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Implantable-cardioverter-defibrillator : clinical advancements in individualized and targeted treatment

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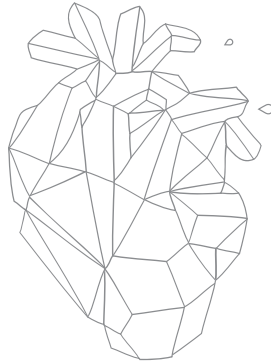
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CHAPTER 2



The Clinical Course of Patients with Implantable Defibrillators; Extended Experience on Clinical Outcome, Device Replacements and Device-Related Complications

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ABSTRACT

Background

Large randomized trials demonstrated the beneficial effect of implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy-defibrillator (CRT-D) treatments in selected patients. Data on long-term follow-up of patients outside the setting of clinical trials are scarce.

Objective

The aim of this study was to evaluate the long-term outcome of ICD and CRT-D recipients.

Methods

All patients who underwent ICD (N=1729 [57%]) or CRT-D (N=1326 [43%]) implantation at the Leiden University Medical Center since 1996 were evaluated. Follow-up visits were performed every 3–6 months, and events were registered. Cumulative incidence curves of device therapy and device-related complications were adjusted for the competing risk of all-cause mortality.

Results

After a median follow-up of 5.1 years (25th–75th percentile 3.1–7.8 years), 842 patients (28%) died. The cumulative incidence of all-cause mortality was 49% (95% confidence interval [CI] 45%–54%) in ICD recipients after 12 years of follow-up and 55% (95% CI 52%–58%) in CRT-D recipients after 8 years of follow-up. A total of 1081 patients (35%) received appropriate defibrillator therapy. The cumulative incidence of appropriate therapy in ICD patients was 58% (95% CI 54%–62%) after 12 years of follow-up and 39% (95% CI 35%–43%) in CRT-D patients after 8 years of follow-up. Twelve-year cumulative incidences of adverse events were 20% (95% CI 18%–22%) for inappropriate shock, 6% (95% CI 5%–8%) for device-related infection, and 17% (95% CI 14%–21%) for lead failure.

Conclusion

After long-term follow-up of ICD (12 years) and CRT-D (8 years) recipients, 49% of ICD recipients and 55% of CRT-D recipients had died. Appropriate ICD therapy was received by the majority (58%) of ICD recipients and by almost 40% of CRT-D recipients.

INTRODUCTION

Implantable cardioverter-defibrillator (ICD) treatment reduces mortality in patients surviving malignant ventricular arrhythmias (secondary prevention) and in selected patients with high risk of malignant ventricular arrhythmias due to underlying heart disease (primary prevention).¹⁻⁶

Currently, the effectiveness of ICD treatment has been confirmed after an extended follow-up of 11 years in a part of the secondary prevention population of the Canadian Implantable Defibrillator Study (CIDS), which enrolled patients with sustained ventricular arrhythmias combined with hemodynamic instability or reduced left ventricular ejection fraction (LVEF).⁷ Long-term ICD treatment (8 years of follow-up) was also deemed effective in the primary prevention population of the second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II), which constituted of patients with previous myocardial infarction and reduced LVEF.⁸ These randomized trials are performed in a defined patient population and therefore may not be representative of routine clinical practice. Little is known about long-term clinical outcome of patients receiving an ICD or cardiac resynchronization therapy-defibrillator (CRT-D) according to the current international guidelines.⁹ Follow-up in observational studies does not exceed 5 years, while many patients live more than a decade after device implantation.¹⁰⁻¹⁵

Therefore, the aim of the present study was to provide an overview of the long-term clinical outcome of ICD and CRT-D recipients in a large cohort outside the setting of a clinical trial. Clinical outcome includes all-cause mortality, device therapy, device replacements, and device-related complications.

METHODS

Patient population

Since 1996, all patients who underwent ICD or CRT-D implantation at Leiden University Medical Center are registered in the departmental cardiology information system (EPD-Vision, Leiden University Medical Center, Leiden, The Netherlands). Registration includes patient characteristics at implantation and at all subsequent follow-up visits. Patients were characterized by depressed LVEF (primary prevention), survival of a cardiac arrest, or occurrence of ventricular arrhythmias combined with syncope (secondary prevention).⁵ Device implantations were based on international guidelines.⁹ Patients with congenital or monogenetic heart disease were excluded from this analysis. The study is a descriptive report of routine clinical practice; all patient information was de-identified and therefore was exempt from the institutional committee on human research approval.

Device implantation and programming

The devices used were manufactured by Biotronik (Berlin, Germany), Boston Scientific (Natick, MA, formerly CPI, Guidant [St Paul, MN]), Medtronic (Minneapolis, MN), or St Jude Medical/Ventritex (St Paul, MN) and include single-chamber ICDs, dual-chamber ICDs, and CRT-Ds. All implantations were performed transvenously. Sensing and pacing thresholds were tested, and a defibrillation threshold test was performed.

