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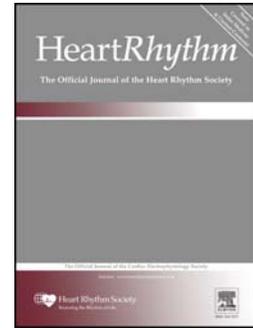
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The Mode of Death in Implantable Cardioverter Defibrillator and Cardiac Resynchronization Therapy – Defibrillator Patients: Results from Routine Clinical Practice

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Abstract

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

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

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

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

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

Key words: mortality, implantable cardioverter defibrillator, mode of death, cardiac resynchronization therapy - defibrillator, sudden cardiac death.

Abbreviations list

ACE = angiotensin-converting enzyme

AT = angiotensin

ATP = antitachycardia pacing

B.p.m. = beats per minute

CI = confidence interval

COPD = chronic obstructive pulmonary disease

CRT = cardiac resynchronization therapy

CRT-D = cardiac resynchronization therapy-defibrillator

HR = hazard ratio

ICD = implantable cardioverter defibrillator

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

SCD = sudden cardiac death

Introduction

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

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

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

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

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Methods

Patients

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

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

Device implantation

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

All devices were programmed with three consecutive zones with limits slightly varying per manufacturer: a monitor zone (lower limit between 150-155 beats per minute (b.p.m.); upper limit

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between 185-190 b.p.m.), an antitachycardia pacing (ATP) shock zone (lower limit between 185-190 b.p.m.; upper limit between 205-210 b.p.m.) and an initial shock zone (≥205-210 b.p.m.). In the monitor zone, no therapy was programmed unless ventricular arrhythmia was detected during follow-up. In the ATP-shock zone, arrhythmias were initially attempted to be terminated by two bursts of ATP and, if arrhythmia continued, defibrillator shocks were used. In case of ventricular arrhythmia faster than the ATP shock zone, device shocks were the initial therapy. Furthermore, atrial arrhythmia detection was set to >170 b.p.m. with supraventricular tachycardia discriminators enabled. Therapy settings were adapted only when clinically indicated.

Follow-up

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

Event subclassification and definitions

Causes of death were categorized according to a modified Hinkle Taler classification and categorized into 3 groups: cardiac, non-cardiac and sudden death.[18] The cardiac group was further categorized into tachyarrhythmic, bradyarrhythmic, heart failure, non-arrhythmic non heart failure, and in cardiac but unable to classify further. The non-cardiac death group was further divided into a vascular and a non-vascular mode of death. Patients who died in their sleep or died unexpectedly without worsening of their clinical situation were categorized as sudden death. Patients who died suddenly but with a clear

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alternative mode of death were categorized as non-sudden (e.g. someone who died suddenly of acute myocardial infarction was categorized as "cardiac, non-arrhythmic non-heart failure" and not as sudden death). Heart failure was diagnosed when patients died of terminal heart failure, progressive failure of cardiac pump function, or cardiac asthma under maximum inotropic drug support. All other causes were categorized as cardiac but unable to classify further. In all cases, the mechanism underlying the immediate demise was selected as the mode of death.

Statistical analysis

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

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

Results

Patients

Since January 1996, 756 (26%) patients received an ICD for primary prevention of SCD, 914 (32%)

patients received an ICD for secondary prevention, and 1189 (42%) patients received a CRT-D. Median

follow-up was 3.4 years (interquartile range, 1.7-5.7 years). Baseline characteristics are summarized in

Table 1.

Mode of death

At the end of follow-up, 662 (23%) patients had died. For 548 (83%) patients the mode of death was

obtained (Table 2). The cumulative incidence of all-cause mortality was 10.0% (95% CI 8.8-11.1%)

after 2 years, 19.6% (95% CI 17.9-21.3%) after 4 years and 39.9% (95% CI 37.0–42.9%) after 8 years.

All-cause mortality was significantly different between the 3 groups and was highest for patients who

received a CRT-D (Figure 1).

