICDs (n=4,673) was 5.0 ± 0.1 years. Event-free rates for a replacement were 94.4% (95% CI 93.6%-95.2%) after 2 years, 73.2% (95% CI 71.4%-75.0%) after 4 years and 25.7 % (95% CI 23.3%-28.1%) after 6 years (Figure 2). Exclusion of the 407 non-battery related replacements, results in a mean battery longevity of 5.5 ± 0.1 years. Event-free rates for replacement because of battery depletion were 99.6 % (95% CI 99.4%-99.8%) after 2 years, 83.7 % (95% CI 81.9%-85.5%) after 4 years and 31.9 % (95% CI 29.2%-34.6%) after 6 years (Figure 2).

Battery longevity per device type and generation

Battery longevity (i.e. only device replacement because of battery depletion) differed significantly between the 3 different types of ICDs and was the longest in dual-chamber ICDs, followed by single chamber ICDs and thereafter by the CRT-D devices (5.8 ± 0.1 years, 5.5 ± 0.2 years and 4.7 ± 0.1 years, respectively, p<0.001; Figure 3).

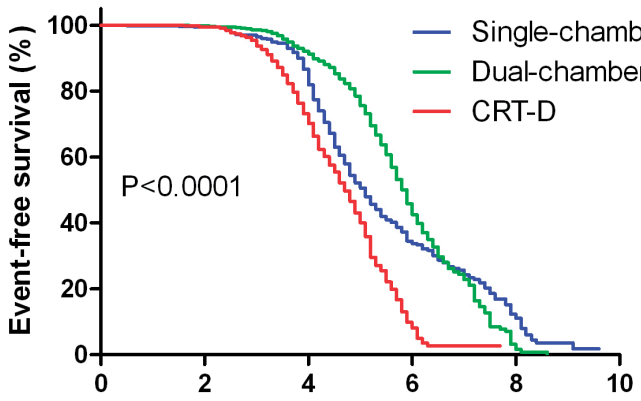
Five hundred and eighty devices (12%) were implanted before 2002 and 4,093 (88%) after 2002.

When analyzed per type of ICD, mean battery longevity (i.e. only device replacement because of battery depletion) was significantly longer in single-chamber ICDs implanted since 2002 as compared with single-chamber ICDs implanted before 2002 (6.7 ± 0.3 vs. 5.0 ± 0.2 years, p<0.001). Similarly, a significantly improved longevity in dual-chamber ICDs (6.0 ± 0.1 vs. 5.0 ± 0.2 years, p<0.001) as well as in CRT-D devices (4.7 ± 0.1 vs. 3.7 ± 0.4 years, p<0.001) was found if devices implanted since 2002 were compared with devices implanted before 2002.



ICDs at risk						
All causes	4673	2925	1371	283	24	0
Battery depletion	4673	2925	1371	283	24	0

Figure 2. Kaplan-Meier curve for event-free rate for a replacement because of all causes (red line) or because of battery depletion alone (green line). Regarding the curve for battery depletion, ICDs were censored in case of ICD explantation for reasons other than battery depletion.



ICDs at risk						
Single-chamber	730	536	333	86	20	0
Dual-chamber	2090	1353	693	180	4	0
CRT-D	1853	1036	345	17	0	0

Figure 3. Kaplan-Meier curve for event-free survival of ICDs, replaced because of battery depletion in single-chamber (blue line), dual-chamber (green line) and CRT-D devices (red line).

Battery longevity per device manufacturer

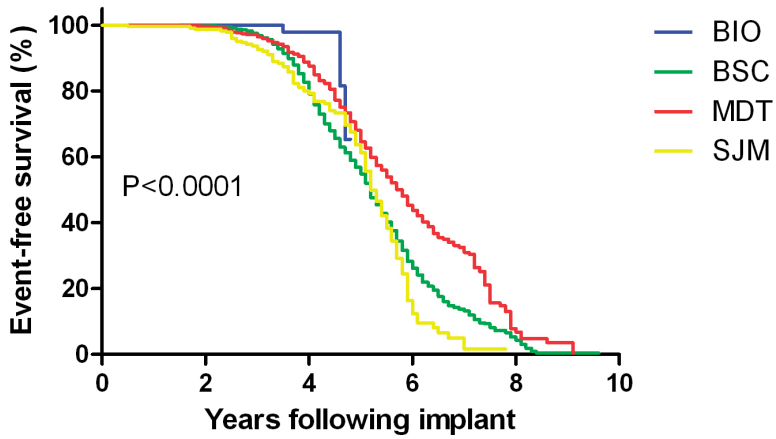
The 4,673 implanted devices in this analysis were produced by four different manufacturers (Table 2). Kaplan-Meier curves for device survival, specifically because of an ERI, demonstrate considerable differences in battery longevity (overall log rank test $p<0.001$; Figure 4). Mean battery longevity was 4.7 ± 0.1 years for Biotronik, 5.3 ± 0.1 years for Boston Scientific, 5.8 ± 0.2 years for Medtronic and 5.0 ± 0.2 years for St Jude Medical devices. All manufacturers demonstrated an improvement in battery longevity since 2002 ($p < 0.05$).

Predictors of battery longevity

Multivariate Cox regression analysis demonstrated that device type, device manufacturer, device generation (i.e. implanted before or since 2002), the percentage of pacing and the pacing output were all highly significant independent predictors of battery longevity (Table 4). Noteworthy, the number of shocks (i.e. appropriate and inappropriate) did not influence the battery longevity.

DISCUSSION

In the present study on the longevity of ICD devices, findings can be summarized as follows: (i) although the majority of devices is replaced because of battery depletion, approximately 30% of devices is explanted because of a non-battery related indication; (ii) CRT-D devices had a significantly shorter battery longevity when compared with single-chamber and dual-chamber devices; (iii) modern ICD generations of all three types of ICDs demonstrated significantly improved mean battery longevity when compared with early generations; (iv) large differences



ICDs at risk						
BIO	540	212	17	0	0	0
BSC	2290	1520	719	131	16	0
MDT	1551	962	507	140	8	0
SJM	292	231	128	12	0	0

Figure 4. Kaplan-Meier curve for event-free survival of ICDs replaced because of battery depletion for the manufacturers (Biotronik (=BIO, blue line), Boston Scientific/Guidant (=BSC, green line), Medtronic (=MDT, red line), St. Jude Medical/Ventritex (=SJM, yellow line).

exist between manufacturers; (v) variables such as device type, device manufacturer, device generation (i.e. implanted before or since 2002), the percentage of pacing and the pacing output were all highly significant independent predictors of battery longevity.

Non-battery related indications for replacement

Approximately 30% of all implanted devices in the current analysis were replaced prior to battery depletion. Due to this considerable part of early replacements, mean device longevity is heavily reduced and many patients are confronted with a premature replacement procedure. Important is that 61% of reasons other than battery depletion consist out of preventable technical issues or device infection resulting in such an early replacement. In addition, other studies demonstrate similar results. For example in a study of Knops et al., 24% of implanted devices had a non-battery related replacement indication. 17 Although there are some remarkable differences between both studies, they clearly demonstrate the necessity of reducing non-battery related indications for replacement in order to improve device longevity. Even if it is not realistic to completely eliminate these causes, major efforts should be made to minimize these occurrences.

Battery related ICD longevity

Another notable outcome from the current analysis is that dual-chamber ICDs have a significantly longer mean battery longevity (i.e. 5.8 ± 0.1 years) as compared to single-

Table 4. Cox proportional hazard ratio model to predict ICD battery depletion

	Univariate			Multivariate		
	HR	95%CI	p-value	HR	95%CI	p-value
Device type						
Single-chamber	Reference		<0.001†	Reference		<0.001
Dual-chamber	0.80	0.69-0.94	0.005†	1.29	1.08-1.54	0.01
CRT-D	2.25	1.91-2.66	<0.001†	2.51	1.94-3.26	<0.001
Manufacturer*						
Medtronic	Reference		<0.001†	Reference		<0.001
Boston Scientific/Guidant	1.52	1.33-1.73	<0.001†	1.35	1.18-1.55	<0.001
St. Jude Medical/Ventritex	1.75	1.42-2.16	<0.001†	3.00	2.41-3.74	<0.001
Device generation <2002 vs. ≥2002	0.59	0.52-0.67	<0.001†	0.34	0.29-0.40	<0.001
Pacing percentage (per 10% increase)	1.16	1.14-1.18	<0.001†	1.14	1.10-1.17	<0.001
Pacing output (per V increase)	1.17	1.09-1.25	<0.001†	1.23	1.14-1.32	<0.001
Number of shocks	1.00	0.98-1.02	0.89			

*CI = confidence interval; HR = hazard ratio. *Biotronik was not included in the analyses since limited data (i.e. 3 battery depletions) made outcomes unreliable, †variable was included in multivariate analysis.*

chamber ICDs (5.5 ± 0.2 years). This is in contrast with previous reports of Hauser et al., in which the service life of pulse generators was 4.7 year for single-chamber devices and 4.0 year for dual-chamber devices.[10, 18]

However, this difference can be explained by the fact that the distribution of device types (i.e. single-chamber, dual-chamber and CRT-D) implanted in our center was unequally distributed over time (Figure 1). As a result, a relatively older compilation of single-chamber devices with a less advanced battery technology was compared with a relatively newer compilation of dual-chamber devices. This 'bias' is resolved when longevity of dual-chamber devices is corrected, among others, for device generation: in univariate analysis having a dual-chamber decreases the risk for battery depletion as compared with single-chamber devices while in multivariate analysis this effect is reversed (HR 1.29 (95% CI 1.08-1.54, p<0.001).

Moreover, in CRT-D devices, battery longevity was remarkably shortened as compared with single-chamber and dual-chamber devices. This is most likely due to their inherent higher percentage of pacing, which diminishes battery longevity significantly.[19, 20]

Given the battery longevity among different manufacturers, devices manufactured by Medtronic provided the longest service time. Since devices were implanted in a prespecified sequence per device type and independently of their manufacturer over the cohort of patients, it can be assumed that no specific bias favoring one certain manufacturer exists. Furthermore, these results were similar to other studies, in which it was considered to be the effect of a more stable and better battery performance and minimization of intracardiac electrogram collection in Medtronic devices.[17, 19, 21]

Implications of ICD longevity on health care

Similar to results of the study of Schaer et al., the latest ICD generations (i.e. implanted since 2002) in the current analysis demonstrated improved battery longevity when compared to older generations (i.e. implanted before 2002).[20] However, despite these advances in battery longevity, a substantial part of ICD recipients will still outlive their first device.[10] Hauser et al. already estimated that mean battery longevity of devices should at least exceed 10 years of service, in order to prevent replacement procedures to occur in the majority of ICD recipients. Although technically feasible because of improved battery platforms and advanced battery saving device algorithms, such longevity reports in clinical practice are, to the best of our knowledge, not published so far. Consequently, an enormous number of ICD recipients will be exposed to the additional risk for complications when undergoing a device replacement procedure because of battery depletion.[13, 22, 23] In addition to impending adverse effects for ICD patients, increased device longevity will also result in improved cost-effectiveness of ICDs and reduction in the burden of growing health care cost worldwide.[15] Therefore, all efforts should be made to increase battery longevity of ICDs in the near-term. Since upcoming improvements in battery technology remain to be proven in real life, the most feasible near-term solution appears to be the provision of devices with larger, longer-life batteries. In a study by Wild et al., 90% of the patients preferred a larger device that could reduce the number of potential replacement procedures instead of a smaller device with the same or reduced longevity.[24] However, ICD manufacturers and physicians (i.e. depending on the organization of the national health care system) have little incentive to provide long-lived pulse generators since frequent replacements increase sales and profits.[10] In order to encourage manufacturers to produce longer-life devices, manufacturers should be rewarded on the basis of the amount of functional service years per ICD implanted. This could result in a substantial reduction of replacement surgery, adverse effects for the patient, increased cost-effectiveness and appropriate compensation for ICD manufacturers.

Limitations

There are several limitations to this study. First of all, battery longevity was only studied in four different manufacturers. Furthermore, although the sequence per device type was prespecified (i.e. at random) for the different manufacturers, annual price-volume agreements resulted in an unequal number of ICDs implanted per different manufacturer. In addition, it is important to be aware of the fact that replaced devices in every longevity analysis are outdated and therefore ICD longevity results may not apply to current or future devices.

