Preventive cardiovascular strategies for patients with advanced kidney disease

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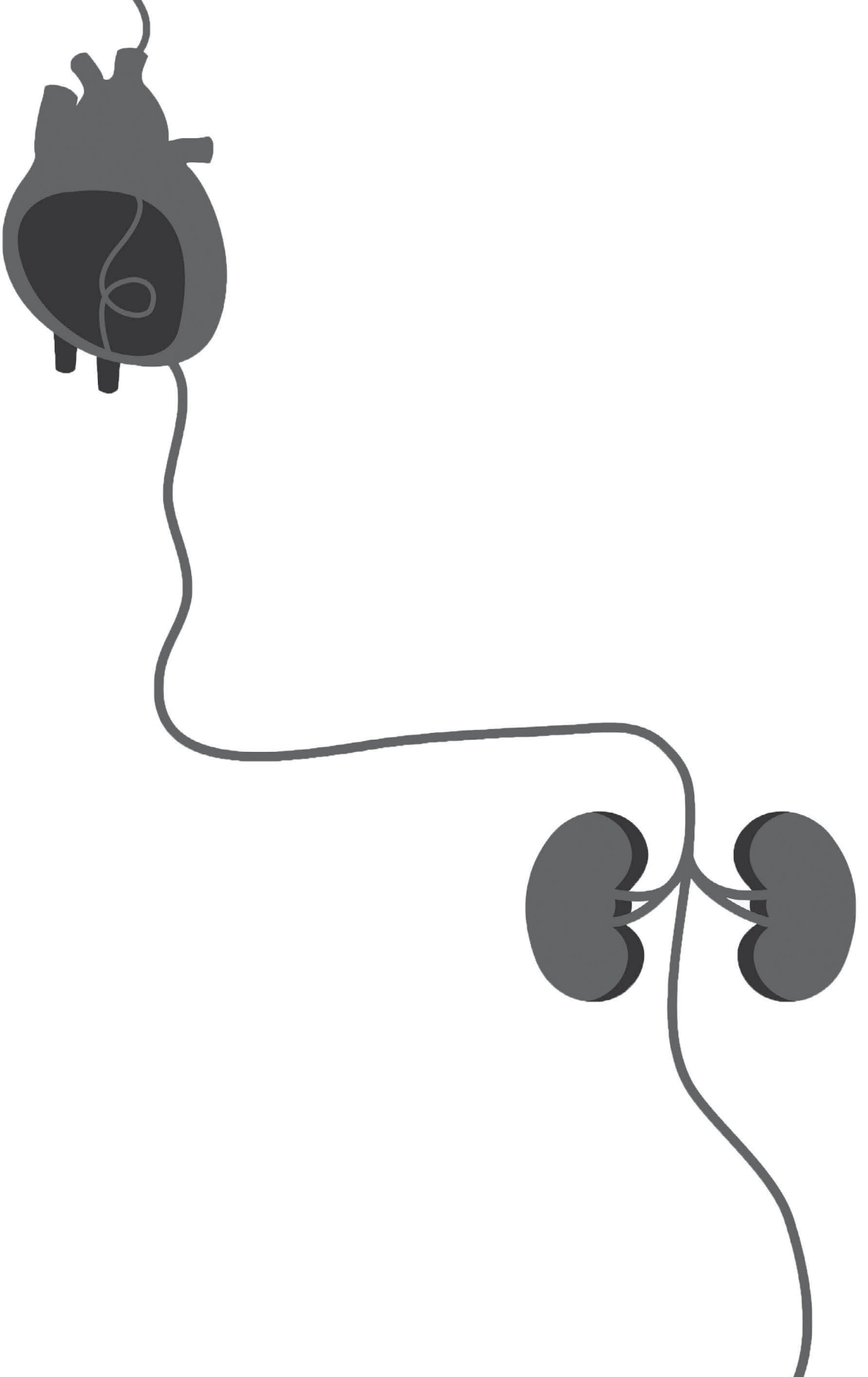
PART II



CHAPTER 3

Prophylactic use of Implantable Cardioverter-Defibrillators in the Prevention of Sudden Cardiac Death in Dialysis Patients: The Prospective Randomized Controlled ICD2 Trial

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ABSTRACT

BACKGROUND End-stage renal disease patients on dialysis are reported to be at high risk of sudden cardiac death (SCD) and, to date, no therapy has been shown to be effective in reducing this. The feasibility and value of prophylactic implantable cardioverter-defibrillator (ICD) implantation to prevent SCD is uncertain.

METHODS We conducted the ICD2 trial, a prospective, randomized controlled study investigating the value and safety of ICD implantation to prevent SCD in 200 patients on dialysis with a left ventricular ejection fraction ≥35%, after adequate screening and optimization of other treatments. The primary endpoint was SCD. Secondary endpoints were all-cause mortality and ICD-related complications.

RESULTS The trial was stopped as per the recommendation of the data and safety monitoring board for futility reasons after inclusion of 188 patients, 97 in the ICD group and 91 in the control group. The median duration of follow-up was 6.8 years (interquartile range, 3.8–8.8). SCD occurred in 19/188 cases (10.1%), 11/97 in the ICD group and 8/91 in the control group. The cumulative SCD incidence at 5 years in the ICD group was 9.7% (95% confidence interval [CI], 3.3 – 16.2%), and in the control group was 7.9% (95% CI, 1.7–14.0%), resulting in a hazard ratio (HR) of 1.32 (95% CI, 0.53 – 3.29, *P* = 0.55). Overall, 99/188 patients died (52.7%), 52/97 in the ICD group and 47/91 in the control group. Five-year survival probability in the ICD group was 50.6% (95% CI, 39.8–61.5%), and in the control group was 54.5% (95% CI, 43.0–66.0%), resulting in an HR of 1.02 (95% CI, 0.69 – 1.52, *P* = 0.92). Among 80 patients who received an ICD, 25 adverse events related to ICD implantation occurred.

CONCLUSIONS In a well-screened and well-treated population undergoing dialysis, prophylactic ICD therapy did not reduce the rate of SCD or all-cause mortality, which remained high.

CLINICAL PERSPECTIVE

What Is New?

- Prophylactic ICD therapy in patients on chronic dialysis with LVEF ≥35% was not associated with a reduced rate of SCD or of all-cause mortality.
- The prevalence of SCD in patients on dialysis was significantly lower compared with reports from the literature and data from epidemiological registries.
- The long follow-up during our trial offers new insights for this patient group: possible survival advantages from ICD implantation are mitigated by competing risks from comorbidities and device-related complications.

What Are the Clinical Implications?

- The findings of this trial do not support routine ICD implantation to prevent death, including SCD, in this population, nor does it support the initiation of a larger study with all-cause death as the primary endpoint.
- The findings of this trial address the knowledge gap regarding ICD therapy in patients on dialysis and may be considered as an evidence-based recommendation for future international guidelines, which are currently lacking.

INTRODUCTION

Patients with end-stage renal disease (ESRD) requiring renal replacement therapy have a 14-fold increased risk of death compared with the general population, with the largest category of cause-specific death believed to be attributable to cardiovascular disease.[1,2] To date, no therapy has been shown to be effective in reducing this mortality.[3] Arrhythmia and cardiac arrest are estimated to cause 30% of the fatalities.[4]

The implantable cardioverter-defibrillator (ICD) was designed to detect and treat life-threatening ventricular arrhythmias by means of defibrillation, cardioversion, or antitachycardia pacing. Several landmark trials have identified high-risk patients who are eligible for ICD implantation for primary or secondary prevention of sudden cardiac death (SCD), namely, those with a reduced systolic left ventricular function or history of ventricular fibrillation or ventricular tachycardia.[5] Patients on dialysis were systematically excluded from these trials, irrespective of their left ventricular function. Therefore, the potential value of prophylactic ICD implantation in patients undergoing dialysis is unknown. It is unclear whether ICD implantation offers a survival advantage or whether competing risks from comorbidities and device-related complications negatively affect outcome, mitigating any benefit.[6]

Literature concerning ICD therapy in ESRD patients is scarce, comprising small retrospective studies with conflicting results.[7–10] A recent matched cohort study in dialysis patients with reduced left ventricular ejection fraction (LVEF) did not observe a significant association between primary prevention ICDs and reduced mortality among ESRD patients receiving dialysis and called for a prospective study.[11] Consequently, international guidelines provide no recommendation on the use of ICD therapy in dialysis patients.[4,12] In this prospective, randomized pilot trial, we sought an evidence-based answer to the question of whether primary prevention of SCD by ICD implantation in dialysis patients with LVEF $\geq$35% is beneficial and safe. Thus, we deliberately selected patients on dialysis who were sufficiently healthy to have a possible meaningful extension to their lives through ICD implantation.

Methods

Study Design

The ICD2 trial (Implantable Cardioverter-Defibrillator in Dialysis Patients) is an investigator-initiated, randomized, prospective, controlled study of ICD therapy versus no ICD in patients on dialysis. The design has been described previously.[13] Per advice of the evaluating medical ethics committee, physicians from 17 centers referred their

patients to the implantation and coordinating center (Leiden University Medical Center), a high-volume, experienced ICD center, because ICD implantation in patients receiving dialysis is reported to have increased complication rates compared with that in ICD recipients without ESRD.[6,14]

The protocol was approved by the hospital's ethics committee in April 2007. The trial is registered at the Netherlands Trial Register (http://www.controlled-trials.com/ISRCTN20479861). All patients provided written informed consent. An independent data and safety monitoring board periodically reviewed the study data for patient safety and efficacy. The first patient was enrolled in June 2007 and the last in January 2018. On the advice of the data and safety monitoring board, the trial was stopped early (February 2018) because of futility.