A total of 107 (14%) primary prevention ICD patients died during follow-up. In 85 (79%) of these

patients, the mode of death was obtained. In absolute terms, most patients died from heart failure

(n=37, 35%), followed by a non-cardiac cause (n=35, 33%). Seven patients (7%) died suddenly (Table

2, Figure 2). In the group with secondary prevention ICD recipients, 253 (28%) patients died during

follow-up and for 197 (78%) patients the mode of death was obtained. Further sub classification

revealed that most patients died from a non-cardiac cause (n=95, 38%), but still a significant number

died from heart failure (n=71, 28%). Twenty patients (8%) died suddenly. In the CRT-D group, 302

(25%) patients died during follow-up. The mode of death was obtained in 266 (88%) of these patients.

Not unexpectedly, most patients died from heart failure (n=131, 43%), but still 30% (n=92) died from a

non-cardiac cause.

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Mortality rates per mode of death

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

Sudden death

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

Discussion

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

All-cause mortality in routine clinical practice

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

In comparison, in the ICD treated arms of major randomized trials, higher annual mortality rates were observed ranging from 5.8%-8.4% in primary prevention patients and from 6.0%-8.2% in secondary prevention patients.[2-4, 6, 8, 20-22] The differences could be explained by either a healthier population at baseline, better (pharmacotherapeutic) treatment during follow-up, or a combination of both. Baseline mean left ventricular systolic function, for example, was higher in primary prevention patients in the current study (LVEF 32%) than in the major primary prevention ICD trials (LVEF 21%-30%).[5, 8, 23, 23, 24] Furthermore, inclusion of patients in the three major secondary prevention trials occurred between 1987 and 1998, while in the current study, patients received an ICD between 1996 and 2010.[4, 6, 20] Also for CRT-D patients, the annual mortality rate was lower in the current analysis when compared with the outcomes of large clinical trials. For instance, in the CARE-HF and COMPANION, annual mortality rates of respectively 9% and 12% were reported.[25, 26] Again, these differences are mainly due to differences in the selection and composition of the patient population. The effect hereof is clearly

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illustrated in the MADIT-CRT Trial, where selection of patients with mild cardiac symptoms resulted in an annual mortality rate of only 3%.[27]

Heart failure mortality

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

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

Interestingly, in the major ICD trials, higher rates of heart failure mortality were observed: in MADIT-2, Greenberg et al reported annual rates for non-sudden cardiac death of 2.5% and in the SCD-HeFT, the cumulative incidence of heart failure mortality after 5-years of follow-up was approximately 13% (value estimated from graph) resulting in an annual rate of approximately 2.6%.[31] Even higher

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incidences were observed in the AVID trial: after 4 years of follow-up, cumulative incidence was approximately 13% (value estimated from graph), resulting in an annual incidence of 3.3%.[7] Comparing the results of the current study with major randomized trials is difficult given the different time periods during which the studies were conducted as well as differences in patients' characteristics.

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

Sudden cardiac death

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

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

Limitations

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

Conclusion

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

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sudden death rates were comparable between primary prevention ICD patients, secondary prevention

ICD patients, and CRT-D patients.

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Figure Legends

Figure 1. Kaplan Meier curve for all-cause mortality in primary prevention ICD recipients (bold line),

in secondary prevention ICD recipients (dashed line) and in CRT-D recipients (dotted line).

Figure 2. Distribution of the mode of death.

Figure 3. Kaplan Meier curve categorized in heart failure death, sudden cardiac death, non-cardiac

death, and other cardiac death. Cumulative mortality is presented for primary prevention ICD recipients

(red line), secondary prevention ICD recipients (blue line) and CRT-D recipients (green line)

separately. Modes of death other than the one described were censored.