CONCLUSION

Although the majority of devices are replaced because of battery depletion, approximately 30% of the devices are replaced for other reasons. Furthermore, device type, device manufacturer, device generation (i.e. implanted before or since 2002), the percentage of pacing and the pacing output had significant influence on battery longevity. Multivariate analysis demonstrated improved battery longevity in modern ICD generations and large.

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8

Chapter 8

Driving Restrictions after Implantable Cardioverter Defibrillator Implantation: an Evidence Based Approach

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ABSTRACT

Aims

Little evidence is available regarding restrictions from driving following implantable cardioverter defibrillator (ICD) implantation or following first appropriate or inappropriate shock. The purpose of the current analysis was to provide evidence for driving restrictions based on real-world incidences of shocks (appropriate and inappropriate).

Methods and results

A total of 2786 primary and secondary prevention ICD patients were included. The occurrence of shocks was noted during a median follow-up of 996 days (IQR, 428–1833 days). With the risk of harm formula, using the incidence of sudden cardiac incapacitation (SCI), the annual risk of harm to others posed by a driver with an ICD was calculated. Based on Canadian data, annual risk of harm to others of 5 in 100 000 (0.005%) was used as a cut-off value. In both primary and secondary prevention ICD patients with private driving habits, no restrictions to drive directly following implantation or an inappropriate shock are warranted. However, following an appropriate shock, these patients are at increased risk to cause harm to others road users and therefore should be restricted to drive for a period of 2 and 4 months, respectively. In addition, all ICD patients with professional driving habits have a substantial elevated risk to cause harm to other road users during the complete follow-up after both implantation and shock and should therefore be restricted to drive permanently.

Conclusion

The current analysis provides a clinically applicable tool for guideline committees to establish evidence-based driving restrictions.

INTRODUCTION

It has been recognized that patients treated with an ICD have an ongoing risk of sudden incapacitation that might cause harm to others when driving a car. Although numerous recommendations exist, thus far evidence is scarce to justify them. As a result, a large variation exists between different countries concerning the legislation of driving restriction after both primary prevention and secondary prevention ICD implantation.[1-3] Since driving restrictions are often being perceived as difficult for patients and their families, clear evidence on the necessity of these restrictions is vital. Furthermore, these restrictions should take into account the indication for ICD implantation (primary or secondary prevention). In the end, however, it must be recognized that the goal of a zero percent risk is unobtainable and that society has to accept a certain level of risk by allowing patients at risk to resume driving.[4-6]

With the constant increase in ICD implants worldwide, clear guidelines regarding driving restrictions in both primary and secondary ICD patients are warranted. In this analysis we determined the risk for ICD therapy following ICD implantation or following previous device therapy (appropriate and inappropriate shock) in relation with driving restriction for private and professional drivers in a large number of primary and secondary ICD patients.

METHODS

Patients

The study population consisted of patients from the South-western part of the Netherlands (comprising 1.500.000 people) who received an ICD for primary prevention or secondary prevention in the Leiden University Medical Centre, the Netherlands. Since 1996, all implant procedures were registered in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Centre). Characteristics at baseline, data of the implant procedure, and all follow-up visits were recorded prospectively. The data collected for the current registry ranged from January 1996 up to September 2009.

Eligibility for ICD implantation in this population was based on international guidelines for primary and secondary prevention. Due to evolving guidelines, indications will have changed over time.[7, 8]

Device implantation and programming

All defibrillator system implantations were performed transvenously, without thoracotomy. Testing of sensing and pacing thresholds and defibrillation threshold testing was performed during the implant procedure. Implanted systems were manufactured by Biotronik (Berlin, Germany), Boston Scientific [Natick, MA, USA, formerly CPI, Guidant (St Paul, MN, USA)], Medtronic (Minneapolis, MN, USA), and St Jude Medical/Ventritex (St Paul, MN, USA).

Defibrillators were programmed as follows: a ventricular arrhythmia monitor zone was programmed in all patients (150-188 bpm). No therapy was programmed in this zone until arrhythmias were detected during follow-up. Ventricular arrhythmias faster than 188 bpm were initially attempted to be terminated with two bursts of antitachycardia pacing (ATP) and, after continuation of the arrhythmia, device shocks were the indicated therapy.

Ventricular arrhythmias faster than 210 bpm were directly attempted to be terminated by device shocks. Furthermore, atrial arrhythmia detection was set to >170 bpm with supraventricular arrhythmia–discriminators enabled. Settings were adapted, only when clinically indicated (e.g. hemodynamic well-tolerated ventricular tachycardia (VT) at high rate; VT in the monitor zone).

According to Dutch legislation, updated in June 2004, private driving was prohibited for the first 2 months after implantation for both primary prevention and secondary prevention ICD patients. Furthermore, private drivers are restricted from driving for a period of 2 months following an appropriate shock and professional drivers are permanently restricted from driving following ICD implantation.[9]

Patient follow-up

Patient check-up was scheduled every 3-6 months, which included device interrogation. In case of unplanned hospitalization or symptomatic episodes of arrhythmia, additional device interrogations were performed. During device interrogation, episodes were assessed for appropriate and inappropriate ICD therapy (ATP or shocks) and verified by an electrophysiologist. Shocks were classified as appropriate when they occurred in response to VT or ventricular fibrillation (VF) and as inappropriate when triggered by sinus tachycardia or supraventricular tachycardia (SVT), T-wave oversensing, or electrode dysfunction. After delivery of an appropriate shock, efforts were made by a trained electrophysiologist to reduce the recurrence rate of arrhythmic events. When clinically indicated, ICD settings and/or antiarrhythmic medication were adjusted.

Since periodical follow-up was performed every 3-6 months, patients without data for the most recent 6 months prior to the end of the study were considered as lost to follow-up. However, these patients were included in the analysis as far as data was acquired.

End-points

The first shock (appropriate or inappropriate) was considered the primary end-point. For the second shock analysis, only those patients who received a first shock were considered at risk for a second shock and only subsequent shocks occurring more than 24 hours after first shock were considered second shocks. Noteworthy, ATP therapy was discarded from the analysis since the number of patients experiencing syncope – and therefore incapacitation – during ATP therapy is low. [10, 11]

Risk assessment

Currently, prospective controlled studies in which ICD patients have been randomized to permit driving are not available. In 1992, a 'risk of harm' formula was developed to quantify the level of risk to drivers with ICDs by the Canadian Cardiovascular Society Consensus Conference.[12, 13] This formula, with the following equation: RH = TD × V × SCI × Ac, calculates the yearly risk of harm (RH) to other road users posed by a driver with heart disease and is directly proportional to:

- proportion of time spent on driving or distance driven in a given time period (TD),
- type of vehicle driven (V),

- yearly risk of sudden cardiac incapacitation (SCI),
- the probability that such an event will result in a fatal or injury producing accident (Ac).

Based on the literature, it is known that on average a private driver spends ~4% (TD = 0.04) and a professional driver spends ~25% (TD = 0.25) of his time driving.[14, 15] In addition, it was shown that more injurious accidents were caused by heavy truck or passenger-carrying vehicles when compared to private automobiles. In the Ontario Road Safety Annual Report, truckers were involved in ~2% of all road accidents but in ~7.2% of all lethal accidents. Based on this data, V = 1 for a professional driver and V = 0.28 for a private driver in the risk of harm formula.[14, 15] Furthermore, less than 2% of reported incidents of driver sudden death or loss of consciousness has resulted in injury or death to other road users or bystanders (Ac = 0.02).[16-18] In this analysis, the yearly risk of sudden cardiac incapacitation was based on the cumulative incidence of ICD shocks (appropriate or inappropriate) which were calculated for different follow-up periods as described previously. However, the actual influence of an ICD shock on the capacity to drive is unknown. According to the literature, 31% of the patients experience syncope or near syncope during an appropriate shock.[19] Since this proportion of patients receiving an appropriate shock will then be incapacitated to drive, it was assumed that the SCI is equal to the cumulative incidence of appropriate ICD shocks times 0.31. So far, no reports exist which describe the proportion of patients experiencing syncope or near syncope during an inappropriate shock. Based on the causes of inappropriate shocks (atrial fibrillation, sinus tachycardia, T-wave oversensing and lead failure) it is less likely that inappropriate shocks coincide with more hemodynamic consequences then appropriate shocks do. With the assumption that 31% of the patients with appropriate shocks experience syncope, it was supposed that at most the same proportion of patients receiving an inappropriate shock will experience syncope. Therefore, similar to appropriate shocks, the SCI is equal to the cumulative incidence of inappropriate ICD shocks times 0.31.

Considering the fact that driving restrictions for ICD patients are implemented as a protection for both ICD patients, as well as other road users, the risk of harm formula is an easy tool to calculate the potential harm brought to other road users on a yearly basis when ICD patients are not restricted to drive.

Unfortunately, data regarding an acceptable level of risk for private and professional drivers with an ICD in society are scarce. However, in Canada an annual risk of death or injury to others of 5 in 100 000 (0.005%) appeared to be in general acceptable.[3] Therefore, this generally accepted level of risk will be used as a cut-off value in the current study.

Private and professional drivers

Criteria to distinguish a private driver from a professional driver were defined on the basis of the Canadian Cardiovascular Society Consensus Conference.[12, 13] According to these criteria, a private driver was defined as follows: 1) driving < 36 000 km per year; 2) spending < 720 h per year driving; 3) driving a vehicle weighting < 11 000 kg, and 4) does not earn a living by driving. Any licensed driver who does not fulfil one of these criteria was considered to be a professional driver.

Statistical analysis

Continuous data are expressed as mean with standard deviation (SD) or median and first and third quartile when appropriate; dichotomous data are presented as numbers and percentages. Cumulative incidences for first and second appropriate shock were determined by the Kaplan-Meier method to take different follow-up times per patient into account. Cumulative incidences were determined for several periods of time after implantation and presented with a 95% confidence interval (CI) as the estimate plus or minus 1.96 times the standard error.

Standard errors were derived from the binomial distribution, and the confidence interval constructed with the normal approximation. The risk of harm formula was used to calculate the yearly risk of harm to other road users posed by an ICD treated driver. With this formula, various outcomes were calculated on basis of distinct ICD indication (i.e. primary and secondary prevention), type of driver (i.e. private and professional driver) and type of vehicle driven (i.e. heavy truck and passenger-carrying vehicle or a private automobile). All statistical analyses were performed with SPSS software (version 18.0, SPSS Inc., Chicago, Illinois).

RESULTS

Patients

Since 1996, data of 2786 consecutive patients receiving an ICD for primary (n=1718, 62%) or secondary (n=1068, 38%) prevention were prospectively collected. One hundred and ninety eight of these patients (n=126 (64%) primary prevention; n=72 (36%) secondary prevention) received an ICD for diagnosed congenital heart disease or monogenetic heart disease. A total of 196 (7.0%) patients were lost to follow-up, however included in the analysis as far as data was acquired. Median follow-up time was 996 days (interquartile range, 428–1833 days). The majority of patients (79% men, mean age 61 years (SD 13 years) had ischemic heart disease. Baseline patient characteristics are summarized in Table 1.

Device therapy in primary prevention patients

In the group of primary prevention patients, median follow-up was 784 days (interquartile range, 363–1495 days). During this follow-up, a total of 190 (10%) patients received an appropriate shock. Median time to first appropriate shock was 417 days (interquartile range, 134 to 960 days). From those 190 patients who received a first appropriate shock, 65 patients (34%) received a second appropriate shock. Median time between first and second appropriate shock was 66 days (interquartile range, 29-379 days). Cumulative incidences for first and second appropriate shock are displayed in Figure 1.

Inappropriate shocks occurred in 175 (10%) patients with a median time of 320 days (interquartile range, 124 to 711days). From the 175 patients with a first inappropriate shock, 47 patients (27%) received a second inappropriate shock. Median time between first and second inappropriate shock was 224 days (interquartile range, 77 to 580 days). Cumulative incidences for first and second inappropriate shock are displayed in Figure 2.

Table 1. Baseline patient characteristics.