Randomization and Masking

Blinded permuted-block randomization with stratification for age and referring center were used to randomize patients, in a 1:1 fashion, to receive an ICD (ICD group) or usual care (control group). Before randomization, a serum laboratory examination, ECG, transthoracic echocardiogram, and multislice coronary computed tomography were performed to rule out severe cardiac pathology that should be treated first.

Study Population

Inclusion criteria were age $\geq$ 55 years and $<$ 81 years, and ESRD treated with hemodialysis or peritoneal dialysis for $\geq$90 days. Patients on dialysis meeting the class I indication for ICD implantation were excluded, acknowledging that these recommendations may not apply to the dialysis population, regardless of LVEF, because such patients were excluded from ICD studies. Also, patients with heart failure (New York Heart Association functional class IV) or a medical condition that made 1-year survival unlikely were excluded.[4,12] Patients with a central venous catheter were not eligible. Patients were also excluded if they were being prepared for a living kidney donation, had an acute myocardial infarction in the past 40 days, had HIV, or were unable to give informed consent.

ICD Implantation

Patients assigned to the ICD group received a Biotronik (Berlin, Germany) device. All patients received a dual-chamber device, except those with chronic atrial fibrillation, who received a single-chamber device. Devices were implanted at Leiden University Medical Center by cardiologists experienced in device implantation. The ICD was implanted

subcutaneously, under local anesthesia, at the contralateral side of the arteriovenous fistula in hemodialysis patients. In patients on peritoneal dialysis, the device was implanted at the site of the dominant arm, so that an arteriovenous fistula could be constructed in the nondominant arm in case of switch to hemodialysis in the future.

ICD Setup

At the onset of the ICD2 study (2007), ICD programming occurred according to conventional settings. The ICD was turned on for the detection and treatment of ventricular fibrillation and ventricular tachycardia. Because antibradycardia pacing can worsen cardiac function, the ICD was programmed to back up DDI pacing at a rate of 30 beats per minute (bpm), with an AV delay of 350 ms. A monitor zone (VT1) was programmed with a detection rate set between 150 and 188 bpm. Antitachycardia pacing within the VT2 zone (188–214 bpm) was turned on to deliver 4 bursts of 6 beats beginning at 80% of the tachycardia cycle length, with 10 ms decrements between bursts. If antitachycardia pacing was unsuccessful, up to 8 discharges of 40 J could be delivered. The device was programmed to deliver a single instance of antitachycardia pacing (One-Shot ATP) and 8 discharges at maximal output (40 J) for the ventricular fibrillation zone (> 214 bpm). However, during the course of the trial, because of advancing insight derived from the MADIT-RIT trials, the ICD settings could be adjusted as deemed appropriate by the implanting cardiologist.[15]

After implantation, a defibrillation threshold test was performed with the patient under conscious sedation (using midazolam and fentanyl) with the induction of ventricular fibrillation. The maximal energy of the device was 40 J. The Holter function was turned on. The implanted ICDs contain a home monitoring function, with daily transmission of device data at 02:00 am.

End Points

The primary end point was sudden cardiac (arrhythmic) death, with assessment of all adverse clinical events. The cause of death was classified as caused by SCD/arrhythmia, other cardiac event, withdrawal of renal replacement therapy, neurological, malignancy, infection, or other cause. Validation of the cause of death was based on information obtained from witnesses, family members, death certificates, hospital records, and autopsy reports, when available. A blinded clinical events committee independently reviewed information on all deaths. The committee classified deaths with respect to suddenness and arrhythmic mechanism using criteria developed by Hinkle and Thaler.[16] SCD was defined as either one

of the following conditions: (1) if a subject, apparently well, was observed to have died within a few minutes (operationally documented as < 1 hour) from onset of symptoms and if the cause of death could not reasonably be attributed on the basis of the full clinical information and the information concerning death to some potentially lethal disease; (2) death was called arrhythmic if the patient was found dead after an unwitnessed event with no other cause of death identifiable and if the patient had been in his or her usual state of health without any new symptoms when last observed.[17] To avoid unblinding, the results of ICD interrogation after death were not used to determine cause-specific death for the primary analysis, because this information was only available for ICD patients.

The first secondary end point was all-cause death. The safety analysis included known device-related complications such as pneumothorax, pocket hematoma, ICD infection, inappropriate shocks, and secondary thrombosis of the vascular access.

Statistical Analysis

In the United States, the annual all-cause mortality rate for patients on dialysis was 21% in 2004.[18] In the Netherlands, the rate was 30% for patients aged 65 to 75 years between 1995 and 2002, with a slight decrease in the 2 years thereafter.[19] We anticipated a further decrease in all-cause mortality because of more intensive medical surveillance and new treatment modalities during the study. We therefore estimated an annual all-cause death rate of 22% in the study. The proportion of SCDs is estimated to be 30% of all-cause death. This is in line with recommendations from the cardiovascular studies of the Unites States Renal Data System, which state that 6.9% of SCDs annually among patients on dialysis should be regarded as a starting point for the design for interventions to reduce the risk of SCD in this population.[18] Several trials comparing ICD with medical therapy as secondary prevention for SCD have shown a significant reduction in SCD of 50%.[20] This reduction was even greater in studies that compared ICD treatment with medical treatment for primary prevention.[21]

On the basis of our experience, we hypothesized that a 70% reduction was likely and would be clinically relevant. We calculated that 200 patients, with a follow-up of 3 years, were required to demonstrate a significant difference with > 80% power and an α=0.05, accounting for an estimated 10% crossover from control to ICD group, dropouts, and censoring because of other causes of death. Power calculation was performed with certified software (PASS 2005, Kaysville, UT[22]).

The main analysis was performed according to the intention-to-treat (ITT) principle.

In the ITT analysis, patients who refused ICD implantation after being randomized to receive the device or in whom an ICD could not be implanted remained in the ICD group. In the per-protocol analysis, patients who refused ICD implantation or could not receive an ICD after being randomized to receive an ICD were excluded. The safety analysis was performed in the per-protocol population.

Patients who survived were censored at the date of termination of the study. Deaths of other causes were censored for the primary outcome at the date of death. Time to SCD or censoring was calculated from the date of randomization and the date of SCD or censoring. Because death of other causes is a competing risk in SCD, we calculated the probability of SCD as a cumulative incidence function, taking death of other causes as a competing risk.[23] Comparison of the primary end point between treatment arms was based on the log-rank test, which compared cause-specific hazards of SCD in the treatment arms, as well as in the presence of competing risks. Cause-specific hazard ratios (HRs), with 95% CIs, for the ICD versus control arms were also calculated under the proportional hazards assumption, again censoring patients who died of other causes.

Overall survival probabilities during follow-up were quantified with Kaplan–Meier curves and were compared with the log-rank test. The HR of ICD treatment versus control group was estimated with Cox regression analysis.

Because the study lasted longer than expected, which is often the case with clinical studies, and because, in theory, advances in clinical practice or changes in ICD development could have affected the outcome, we performed an additional analysis to evaluate the fate of patients who were included in the first half versus the second half of the study. We checked the assumed proportionality over follow-up of the mortality hazards in the ICD and control groups by inspection of Schoenfeld residuals and the proportionality test of Grambsch and Therneau.[24] We also compared the effect of ICD therapy on death in the subgroup of patients included in the first 5 years of the trial (July 2007 to July 2012) and of patients included after July 2012, using the Cox model interaction test.

RESULTS

Participants and procedural information

A total of 220 dialysis patients who were referred from 17 participating medical centers provided informed consent and were screened. Of these, 32 patients were not randomized, and 14 patients were excluded for medical reasons. Another 4 patients

were scheduled for kidney transplantation over the short-term. After reconsideration, 11 patients withdrew their consent because they found the intervention too stressful. Finally, 3 patients withdrew consent because of driving license restrictions after ICD implantation, even though they were informed extensively of the restrictions before randomization. The remaining 188 patients were eligible for inclusion and were randomized to receive an ICD (97 patients) or usual care (91 patients); these patients were included in the ITT analysis (**Figure 3.1**). No patients were lost to follow-up.