In the early years (1996–2000), the majority of the devices were programmed with a single zone in which shocks were programmed to terminate ventricular arrhythmias exceeding 185 beats/min. After a transitional period, defibrillators were programmed with 3 zones since 2004: ventricular arrhythmias from 150 to 188–190 beats/min were detected in a monitoring zone in which no therapy was programmed (30–32 intervals were needed for detection [NID] or 8/10 with a 2.5-second initial delay, depending on the manufacturer); ventricular arrhythmias faster than 188–190 beats/min were detected in the ventricular tachycardia zone, programmed with 2–4 bursts of antitachycardia pacing (ATP) to terminate the arrhythmias, followed by shock if the arrhythmia persists (22–30 intervals were needed for NID or 8/10 with a 2.5-second initial delay, depending on the manufacturer); the final zone was programmed to detect arrhythmias exceeding 220–231 beats/min, in which case defibrillator shock was the initial therapy (12–30 NID intervals were needed for or 8/10 with a 1.0-second initial delay, depending on the manufacturer). In the latter zone, ATP during charging was programmed since 2008–2009, depending on the manufacturer. ICD programming was adjusted to the needs of the patient, when clinically indicated. In addition, supraventricular tachycardia discriminators were enabled and atrial arrhythmia detection was set to >170 beats/min.

Follow-up and device interrogation

Patients were clinically assessed, and devices were interrogated under supervision of electrophysiologists or device cardiologists. During device interrogation, stored episodes were analysed and defibrillator interventions were registered. Defibrillator therapy was classified on the basis of intracardiac electrograms and was considered appropriate only when occurring in response to ventricular tachycardia or ventricular fibrillation; other triggers for defibrillator therapy were considered inappropriate. Other device-related complications (not related to the initial implantation procedure) were assessed. A device-related infection was defined as an infection requiring device explantation. Lead failures included mechanical (micro-)dislodgment and/or electrical malfunctioning requiring lead intervention or lead inactivation of any lead, occurring >30 days after the initial lead implantation procedure.

Periodical follow-up visits were performed every 3–6 months or more frequently when indicated; all visits up to May 2012 were included. According to Dutch health care regulations, the implanting centre is responsible for adequate patient follow-up. Therefore, ICD recipients were tracked when follow-up visits were missed and referred to other centres only because of geographical reasons. Data on patients referred to surrounding centres were tracked. In the case of emigration or transmigration resulting in referral to centres far afield, or when follow-up visits were not performed for >12 months, follow-up was considered incomplete. However, these patients were included in the analysis as far as data were acquired. In the case of heart transplantation or premature termination of ICD treatment, follow-up was ended at the time of intervention. Survival status was retrieved from regularly updated municipal civil registries. In all deceased, the cause of death was retrieved from hospital letters or follow-up reports if present, and otherwise from the contacted general practitioner. In the Netherlands each patient has a general practitioner which is comparable with a Family doctor.

End points

All-cause mortality, appropriate defibrillator therapy (ATP and shock), and appropriate defibrillator shock were considered primary end points. Secondary end points were device replacements and device-related complications (inappropriate shock, device-related infections, and lead failure).

Statistical analysis

All statistical analyses were performed using the statistical software program SPSS 20.0 (IBM Corp., Chicago, IL). Continuous data are expressed as mean \pm SD or as median with 25th–75th percentile, when appropriate. Categorical data are presented as number and percentage. Clinical characteristics at baseline were compared using the independent sample Mann-Whitney U test for continuous variables and the χ^2 test with Mantel-Haenszel odds ratio for categorical variables. A P value of $<.05$ was considered statistically significant. Cumulative event rates were calculated using cumulative incidence curves with log-rank statistics; event rates of appropriate therapy, appropriate shock, and device-related complications were adjusted for the competing risk of all-cause mortality.¹⁶ In addition, a multivariate Cox regression analysis was used, adjusted for predefined clinical characteristics (ICD indication, CRT treatment, creatinine clearance, history of atrial fibrillation/flutter, sex, age, aetiology of heart failure, LVEF, and New York Heart Association [NYHA] functional class).

RESULTS

Patients

Since 1996, 3352 patients underwent ICD or CRT-D implantation. Of these 3352 patients, 297 (9%) were diagnosed with congenital or monogenetic heart disease. The present study population included 3055 patients (1729 ICD recipients [57%] and 1326 CRT-D recipients [43%]). Follow-up was complete in 2874 patients (94%), and in the remaining 181 patients (6%), follow-up was incomplete.