	Total (n = 2786)	Primary prevention (n = 1718)	Secondary prevention (n = 1068)
Clinical characteristics			
Age (years)	61±13	62±13	61±14
Male (%)	2192 (79)	1336 (78)	856 (80)
Left ventricular ejection fraction (%)	33±15	31±14	39±16
QRS, mean (SD), ms	125±34	129±35	119±32
Renal clearance, mean (SD), ml/min	81±37	81±36	82±39
Ischemic heart disease (%)	1800 (65)	1077 (63)	723 (68)
History of atrial fibrillation/flutter (%)	683 (25)	447 (26)	236 (22)
Medication			
ACE inhibitors/AT II antagonist (%)	2107 (76)	1407 (82)	700 (66)
Aspirin (%)	1107 (40)	649 (38)	458 (43)
Beta-blocker (%)	1513 (54)	1074 (63)	439 (41)
Diuretics (%)	1738 (62)	1221 (71)	517 (48)
Statins (%)	1610 (58)	1075 (63)	535 (50)
Antiarrhythmic medication *			
Amiodarone (%)	497 (18)	221 (13)	276 (26)
Sotalol (%)	386 (14)	184 (11)	202 (19)

*ACE = angiotensin-converting enzyme; AT = angiotensin; SD = standard deviation. * Patients could be taking >1 antiarrhythmic drug.*

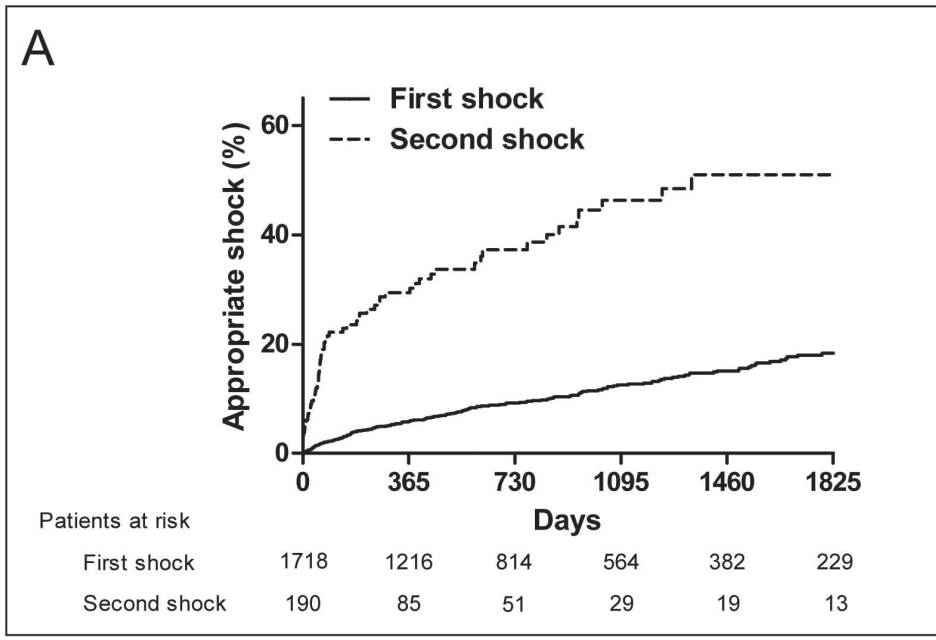
Device therapy in secondary prevention patients

In the group of secondary prevention patients, median follow-up time was 1442 days (interquartile range, 618–2469 days). During this follow-up, a total of 342 (32%) patients received an appropriate shock. Median time to first appropriate shock was 509 days (interquartile range, 141 to 1137 days). From those 342 patients with a first appropriate shock, 166 (49%) patients received a second appropriate shock. Median time between the first and second appropriate shock was 400 days (interquartile range, 107-1072 days). Cumulative incidences for first and second appropriate shock are displayed in Figure 1.

Inappropriate shocks occurred in 177 (17%) patients with a median time of 639 days (interquartile range, 190 to 1676 days). From the 177 patients with a first inappropriate shock, 60 patients (34%) received a second inappropriate shock. Median time between first and second inappropriate shock was 243 (interquartile range, 47 to 435 days). Cumulative incidences for first and second inappropriate shock are displayed in Figure 2.

Risk assessment in primary prevention ICD patients

In the risk of harm formula (RH = TD × V × Ac × SCI), the annual risk of harm per specific time point is calculated with the prespecified variables TD, V, and Ac and with the SCI. SCI equals the cumulative incidence of ICD shocks multiplied by the proportion of



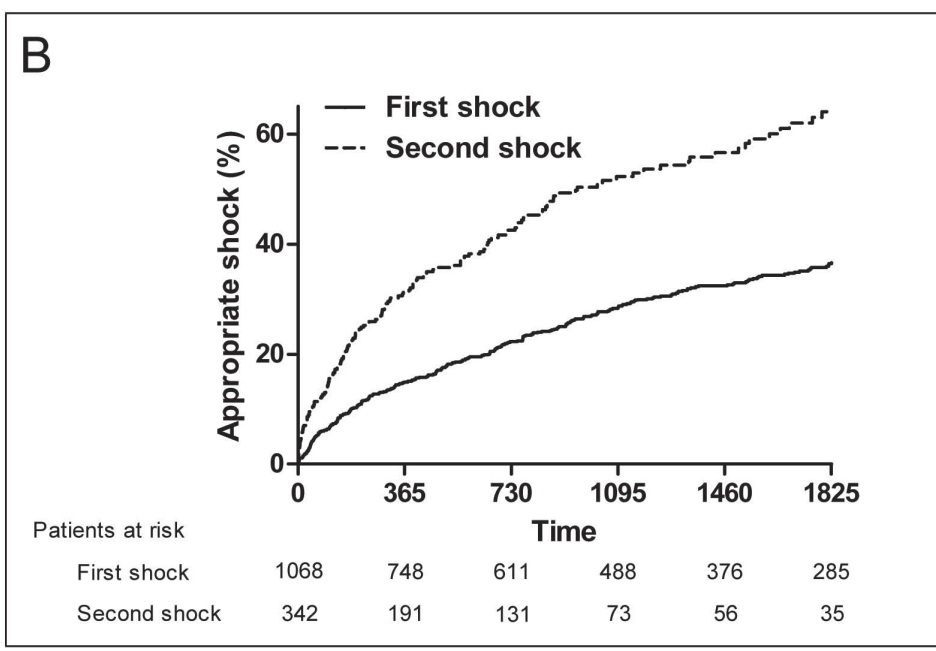
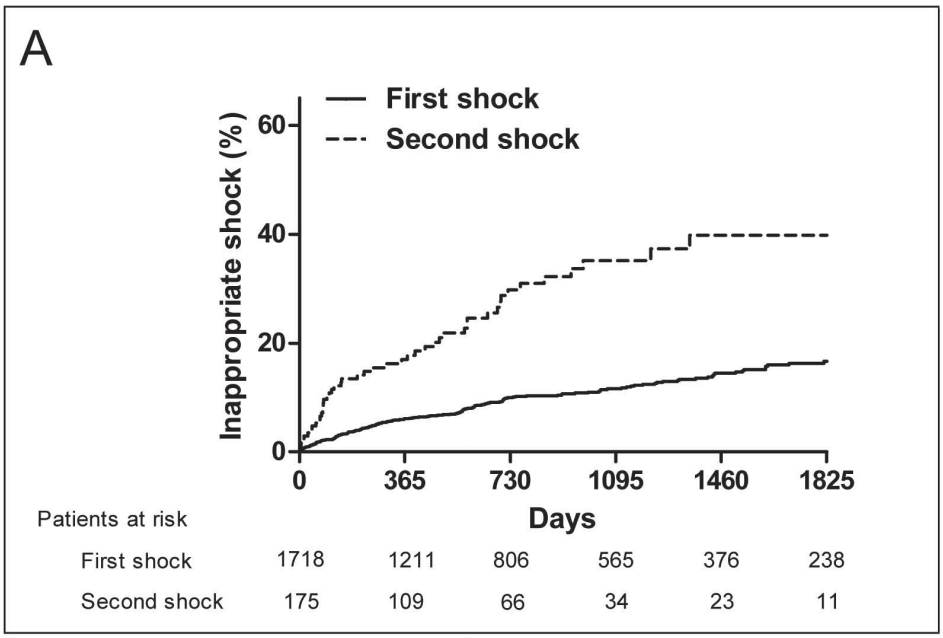


Figure 1. Kaplan-Meier curve for first and second appropriate shock in primary (panel A) and secondary (panel B) prevention ICD patients. Only patients who received a first appropriate shock were included in the analysis for the second appropriate shock. The time to the occurrence of a second appropriate shock was counted (in days) from the first appropriate shock.



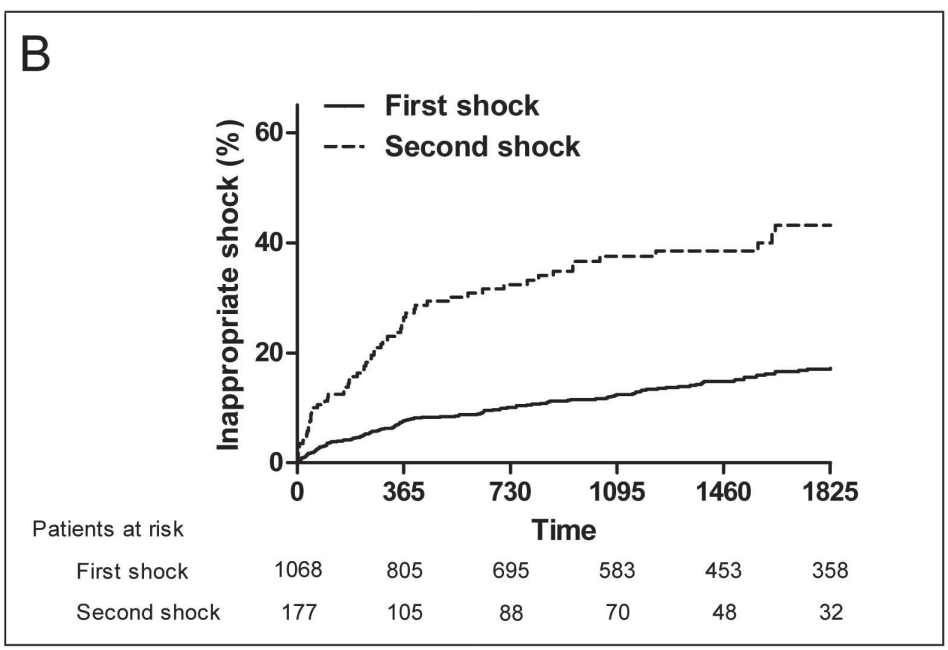


Figure 2. Kaplan-Meier curve for first and second inappropriate shock in primary (panel A) and secondary (panel B) prevention ICD patients. Only patients who received a first inappropriate shock were included in the analysis for the second inappropriate shock. The time to the occurrence of a second inappropriate shock was counted (in days) from the first inappropriate shock.

patients experiencing syncope (31%). For instance, for primary prevention ICD patients the cumulative incidence for an appropriate shock at one month following implantation is 0.9%. Since the formula uses yearly incidences, the monthly incidence is converted to a yearly incidence of 10.8% (0.9% × 12) and hereafter multiplied by the proportion of patients experiencing syncope or near syncope during an ICD (i.e. 31%) shock. Therefore, SCI in this example equals 0.03 (0.009 × 12 × 0.31). Accordingly, the risk of harm to other road users per 100 000 ICD patients for primary prevention ICD patients with private driving habits one month after implantation is calculated as follows: 0.04 × 0.28 × 0.02 × 0.009 × 12 × 0.31 = 0.75. After one year, the cumulative incidence for appropriate shocks in these patients is 6.0% following implantation. Consequently, the risk of harm to other road users for these patients declines to 0.43 (RH = 0.04 × 0.28 × 0.02 × 0.062 × 0.31) per 100 000 ICD patients per year (Figure 1 and Figure 3). Directly after implantation, the risk of harm to other road users in primary and secondary prevention ICD patients with private driving habits remains below the acceptable cut-off value of 5 per 100 000 ICD patients. Also after experiencing a first inappropriate shock the risk of harm to other road users remains below the accepted cut-off value (Figure 4).

Following an appropriate shock, the annual risk of harm declines from 8.0 (RH = 0.04 × 0.28 × 0.02 × 0.096 × 12 × 0.31) after one month to 2.1 (RH = 0.04 × 0.28 × 0.02 × 0.302 × 0.31) per 100 000 ICD patients after one year (Figure 1 and Figure 3). In Figure 3 it is shown that the risk of harm declines below the accepted cut-off value after 4 months following an appropriate shock in primary prevention ICD patients with private driving habits. However, following an inappropriate shock, the risk of harm in these patients is again directly below the accepted cut-off value (Figure 4).