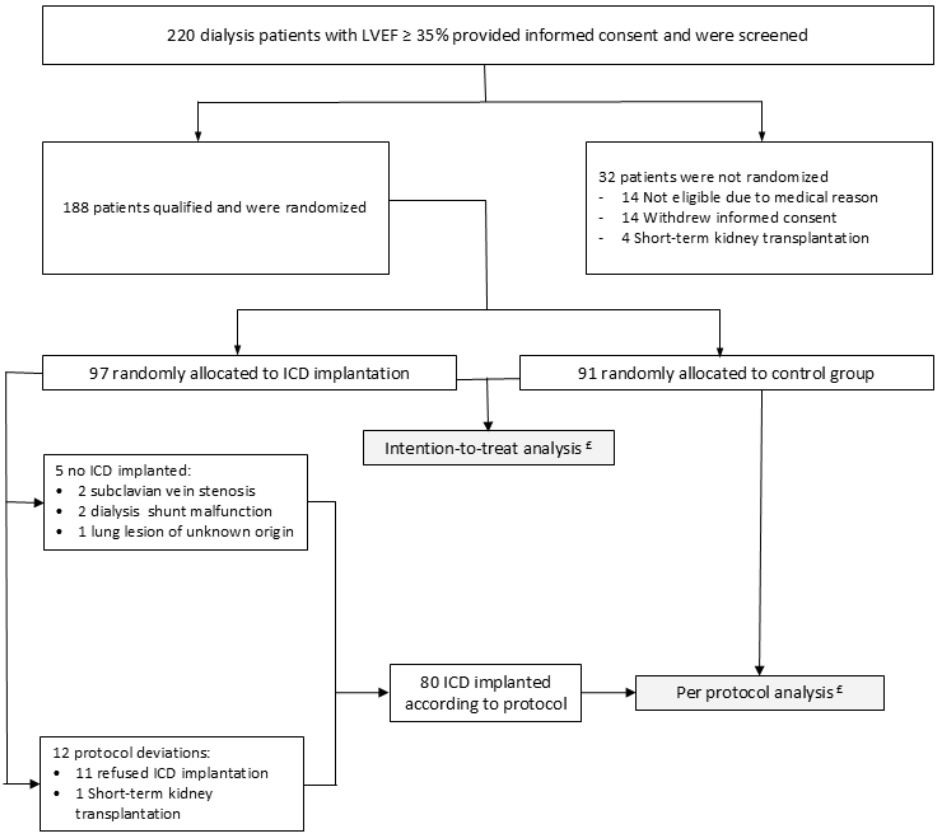

Figure 3.1 Study flow chart.
ICD indicates implantable cardioverter defibrillator. LVEF, left ventricular ejection fraction.
£There were no cases of lost to follow-up.

Protocol deviations in the ICD group

Protocol deviations occurred in 17 patients in the ICD group, who were excluded from the per-protocol analysis. In 5 patients, the ICD could not be implanted for medical reasons: the procedure was aborted in 2 patients because of subclavian vein stenosis, which made implantation impossible; in another 2 cases, malfunction of the arteriovenous fistula occurred between randomization and planned ICD implantation, after which a central venous catheter was used for dialysis treatment (an exclusion criterion); and a suspect lung lesion was found during screening in 1 patient. Eleven patients refused ICD implantation despite having provided earlier consent and having had extensive counseling about the procedure before randomization; they did not withdraw informed consent and were followed up during the study. One patient did not undergo ICD implantation because of unexpected early kidney transplantation.

ICD Data

The implantation procedure took a mean (SD) of 70 (20) minutes (range, 34−116 minutes), and the right pectoral region was used in 58 patients (72.5%). The following devices were used: Lumax 540 DR-T (n=27; 33.8%), Lumax 740 DR-T (n=16; 20.0%), LUMAX 340 DR-T (n=13; 16.3%), ILESTO 7 DR-T ProMRI DF1 (n=11; 13.8%), IPERIA 7 ProMRI DR-T DF4 (n=10; 12.5%), Ilivia 7 ProMRI DR-T DF4 (n=2; 2.5%), and Lumax 540 VR-T (n=1; 1.3%). The right atrial lead was implanted in 78 of 80 patients. The types and numbers of implanted right atrial and right ventricular leads are listed in **Supplemental Table 3.1**. The median energy delivered during defibrillation threshold testing was 20 J (interquartile range [IQR], 15–20 J; range, 14–34 J).

Intention-to-treat analysis

The median age was 67 years (interquartile range [IQR], 62 – 74); 76.1% were men, and 71.3% were on hemodialysis. Most of the hemodialysis patients (105/134; 78.4%) underwent three sessions per week. Treatment groups were well balanced for baseline characteristics (**Table 3.1**). During a median follow-up of 6.8 years (IQR, 3.8–8.8), 54 patients (28.7%) underwent kidney transplantation, 29 (29.9%) in the ICD group and 25 (27.5%) in the control group (P = 0.71). The median number of hospital admissions was 5 (IQR, 3 – 7; range, 0 − 24) in the ICD group and 5 (IQR, 2 – 8; range, 0 − 21) in the control group.

Ninety-nine patients (52.7%) died: 52 (53.6%) in the ICD group and 47 (51.6%) in the control group. SCD occurred in 19/188 patients (10.1%), 11 in the ICD group (11.3%) and eight in the control group (8.8%) (**Table 3.2**). Peritoneal dialysis was the dialysis modality in 5/19 (26.3%) cases of SCD, two in the ICD group and three in the control group (**Supplemental Table 3.2**). Cause of death was evenly distributed between treatment groups (**Table 3.2**). The most prevalent cause was attributed to infectious disease followed by SCD. The overall cumulative incidence of SCD at 5 years was 8.9% (95% CI, 4.4–13.3; **Supplemental Figure 3.1**); 9.7% (95% CI, 3.3 – 16.2) in the ICD group and 7.9% (95% CI, 1.7 – 14.0) in the control group (HR 1.32; 95% CI, 0.53 – 3.29, *P* = 0.55) (**Figure 3.2**).

Overall survival probability at 5 years was 52.4% (95% CI, 44.5 – 60.3) (**Supplemental Figure 3.2**): 50.6% (95% CI, 39.8 – 61.5) in the ICD group and 54.5% (95% CI, 43.0 – 66.0) in the control group (HR, 1.02; 95% CI, 0.69 – 1.52; *P* = 0.92) in the control group (**Figure 3.3**). Thus, ICD implantation was not associated with a reduced incidence of SCD or improved overall survival.

There were no significant differences in the effect of ICD therapy on survival in subgroup analyses, stratified according to age (*P* = 0.87), sex (*P* = 0.29), history of diabetes (*P* = 0.33), history of coronary artery disease (*P* = 0.89), dialysis modality (*P* = 0.21) and dialysis duration (*P* = 0.25) (**Figure 3.4**).

Table 3.1 Baseline Characteristics (intention-to-treat population).

	ICD group (n = 97)	Control group (n = 91)
Men, n (%)	74 (76.3)	69 (75.8)
Age, y, median (IQR)	67 (62–74)	68 (61–74)
Body mass index, kg/m^2, mean (SD)	28.0 (5.4)	27.2 (4.7)
Systolic blood pressure, mmHg, mean (SD)	139 (22)	138 (21)
Diastolic blood pressure, mmHg, mean (SD)	75 (11)	74 (11)
Heart rate, bpm, mean (SD)	70 (13)	73 (13)
Dialysis		
Duration, months, median (IQR)	17 (10–27)	15 (10–27)
Modality, n (%)		
- Hemodialysis	71 (73.2)	63 (69.2)
- Peritoneal dialysis	26 (26.8)	28 (30.8)
Kt/V urea/week, median (IQR)		
- Hemodialysis	4.3 (3.6–5.2)	4.5 (3.8–5.1)
- Peritoneal dialysis	2.2 (2.0–2.5)	2.6 (2.1–3.4)
Hemodialysis, days/week, median (IQR)	3 (3–3)	3 (3–3)

Table 3.1 *(Continued)*

	ICD group (n = 97)	Control group (n = 91)
Symptoms, n (%)		
NYHA I	59 (60.8)	56 (61.5)
NYHA II	25 (25.8)	25 (27.5)
NYHA III	9 (9.3)	6 (6.6)
Angina pectoris	11 (11.3)	14 (15.4)
Palpitations	23 (23.7)	21 (23.1)
Edema	9 (9.3)	12 (13.2)
Orthopnea	7 (7.2)	5 (5.5)
Intermittent claudication	19 (19.6)	14 (15.4)
Medical history, n (%)		
Diabetes mellitus	34 (35.1)	38 (41.8)
Atrial fibrillation or flutter	25 (25.7)	17 (18.7)
Percutaneous transluminal coronary angioplasty	14 (14.4)	16 (17.6)
Coronary artery bypass graft	12 (12.4)	13 (14.3)
Myocardial infarction	23 (23.7)	27 (29.7)
Heart failure	4 (4.1)	5 (5.5)
Transient ischemic attack/cerebrovascular accident	13 (13.4)	18 (19.8)
Hypertension	80 (82.5)	71 (78.0)
Hypercholesterolemia	54 (55.7)	43 (47.3)
Cardiovascular risk profile, n (%)		
Family history of premature cardiovascular disease	34 (35.1)	30 (33.0)
History of smoking	61 (63.9)	66 (72.5)
Medication use, n (%)		
Beta-blocker	57 (58.8)	51 (56.0)
Angiotensin-converting enzyme inhibitor	20 (20.6)	19 (20.9)
Angiotensin receptor blocker	33 (34.0)	24 (26.4)
Calcium antagonist	37 (38.1)	29 (31.9)
Statin	58 (59.8)	58 (63.7)
Insulin	16 (16.5)	20 (22.0)
Erythropoietin	82 (84.5)	72 (79.1)
Cause of end-stage renal disease, n (%)		
Diabetic nephropathy	23 (23.7)	21 (23.1)
Hypertension	37 (38.1)	27 (29.7)
Cystic kidney	4 (4.1)	6 (6.6)
Glomerulonephritis	14 (14.4)	9 (9.9)
Other/unknown	19 (19.6)	28 (30.8)
Echocardiography, left ventricular ejection fraction, n (%)		
≥55%	58 (59.8)	45 (49.5)
≥45% and <55%	26 (26.8)	30 (33.0)
≥35% and <45%	13 (13.4)	16 (17.6)
Left ventricular hypertrophy	42 (43.3)	43 (47.3)