At implantation, patients had a mean age of 63 ± 12 years, the majority was men (79%), and they had ischemic heart disease (68%) and reduced LVEF (primary prevention: $29\% \pm 11\%$; secondary prevention: $38\% \pm 15\%$). As indicated by Table 1, ICD recipients were younger (61 years vs 65 years), more likely to have ischemic heart disease (74% vs 60%), had more preserved LVEF (37% vs 26%), and shorter QRS duration (112 ms vs 149 ms).

Mortality and defibrillator therapies in ICD recipients

During a median follow-up of 5.8 years (25th–75th percentile 3.3–8.9 years), 438 patients with ICD (25%) died. The 12-year cumulative incidence of all-cause mortality was 49% (95% confidence interval [CI] 45%–54%; Table 2). As illustrated in Figure 1A, the 12-year cumulative incidence of all-cause mortality was lower in primary prevention ICD recipients than in secondary prevention ICD recipients (42% [95% CI 30%–55%] vs 53% [95% CI 48%–58%]; log rank, $P = .004$).

Table 2 lists the cumulative incidences of appropriate therapy and appropriate shock in ICD recipients during follow-up. A total of 13,682 appropriate ICD therapies (ATP or shock) were received by 711 patients (41%), and 512 (30%) patients received >1 ICD intervention (Figure 2).

Table 1. Baseline characteristics of ICD and CRT-D recipients

	ICD recipients N=1729	CRT-D recipients N=1326	p-value
Clinical parameters			
Age, years	61±13	65±10	<0.001
Male gender	1409 (82%)	1016 (77%)	0.001
Primary prevention	814 (47%)	1153 (87%)	<0.001
Ischemic heart disease	1279 (74%)	798 (60%)	<0.001
NYHA functional class III/IV	242 (14%)	862 (65%)	<0.001
LVEF, %	37±15	26±9	<0.001
QRS duration, ms	112±27	149±33	<0.001
History of atrial fibrillation/flutter	503 (22%)	419 (32%)	<0.001
Creatinine clearance, ml/min	84±38	74±34	<0.001
Hypertension	692 (40%)	585 (44%)	0.03
Diabetes	341 (20%)	318 (24%)	0.005
History of smoking	935 (54%)	634 (48%)	0.001
Medication			
ACE inhibitors /AT II antagonists	1279 (75%)	1165 (88%)	<0.001
Aldactone	363 (21%)	603 (46%)	<0.001
Amiodarone	298 (17%)	218 (16%)	
Beta-blockers	923 (53%)	930 (70%)	<0.001
Sotalol	275 (16%)	115 (9%)	<0.001
Calcium antagonists	162 (9%)	82 (6%)	0.001
Diuretics	774 (45%)	1074 (81%)	<0.001
Statins	1071 (62%)	802 (61%)	

ICD=implantable cardioverter-defibrillator; CRT-D=cardiac resynchronization therapy-defibrillator; NYHA=New York Heart Association; LVEF=left ventricular ejection fraction; ACE=angiotensin-converting enzyme; AT=angiotensin; SD=standard deviation. Categorical variables are expressed by N (%), and continuous variables presented as mean±SD.

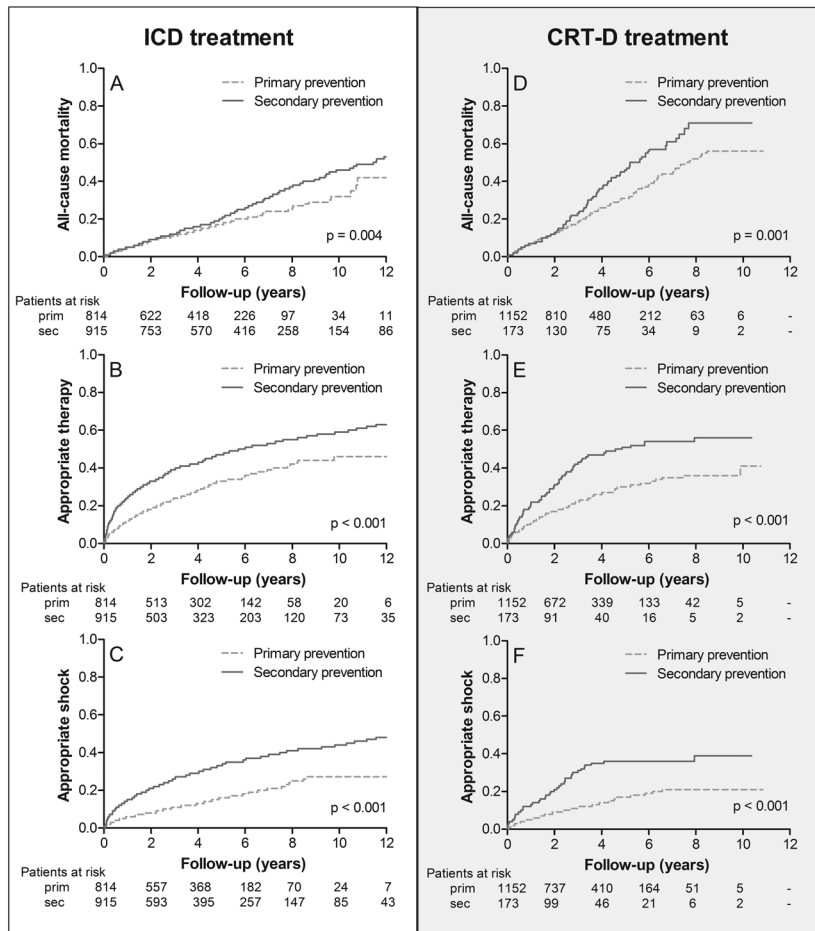
The 12-year cumulative incidence of appropriate therapy was 46% (95% CI 40%–52%) in primary prevention patients as compared with 63% (95% CI 59%–67%) in secondary prevention patients (log rank, $P < .001$; Figure 1B).