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Table 1. Baseline characteristics.

|	Primary ICD patients (n = 756)	Mean difference±	Secondary ICD patients (n = 914)	Mean difference‡	CRT-D patients (n =1189)	Mean difference§	p-value
Clinical characteristics							
Age, mean (SD), years	60 ± 12	MD: -1.6 (95% CI -3.0; -0.2)	62 ± 14*	MD: -3.5 (95% CI -4.7; -2.2)	65 ± 10*†	MD: 5.1 (95% CI 3.7; 6.4)	<0.001
Male (%)	627 (83%)	OR: 1.2 (95% CI 0.94-1.54)	733 (80%)	OR: 1.24 (95% CI 1.00 – 1.53)	911 (77%)*	OR: 1.48 (95% CI 1.18 – 1.87)	<0.001
Left ventricular ejection fraction (%)	32 ± 13	MD: -7.5 (95% CI -9.1; -6.0)	40 ± 15*	MD: 13.9 (95% CI 12.5; 15.2)	26 ± 9*†	MD: -6.3 (95% CI -7.7; -4.9)	<0.001
QRS, mean (SD), ms	109 ± 25	MD: -5.5 (95% CI -9.1; -1.9)	115 ± 29*	MD: -30.9 (95% CI -34.1; -27.7)	146 ± 33*†	MD: 36.4 (95% CI 33.0; 39.7)	<0.001
Renal clearance. mean (SD), mL/min	85 ± 36	MD: 3.1 (95% CI 1.4; 7.5)	82 ± 40	MD: 7.5 (95% CI 3.5; 11.5)	74 ± 40*†	MD: -10.6 (95% CI -14.8; -6.4)	<0.001
Ischemic heart disease (%)	584 (77%)	OR: 1.35 (95% CI 1.08 – 1.69)	654 (72%)*	OR: 2.11 (95% CI 1.72 – 2.59)	734 (62%)*†	OR: 0.47 (95% CI 0.39 – 0.58)	<0.001
History of atrial fibrillation/flutter (%)	160 (21%)	OR: 0.98 (95% CI 0.77 – 1.24)	197 (21%)	OR: 0.61 (95% CI 0.50 – 0.74)	370 (31%)*†	OR: 1.69 (95% CI 1.36 – 2.09)	<0.001
Medication							
ACE-inhibitors/AT II antagonist (%)	626 (83%)	OR: 2.36 (95% CI 1.86 – 2.98)	614 (67%)*	OR: 0.30 (95% CI 0.24 – 0.37)	1038 (87%)*†	OR: 1.43 (95% CI 1.11 – 1.85)	<0.001
Beta-blocker (%)	476 (63%)	OR: 2.35 (95% CI 1.93 – 2.86)	385 (42%)*	OR: 0.40 (95% CI 0.33 – 0.48)	769 (65%)†	OR: 1.07 (95% CI 0.89 – 1.30)	<0.001
Diuretics (%)	454 (60%)	OR: 1.83 (95% CI 1.50 – 2.23)	412 (45%)*	OR: 0.14 (95% CI 0.12 – 0.18)	1013 (85%)*†	OR: 3.84 (95% CI 3.09 – 4.77)	<0.001
Statins (%)	540 (71%)	OR: 2.30 (95% CI 1.87 – 2.82)	479 (52%)*	OR: 0.66 (95% CI 0.56 – 0.79)	741 (62%)*†	OR: 0.66 (95% CI 0.54 – 0.80)	<0.001
Anti-arrhythmic medication							
Amiodarone* (%)	78 (10%)	OR: 0.37 (95% CI 0.28 – 0.49)	217 (24%)*	OR: 1.49 (95% CI 1.21 – 1.85)	205 (17%)*†	OR: 1.80 (95% CI 1.36 – 2.37)	<0.001
Sotalol* (%)	101 (13%)	OR: 0.64 (95% CI 0.49 – 0.84)	177 (19%)*	OR: 2.44 (95% CI 1.88 – 3.15)	106 (9%)*†	OR: 0.64 (95% CI 0.48 – 0.86)	<0.001

ACE = angiotensin-converting enzyme; AT = angiotensin; CI = confidence interval; CRT-D = cardiac resynchronization therapy defibrillator; ICD = implantable cardioverter defibrillator; MD = mean difference; OR = odds ratio; SD = standard deviation. *Patients could be taking >1 antiarrhythmic drug. * p<0.05 versus primary ICD patients; † p<0.05 versus secondary ICD patients; ± mean difference or odds ratio between primary ICD patients and secondary ICD patients; ‡ mean difference or odds ratio between secondary ICD patients and CRT-D patients; § mean difference or odds ratio between CRT-D patients and primary ICD patients. Mean differences were calculated for continuous variables and odds ratios for categorical variables to illustrate the statistical differences between the groups.