Table 3.1 *(Continued)*

	ICD group (n = 97)	Control group (n = 91)
Laboratory examination, median (IQR)		
Hemoglobin, mmol/L	7.6 (6.9–8.0)	7.7 (7.0–8.1)
Haematocrit, %	0.378 (0.346–0.402)	0.384 (0.355–0.402)
Erythrocytes, ×1012/L	3.83 (3.55–4.23)	4.07 (3.74–4.32)
MCV, fL	97 (93–100)	95 (91–98)
MCH, fmol	1.93 (1.84–2.00)	1.89 (1.81–1.98)
MCHC, mmol/L	20.0 (19.6–20.4)	19.9 (19.6–20.4)
Leukocytes, ×109/L	7.6 (6.0–9.4)	7.4 (6.0–9.1)
Sodium, mmol/L	140 (138–142)	140 (137–142)
Potassium, mmol/L	4.8 (4.4–5.2)	4.6 (4.2–5.2)
Urea, mmol/L	18.0 (13.8–21.9)	18.1 (13.0–22.1)
Creatinine, µmol/L	624 (470–762)	575 (462–738)
Calcium, mmol/L	2.37 (2.27–2.46)	2.35 (2.29–2.50)
Inorganic phosphate, mmol/L	1.54 (1.27–1.71)	1.44 (1.15–1.70)
Albumin, g/L	42 (40–45)	43 (40–46)
C-reactive protein, mg/L	5.0 (2.9–10.0)	5.0 (2.9–12.6)
Heart rhythm, n (%)		
Sinus rhythm	89 (91.8)	83 (92.2)
Atrial fibrillation	7 (7.2)	5 (5.6)
Atrial flutter	0	2 (2.2)
Nodal rhythm	1 (1.0)	0

ICD indicates implantable cardioverter defibrillator; IQR, interquartile range; Kt/V, K dialyzer clearance of urea; t, dialysis time; V, volume of distribution of urea; NYHA, New York Heart Association; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume.

Table 3.2 Causes of Death (Based on Crude Rates) in the ICD and Control Groups (intention-to-treat population).

	n (%)	
	ICD group (n = 97)	**Control group (n = 91)**
Sudden cardiac death	11 (11.3)	8 (8.8)
Cardiac (non-sudden cardiac death)	5 (5.2)	3 (3.3)
Withdrawal of renal replacement therapy	7 (7.2)	8 (8.8)
Neurological	4 (4.1)	2 (2.2)
Malignancy	5 (5.2)	6 (6.6)
Infectious	15 (15.5)	14 (15.4)
Abdominal sepsis	5 (5.2)	1 (1.1)
Sepsis based on ulcus cruris/osteomyelitis	2 (2.1)	5 (5.5)
(Aspiration) pneumonia	6 (6.2)	5 (5.5)
Urosepsis	0	1 (1.1)
Unknown origin of sepsis	2 (2.1)	2 (2.2)
Other	5 (5.2)	6 (6.6)
Total	52 (53.6)	47 (51.6)

ICD indicates implantable cardioverter defibrillator.

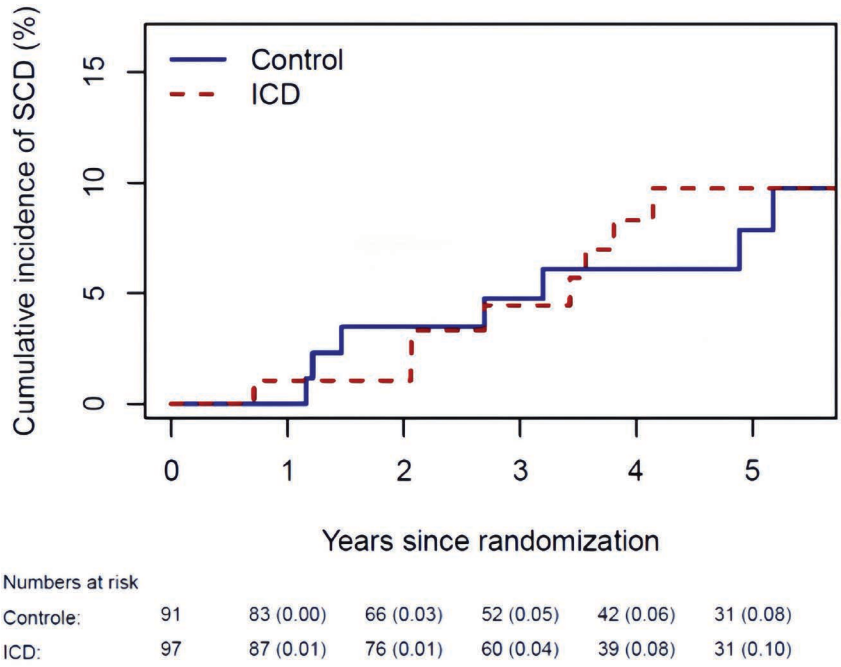

Figure 3.2 Five-year cumulative incidence of SCD per treatment group (intention-to-treat analysis).

The difference in SCD incidence was non-significant (*P* = 0.55, log-rank test).

ICD indicates implantable cardioverter defibrillator; SCD, sudden cardiac death.

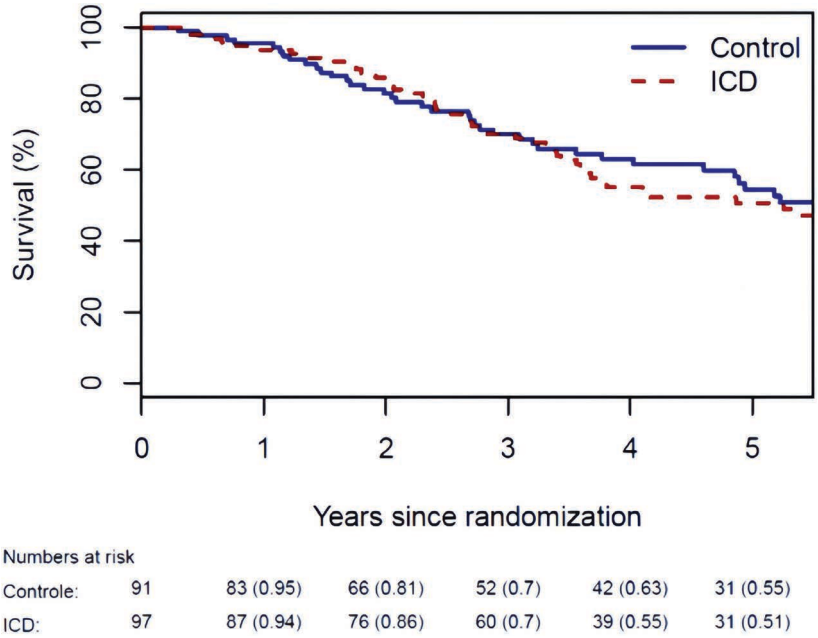

Figure 3.3 Kaplan–Meier curves for survival per treatment group (intention-to-treat analysis).
The difference in survival was non-significant (*P* = 0.92, log-rank test).
ICD indicates implantable cardioverter defibrillator.

There were no statistically significant interactions in the various subgroups. The solid vertical line represents the overall HR (1.02). The horizontal lines indicate 95% confidence intervals around estimated hazard ratios (solid squares). Yr denotes years.

Eleven patients (13.8%) received appropriate ICD therapy. Four patients received one or more ICD shocks following detection of ventricular fibrillation, and in eight patients (transient) ventricular tachycardia was detected, of which three were terminated by means of ICD shock.

Using the Grambsch and Therneau proportionality test, the assumed proportionality of the mortality hazards in the ICD and control groups over follow-up was assessed.[24] Proportionality was not rejected (*P* = 0.64), and indeed, the estimated log (HR) did not change appreciably during follow-up. Comparison of the effect of ICD therapy on mortality in the subgroups of patients included in the first 5 years of the trial (July 2007 to July 2012) and of patients included after July 2012 was not significant in either subgroup ($P > 0.75$) and did not differ significantly between these subgroups (Cox model interaction test, *P* = 0.72), showing no evidence for heterogeneity in the results.