Appropriate defibrillator shocks were received by 461 patients with ICD (27%), and 274 patients received >1 ICD shock; overall, 1.621 ICD shocks were experienced. After 12 years of follow-up, the cumulative incidence of appropriate shock was 27% (95% CI 21%–33%) in primary prevention patients as compared with 48% (95% CI 44%–52%) in secondary prevention patients (log rank, $P < .001$; Figure 1C).

Table 2. Overview of clinical outcome, device replacements and device-related complications of defibrillator recipients during long-term follow-up.

Follow-up	1 year	4 years	8 years	12 years
Clinical outcome†				
All-cause mortality	5% (4–6)	15% (13–17)	34% (30–37)	49% (45–54)
	7% (5–8)	27% (24–30)	55% (52–58)	
Appropriate ICD therapy	19% (17–21)	36% (34–38)	49% (45–53)	58% (54–62)
	12% (10–14)	29% (27–31)	39% (35–43)	
Appropriate ICD shock	10% (8–12)	22% (20–24)	34% (32–36)	41% (37–45)
	6% (4–8)	17% (15–19)	23% (19–27)	
Device replacements‡				
Mean replacements	0.02 (0.13)	0.22 (0.43)	1.21 (0.53)	1.83 (0.66)
Device-related complications‡				
Inappropriate ICD shock	6% (5–7)	12% (10–13)	17% (15–19)	20% (18–22)
Device infection	1% (1–2)	2% (2–3)	5% (4–6)	6% (5–8)
Lead failure	2% (1–2)	6% (5–7)	13% (11–15)	18% (14–21)

CI=confidence interval; SD=standard deviation. † Indicates cumulative incidence (95%CI). ‡ indicates mean (SD) for patients alive at the specified follow-up points.

Figure 1. Cumulative incidence curves of all-cause mortality and ICD interventions.

All-cause mortality and ICD interventions in ICD and CRT-D recipients. Panel A: All-cause mortality in ICD recipients. Panel B: Appropriate therapy in ICD recipients. Panel C: Appropriate shock in ICD recipients. Panel D: All-cause mortality in CRT-D recipients. Panel E: Appropriate therapy in CRT-D recipients. Panel F: Appropriate shock in CRT-D recipients.

Mortality and defibrillator therapies in CRT-D recipients

A total of 404 CRT-D recipients (30%) died during a median follow-up of 4.5 years (25th–75th percentile 2.7–6.6 years). The 8-year cumulative incidence of all-cause mortality was 55% (95% CI 52%–58%; Table 2). After 8 years, the cumulative incidence of all-cause mortality was lower in primary vs secondary prevention CRT-D recipients (52% [95% CI 46%–57%] vs 71% [95% CI 60%–80%]; log rank, $P = .001$; Figure 1D).

A total of 4,367 appropriate ICD therapies were received, in which 705 appropriate shocks were experienced by 370 CRT-D recipients (28%) and 239 received >1 ICD intervention (Figure 2). As illustrated in Figures 1E and 1F, the 8-year cumulative incidence of appropriate therapy was 36% (95% CI 32%–40%) in primary prevention and 56% (95% CI 46%–66%) in secondary prevention

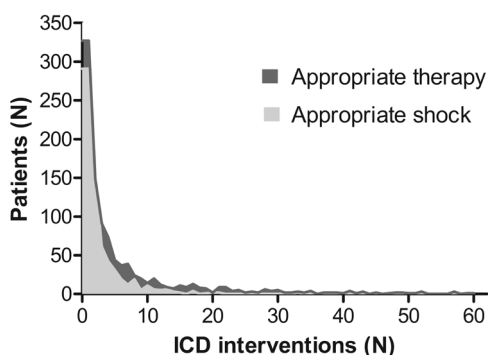
CRT-D recipients (log rank, $P < .001$). In addition, the 8-year cumulative incidence of appropriate shock was 21% (95% CI 17%–28%) and 39% (95% CI 29%–49%) in primary and secondary prevention CRT-D recipients, respectively (log rank, $P < .001$).