Due to the heavy type of vehicle driven and the hours spent driving, the annual risk of harm following both implantation and appropriate shock was found to be 22.3 times higher in primary prevention ICD patients with professional driving habits as compared to private drivers. Consequently, the risk of harm to other road users following implantation or shock remains above the acceptable cut-off value during the complete follow-up.

Risk assessment in secondary prevention ICD patients

In secondary prevention ICD patients with private driving habits the annual risk of harm based on an appropriate shock was found to be 1.8 (RH=0.04*0.28*0.02*0.022*12*0.31) per 100 000 ICD patients 1 month following implantation (Figure 1 and Figure 2). Similar to primary prevention ICD patients with private driving habits, the risk of harm to other road users of these patients remained below the cut-off value of 5 per 100 000 ICD patients during follow-up. Also if the risk of harm to other road users after implantation was based on the cumulative incidence of inappropriate shocks, outcomes were directly following implantation below the accepted cut-off value (Figure 4).

However, after an appropriate shock, the risk of harm to other road users declined from 6.9 (RH=0.04*0.28*0.02*0.083*12*0.31) to 2.2 (RH=0.04*0.28*0.02*0.315*0.31) casualties on an annual basis per 100 000 ICD patients 1 month and 12 months following appropriate shock respectively. This risk following appropriate shock declined below the accepted cut-off value after 2 months in the group of secondary prevention ICD patients with private

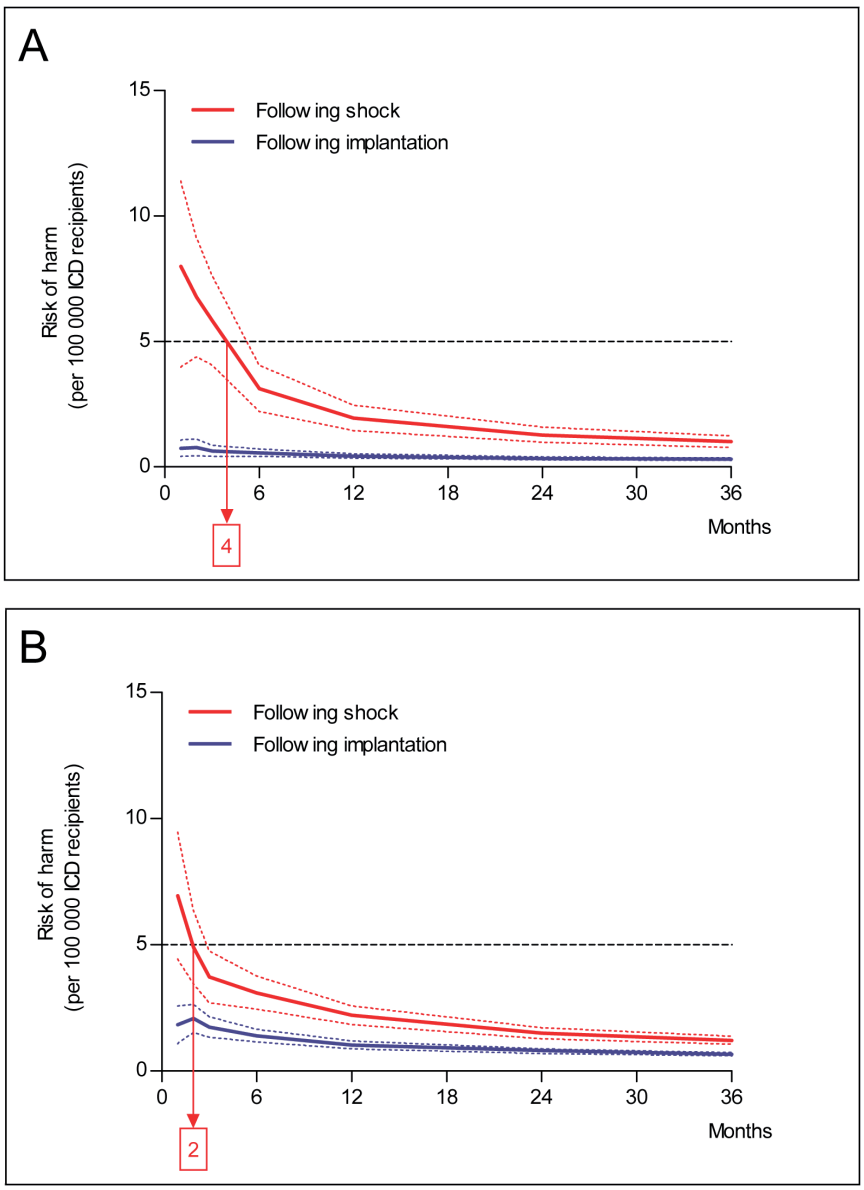


Figure 3. The annual Risk of Harm to other road users (Y-axis) in primary (panel A) and secondary (panel B) prevention ICD patients based on the cumulative incidence of appropriate shocks is illustrated. Risk of harm (solid lines) is calculated in the months (X-axis) following implantation or appropriate shock. The horizontal dotted line represents the cut-off value for the accepted level of risk of harm (5 per 100 000). Blue and red dotted lines represent the range of the risk of harm, based on the confidence interval of the cumulative incidence for appropriate shocks. In primary prevention ICD patients (panel A), driving is acceptable directly following implantation (blue line) and should be restricted for 4 months following appropriate shock (red line). In secondary prevention ICD patients (panel B), driving is acceptable directly following implantation (blue line) and should be restricted for 2 months following appropriate shock (red line).

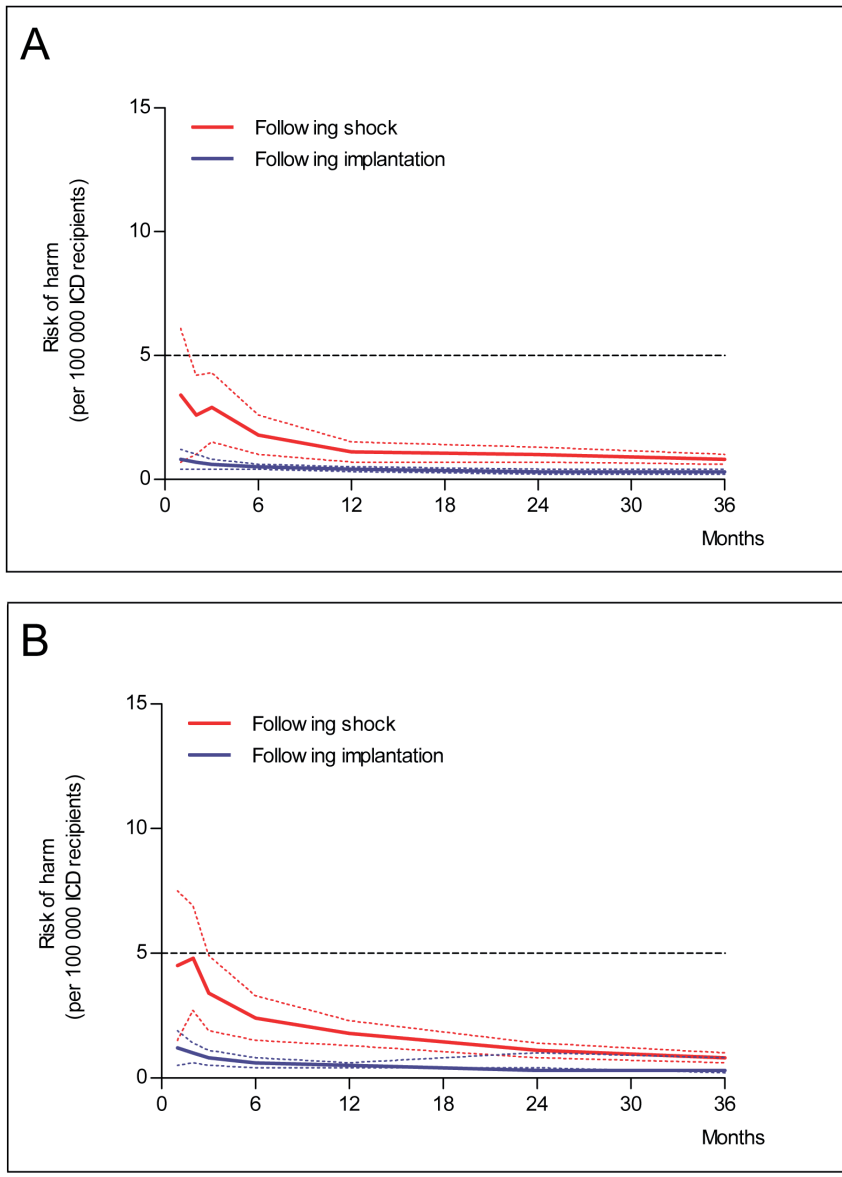


Figure 4. The annual Risk of Harm to other road users (Y-axis) in primary (panel A) and secondary (panel B) prevention ICD patients based on the cumulative incidence of inappropriate shocks is illustrated. Risk of harm (solid lines) is calculated in the months (X-axis) following implantation or inappropriate shock. The horizontal dotted line represents the cut-off value for the accepted level of risk of harm (5 per 100 000). Blue and red dotted lines represent the range of the risk of harm, based on the confidence interval of the cumulative incidence for inappropriate shocks. In primary prevention ICD patients (panel A), driving is acceptable directly following implantation (blue line) as well as directly following inappropriate shock (red line). Similar results were found in secondary prevention ICD patients (panel B), were driving is again acceptable directly following implantation (blue line) as well as directly following inappropriate shock (red line).

driving habits (Figure 1 and Figure 2). Following an inappropriate shock, the risk of harm in these patients is again directly below the accepted cut-off value (Figure 4).

Professional driving in secondary prevention ICD patients was above the cut-off value following both implantation and shock during the complete follow-up.

DISCUSSION

In this evidence based assessment of driving restrictions using the risk of harm formula, the findings can be summarized as follows: 1) following device implantation, primary and secondary prevention ICD patients with private driving habits have an acceptable risk of harm and therefore can be directly permitted to drive; 2) after an inappropriate shock, the level of risk remains below the accepted cut-off value and therefore no restrictions should be applied in all ICD patients with private driving habits; 3) in the case of an appropriate shock, primary and secondary preventions ICD patients with private driving habits should be restricted to drive for 4 and 2 months respectively; 4) ICD patients with professional driving habits do not reach an acceptable level of risk during follow-up and therefore should be permanently restricted to drive.

Risk of driving in primary prevention ICD patients

With increasing rates of primary prevention ICD implantations worldwide, clear guidelines regarding driving restrictions are essential. Although the risk for sudden incapacitation while driving is considered lower in this group of ICD patients than in secondary prevention ICD patients, no distinction is made in driving restrictions following ICD treatment. These differences in event rates are based on mortality data, rates of sudden cardiac death, and rate of ICD discharges reported from primary prevention trials.[20-27] With the lack of randomized controlled trials concerning ICD patients and the risk of driving, recommendations of the European Society of Cardiology (ESC) and American Heart Association (AHA) on driving restrictions in the group of primary prevention ICD patients are based on data from these trials.[1, 3]

The current study shows a cumulative incidence of 6.0% appropriate shocks after 1 year. Furthermore, ICD discharges were highest in the first period following implantation and showed a slight decline in the years thereafter (Figure 1). These data are not comparable with the MADIT I trial which described a shock rate of 30.0% on an annual basis during two years follow-up or with the MADIT II trial which described a shock rate of 11.7% on an annual basis during three years follow-up. However the appropriateness of the defibrillator discharges could not be assessed reliably in the MADIT I trial.[26, 28] Furthermore, with regard to the MADIT II trial, devices were unable to deliver ATP therapy which could lead to a higher shock rate. In the SCD-HeFT trial, the annual rate of appropriate ICD discharge during 5 years of follow-up was 7.5% per year.[20] In the DEFINITE trial, a shock rate of 7.4% occurred on an annual basis, however only 44.9% of discharges were appropriate.[25] Data of the SCD-HeFT and DEFINITE trials are comparable with data from the current study.