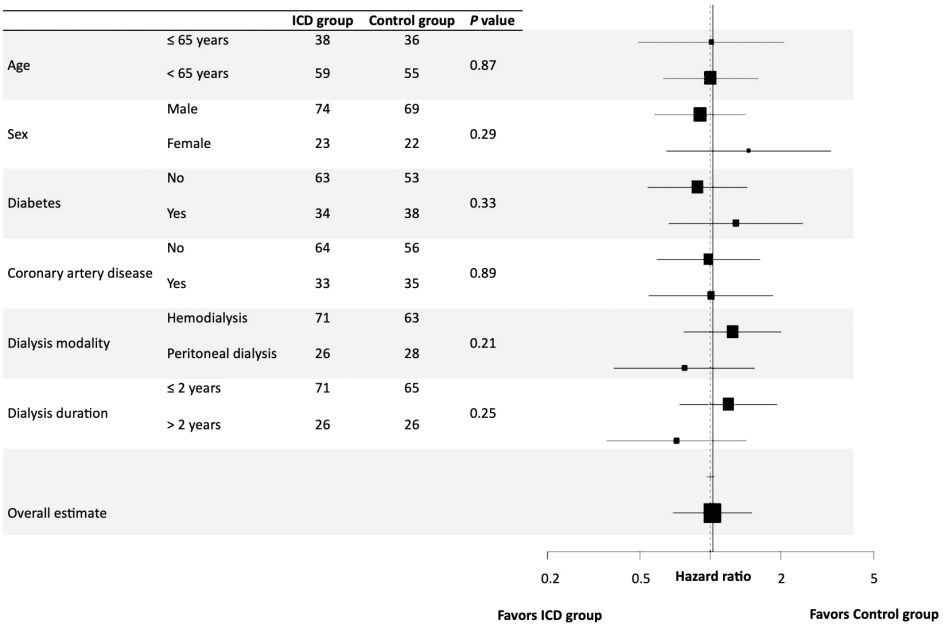

Figure 3.4 Forest plot of hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality in the ICD group compared with the control group, according to selected clinical characteristics.

Per-protocol analysis

The baseline characteristics patients in the per-protocol analysis, which are detailed in **Supplemental Table 3.3**, did not differ significantly between the two groups. Median duration of follow-up was 3.8 years (IQR, 3.8–8.6), during which 28.7% (49/171) of the patients underwent kidney transplantation (24 [30.0%] in the ICD group and 25 [27.5%] in the control group). The per-protocol analysis yielded similar results to the ITT analysis (**Supplemental Results, Supplemental Table 3.4, Supplemental Figures 3.3 –3.6**). Also, in this per-protocol analysis, there was no evidence of heterogeneity in results for patients included in the first versus the second half of the study.

Adverse events

A total of 25 adverse events occurred in 22 patients (27.5%) who received an ICD (**Table 3.3**). Short-term complications, directly related to the implantation procedure, occurred in 10 (12.5%) patients. Eleven re-interventions occurred in 10 patients. A detailed description of ICD-related complications is provided in **Supplemental Results**.

ICD explantation occurred in six patients (7.5%). In four patients, this was due to recurrent bacteremia; in three of these patients there was no obvious relation to the ICD, whereas the fourth patient developed *Staphylococcus aureus* bacteremia following ICD pocket infection. In one patient, in which right ventricular lead dysfunction was already apparent, ICD extraction was indicated for a non-functioning dialysis shunt; surgical creation of a new arteriovenous fistula, ipsilateral to the ICD implantation site, was carried out. The pulse generator was explanted in one patient because of ICD malfunctioning leading to inappropriate shocks. Finally, an arteriovenous shunt for hemodialysis was surgically created in one patient in a referring center, although contraindicated in international guidelines, ipsilateral to the ICD, leading to discomfort and angioedema of the arm due to a total occlusion of the proximal subclavian vein; the ICD and lead were subsequently extracted. There were no cases of pneumothorax or death due to ICD implantation.

Table 3.3 Adverse Events (Based on Crude Rates) in the ICD Group (n = 80).

ICD-related adverse events	
	n (%)
Directly related to ICD implantation procedure	10 (12.5)
Pocket hematoma	2 (2.5)
Pocket infection	3 (3.8)
Post-ICD implantation bacteremia	1 (1.3)
Pneumothorax	0
Lead dysfunction	10 (12.5)
Lead dislocation	3 (3.8)
Lead perforation	1 (1.3)
Lead malfunction	6 (7.5)
Inappropriate shocks	4 (5.0)
Subclavian vein stenosis	3 (3.8)
ICD explantation	6 (7.5)
Due to bacteremia	4 (5.0)
- Directly related to ICD implantation	1 (1.3)
- Probably not related to ICD implantation	3 (3.8)

ICD indicates implantable cardioverter defibrillator.

DISCUSSION

In this prospective randomized study in selected dialysis patients with LVEF ≥35% and without a class I ICD indication, ICD implantation was not associated with a reduced rate of SCD or all-cause mortality, despite the fact that 13.8% of the ICD recipients received appropriate therapy for ventricular tachyarrhythmia. However, although in line with expectations, the complication rates were non-negligible. In a retrospective analysis of 75 patients on hemodialysis who experienced 84 sudden cardiac arrest events with a wearable cardioverter-defibrillator, the initial rhythm was a shockable type in 78.6%.[25] Accordingly, one would expect a substantial benefit of ICD therapy in this population. Recent studies using implantable loop recorders in hemodialysis patients suggest a higher than expected rate of bradyarrhythmic deaths. However, an ICD with backup pacing should treat these as well.[26,27] A recent matched cohort study in dialysis patients with reduced LVEF did not observe a significant association between primary prevention ICDs and reduced mortality among ESRD patients receiving dialysis.[11] A possible explanation for the lack of effectiveness of ICD therapy in the present study could be that any survival benefit associated with ICDs was mitigated by competing causes of death, such as infection, malignancy, or nonarrhythmic cardiac death. In support of this, Khan et al. retrospectively explored the effect of ICD therapy on survival in 78 patients with chronic kidney disease with LVEF < 35% and suggested that patients requiring renal replacement therapy might not benefit from ICD therapy.[8] In light of these conflicting data, a prospective randomized study was called for, weighing the possible benefits against the chance of complications. Patients on dialysis who met the class I indication for ICD implantation were excluded, with the acknowledgment that these recommendations might not apply to the dialysis population, regardless of LVEF, given that such patients were excluded from ICD studies.

We deliberately chose to investigate a subpopulation, patients on dialysis with LVEF ≥35%, who might benefit from ICD therapy and receive a meaningful extension of their life span. Physicians were already hesitant to refer these vulnerable patients to our trial. Implanting a device in patients with significant comorbidity was considered unfeasible and unethical because no pilot data were available.

We performed adequate screening and treatment to avoid the bias that we randomized patients who were too sick to benefit or who had major disease that could and should have been treated first. Nevertheless, total mortality was still high, as more than half of the population died during the follow-up period. The most prevalent cause of death was adjudicated to be attributable to infections, followed by SCD. However, we found a

significantly lower prevalence of SCD (10.1%) than in reports from the literature (22%–26%).[28,29] The incidence of SCD was also lower in the present study than in the United States Renal Data System registry.[1] This could be related to our selection criteria but could also be related to misclassification in the latter, in which SCD as a cause of death was not adjudicated. Epidemiological registries are known to lack sufficient clinical data and systemic adjudication, which makes ascertainment of the primary cause of death, especially SCD, difficult. For example, cerebrovascular accident, pulmonary embolism, and aortic dissection can be mistaken for SCD if death is not witnessed and no autopsy data are available.[30]

Although ICD implantation in this vulnerable population was feasible, considerable adverse events related to ICD implantation occurred in 27.5% of the patients, a rate that is in line with observational data in patients with renal failure.[14,31] Dasgupta et al. performed a case–control study in which the incidence of complications related to cardiac rhythm management was compared in patients with and without ESRD and reported complication rates of 39% in patients with ESRD versus 11% in control subjects; dialysis access was compromised in 19% of patients when device placement was performed contralaterally.[14] Such increased device-related complication rates in patients with ESRD have been attributed to increased bleeding and device-related infections in retrospective analyses, as was also confirmed in the current study.[31] The use of alternatives to transvenous ICD (e.g. subcutaneous ICD) might be better suited in patients with ESRD requiring dialysis, but this technology has yet to be proven in large-scale series.[32]

The current trial is, to the best of our knowledge, the first prospectively studied cohort of dialysis patients undergoing ICD implantation and has the potential to affect healthcare costs, because the results may be considered for future guidelines. Patients undergoing peritoneal dialysis were well represented. The long follow-up during our trial offers new insights into the possible long-term risk of ICD-related complications. However, certain limitations must be noted. The study was terminated early because of futility. At the outset, we postulated that recruitment of 200 subjects would take 24 months, with a mean follow-up of 4 years. This appeared an underestimation, because patient accrual was slower, mostly because some nephrologists were hesitant to participate. Also, per advice of the medical ethics committee, patients from 17 centers referred their patients to the implantation and coordinating center (Leiden University Medical Center), a high-volume, experienced ICD center, because ICD implantation in patients receiving dialysis has increased complication rates compared with ICD recipients without ESRD.[6,14] This

approach ensured quality and good outreach to other centers but slowed the study down. Another important hurdle was the invasive nature of the treatment in patients who already had to cope with a high burden of (co)morbidity. Furthermore, driving license restrictions after ICD implantation adversely affected enrollment.[33]

The probability that the inclusion of the planned additional 12 patients would change the findings is negligible. An advantage of the extended inclusion period is that longer follow-up was available, which is a strength of this study. Advancements in clinical practice and ICD development during the 11-year course of the trial did not affect the outcome significantly, because mortality of patients included in the first half of the study was similar to that of patients included in the second half of the study. The trial was also limited by the number of protocol deviations. However, the findings of the per-protocol analyses were in agreement with the ITT analyses. Finally, we deliberately selected patients undergoing dialysis who were sufficiently healthy to have a possible meaningful extension to their lives by ICD implantation, and we performed adequate screening and treatment to avoid the possible criticism that we randomized patients who were too sick and would not benefit anyway or who had major disease that should have been treated first.