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Table 2. Causes of death of ICD patients.

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

COPD = chronic obstructive pulmonary disease, ICD = implantable cardioverter defibrillator.
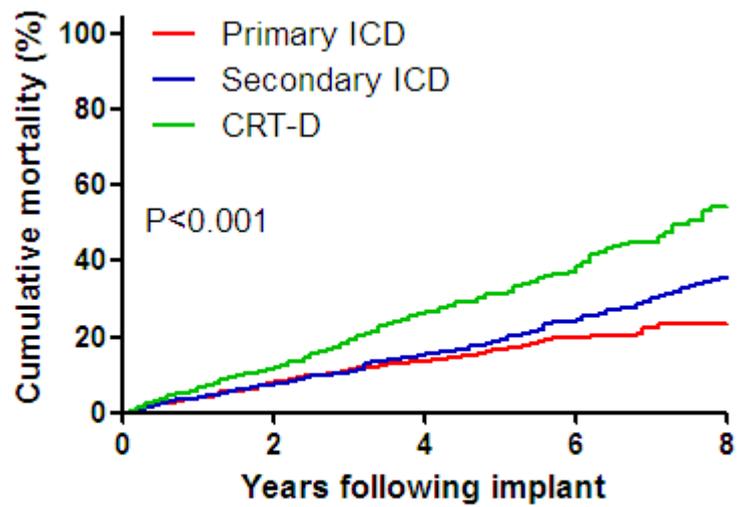
Patients at risk					
Primary ICD	756	545	298	149	59
Secondary ICD	914	715	543	378	227
CRT-D	1189	794	386	143	29

Primary prevention ICD patients

20%

34%

33%

7%

6%

Secondary prevention ICD patients

22%

28%

4%

8%

38%

CRT-D patients

12%

43%

31%

7%

7%

| | Heart failure | | Sudden death | | Unknown |
| | Other cardiac death | | Non-cardiac death | | |
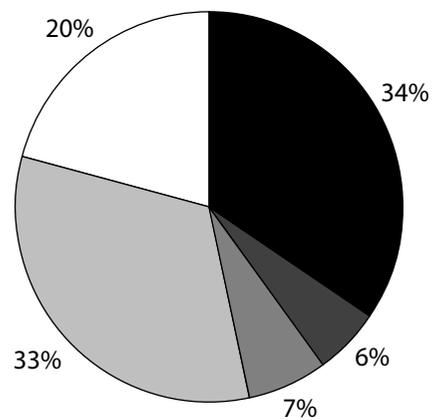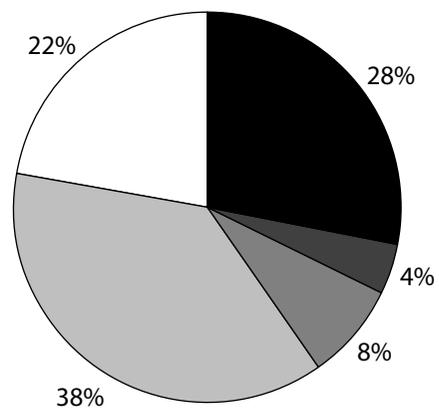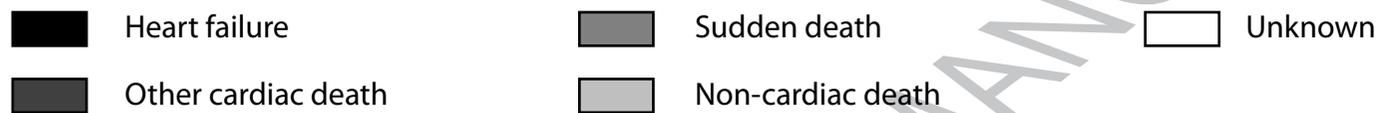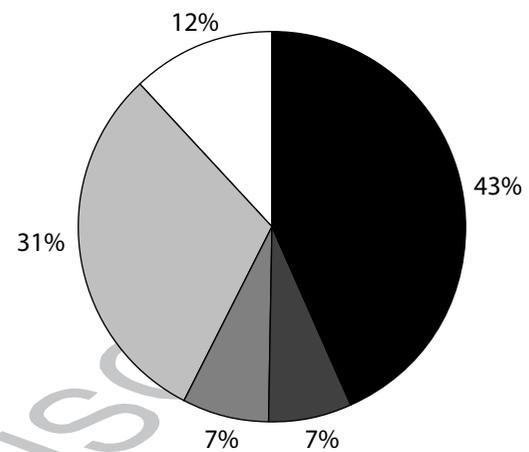
Heart failure death