Clinical outcome of ICD in subpopulations

Table 3 summarizes the results of a subgroup analysis in specific ICD populations; a multivariate model shows that the risk of all-cause mortality is 24% lower in female defibrillator recipients ($P = .006$) and increases with age (age 65–74 years: hazard ratio [HR] 1.31; $P = .003$) and age ≥ 75 years: HR 1.62; $P < .001$). Patients with non-ischemic heart disease are 23% less likely to die ($P = .003$). The risk of all-cause mortality is also higher in patients with lower LVEF (HR 0.65; $P < .001$) or higher NYHA functional class (HR 1.36; $P < .001$).

In addition, the occurrence of appropriate therapy was analysed in specific ICD subpopulations (Table 3). The 10-year cumulative incidence of appropriate ICD therapy was comparable in patients with ischemic (58%; 95% CI 54%–63%) and non-ischemic (55%; 95% CI 49%–61%) heart disease ($P = .07$). In a multivariate analysis, only female sex (HR 0.80; $P = .01$) and LVEF $\geq 25\%$ (HR 0.76; $P < .001$) were associated with a reduced risk of appropriate ICD therapies.

Figure 2. The number and distribution of effective ICD interventions



Number of effective ICD therapies (ATP and Shock) and ICD shock received by patients. Five % of the patients received > 62 ICD interventions and are not included in the figure.

Device replacements

During follow-up, 1339 devices were replaced in 3055 ICD recipients. A total of 1050 patients (34%) received at least 1 device replacement (Figure 3). After 12 years of follow-up, patients had undergone a mean of 1.8 ± 0.7 device replacements. ICD recipients required their first device replacements after a mean follow-up of 5.6 years (95% CI 5.4–5.7 years), whereas CRT-D recipients required their device replacements after a mean follow-up of 4.9 years (95% CI 4.8–5.0 years) (log rank, $P < .001$).

Table 3. Subgroup analysis of long-term clinical outcome of ICD recipients

	All-cause mortality		Appropriate ICD therapy	
	Cumulative incidence†	Multivariate‡	Cumulative incidence†	Multivariate‡
	10 year	p-value	10 year	p-value
Gender				
Male	50% (46-53)	Reference	59% (55-63)	Reference
Female	43% (36-50)	0.01	51% (44-58)	0.80 (0.68-0.95)
Age				
<65 years	33% (29-37)	Reference	57% (52-62)	Reference
65 – 74 years	60% (54-65)	1.31 (1.10-1.56)	58% (53-64)	1.03 (0.89-1.19)
≥75 years	84% (73-94)	<0.001	51% (42-61)	0.99 (0.80-1.22)
Aetiology of heart failure				
Ischemic heart disease	55% (50-59)	Reference	58% (54-63)	Reference
Non-ischemic heart disease	41% (35-47)	<0.001	55% (49-61)	1.08 (0.94-1.25)
LV ejection fraction				
LVEF<25%	62% (56-67)	Reference	69% (61-77)	Reference
LVEF≥25%	42%(38-46)	<0.001	53% (49-57)	0.76 (0.66-0.87)
NYHA functional class				
NYHA I-II	42% (38-46)	Reference	59% (54-63)	Reference
NYHA III-IV	61% (56-66)	<0.001	55% (47-62)	1.03 (0.88-1.21)

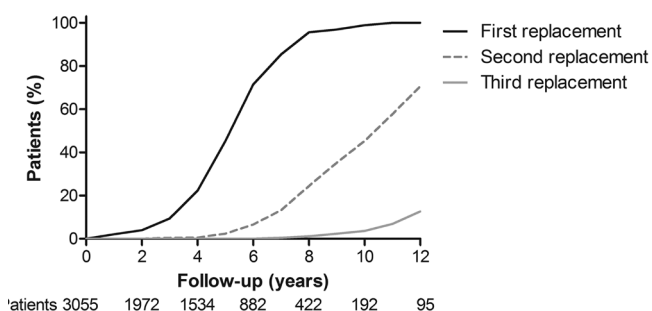
HR=hazard ratio; CI=confidence interval; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association. † Indicates cumulative incidence (95%CI) as estimated by Kaplan Meier analysis. ‡ indicates HR (95%CI) estimated by Cox regression analysis.

Device-related complications

Inappropriate shock was experienced by 397 patients (13%) during follow-up. As indicated by Table 2, the 12-year cumulative incidence of inappropriate device shock was 20% (95% CI 18%–22%). After 8 years of follow-up, CRT-D recipients received an inappropriate shock less frequently than did ICD recipients (ICD: 20% [95% CI 18%–22%] vs CRT-D: 12% [95% CI 10%–14%]; log rank, $P = .001$).