Because we did not include dialysis patients with LVEF $<$ 35%, our recommendation is limited to dialysis patients with LVEF $\geq$35%. We cannot exclude the appropriateness of a trial studying ICD implantation in ESRD patients with LVEF $<$ 35%, recognizing that nonrandomized signals suggest absence of benefit.

In conclusion, prophylactic ICD therapy was feasible in a selected well-screened and well-treated population undergoing dialysis, but it was not associated with a reduced rate of SCD or all-cause death, which remained high. The findings of this study do not support routine ICD implantation to prevent death, including SCD, in this population, nor do they support the initiation of a larger study with all-cause death as the primary end point.

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SUPPLEMENTAL MATERIALS CHAPTER 3

Supplemental Results

Per-protocol analysis

Data from 171 patients were analysed according to the per-protocol analysis, 80 in the ICD group and 91 in the control group (**Figure 3.1** in the main manuscript). The baseline characteristics are detailed in **Supplemental Table 3.3**. Median duration of follow-up was 3.8 years (IQR 3.8–8.6), during which 28.7% (49/171) of the patients underwent kidney transplantation, 25/91 (27.5%) in the control group and 24/80 (30.0%) in the ICD group.

Eighty-nine patients (52.0%) died during follow-up (**Supplemental Table 3.4**). Rates of death did not differ between treatment groups: 42 deaths (52.5%) in the ICD group and 47 (51.6%; *P* = 0.91) in the control group. Cause of death was evenly distributed between the groups, with the most prevalent attributed to infection, followed by SCD (17/171 [9.9%]), 9 (11.3%) in the ICD group and 8 (8.8%; *P* = 0.60) in the control group. Peritoneal dialysis was the dialysis modality in 5/17 cases of SCD (29.4%), two in the ICD group and three in the control group.

The overall cumulative incidence of SCD at 5 years was 8.3% (95% CI 3.7–12.8) (**Supplemental Figure 3.3**). In the control group, the cumulative incidence of SCD at 5 years was 7.9% (95% 1.7–14) and in the ICD group 8.7% (95% CI 2.0–15.4), HR 1.29; *P* = 0.60) (**Supplemental Figure 3.4**).

Overall survival probability at 5 years was 53.7% (95% CI 45.4–62.1) (**Supplemental Figure 3.5**). For the treatment group, 5-year probability of survival was 53.1% (95% CI 41.2–65.0) in the ICD group and 54.5% (95% CI 43.0–66.0) in the control group (HR 1.02; *P* = 0.93) (**Supplemental Figure 3.6**).

In brief, as also seen in the ITT population, ICD implantation did not result in a substantial difference as compared to the control group regarding the incidence of SCD, nor in the overall survival in the PP population.

ICD-related complications

ICD 3: ICD was implanted on July 30, 2007. Periodic ICD interrogation in December 2011 revealed an increase in RV impedance from 523 to 1500 Ω. In March 2012 RV lead impedance was > 3000 Ω. In December 2012 ICD therapy was turned off. In May

2013 the ICD was ICD battery was almost completely depleted (elective replacement indicator [ERI]). In November 2013 pacing function was also turned off. On October 24, 2014 patient received eight inappropriate ICD shocks, although device was detection and therapy were turned off. ICD explantation occurred on October 24, 2014.

ICD 9: ICD was implanted on September 9, 2009. On September 14, 2009 four inappropriate ICD shocks occurred because of RV-lead dysfunction. Patient underwent RV-lead replacement on September 15, 2009.

ICD 29: ICD was implanted on September 9, 2008. Peri-procedural, during placement of RV lead, the patient developed acute thoracic pain due to RV lead perforation. An emergency echocardiogram was performed which showed pericardial effusion (1.5 cm), without hemodynamic instability. The perforation was conservatively treated.

ICD 30: ICD was implanted on September 12, 2008. Directly after ICD implantation the RV impedance was 609 Ω). On September 3, 2009 a sudden increase in RV-lead impedance was detected via Home Monitoring (1302 Ω). Periodic ICD interrogation in December 2009 showed a daily increase in RV impedance. On March 15, 2011 the RV-lead impedance was 3000 Ω. ICD generator was explanted because of lead-dysfunction on September 12, 2011. On June 19, 2012 both RA and RV lead were extracted because of *Staphylococcus aureus* bacteraemia without signs of endocarditis.

ICD 48: ICD was implanted on May 26, 2015. On June 3, 2015 patient developed acute pain and swelling in ICD pocket, without fever or pus effusion. No specific triggering factor could be identified. Laboratory analysis revealed an international normalised ratio (INR) of 3.6. Pocket haematoma treatment was conservative. Oral anticoagulants were discontinued for 5 days.

ICD 57: ICD was implanted via the right subclavian vein on September 30, 2009. Patient was admitted November 5, 2009 for RA and RV lead repositioning after dislocation in the context of Twiddler syndrome.

Four years later, following a traumatic event, the AV shunt on the left arm became unusable, after which an arteriovenous shunt was created ipsilateral to ICD implantation site. Patient suffered from pain and oedema in the right arm due to venous occlusion. Subsequently, the right-sided AV-shunt was ligated.

ICD 61: ICD was implanted on November 16, 2009. On September 29, 2010 an inappropriate shock occurred following atrial tachycardia. Patient was treated with beta-blocker.

ICD 82: ICD was implanted on September 7, 2010. Defibrillation threshold test was performed after which atrial fibrillation occurred. Post-implantation successful electrical cardioversion was performed via ICD.

On June 30, 2015 VF–oversensing occurred and was registered via Home Monitoring. The defibrillator was charged, but the discharged was aborted. In order to prevent inappropriate shock delivery the defibrillation function was turned off until ICD- and RV lead replacement on September 11, 2015. Procedure was uncomplicated.

ICD 89: ICD was implanted on December 3, 2010. On July 16, 2015 inappropriate ICD therapy was delivered following atrial fibrillation with rapid ventricular response, first in the form of ATP followed by two inappropriate shocks. Patient was admitted in the hospital during which he developed a urinary tract infection under immunosuppression, a delirium, hyperglycaemic dysregulation and a hyperkalaemia.

ICD 121: ICD was implanted on July 3, 2012. Device interrogation 1 day after implantation revealed showed no atrial sensing and no atrial capture. X-ray examination of the thorax showed dislocation of atrial lead. Subsequently, the ICD was VVI programmed.

ICD 125: ICD was implanted on October 25, 2012. Following a sudden movement of the right arm a swelling occurred at the site of the ICD pocket. The pocket haematoma was treated conservatively.

ICD 133: ICD was implanted on February 7, 2013. Patient was admitted on May 16, 2017 because of urosepsis. Blood culture revealed *Enterococcus faecalis*. Both transthoracic and transoesophageal echocardiogram were performed and revealed a structure on the ICD-lead suggestive for vegetation. Uncomplicated removal of the complete ICD system was performed on May 30, 2017.

ICD 136: ICD was implanted on March 19, 2013. In June 2014 complaints of malaise and fever. Blood culture revealed *Staphylococcus epidermidis* bacteraemia. Treatment with antibiotics was started. Both transthoracic and transoesophageal echocardiogram showed a signs of endocarditis (vegetation). On July 8, 2014 the complete ICD system was removed.

ICD 137: ICD was implanted on March 19, 2013. On April 9, 2013 patient was admitted in referring hospital because of fever with signs of pocket infection with spontaneous evacuation of pus. On April 13, 2013 uncomplicated ICD explantation occurred because

of recurrent positive blood cultures with *S. aureus* in spite of adequate flucloxacillin treatment.

ICD 139: ICD was implanted on April 17, 2013. Patient was admitted June 3,2013 because of suspected ICD pocket infection. One blood culture was positive for Staphylococcus aureus. Patient was treated with flucloxacillin and was discharged 4 days after admission.

ICD 156: ICD was implanted on April 8, 2014. In September 2016 RV lead oversensing was observed during periodic ICD interrogation. On September 30, 2016 patient was admitted for RV lead extraction and implantation of a new RV shock-lead.

ICD 159: ICD was implanted on May 15, 2014. Post-implantation signs of pocket infection with evacuation of pus. This was successfully treated with flucloxacillin.

ICD 166: ICD was implanted on September 18, 2014. Device interrogation 1 day after ICD implantation revealed RA-lead dysfunction with capture only occurring with maximum output. ICD was VVI programmed.