P<0.001
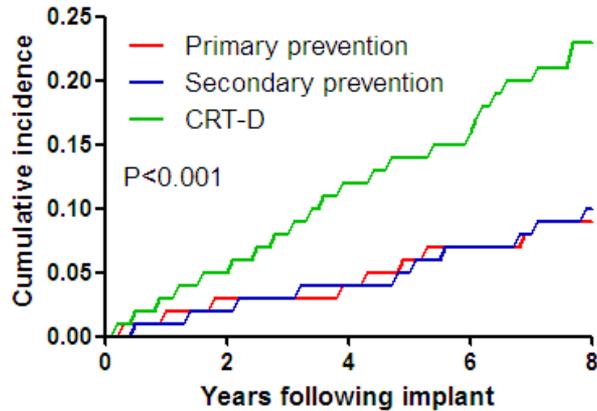
Patients at risk					
Primary ICD	756	545	298	149	59
Secondary ICD	914	715	543	378	227
CRT-D	1081	794	386	143	29

Sudden death
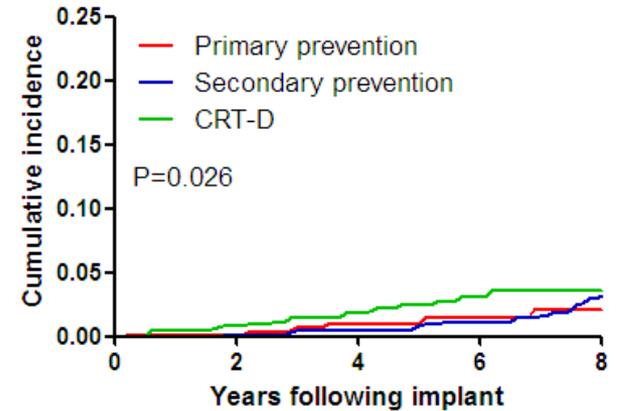
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Patients at risk					
Primary ICD	756	545	298	149	59
Secondary ICD	914	715	543	378	227
CRT-D	1081	794	386	143	29

Non-cardiac death
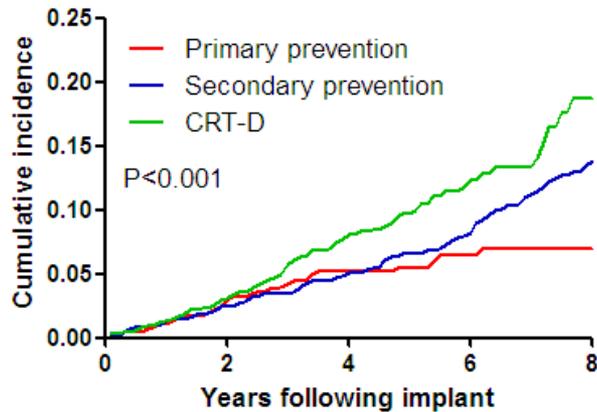
P<0.001

Patients at risk					
Primary ICD	756	545	298	149	59
Secondary ICD	914	715	543	378	227
CRT-D	1081	794	386	143	29

Other cardiac death

P=0.051

Patients at risk					
Primary ICD	756	545	298	149	59
Secondary ICD	914	715	543	378	227
CRT-D	1081	794	386	143	29