In the current analysis 10% of the primary prevention ICD patients received an inappropriate shock which is more or less comparable with the 11.5% of the MADIT II trial.[29]

Currently, ESC and AHA recommend primary prevention ICD patients with private driving habits not to drive for 1 month and 1 week respectively. It should be noted that this is not because of an increased risk of SCI, but to improve recovery from implantation of the defibrillator.[1-3] The current study demonstrates that the risk of harm for private drivers remains well below the acceptable cut-off level after implantation and therefore is in agreement with these recommendations (Figures 3 and 4). In addition, for professional drivers the outcomes of the risk of harm formula in the current analysis are unfavourable during the entire period of ICD implantation. As a result, based on the outcomes of this study, these drivers should be permanently restricted from driving which is in line with the current recommendations of the ESC and AHA.[1-3]

Risk of driving in secondary prevention ICD patients

Secondary prevention ICD patients have already experienced a life-threatening arrhythmia (e.g. VT or VF). The probability that patients will experience a recurrent arrhythmia is therefore an important factor determining the risk of harm, both with respect to themselves as well as others in car accidents. With regard to inappropriate shocks, only 17% of the secondary prevention ICD patients in the current analysis received such a shock. This proportion is more or less comparable with the 15% found in secondary prevention ICD patients included in the PainFREE Rx II trial.[30] However, the 5 year cumulative incidence of appropriate shock ranged between 55% and 70% in various trials, compared with a 36% cumulative incidence of appropriate shock in the current analysis.[19, 31-34] This difference is at least in part explained by the ATP therapy which was less frequently applied in the older secondary prevention studies which could prevent degeneration of VT in VF resulting in a lower cumulative incidence of appropriate shock therapy in the present study. Almost similar to Lubinski et al., the probability of arrhythmic episodes resulting in appropriate shocks in the current analysis was 2.2% in the first month, 2.9% in the second month, and remained below 2% per month in the months thereafter.[35] However, it was assumed that the risk for road accidents is just a fraction of the monthly probability of appropriate shocks, as described previously. Therefore, in patients with defibrillators implanted for secondary prevention, the risk of symptoms that may lead to incapacity while driving is low. Consequently in the current analysis, the risk of harm to other road users, based on both the cumulative incidence of appropriate and inappropriate shocks, remains below the acceptable risk. Therefore, no driving restrictions for secondary prevention ICD patients with private driving habits following implantation should be implemented. However, this outcome is in contrast with the current guidelines for secondary ICD patients with private driving habits, where the ESC and AHA recommend a 3 and 6 months driving restriction respectively.[1-3]

With respect to professional drivers, outcomes of the risk of harm formula are unfavourable during the entire period. Therefore, similar to primary prevention patients, secondary ICD patients should be restricted from professional driving.

Risk of driving following appropriate or inappropriate shock

A particularly difficult issue for patients and physicians is the consideration of driving restrictions in an ICD patient who has received an appropriate ICD shock. Following appropriate ICD therapy, guidelines of the ESC and AHA prescribe a 3 and 6 month

period of driving restriction in ICD patients respectively.[1, 3, 36] When patients experience an appropriate shock for a spontaneous ventricular arrhythmia during follow-up, the risk of driving is determined by the probability of a subsequent arrhythmic event and by the likelihood of symptoms of impaired consciousness. However, symptoms of impaired consciousness during the first appropriate ICD therapy are not unambiguously predictive for future syncope during subsequent shocks.[31, 37] In a study of 125 ICD patients by Freedberg et al., the median freedom from ICD therapy for the second shock was only 22 days, with a one year cumulative incidence of a second appropriate shock being 79%.[19] These were all secondary prevention ICD patients and the cumulative incidence for a second appropriate shock shows large dissimilarity when compared with the one year cumulative incidence of 32% observed in the secondary prevention group in the present study. However, since these are all older devices without the option of ATP, shock rates in the study by Freedberg et al. are probably comparable with cumulative incidence of all ICD therapy in the current analysis.

Finally, substituting these cumulative incidences for appropriate shock in the risk of harm formula results in a significant increase in the risk of harm to other road users when ICD patients are allowed to drive in the period following this shock. This risk of harm to others is above the cut-off value of 5 per 100 000 on an annual basis for a period of 4 months and 2 months following appropriate shock in primary and secondary ICD patients respectively (Figure 3). These outcomes are more or less in line with the guidelines of the ESC and AHA.[1-3]

Since, to our knowledge, the incidence of syncope following an inappropriate shock is unknown, calculating the corresponding risk of harm is problematic. Therefore, it was assumed that the incidence of syncope or near syncope during an inappropriate shock is equal to the incidence of syncope or near syncope during an appropriate shock. Even with this apparent defensive approach in which the potential risk of harm could be overestimated, the actual risk of harm following an inappropriate shock remained below the acceptable cut-off value for both primary and secondary ICD patients. Therefore, in line with the current guidelines of the ESC and AHA, no driving restrictions following an inappropriate shock should be applied in these patients. [1-3] However, it is needless to say that all efforts should be made to prevent subsequent inappropriate shock before those patients should be permitted to drive again.

Private and professional drivers

It is however important to recognize the difference between the Canadian and European classification of private and commercial drivers. In Canada a private driver is defined as one who drives less than 36000 km per year or spends less than 720 h driving per year, drives a vehicle weighing < 11 000 kg, and does not earn a living by driving. A commercial driver is defined as any licensed driver who does not fulfill the definition of a private driver. In Europe, two groups of drivers are defined: Group 1 comprises drivers of motor cycles, cars, and other small vehicles with or without a trailer. Group 2 includes drivers of vehicles over 3.5 metric tons or passenger-carrying vehicles exceeding eight seats excluding.[3]

As the risk of harm estimations are based on the Canadian data it may be necessary to reevaluate the strict European rules. For example a private driver with a motor-home exceeding the 3.5 metric ton limit automatically is a group 2 driver and restricted from driving after ICD implant which seems to be an unnecessary restriction.

Clinical implications

Recently, EHRA and AHA provided consensus documents on driving restriction for ICD patients. Since no data from routine clinical practice was available at that time, restrictions were based on data from randomized clinical trials, which to a certain extent differ from routine clinical practice. This study is the first to provide accurate data on the incidences of appropriate and inappropriate shocks during follow-up in routine clinical practice and based on this, established driving restrictions. However, it is of course up to the guideline committees and national regulatory authorities to determine final driving restrictions for ICD patients. It should be emphasized that for the current study, an acceptable risk of harm of 5 per 100 000 ICD patients was used based on Canadian consensus. Increasing or decreasing this cut-off value may hold significant consequences for the recommendations. Moreover, in the current formula, Ac was considered 2% (i.e. 2% of reported incidents of driver sudden death or loss of consciousness has resulted in injury or death to other road users or bystanders). This data is derived from the Ontario Road Safety Annual Report since exact data usable for the formula are scarce. It should be noted that differences in these data will exist between different countries or areas affected by population density, driving habits, and type of vehicle driven. This could affect the risk of harm to other road users. However, if available, data from other countries can be implemented in the formula.[2] Finally, guidelines committees and national regulatory authorities must taken into account the serious impact of driving restrictions on patient's life and the fact that ICD patients will ignore (too rigorous) driving restrictions.[38-40]

Limitations

This was a prospective observational study assessing the incidence of SCI in ICD patients. Since patients received ICDs in a single center over a long period of time, evolving guidelines could have created a heterogeneous population. Moreover, median follow-up time was 2.1 years in primary prevention and 4.0 years in secondary prevention ICD patients which resulted in relatively broad confidence intervals of the cumulative incidences at long-term follow-up. In addition, ATP was discarded from the analysis since, according to the literature, minority of patients receiving ATP experience syncope.[10, 11] As a result, calculated risk of harm to others might be underestimated. Moreover, ICD programming was not homogeneous since ICD settings were adapted when clinically indicated. Finally, only the first and second shock (appropriate or inappropriate) of the ICD patients were taken into account. Although patients sometime received more than two shocks, the number of patients receiving three or more shocks was small and had limited follow-up making assessment of the SCI unreliable.

CONCLUSION

The current study provides reports on the cumulative incidences of SCI in ICD patients following ICD implantation and following first appropriate or inappropriate shock. The risk of harm to others was assessed using this SCI multiplied by the estimated risk of syncope, which resulted in specific outcomes for the risk of harm to other road users per different scenario (Figure 5). This study may serve as a basis and founding of driving recommendations which can be used by national regulatory authorities.

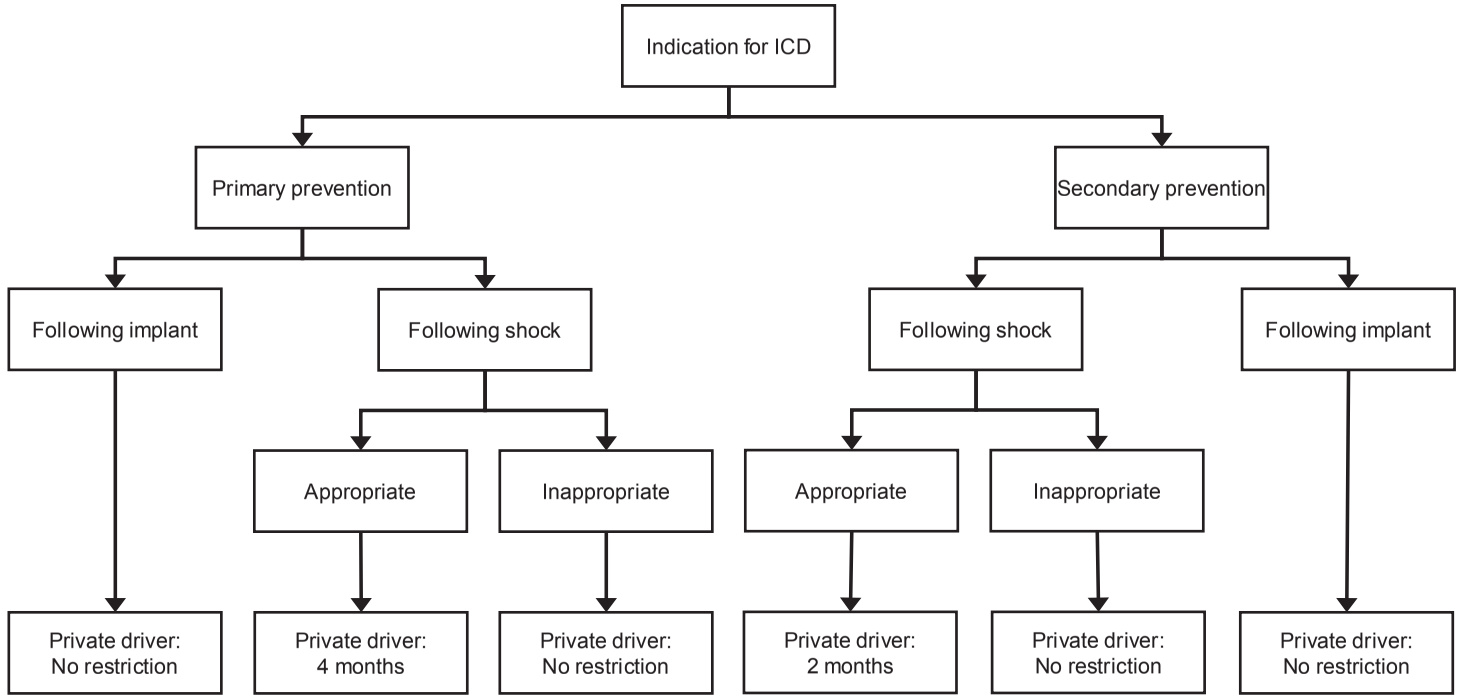


Figure 5. Flowchart demonstrating the recommended driving restrictions for ICD patients with private driving habits.

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Chapter 9

Primary Prevention Implantable Cardioverter Defibrillator Treatment: how to Identify Patients most Likely to Benefit?