One hundred six patients (3%) suffered from a device-related infection requiring device extraction. The 12-year cumulative incidence of device-related infection was 6% (95% CI 5%–8%; Table 2). Device-related infection occurred more frequently in CRT-D than in ICD recipients (8-year cumulative incidence, ICD: 6% [95% CI 4%–7%] vs CRT-D: 8% [95% CI 5%–10%]; log rank, $P = .01$). Furthermore, during follow-up, 210 patients (7%) experienced lead failure, necessitating lead intervention (repositioning, replacement, or extraction; $N = 180$ [85%]) or lead inactivation ($N = 31$ [15%]). The 8-year cumulative incidence of lead failure was 10% (95% CI 7%–12%) in ICD recipients and 19% (95% CI 14%–23%) in CRT-D recipients (log rank, $P < .001$). The shock lead failed in 106 patients (50%); of these failing right ventricular (RV) leads, 47 (44%) were leads with a known high failure rate (38 Sprint Fidelis leads [Medtronic Inc., Minneapolis, MN, USA] and 9 Riata leads [St. Jude Medical Inc., St. Paul, MN, USA]). The failure rates of RV leads with known high failure rates were significantly higher than those of RV leads without known high failure rates (log rank, $P < .001$). The 10-year cumulative incidence of RV lead failure was 7% (95% CI 5%–9%) for the RV lead without known high failure rates as compared to 34% (95% CI 11%–56%) for the RV lead with known high failure rates.

Figure 3. Required device replacements during follow-up.



Proportion of patients requiring device replacements, in percentage of all device recipients alive at the specified time point.

DISCUSSION

The main findings of the present study on 8–12-year outcome of ICD and CRT-D recipients can be summarized as follows: (1) of all ICD recipients, 49% had died and 58% had received appropriate ICD therapy after 12 years of follow-up; (2) of all CRT-D recipients, 55% had died and 39% had received appropriate defibrillator therapy after 8 years of follow-up; (3) after 12 years, patients required an average of 1.8 device replacements; (4) inappropriate shocks had been experienced by 20% of the patients; (5) 6% had suffered from device-related infection and 17% from lead failure.

The present study was performed in a large cohort of ICD and CRT-D recipients outside the setting of a clinical trial. The aim was not to highlight or explain differences in clinical outcome subgroups receiving an implantable defibrillator, but rather to provide insight into long-term clinical course of defibrillator recipients in general practice.

Mortality in ICD and CRT-D recipients

Large randomized trials have demonstrated that ICD implantation improves survival by primary and secondary prevention of sudden cardiac death. Only 2 of the pivotal trials on ICD treatment published results of extended follow-up of study patients.^{7,8} These studies are performed in a selected patient population that may not be representative of the patients receiving their ICD in routine clinical practice nowadays. Hence, comparisons between these studies must be interpreted with caution. In the MADIT-II, 44% of the primary prevention ICD recipients died after 8 years, which seems comparable with the 8-year cumulative incidence of 40% observed in this study.⁸ Of the secondary prevention patients, 27% had died after 8 years of follow-up in the CIDS, while a 12-year cumulative incidence of all-cause mortality of 56% in secondary prevention ICD patients was observed in the present study.⁷ This may be due to differences in severity of heart failure (NYHA functional class ≥ 3 : present study: 18% vs CIDS: 5%). Other observational studies reported similar mortality rates, although most follow-up periods did not exceed 5 years in these studies.^{10–15}

The incidence of all-cause mortality of ICD recipients was higher in the secondary prevention population; this has not been described before and was only apparent after stratifying for ICD and CRT-D treatments. However, closely reviewing the 3-year mortality rates observed in primary and secondary prevention trials demonstrates a comparable trend.¹⁷ After 8 years, we observed a mortality of 52% in primary prevention CRT-D recipients. Yet, only 12% of the REVERSE population had died after 5 years; however, this trial included only patients with mild heart failure.¹⁸ Also, the mortality rate in the MADIT-CRT study population was markedly lower (18%–36% after 7 years).¹⁹ Again, the patients enrolled in this trial suffered from less severe symptoms of heart failure (NYHA functional class ≥ 3 : 10%).

In the present study, male sex, increasing age, ischemic heart disease, reduced LVEF (<25%), and NYHA functional class >3 were independently associated with an increased mortality.