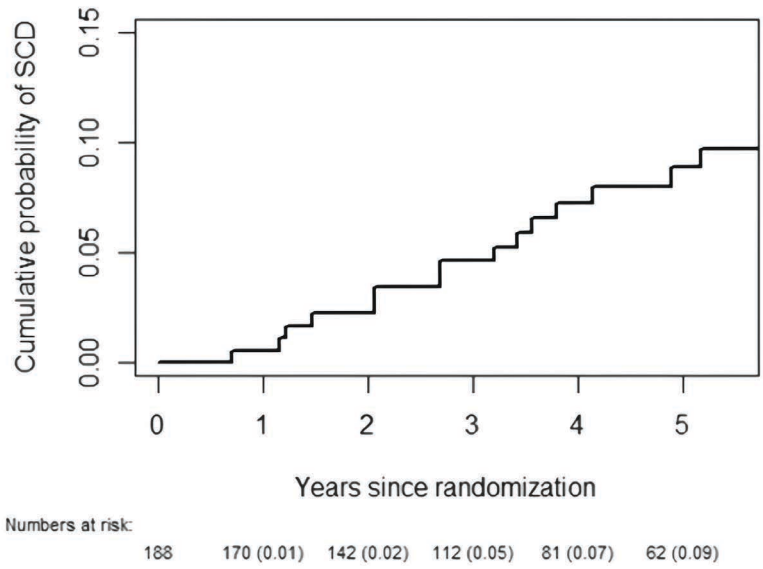
ICD 167: ICD was implanted right-sided on September 12, 2014. Patients developed ipsilateral oedema of the right arm. Visualisation of subclavian vein showed a significant stenosis near the bifurcation with the superior vena cava. Conservative treatment.

ICD 169: ICD was implanted on September 11, 2014. Device interrogation 2 months after ICD implantation revealed RA-lead dysfunction as atrial sense was absent. X-ray examination of the thorax confirmed atrial lead dislocation. Subsequently, the ICD was VVI programmed.

ICD 174: ICD was implanted on May 28, 2015. Afterwards, that evening patient developed fever. Antibiotic treatment with flucloxacillin and ceftazidime was started. Blood cultures showed *Enterobacter aerogenes*, after which switch to ciprofloxacin. Infection was successful treated.

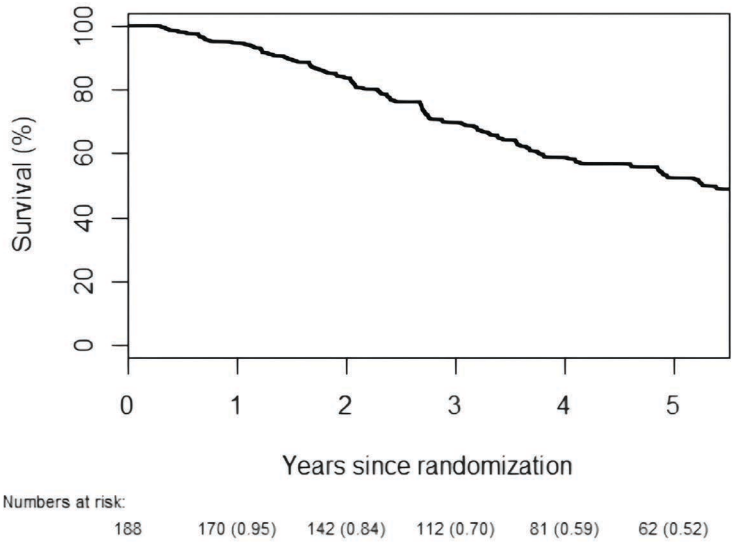
ICD 195: ICD was implanted on April 12, 2016 in a patient treated with peritoneal dialysis. Implantation location was the right pectoral region. Because of clinical reasons the dialysis modality was changed from peritoneal dialysis to hemodialysis. In July 2016 an arteriovenous shunt was surgically created in the right arm. After shunt maturation, the patient developed an oedematous right arm. This was bothersome and it impeded the puncture of the shunt for dialysis. Therefore, dialysis temporarily occurred via central venous catheter.

A venogram showed a mild stenosis in the transition from the subclavian vein to the vena cava superior with extensive collateral formation. The shunt had a high shunt flow of > 3 L/min. The mild stenosis with this very high supply was responsible for the oedema of the arm. During a 3-day admission the ICD and leads were removed, and an attempt was made to dilate the venous trajectory on the right-pectoral side, using rotablation and cutting balloon. The procedure was complicated by bleeding in the ICD pocket. Afterwards, a banding procedure of the shunt took place during an elective admission, after which the oedema diminished.

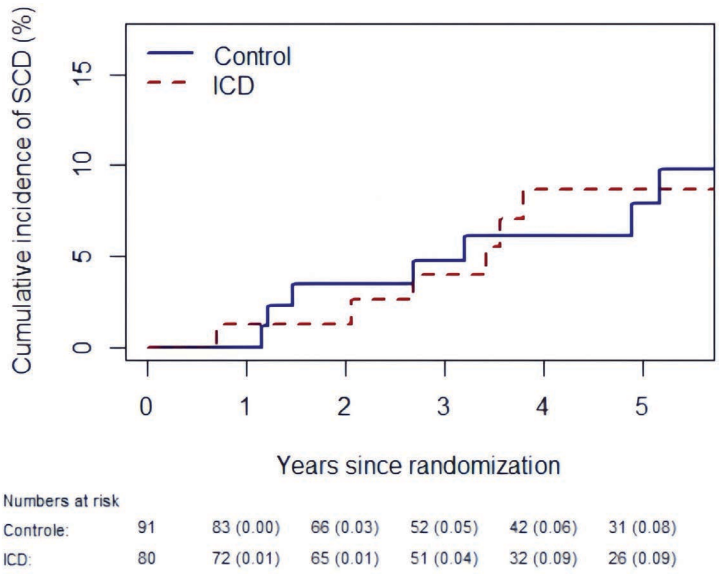


Supplemental Figure 3.1 Five-year overall cumulative incidence of SCD (intention-to-treat analysis).

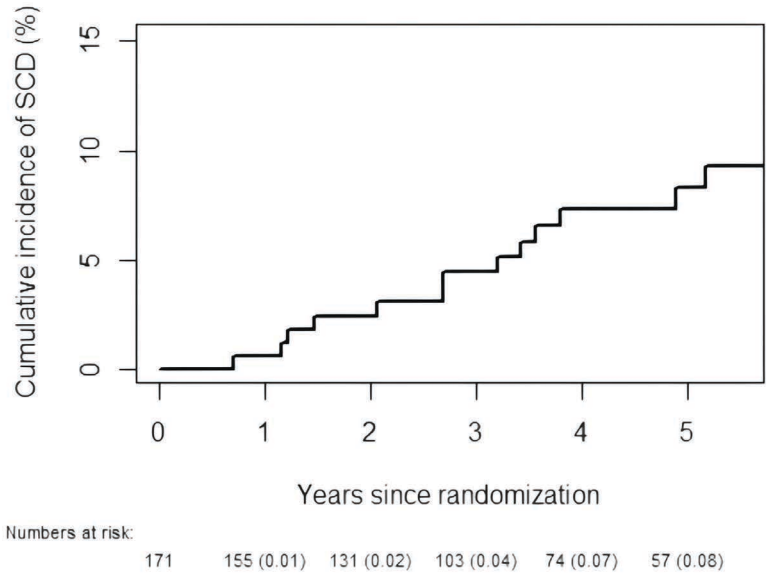
SCD indicates sudden cardiac death.



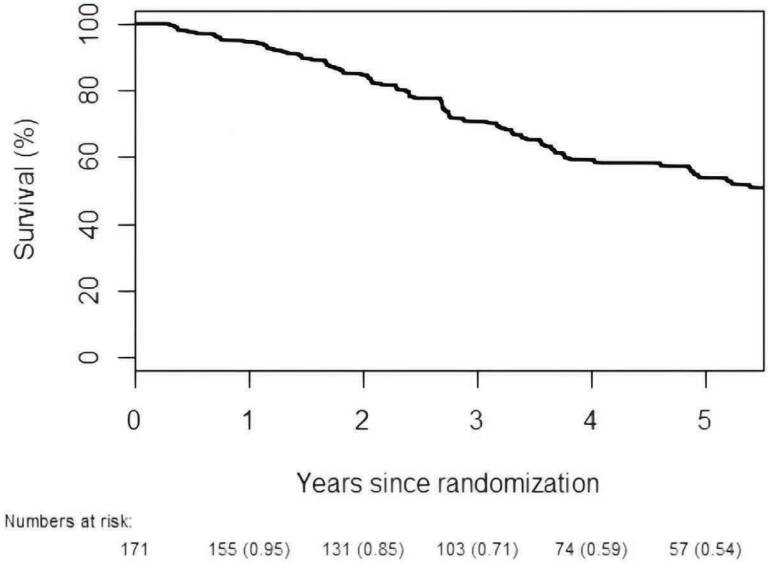
Supplemental Figure 3.2 Kaplan–Meier curves for overall survival (intention-to-treat analysis).