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INTRODUCTION

Sudden cardiac death (SCD) is defined as death from an unexpected circulatory arrest, mostly due to a cardiac arrhythmia in patients with coronary artery disease, occurring within an hour of the onset of symptoms.[1] Approximately 50% of all deaths in patients with ischemic heart disease are unexpected, occurring shortly after onset of symptoms. Concomitantly with the rising number of patients with ischemic heart disease - especially in the Western world - annual worldwide mortality rates due to SCD has risen to an estimated 7 million patients.[2-4]

An effective treatment to prevent arrhythmic death is implantation of an implantable cardioverter defibrillator (ICD). Large randomized trials have proven the beneficial effect of ICD therapy in patients at high risk for SCD. The first trials demonstrated benefit in patients who survived a life-threatening ventricular arrhythmia (secondary prevention).[5-7] However, since the chance of surviving such an event is low (estimated at 6%), focus shifted to the identification of patients at high risk, prior to a first life-threatening event (primary prevention).[8] A clear example hereof is the MADIT II trial, which demonstrated that post infarct patients with a left ventricular ejection fraction (LVEF) of less than 30% had a significant better survival if they underwent ICD implantation compared with conventional medical therapy only.[9] In addition, the SCD-HeFT trial demonstrated that both ischemic and non-ischemic symptomatic heart failure patients with an LVEF ≤ 35% had an improved survival if treated with a defibrillator.[10]

Following the inclusion of primary prevention ICD treatment in the international guidelines, the implanted population changed from survivors of ventricular arrhythmias to patients with a low LVEF due to prior myocardial infarction.[11, 12] As a consequence , the total number of worldwide ICD implantations significantly increased to 275 000 in 2008.[13]

Clinical trials: identification of primary prevention ICD patients most likely to benefit

Although the large randomized trials clearly demonstrated the positive effect of ICD treatment on total mortality, these positive results are not observed in all patients currently indicated. A clear example is the analysis of mortality data from the MADIT-II trial, including patients with ischemic heart disease and a reduced LVEF without prior ventricular arrhythmias.[14] Benefit from ICD treatment was not observed in patients (5%) with severe renal failure (defined as blood urea nitrogen (BUN) ≥50 mg/dl or serum creatinine ≥2.5 mg/dl). After exclusion of these patients, 17 pre-specified potential risk factors were assessed for their predictive value for all-cause mortality in the non-ICD arm of the trial. This resulted in the following 5 risk factors: age > 70 years, New York Heart Association (NYHA) functional class > II, BUN > 26mg/dL, atrial fibrillation, and QRS duration > 120ms. All patients were grouped by the number of risk factors (0, 1, 2 or ≥3) and the effect of ICD treatment was assessed per group. The results showed a beneficial effect in patients with 1 or 2 risk factors (52% of patients) but no effect in patients without risk factors or with three or more risk factors (43% of patients). This implies that the patient who benefit most from ICD treatment should be at high enough risk for SCD (e.g. at least one risk factor) but not at too high a

risk for mortality from other causes (e.g. three or more risk factors). Additionally, the results show that in 48% of MADIT II patients, no benefit could be observed! An analysis of the SCD-HeFT trial showed similar results in a population with poor LVEF and symptomatic heart failure (NYHA functional class II or III) due to ischemic or non-ischemic heart disease.[15] A total of 2483 patients were included and stratified into 5 different risk-groups according to their predicted mortality calculated from their baseline variables. In the highest-risk patients (20% of patients included) a four-years mortality of 50% was observed and ICD implantation had no beneficial effect on survival. These outcomes again suggest that patients with a high risk for mortality do not benefit from primary prevention ICD treatment.

Routine clinical practice: identification of primary prevention ICD patients most likely to benefit

More recently, efforts have been made to construct a risk model on an ICD treated population in a real world population outside the setting of a clinical trial. Initially, risk models were constructed to identify patients at high risk for all-cause mortality, implying that these patients may have less ICD benefit. The analysis was performed with data from a 1036 (68% ischaemic) primary prevention patients registry with a mean follow-up of 873 ± 677 days. The risk score consisted of simple baseline variables such as age, LVEF and renal clearance which could stratify ischemic and non-ischemic patients in low (6 years mortality of <5%), intermediate, and high risk (6 years mortality of >45%) for mortality and therewith create an individual patient-tailored estimation on mortality risk which could aid clinicians in daily practice.[16] Although, according to the large studies mentioned above, high mortality risk can be expected to point out patients at low benefit, one could take it to a higher analytical level and by trying identify death prior to ICD discharge as the ideal end-point for non-benefit. At our center, we developed a tool to identify patients with ischemic heart disease who, although currently indicated for ICD treatment, will have a high risk of dying prior to actually receiving a potentially life-saving ICD shock.[17] In this study, a total of 900 primary prevention ICD patients with ischemic heart disease were followed for 669 days (IQR 363 – 1322 days). During follow-up 150 (17%) patients died of whom 114 (76%) patients did not receive appropriate device therapy and therewith had no clear benefit from ICD treatment. Accordingly, the following 5 independent predictors of death without appropriate ICD therapy were selected: NYHA ≥III, age ≥75, diabetes mellitus, LVEF ≤25%, and a history of smoking and included in a risk score model for death without appropriate ICD therapy (non benefit). The score was named the FADES score (acronym for Functional class, Age, Diabetes, Ejection fraction, Smoking) and after the determination of the individual patient risk scores cut-offs were determined for a population at low, intermediate and high risk of death without prior appropriate ICD therapy. Five-year cumulative incidence for death without prior appropriate therapy (non benefit) was 10% in low risk patients, 17% in intermediate risk patients and 41% in high risk patients. These results demonstrate that especially in the high risk patient group, which comprises 23% of the total primary prevention ICD population, a significant number of patients had no benefit of ICD therapy. However, it is important to realize that patients classified as high risk for death without prior appropriate ICD therapy do not per se receive no appropriate

ICD therapy at all. Paradoxically, factors as advanced age, depressed ejection fraction, and smoking are also identified as predictors of sudden cardiac death or appropriate ICD therapy.[14, 15, 18] Nevertheless, following potentially life-saving ICD therapy, life expectancy in those high-risk patients remains short: within 5 years following ICD therapy 61% of the high risk patients died. Consequently, the FADES score may offer additional inputs to improve patient care.

The potential of ICD treatment

A meta-analysis of all randomized clinical trials on primary prevention ICD treatment reported a number needed to treat of 13 (e.g. 13 ICD's to prevent one death).[19] Taking into consideration that within the currently indicated population, it may be relatively easy to identify patients who do not benefit from ICD therapy, one can imagine the high potential of ICD's, if better allocated than currently according to the guidelines directed clinical practice. Consequently, this will improve the cost-effectiveness of ICD therapy even more and optimize the utilization of limited financial resources and trained personnel which is so evidently needed.[20]

CONCLUSION

ICD therapy in primary prevention patients is effective en may save many patients from dying suddenly. However the challenge will be to develop and implement criteria allowing better identification of high risk patients and to limit the number of implants in patients who will not benefit. This is important not only from a cost perspective but also because ICD therapy is not harmless. In other words inappropriate shocks, infections and device or lead malfunction are serious issues.

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Chapter 10

Summary, Conclusions and Future Perspectives

SUMMARY

The general introduction of this thesis (**Chapter 1**) gives an overview of epidemiology and impact of sudden cardiac death (SCD) and describes its most important risk factors. The chapter further focusses on the development of the implantable cardioverter defibrillator (ICD) and major studies establishing the beneficial effect of ICD therapy as primary and secondary prevention strategy for SCD are specified. Additionally, the chapter shows the combination of an ICD with cardiac resynchronization therapy (CRT-D) as a frequent treatment in heart failure patients and, finally, shortly indicates potential complications and the socio-economic impact of device treatment. Although the beneficial effects of ICD therapy and CRT are extensively proven in clinical trials, much still remains unclear about the wide optimal allocation of these therapies in routine clinical practice. Therefore the aim of this thesis was to examine several important and unresolved issues regarding ICD and CRT treatment in daily clinical care by studying a large cohort of ICD and CRT-D recipients outside the setting of a clinical trial. The first part (**Part I**) of this thesis was focused on the clinical characteristics and outcomes of the population indicated for defibrillator treatment. In the second part (**Part II**), the social and economic implications of ICD and CRT-D therapy were examined.

Part I: Clinical aspects of implantable defibrillator treatment

In **Chapter 2** the mode of death of 2,859 ICD and CRT-D patients in routine clinical practice were assessed. For patients who died during follow-up, the mode of death was retrieved from hospital and general practitioner records and categorized according to a predetermined classification: heart failure death, other cardiac death, sudden death, non-cardiac death, and unknown death. During a median follow-up of 3.4 years, 107 (14%) primary prevention ICD, 253 (28%) secondary prevention ICD, and 302 (25%) CRT-D recipients died. The 8-year cumulative incidence of all-cause mortality was 39.9%. Heart failure death and non-cardiac death were the most common modes of death for all groups. Sudden death accounted for approximately 7-8% of all deaths.

This study demonstrated that heart failure and non-cardiac death are the most common modes of death in ICD and CRT-D patients and that the proportion of patients who died suddenly was low and comparable for all groups.

In **Chapter 3** the requirement for pocket related surgical re-interventions following 3,161 ICD implantations was evaluated and the effect of device replacement on the occurrence of re-interventions was assessed. In total, 145 surgical re-interventions were required in 122 (3.9%) patients, with a median time to first re-intervention of 75 days. The three years cumulative incidence of first re-intervention was 4.7% and the incidence of re-intervention was 1.9 per 100 ICD-years. Event rate comparison of replacement ICDs versus first implanted ICDs showed a more than doubled need for re-interventions in replacement ICDs (rate ratio 2.2). Further sub-division by the consecutive number of ICD replacements, shows an increase in the annual need for surgical re-intervention, ranging from 1.5% in the first implanted ICD, to 8.1% in the fourth implanted ICD.

This study showed the effect of ICD replacement on the requirement of pocket related surgical re-interventions.

In **Chapter 4** we assessed the impact of upgrading ICD therapy to CRT-D, in 115 heart failure patients, on the occurrence of ventricular arrhythmias (VAs) and appropriate ICD therapies. Episodes of VA, triggering device therapy (anti-tachycardia pacing and shocks) were recorded before and after upgrade for the overall population. In addition, these outcomes were compared between CRT responders and non-responders during the follow-up period after CRT response, defined as a LV end-systolic volume reduction of ≥15%, was assessed. It was found that in CRT responders (n=70), the frequency of VAs requiring appropriate device therapy demonstrated a trend toward a decrease from 0.51±0.79 to 0.30±0.59 per patient per year after CRT-D upgrade (p=0.052). In CRT non-responders (n=45), the frequency of VAs requiring appropriate device therapy significantly increased from 0.40±0.69 to 1.21±2.53 per patient per year after CRT-D upgrade (p=0.014).

This study clearly demonstrated that after an upgrade from ICD to CRT-D, non-responders to CRT showed a significant increase in VAs burden, requiring appropriate device therapy.

Chapter 5 assessed what proportion of 1,742 transvenously implanted ICD recipients would have been suitable for an ICD with a subcutaneous lead (S-ICD) and what the characteristics of these patients were. Patients without a preexistent indication for pacing were defined suitable for an S-ICD if they did not require atrial and/or right ventricular pacing, received successful antitachycardia pacing without a subsequent shock or an upgrade to a CRT-D device. During a median follow-up of 3.3 years, 627 (36%) patients reached an endpoint. The cumulative incidence of ICD recipients, suitable for an initial S-ICD implantation was 60% after 5 years. Significant predictors for the unsuitability of an S-ICD were: older age, secondary prevention, severe heart failure, atrial fibrillation, and a wide QRS.

This study shows that after 5 years of follow-up, more than half of the ICD recipients would have been suitable for S-ICD implantation and that several baseline clinical characteristics could be useful in the selection of those patients.

Part II: Socio-economic implications of implantable defibrillator treatment

The purpose of **Chapter 6** was to assess the cost-effectiveness of prophylactic ICD implantation in the real world. Using a Markov model, lifetime cost, life years (LYs), and gained quality-adjusted life years (QALYs) were estimated for device recipients and control patients. Based on data retrieved from our own center, prophylactic ICD implantation adds an estimated mean of 2.07 LYs and 1.73 QALYs. Increased lifetime cost for single-chamber and dual-chamber ICD recipients were estimated at €60,788 and €64,216 respectively. This resulted in an estimated incremental cost-effectiveness rate of €35,154 per QALY gained for single-chamber ICD recipients and an estimated incremental cost-effectiveness rate of €37,111 per QALY gained in dual-chamber ICD recipients.

This study demonstrated that, based on data and detailed costs derived from routine clinical practice, ICD therapy in selected patients with a reduced LVEF appears to be cost-effective.

In **Chapter 7** the ICD service life was studied in a cohort of 3,194 device recipients, and reasons for ICD replacement were assessed and categorized as battery depletion and non-battery depletion. During follow-up, 4,673 ICDs were implanted of which 1,479 ICDs (33%) were replaced. Mean device longevity was 5.0±0.1 years. A total of 1,072 (72%) ICDs were replaced because of battery depletion. Mean battery longevity of an ICD was 5.5±0.1 years. When divided into different types, mean battery longevity was 5.5±0.2 years for single-chamber ICDs, 5.8±0.1 for dual-chamber ICDs and 4.7±0.1 years for cardiac resynchronization therapy-defibrillators (CRT-Ds) ($p<0.001$). Devices implanted after 2002 had a significantly better battery longevity as compared to devices implanted before 2002 (5.6±0.1 vs. 4.9±0.2 years, $p<0.001$). In addition, large differences in battery longevity between manufacturers were noted (overall log rank test $p<0.001$).