Appropriate device therapy

The present study showed that 42% of primary prevention and 63% of secondary prevention ICD

recipients received appropriate ICD therapy during 12 years of follow-up. This seems comparable with the results of extended follow-up of the CIDS, which reported ICD therapy in 70% of the secondary prevention patients after 11 years.⁷ Also, previous primary prevention observational studies showed similar incidences of appropriate therapy after 5–7 years of follow-up.^{11–13,19} Appropriate shocks were observed in 24% of the primary prevention patients and 47% of the secondary prevention patients over 12 years, which seems comparable with the 28% appropriate shocks reported by Ronn et al after 6 years in secondary prevention patients.¹⁰ Furthermore, the large ALTITUDE registry reported 33%–38% appropriate shocks after 5 years. However, comparisons with this registry should be interpreted with caution since the distribution of primary and secondary prevention patients is unknown.¹⁵ Appropriate device therapies occurred more frequently in patients with a lower LVEF, but also in female patients. To date, studies of sex differences in ICD treatment have shown conflicting results.²⁰

Device-related complications

Inappropriate device therapies are the most common adverse event of defibrillator treatment, which may result in proarrhythmic risk, heart failure progression, reduction of battery life, and psychological distress. Initial clinical trials have reported an incidence of inappropriate shocks of 13%–22% after a follow-up of 2–2.5 years.^{2,21} Through implementation of ATP, adjustments in zone cut-offs, and supraventricular tachycardia discrimination algorithms, the occurrence of inappropriate defibrillator shocks can be reduced.^{22,23} These strategies may have contributed to the lower occurrence of inappropriate shocks observed in the present study. Recently, Moss et al (MADIT-RIT) reported a method to further reduce inappropriate shock in primary prevention patients by delayed therapy (first ICD shock delayed by 60 seconds) or high rate therapy (ICD shock is initial therapy in ventricular arrhythmias >200 beats/min), which resulted in a 50% reduction of inappropriate shocks (without increased occurrence of syncope) and an additive reduction of all-cause mortality of 55%.²⁴ Implementation of these algorithms will hopefully lead to further reduction of inappropriate shocks in future ICD or CRT-D recipients.

Large registries have described an annual rate of device-related infections of 1.5%–2.4%.²⁵ The present study observed 6% device-related infections after 12 years of follow-up, which corresponds to an annual infection rate of 0.8%.

After 12 years of follow-up, the incidence of lead failure was 17%; during the initial years of follow-up, results were in line with other cohort studies.^{26,27} Although 29% of the failing leads included leads with known high failure rate, the long-term durability of leads requires improvement.

Clinical perspectives

The present patient population illustrates that appropriate defibrillator interventions frequently occur in patients receiving an ICD and CRT-D according to contemporary international guidelines. Even after long-term follow-up without defibrillator interventions, patients remain at high risk for potentially life-threatening ventricular arrhythmias. The high event rates of defibrillator therapy observed in this study emphasizes the efficacy of ICD and CRT-D implantation in the long term. However, the device-related complication rate in the long term is worrisome. Awareness of the burden of inappropriate defibrillator shocks already exists. According to the recently published

and ongoing studies, the incidence of inappropriate shocks might be reduced in the near future by changes in device settings.²⁴ Furthermore, the lead failure rates in the long term are alarming and warrant efforts from both the industry and medical professionals to improve lead durability.

Study limitations

This was an observational study to assess the prolonged clinical outcome of ICD recipients in routine clinical practice. Since the study is performed outside the setting of a clinical trial, results are not limited by inclusion of a selected patient population and therefore might be more representative of contemporary general practice. Results are based on a large patient cohort that is prospectively and accurately followed; however, the results are of a single-centre origin and therefore the generalizability may be limited. Evolving guidelines and the prolonged period of data collection could have created a heterogeneous study population. Since cumulative event rates were examined over a long period of time, the results underrate the developments made in ICD treatment (i.e., reduction in inappropriate shock rate by device algorithms, ICD programming, and improved battery life) by recent clinical trials.

CONCLUSION

After long-term follow-up of ICD (12 years) and CRT-D (8 years) recipients, 49% of ICD recipients and 55% of CRT-D recipients had died. Appropriate ICD therapy was received by the majority (58%) of ICD recipients and by almost 40% of CRT-D recipients. During 12 years, patients underwent a mean of 1.8 device replacements, 20% received inappropriate shocks, 6% suffered from device-related infections, and 17% experienced lead failure. The complication rates, especially of inappropriate shocks and lead failure, are worrisome and require effort from physicians and industry.