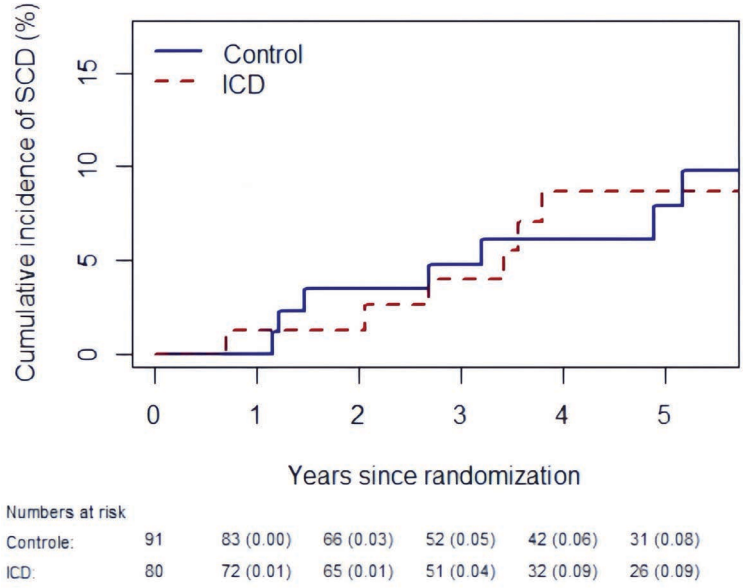
Supplemental Figure 3.3 Five-year overall cumulative incidence of SCD (per-protocol population).
SCD indicates sudden cardiac death.



Supplemental Figure 3.4 Five-year cumulative incidence of SCD per treatment group (per-protocol population).
The difference in SCD incidence was non-significant (*P* = 0.60, log-rank test).
ICD indicates implantable cardioverter defibrillator; PP, per protocol, SCD, sudden cardiac death.



Supplemental Figure 3.5 Kaplan–Meier curves for overall survival (per-protocol population).



Supplemental Figure 3.6 Kaplan–Meier curves for survival per treatment group (per-protocol population).

The difference in survival was non-significant (*P* = 0.93, log-rank test).

ICD indicates implantable cardioverter defibrillator.

Supplemental Table 3.1 Right atrial and right ventricular leads implanted (per-protocol population).

ICD leads	n (%) *
Right atrial	
Not applicable	2 (2.5)
Sweet Tip Rx 4243	13 (16.3)
Solia Pro MRI S53	11 (13.8)
Fineline II EZ Sterox 4473	15 (18.8)
Flextend II 4096	3 (3.8)
CapSure Sense MRI SureScan 4574-53	16 (20.0)
Siello S 53	1 (1.3)
CapsureFix Novus 4076-52	10 (12.5)
CapsureFix MRI 5086MRI52	4 (5.0)
Ingevity MRI 7740	5 (6.3)
Right ventricular	
Linox S 65	51 (63.8)
Linox SD 65/16	9 (11.3)
Linox SD 75/16	1 (1.3)
Protego ProMRI S 65	18 (22.5)
Plexa ProMRI S65 DF-4	1 (1.3)

* Among 80 patients that underwent ICD-implantation.

Supplemental Table 3.2 Sudden Cardiac Deaths According to Dialysis Modality (intention-to-treat analysis).

	Sudden Cardiac Death, n (%)		
	ICD group (n = 97)	Control group (n = 91)	Total (n = 188)
Hemodialysis	9 (9.3)	5 (5.5)	14 (7.4)
Peritoneal dialysis	2 (2.1)	3 (3.3)	5 (2.7)
Total	11 (11.3)	8 (8.8)	19 (10.1)

Supplemental Table 3.3 Baseline Characteristics (per-protocol population).

	ICD group (n = 80)	Control group (n = 91)
Male	61 (76.3)	69 (75.8)
Age, years	67 (63–74)	68 (61–74)
Body mass index, kg/m^2	28.2 (5.6)	27.2 (4.7)
Heart rate, bpm	70 (12)	73 (13)
Systolic blood pressure, mmHg	141 (23)	138 (21)
Diastolic blood pressure, mmHg	75 (11)	74 (11)
Dialysis		
Duration of dialysis, months	16 (9–24)	15 (10–27)
Dialysis modality		
- Hemodialysis	57 (71.2)	63 (69.2)
- Peritoneal dialysis	23 (28.8)	28 (30.8)
Kt/V urea/week		
- Hemodialysis	4.3 (3.6–4.9)	4.5 (3.8–5.1)
- Peritoneal dialysis	2.1 (1.9–2.5)	2.58 (2.1–3.4)
Hemodialysis, days/week	3 (3–3)	3 (3–3)
Symptoms, n (%)		
NYHA I	50 (62.5)	56 (61.0)
NYHA II	20 (25.0)	25 (27.5)
NYHA III	6 (7.5)	6 (6.6)
Angina pectoris	8 (10.0)	14 (15.4)
Palpitations	17 (21.3)	21 (23.1)
Oedema	7 (8.8)	12 (13.2)
Orthopnoea	7 (8.8)	5 (5.5)
Intermittent claudication	15 (18.8)	14 (15.4)
Medical history, n (%)		
Diabetes mellitus	27 (33.8)	38 (41.8)
Atrial fibrillation or flutter	20 (25.1)	17 (18.7)
Percutaneous transluminal coronary angioplasty	9 (11.3)	16 (17.6)
Coronary artery bypass graft	8 (10.0)	13 (14.3)
Myocardial infarction	16 (20.0)	27 (29.7)
Heart failure	2 (2.5)	5 (5.5)
Transient ischemic attack/cerebrovascular accident	13 (16.3)	18 (19.8)
Hypertension	66 (82.5)	71 (78.0)
Hypercholesterolemia	45 (56.3)	43 (47.3)
Family history of premature cardiovascular disease	28 (35.0)	30 (33.0)
History of smoking	50 (62.5)	66 (72.5)
Medication use, n (%)		
Beta-blocker	45 (56.3)	51 (56.0)
Angiotensin-converting enzyme inhibitor	15 (18.8)	19 (20.9)
Angiotensin receptor blocker	27 (33.8)	24 (26.4)
Calcium channel blockers	30 (37.5)	29 (31.9)
Statin	47 (58.8)	58 (63.7)
Insulin	14 (17.5)	20 (22.0)
Erythropoietin	71 (88.8)	72 (79.1)

Supplemental Table 3.3 *(Continued)*

	ICD group (n = 80)	Control group (n = 91)
Cause of end-stage renal disease		
Diabetic nephropathy	20 (25.0)	21 (23.1)
Hypertension	27 (33.8)	27 (29.7)
Cystic kidney	3 (3.8)	6 (6.6%)
Glomerulonephritis	13 (16.3)	9 (9.9%)
Other/unknown	17 (21.3)	28 (30.8%)
Echocardiography, n (%)		
LVEF ≥55%	51 (63.8)	45 (49.5)
LVEF ≥45% and <55%	21 (26.3)	30 (33.0)
LVEF ≥35% and <45%	8 (10.0)	16 (17.6)
Left ventricular hypertrophy	37 (46.3)	43 (47.3)
Laboratory examination, median (IQR)		
Hemoglobin, mmol/L	7.5 (6.8–7.9)	7.7 (7.0–8.1)
Haematocrit, %	0.37 (0.35–0.40)	0.38 (0.36–0.40)
Erythrocytes, $\times 10^{12}$/L	3.81 (3.48–4.15)	4.07 (3.74–4.32)
Mean corpuscular volume, fL	97 (93–101)	95 (91–98)
Mean corpuscular hemoglobin, fmol	1.94 (1.84–2.02)	1.89 (1.81–1.98)
Mean corpuscular hemoglobin concentration, mmol/L	20.0 (19.6–20.4)	19.9 (19.6–20.4)
Leukocytes, $\times 10^{9}$/L	7.5 (6.2–8.7)	7.4 (6.0–9.1)
Sodium, mmol/L	140 (138–142)	140 (137–142)
Potassium, mmol/L	4.9 (4.4–5.2)	4.6 (4.2–5.2)
Urea, mmol/L	18.1 (13.1–21.9)	18.1 (13.0–22.1)
Creatinine, µmol/L	607 (454–767)	576 (462–738)
Calcium, mmol/L	2.36 (2.27–2.46)	2.35 (2.29–2.50)
Inorganic phosphate, mmol/L	1.51 (1.26–1.71)	1.44 (1.15–1.70)
Albumin, g/L	42 (40–45)	43 (40–46)
C-reactive protein, mg/L	5.0 (2.9–10.2)	5.0 (2.9–12.6)
Electrocardiogram heart rhythm, n (%)		
Sinus rhythm	75 (93.8)	83 (92.2)
Atrial fibrillation	4 (5.0)	5 (5.6)
Atrial flutter	0	2 (2.2)
Nodal rhythm	1 (1.3)	0

ICD, implantable cardioverter defibrillator; Kt/V, K dialyser clearance of urea; *t,* dialysis time; *V,* volume of distribution of urea; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Supplemental Table 3.4 Causes of Death (Based on Crude Rates) in the ICD and Control Groups (per-protocol population).

	Causes of Death, n (%)	
	ICD group (n = 80)	**Control group (n = 91)**
Sudden cardiac death	9 (11.3%)	8 (8.8%)
Cardiac: non-sudden cardiac death	5 (6.3%)	3 (3.3%)
Withdrawal of renal replacement therapy	6 (7.5%)	8 (8.8%)
Neurological	2 (2.5%)	2 (2.2%)
Malignancy	4 (5.0%)	6 (6.6%)
Infections	12 (15.0%)	14 (15.4%)
Other	4 (5.0%)	6 (6.6%)
Total	42 (52.5%)	47 (51.6%)

ICD indicates implantable cardioverter defibrillator.

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