This study showed that the majority of ICDs were replaced because of battery depletion and that large differences in device longevity exist between different ICD types, generation, and manufacturers.

Chapter 8 provides evidence for driving restrictions in primary and secondary ICD recipients with private or professional driving habits using real-world incidences of appropriate and inappropriate shocks. A total of 2,786 ICD patients were included and the occurrence of shocks was noted during a median follow-up of 996 days. In both primary and secondary prevention ICD patients with private driving habits, no restrictions to drive directly following implantation or an inappropriate shock are warranted. However, following an appropriate shock, these patients are at increased risk to cause harm to others road users and therefore should be restricted to drive for a period of 2 and 4 months, respectively. In addition, all ICD patients with professional driving habits have a substantial elevated risk to cause harm to other road users during the complete follow-up after both implantation and shock and should therefore be restricted to drive permanently.

This study provides a clinically applicable tool for guideline committees to establish evidence-based driving restrictions.

Chapter 9 is an editorial describing the challenge to develop and implement criteria allowing better identification of high risk patients for sudden cardiac death and to limit the number of implants in patients who will not benefit from primary prevention ICD therapy. This is important not only from a cost perspective but also because ICD therapy is not harmless. In other words, inappropriate shocks, infections, and device or lead malfunction are serious issues and well-defined criteria are needed to warrant that the survival benefit of primary prevention ICD therapy outweighs those drawbacks of complications and cost.

CONCLUSIONS

Although both ICD and CRT have proven to be an effective treatment strategy for selected patients in large clinical trials, many issues of the effects of defibrillator treatment in routine clinical practice remain unclear. In the current thesis, some of these unresolved questions are clarified based on data from a large cohort of ICD and CRT-D patients with long-term follow-up in routine clinical practice.

The first part of the thesis focusses on the clinical aspects of patients treated with a defibrillator. Even though the mode of death of defibrillator patients is extensively reported in randomized control trials, data outside the setting of a clinical trial is lacking. Based on a large number of patients from routine clinical practice the mode of death in ICD and CRT-D recipients was assessed and the most common modes of death turned out to be heart failure and non-cardiac death in primary prevention ICD, secondary prevention ICD, and CRT-D recipients. Furthermore, in defibrillator replacement patients, it was demonstrated that device replacement is associated with a doubled risk for pocket related surgical re-interventions and that every consecutive replacement increases the risk for re-intervention. Additionally, in the subpopulation who underwent upgrade from ICD to CRT-D, due to progression of heart failure, the incidence of ventricular arrhythmias was analyzed. Most strikingly was the difference in the burden of ventricular arrhythmias following an upgrade in both CRT-responders (decrease of ventricular arrhythmias) and CRT non-responders (increase of ventricular arrhythmias). In the last fragment of the first part, the suitability for the recently developed subcutaneous ICD was studied in our cohort and showed that more than half of the current ICD recipients are eligible for this type of device with potentially less associated device related-complications.

The second part of the thesis comprised the implications of large scale defibrillator treatment for both patients and society. First of all, the cost-effectiveness of primary prevention ICD implantation in the real world was assessed. Although ICD therapy in these selected patients appears to be cost-effective, improvement in device longevity and a reduction in the cost of the defibrillator system could have a large beneficial impact on the actual cost-effectiveness. However, in a subsequent analysis, modern ICD generations demonstrated only moderate improvement of longevity and more efforts should be made to prolong the battery life of defibrillator devices. Importantly, this could result in a decrease of pocket related complications, reduced mortality and improved cost-effectiveness ratios. Another important aspect for ICD recipients and society are the restrictions to drive following ICD implantation and therapy. While little evidence is available, legislation in many countries prohibits patients to drive following defibrillator implantation consequently limiting for instance severe heart failure patients in their daily movement. In the last fragment of the second part different approaches for the identification of primary prevention patients with the largest benefit of ICD treatment were discussed.

FUTURE PERPECTIVES

Following the inclusion of primary prevention defibrillator treatment in the international guidelines of cardiology, an enormous increase in the number of implanted defibrillator devices occurred in the last decade. As a result, the implanted population changed from survivors of ventricular arrhythmias to patients with a reduced LVEF with or without symptomatic drug refractory heart failure. Noteworthy is that a significant proportion of these defibrillator patients do not receive potentially life-saving therapy during follow-up and therewith have no benefit from defibrillator implantation. On the other hand, patients at high risk for sudden cardiac death, without an indication for defibrillator therapy according to the current guidelines, will have to be identified. Given the serious drawbacks, such as inappropriate shock, lead failure, and cardiac device infections associated with this therapy, better patient selection prior to defibrillator implantation is required. In addition, the population eligible for primary prevention defibrillator treatment is of such magnitude that treatment of every patient will strain financial resources and the pool of trained personnel. This once more stresses the necessity of optimal allocation of defibrillator treatment. Accordingly, future research for defibrillator devices in routine clinical practice should focus on both diminishing the adverse events of this treatment by enhancing defibrillator longevity, improving antitachycardia algorithms, and reducing the proportion of lead failures as well as on the development and implementation of criteria that allow better identification of high risk patients and to limit the number of defibrillator implants in patients who will not benefit.

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Chapter 11

Samenvatting, Conclusies en Toekomstperspectief

SAMENVATTING

De algemene introductie van dit proefschrift (**hoofdstuk 1**) geeft een overzicht van de epidemiologie en de gevolgen van plotse hartdood (SCD, Sudden Cardiac Death) en beschrijft de belangrijkste risicofactoren hiervan. Het hoofdstuk richt zich onder meer op de ontwikkeling van de Implanteerbare Cardioverter Defibrillator (ICD) en specificeert de belangrijke studies die hebben bijgedragen aan het vaststellen van het gunstige effect van ICD-therapie als primaire en secundaire preventie voor SCD. Daarnaast wordt de combinatie van een ICD met cardiale re-synchronisatie therapie (CRT-D) als een frequente behandeling bij patiënten met hartfalen toegelicht en zullen kort de mogelijke complicaties en sociaaleconomische effecten van ICD therapie worden aangestipt. Ondanks het feit dat de gunstige effecten van ICD therapie en CRT uitvoerig zijn bewezen in klinische studies, bestaan er nog veel onduidelijkheden over de optimale allocatie van deze therapieën in de dagelijkse klinische praktijk. Dientengevolge, is het doel van dit proefschrift om een aantal belangrijke en onopgeloste kwesties met betrekking tot ICD en CRT-behandeling in de klinische praktijk te beantwoorden door middel van het onderzoeken van een groot cohort van ICD en CRT-D patiënten buiten de setting van een klinische studie. Het eerste deel (**deel I**) van dit proefschrift is gericht op de klinische kenmerken en uitkomsten van patiënten die behandeld worden met een ICD. In het tweede deel (**deel II**), worden de sociale en economische gevolgen van de brede toepassing van ICD en CRT-D therapie onderzocht.

Deel I: Klinische aspecten van implanteerbare defibrillator behandeling

In **hoofdstuk 2** werd de doodsoorzaak van 2859 patiënten met een ICD of CRT-D in de klinische setting geanalyseerd. Bij de patiënten die gedurende de follow-up overleden, werd de doodsoorzaak via het betreffende ziekenhuis of via de huisarts achterhaald en gecategoriseerd aan de hand van de vooraf bepaalde indeling: hartfalen dood, andere hartdood, plotse dood, niet-cardiale dood, en onbekende dood. Gedurende een mediane follow-up van 3,4 jaar, overleden 107 (14%) primaire preventie ICD patiënten, 253 (28%) secundaire preventie ICD patiënten, en 302 (25%) CRT-D patiënten. De 8-jaar cumulatieve incidentie van de totale mortaliteit was 39.9%. Hartfalen dood en niet-cardiale dood waren de meest voorkomende doodsoorzaken voor alle groepen. Plotse hartdood was goed voor ongeveer 7-8% van alle sterfgevallen.

Deze studie toonde aan dat hartfalen dood en niet-cardiale dood de meest voorkomende vormen van overlijden zijn in ICD en CRT-D patiënten en dat het aandeel van de patiënten die plotseling overlijd relatief laag was en vergelijkbaar is voor alle groepen.

In **hoofdstuk 3** werd de noodzaak tot pocket gerelateerde chirurgische re-interventie na ICD implantatie (n=3161) geëvalueerd en werd onderzocht of er sprake is van een relatie tussen het aantal ICD implantaties per patiënt en de frequentie van chirurgische re-interventie. In totaal werden er 145 chirurgische re-interventies verricht in 122 (3.9%) patiënten, met een mediane tijd tot de eerste re-interventie van 75 dagen. De cumulatieve incidentie drie jaar na de eerste re-interventie was 4.7% en de incidentie van re-interventie was 1.9 per

100 ICD-jaren. Vergelijking tussen de event rates van chirurgische re-interventie in initieel geïmplanteerde ICD's versus vervangen ICD's toonde een meer dan verdubbelding in de noodzaak tot re-interventies aan in vervangen ICD's (rate ratio 2.2). Verdere onderverdeling op basis van het volgnummer van de geïmplanteerde ICD per patiënt, toont een toename van de jaarlijkse noodzaak tot chirurgische re-interventie, variërend van 1,5% in de eerste geïmplanteerde ICD, tot 8,1% in het vierde geïmplanteerde ICD.

In deze studie werd het effect van ICD vervanging op de noodzaak tot pocket gerelateerde chirurgische re-interventies onderzocht.

In **hoofdstuk 4** hebben we, bij 115 patiënten met hartfalen, de impact van het upgraden van een ICD systeem naar een CRT-D systeem op het optreden van ventriculaire aritmieën en terechte ICD therapie onderzocht. Episodes van ventriculaire aritmieën die resulteerde in therapie (anti-tachycardia pacing en/of defibrillatie) voor en na het upgraden van de geïmplanteerde cardioverter defibrillator werden in de gehele populatie geregistreerd. Daarnaast werden deze resultaten vergeleken tussen CRT responders en non-responders in de follow-up periode nadat er was vastgesteld of er sprake was van een CRT respons welke werd gedefinieerd als een linker ventrikel eind-systolische volume vermindering van ≥ 15%. Het bleek dat in CRT responders (n=70), de frequentie van ventriculaire aritmieën die resulteerde in terechte therapie, een dalende trend van 0,51 ± 0,79 naar 0,30 ± 0,59 therapieën per patiënt per jaar liet zien na CRT-D upgrade (p = 0.052). In CRT non-responders (n=45), was de frequentie van ventriculaire aritmieën die resulteerde in terechte therapie aanzienlijk toegenomen, van 0,40 ± 0,69 tot 1,21 ± 2,53 per patiënt per jaar na CRT-D upgrade (p = 0.014).

Dit onderzoek heeft duidelijk aangetoond dat er, na de upgrade van ICD naar CRT-D, in non-responders een significante toename van het aantal ventriculaire aritmieën is die resulteerde in terechte therapie.

In **hoofdstuk 5** werd onderzocht welk deel van 1742 transveneus geïmplanteerde ICD patiënten geschikt zou zijn geweest voor implantatie van een subcutane ICD (S-ICD) en welke patiënten karakteristieken deze groep kenmerkte. Patiënten zonder pre-existente indicatie voor pacing werden geschikt geacht voor een S-ICD indien er: geen atriale en/of rechterventrikel pacing nodig was, bij een ventriculaire aritmie succesvolle anti-tachycardie pacing zonder defibrillatie plaatsvond en er geen upgrade naar een CRT-D geschiedde. Gedurende een mediane follow-up van 3,3 jaar bereikte 627 (36%) patiënten een van bovenstaande eindpunten. De cumulatieve incidentie van ICD patiënten, geschikt voor S-ICD implantatie was 60% na 5 jaar. Significante voorspellers voor de ongeschiktheid van een S-ICD betroffen de volgende patiënten karakteristieken: hogere leeftijd, secundaire preventie, ernstig hartfalen, atriumfibrilleren, en een breed QRS complex.

Deze analyse toont aan dat, na 5 jaar follow-up, meer dan de helft van de huidige ICD patiënten geschikt zou zijn geweest voor S-ICD implantatie en dat verschillende patiënten karakteristieken nuttig zouden kunnen zijn bij de selectie van deze groep patiënten.