REFERENCES

1. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352(3):225-37.
2. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004;350(21):2151-8.
3. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346(12):877-83.
4. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. *N Engl J Med* 1997;337(22):1576-83.
5. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, et al. Canadian implantable defibrillator study (CIDS) : a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000;101(11):1297-302.
6. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996;335(26):1933-40.
7. Bokhari F, Newman D, Greene M, Korley V, Mangat I, Dorian P. Long-term comparison of the implantable cardioverter defibrillator versus amiodarone: eleven-year follow-up of a subset of patients in the Canadian Implantable Defibrillator Study (CIDS). *Circulation* 2004;110(2):112-6.
8. Goldenberg I, Gillespie J, Moss AJ, Hall WJ, Klein H, McNitt S, et al. Long-term benefit of primary prevention with an implantable cardioverter-defibrillator: an extended 8-year follow-up study of the Multicenter Automatic Defibrillator Implantation Trial II. *Circulation* 2010;122(13):1265-71.
9. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, 3rd, Freedman RA, Gettes LS, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *Circulation* 2008;117(21):e350-408.
10. Ronn F, Kesek M, Hoglund N, Jensen SM. Long-term follow-up of patients treated with ICD: benefit in patients with preserved left ventricular function. *Scandinavian cardiovascular journal* : SCJ 2008;42(2):125-9.
11. Tandri H, Griffith LS, Tang T, Nasir K, Zardkoohi O, Reddy CV, et al. Clinical course and long-term follow-up of patients receiving implantable cardioverter-defibrillators. *Heart Rhythm* 2006;3(7):762-8.
12. van Welsenes GH, van Rees JB, Borleffs CJ, Cannegieter SC, Bax JJ, van Erven L, et al. Long-term follow-up of primary and secondary prevention implantable cardioverter defibrillator patients. *Europace* 2011;13(3):389-94.
13. Wilson D, Shi B, Harding S, Lever N, Larsen P. Implantable cardioverter-defibrillators: a long-term view. *Internal medicine journal* 2012;42(5):554-61.
14. Bradshaw PJ, Stobie P, Briffa T, Hobbs MS. Use and long-term outcomes of implantable cardioverter-defibrillators, 1990 to 2009. *Am Heart J* 2013;165(5):816-22.
15. Saxon LA, Hayes DL, Gilliam FR, Heidenreich PA, Day J, Seth M, et al. Long-term outcome after ICD and CRT implantation and influence of remote device follow-up: the ALTITUDE survival study. *Circulation* 2010;122(23):2359-67.
16. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Statistics in medicine* 2007;26(11):2389-430.
17. Betts TR, Sadarmin PP, Tomlinson DR, Rajappan K, Wong KC, de Bono JP, et al. Absolute risk reduction in total mortality with implantable cardioverter defibrillators: analysis of primary and secondary prevention trial data to aid risk/benefit analysis. *Europace* 2013;15(6):813-9.
18. Gold MR, Daubert JC, Abraham WT, Hassager C, Dinerman JL, Hudnall JH, et al. Implantable Defibrillators Improve Survival in Mildly Symptomatic Heart Failure Patients Receiving Cardiac Resynchronization Therapy: Analysis of the Long-Term Follow-Up of REVERSE. *Circulation. Arrhythmia and electrophysiology* 2013.
19. Alsheikh-Ali AA, Homer M, Maddukuri PV, Kalsmith B, Estes NA, 3rd, Link MS. Time-dependence of appropriate implantable defibrillator therapy in patients with ischemic cardiomyopathy. *J Cardiovasc Electrophysiol* 2008;19(8):784-9.
20. van der Heijden AC, Thijssen J, Borleffs CJ, van Rees JB, Hoke U, van der Velde ET, et al. Gender-specific differences in clinical outcome of primary prevention implantable cardioverter defibrillator recipients. *Heart* 2013;99(17):1244-9.
21. Daubert JP, Zareba W, Cannom DS, McNitt S, Rosero SZ, Wang P, et al. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms, predictors, and survival impact. *J Am Coll Cardiol* 2008;51(14):1357-65.
22. Wathen MS, DeGroot PJ, Sweeney MO, Stark AJ, Otterness MF, Adkisson WO, et al. Prospective randomized multicenter trial of empirical antitachycardia pacing versus shocks for spontaneous rapid ventricular tachycardia in patients with implantable cardioverter-defibrillators: Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx II) trial results. *Circulation*

- 2004;110(17):2591-6.
23. Wilkoff BL, Williamson BD, Stern RS, Moore SL, Lu F, Lee SW, et al. Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients: results from the PREPARE (Primary Prevention Parameters Evaluation) study. *J Am Coll Cardiol* 2008;52(7):541-50.
 24. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, et al. Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med* 2012;367(24):2275-83.
 25. Greenspon AJ, Patel JD, Lau E, Ochoa JA, Frisch DR, Ho RT, et al. 16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillators in the United States 1993 to 2008. *J Am Coll Cardiol* 2011;58(10):1001-6.
 26. Borleffs CJ, van Erven L, van Bommel RJ, van der Velde ET, van der Wall EE, Bax JJ, et al. Risk of failure of transvenous implantable cardioverter-defibrillator leads. *Circulation. Arrhythmia and electrophysiology* 2009;2(4):411-6.
 27. Kleemann T, Becker T, Doenges K, Vater M, Senges J, Schneider S, et al. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of >10 years. *Circulation* 2007;115(19):2474-80.