Deel II: Socio-economische gevolgen van een implanteerbare defibrillator behandeling

Het doel van **hoofdstuk 6** was om de kosteneffectiviteit van profylactische ICD implantatie in de klinische praktijk te beoordelen. Met behulp van een Markov-model werden de levensduurkosten, gewonnen levensjaren, en behaalde kwaliteits-gewonnen levensjaren (QALY's) voor ICD patiënten en een controle groep geschat. Gebaseerd op gegevens uit ons eigen centrum, voegt profylactische ICD implantatie naar schatting een gemiddelde van 2,07 LYs en 1,73 QALY's per patiënt toe. De levensduurkosten voor een een-kamersysteem en twee-kamersysteem ICD werden geschat op respectievelijk €60.788 en €64.216. Dit resulteerde in een geschatte kosteneffectiviteit van €35.154 per gewonnen QALY voor een-kamersysteem ICD en van €37.111 per gewonnen QALY voor een twee-kamersysteem ICD.

Deze studie toonde aan dat, op basis van data en gedetailleerde kosten verkregen uit de klinische praktijk, blijkt dat ICD therapie bij geselecteerde patiënten met een verminderde LVEF kosteneffectief is.

In **hoofdstuk 7** werd de levensduur van een ICD aan de hand van een cohort van 3194 patiënten berekend en werden de oorzaken voor ICD vervanging beoordeeld en gecategoriseerd naar batterij gerelateerd en niet batterij gerelateerd. Gedurende de follow-up, werden er 4673 ICD's geïmplanteerd waarvan er uiteindelijk 1479 (33%) werden vervangen. De gemiddelde levensduur van de ICD was 5,0±0,1 jaar. Een totaal van 1.072 (72%) ICD's werden vervangen als gevolg van uitputting van de ICD batterij. De gemiddelde batterijlevensduur kwam uit op 5,5±0,1 jaren. Onderverdeling op basis van de verschillende ICD's resulteerde in een gemiddelde levensduur van 5,5±0,2 jaren voor een een-kamersysteem, 5,8±0,1 jaren voor een twee-kamersysteem en 4,7±0,1 jaren voor een biventriculaire ICD (CRT-D) ($p < 0,001$). Er was sprake van een significant betere levensduur van ICD's welke na 2002 zijn geïmplanteerd ten opzichte van ICD's die voor 2002 zijn geïmplanteerd (5,6±0,1 versus 4,9±0,2, $p < 0,001$). Verder werden er grote verschillen in de batterijlevensduur van de ICD van verschillende fabrikanten opgemerkt (algemeen log rank test $p < 0,001$).

Dit onderzoek toonde aan dat de meerderheid van ICD's werd vervangen als gevolg van batterij uitputting en dat er sprake is van significante verschillen in de levensduur van het apparaat tussen de verschillende ICD systemen, generaties en fabrikanten.

Hoofdstuk 8 is een analyse waarin het wel of niet toepassen van rijrestricties voor primaire en secundaire ICD patiënten met particulier of professioneel rijgedrag aan de hand van incidenties van terechte en onterechte ICD defibrillatie in de klinische praktijk werd berekend. Een totaal van 2786 ICD patiënten werden geïncludeerd en het optreden van ICD defibrillatie werd gedurende een mediane follow-up van 996 dagen genoteerd. In zowel primaire als secundaire preventie ICD patiënten met particulier rijgedrag bleken rijrestricties zowel direct na de implantatie als na een onterechte defibrillatie niet gerechtvaardigd. Echter, na een terechte defibrillatie, is er sprake van een verhoogd risico op het toebrengen van schade aan andere weggebruikers waardoor respectievelijk een rijrestrictie van 2 en 4 maanden zou moeten gelden. Verder is er, gedurende de volledige follow-up, na zowel

ICD implantatie als terechte defibrillatie, bij alle ICD patiënten met professioneel rijgedrag sprake van een aanzienlijk verhoogd risico op het toebrengen van schade aan andere weggebruikers waardoor een permanente rijrestrictie voor deze groep dient te gelden.

Deze analyse geeft een klinisch toepasbaar wetenschappelijk onderbouwd model wat kan dienen als hulpmiddel voor een richtlijnencommissie bij het vaststellen van rijrestricties in ICD patiënten.

Hoofdstuk 9 is een editorial welke de uitdaging beschrijft om criteria voor een betere identificatie van patiënten met hoog risico op plotse hartdood te ontwikkelen en te implementeren en het aantal implantaties bij patiënten die niet zullen profiteren van primaire preventie ICD therapie te beperken. Dit is niet alleen van belang vanuit een kostenoogpunt, maar ook omdat ICD therapie nadelig kan zijn voor patiënten. Met andere woorden, ongewenste schokken, infecties, en apparaat of lead malfuncties zijn ernstige problemen en goed gedefinieerde criteria zijn nodig om te rechtvaardigen dat het overlevingsvoordeel van primaire preventie ICD therapie opweegt tegen de nadelen van de complicaties en kosten.

CONCLUSIES

Hoewel zowel ICD als CRT in grote gerandomiseerde studie hebben bewezen een effectieve behandelingsstrategie te zijn voor geselecteerde patiënten, blijven er onduidelijkheden bestaan over de effecten van defibrillator behandeling in de dagelijkse klinische praktijk. In het huidige proefschrift worden een aantal van deze onopgeloste vragen, met behulp van gegevens van een groot cohort van ICD en CRT-D patiënten met een lange follow-up in de klinische praktijk, opgehelderd.

Het eerste deel van het proefschrift richt zich op de klinische aspecten van de patiënten met een implanteerbare defibrillator. Ondanks het feit dat in gerandomiseerde controle studies de oorzaak van overlijden van patiënten met een ICD of CRT-D uitgebreid is gerapporteerd, ontbreken dergelijke rapportages buiten de setting van een gerandomiseerde trial. Met behulp van een groot aantal patiënten uit de klinische praktijk werd de doodsoorzaak van ICD en CRT-D patiënten onderzocht en bleken de meest voorkomende oorzaken van overlijden, hartfalen en niet cardiale dood te betreffen in zowel primaire preventie ICD, secundaire preventie ICD en CRT-D patiënten. Verder werd aangetoond dat er, bij patiënten die een defibrillator vervanging ondergingen, sprake is van een dubbel risico op het ondergaan van pocket gerelateerde chirurgische re-interventie na defibrillator vervanging en dat iedere volgende defibrillator vervanging het risico van re-interventie verhoogd. Daarnaast werd in een subpopulatie, die een upgrade van ICD naar CRT-D onderging vanwege progressie van hartfalen, de incidentie van ventriculaire aritmieën geanalyseerd. Het meest opvallende was het verschil in de incidentie van ventriculaire aritmieën na een upgrade in zowel CRT-responders (afname van het aantal ventriculaire aritmieën) en CRT non-responders (toename van het aantal ventriculaire aritmieën). In het laatste fragment van het eerste deel, werd de toepasbaarheid voor de recent ontwikkelde subcutane ICD in ons cohort bestudeerd en werd aangetoond dat meer dan de helft van de huidige ICD patiënten hiervoor in aanmerking zou kunnen komen waardoor er mogelijk minder defibrillatorsysteem geassocieerde complicaties zouden hoeven optreden.

Het tweede deel van het proefschrift bestaat uit de gevolgen van het op grote schaal toepassen van implanteerbare defibrillator behandeling voor zowel patiënten als voor de maatschappij. Allereerst werd de kosteneffectiviteit van primaire preventie ICD implantatie in de praktijk onderzocht. Hoewel ICD therapie bij deze geselecteerde patiënten kosteneffectief lijkt te zijn, zouden verbetering van de levensduur en een vermindering van de kosten van de ICD een gunstig effect op de werkelijke kosteneffectiviteit kunnen hebben. Echter, in een latere analyse bleek dat modernere ICD generaties slechts een geringe verbetering van de levensduur toonden, waardoor het duidelijk is dat er meer inspanningen nodig zijn om met name de levensduur van de ICD batterij te verlengen. Belangrijk is dat dit uiteindelijk kan resulteren in een daling van het aantal pocket gerelateerde complicaties, de mortaliteit en een verbeterde kosteneffectiviteitsratio. Een ander belangrijk aspect voor zowel ICD patiënten als wel voor de maatschappij zijn de rijrestricties die direct na ICD implantatie en na therapie van toepassing zijn. Ondanks het beperkte bewijs hiervoor, gelden er in veel landen rijrestricties na implantatie van een defibrillator welke als gevolg hebben dat bijvoorbeeld ernstig hartfalen patiënten in hun bewegingsvrijheid worden beperkt. In het laatste fragment van het tweede deel worden verschillende strategieën voor de identificatie van primaire preventie patiënten met het grootste voordeel van ICD therapie besproken.

TOEKOMSTPERSPECTIEVEN

Na het toevoegen van primaire preventie defibrillatorbehandeling in de internationale richtlijnen van de cardiologie, vond een enorme toename van het aantal geïmplanteerde defibrillatorsystemen plaats in het laatste decennium. Dientengevolge veranderde de geïmplanteerde patiëntenpopulatie van voornamelijk overlevenden van ventriculaire aritmieën naar patiënten met een verminderde LVEF met of zonder symptomatisch hartfalen. Opmerkelijk is dat een aanzienlijk deel van deze patiënten met een geïmplanteerde defibrillator geen potentieel levensreddende therapie ontvangen gedurende de follow-up en daarmee dus geen voordeel hebben van defibrillator implantatie. Anderzijds, is het juist weer noodzakelijk om patiënten met een hoog risico op plotse hartdood, zonder volgens de huidige richtlijnen in aanmerking te komen voor een behandeling met een geïmplanteerde defibrillator, te identificeren. Gezien de ernstige nadelen, zoals onterechte shocks, leadproblemen, en defibrillatorsysteeminfecties die geassocieerd zijn met deze therapie, is een betere selectie van patiënten voorafgaand aan de defibrillator implantatie vereist. Bovendien is de populatie die in aanmerking komt voor primaire preventie defibrillator implantatie van een dusdanige omvang dat behandeling van ieder patiënt zowel de beschikbare financiële middelen als ook het hiervoor opgeleide personeel zal uitputten. Dit benadrukt des te meer de noodzaak voor optimale allocatie voor de behandeling met implanteerbare defibrillatorsystemen. Dientengevolge zal toekomstig onderzoek voor implanteerbare defibrillatorsystemen in de klinische praktijk zich moeten focussen op zowel het verminderen van de nadelige gevolgen van deze behandeling; door het verlengen van de levensduur, het verbeteren van antitachycardie pacing algoritmes, en het verminderen van leadproblemen, alsook op de ontwikkeling en implementatie van criteria die het mogelijk maken hoog risico patiënten goed te identificeren en het aantal implantaties van defibrillatorsystemen bij patiënten die niet zullen profiteren te beperken.

12

Chapter 12

List of publications, Dankwoord and Curriculum Vitae

LIST OF PUBLICATIONS

1. **Thijssen J**, Borleffs CJ, de Bie MK, van Rees JB, van Welsenes GH, van EL, Bax JJ, Cannegieter SC, Schalij MJ. Recurrent implantable cardioverter-defibrillator replacement is associated with an increasing risk of pocket-related complications. *Pacing Clin Electrophysiol* 2010;33:1013-9.
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CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 2 januari 1983 in Katwijk. In 2001 behaalde hij het eindexamen VWO aan het Da Vinci College te Leiden. In 2002 startte hij met de studie Geneeskunde aan de Universiteit van Leiden. Tijdens zijn studie was hij onder meer actief als bestuurslid binnen de Medische Faculteit der Leidse Studenten (M.F.L.S.) en volgde hij een Summer class Fysische Antropologie aan de faculteit Geneeskunde Leiden. Direct na het behalen van zijn artsexamen in 2009, startte hij in het Leids Universitair Medisch Centrum zijn promotieonderzoek onder leiding van Prof. dr. M.J. Schalij. Een selectie van de resultaten hiervan staan beschreven in dit proefschrift.

Per 1 september 2012 is hij in opleiding tot cardioloog in het Leids Universitair Medisch Centrum (opleider: Prof. dr. M.J. Schalij). Recent heeft hij zijn vooropleiding Interne Geneeskunde in het Rijnland ziekenhuis in Leiderdorp (opleider: dr. M.J.M.F. Janssen) afgerond en is hij momenteel bezig met het B-jaar cardiologie in het Rijnland ziekenhuis in Leiderdorp (opleider: C.J.H.J. Kirchhof).