# Improvements in implantable cardioverter defibrillator patient stratification

Welsenes, G.H. van

# Chapter 2

## Long-term follow-up of primary and secondary prevention implantable cardioverter defibrillator patients

Guido H. van Welsenes, MS, Johannes B. van Rees, MD, C. Jan Willem Borleffs, MD, PhD, Suzanne C. Cannegieter, MD, PhD, Jeroen J. Bax, MD, PhD, Lieselot van Erven, MD, PhD, Martin J. Schalij, MD, PhD.

*Department of Cardiology and the Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands.*

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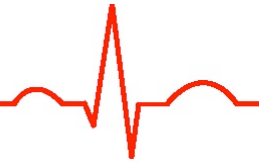
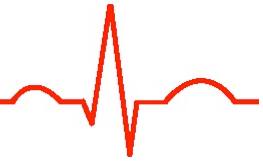



## Abstract

**Aims:** The beneficial effects of implantable cardioverter defibrillators (ICDs) in primary and secondary prevention patients are well established. However, data on potential differences between both groups in mortality and ICD therapy rates during long-term follow-up are scarce. The aim of the study was to assess differences in mortality and ICD therapy between secondary and primary prevention ICD recipients.

**Methods and results:** With exception of patients with congenital monogenetic cardiac disease, all patients treated with an ICD, regardless of the underlying cardiac pathology, from 1996 to 2008 at the Leiden University Medical Center were included in the current analysis. The study population was grouped by type of prevention (secondary or primary) for sudden cardiac death. Primary end-point was all-cause mortality. Secondary end-point was the occurrence of device therapy (appropriate or inappropriate). A total of 2134 (80% men, mean age 63±12 years) ICD recipients were included. Thirteen-hundred-and-two (61%) patients received an ICD for primary prevention of sudden cardiac death and 832 (39%) patients for secondary prevention. During a mean follow-up of 3.4±2.8 years, 423 (20%) patients died. The 5-year cumulative incidence of mortality was 25% (95%CI 21-29%) for primary prevention patients and 23% (95%CI 20-26%) for secondary prevention patients. Secondary prevention patients exhibited a 74% increased risk for appropriate therapy as compared to primary prevention patients (HR 1.7, $p<0.001$). Comparable risk for inappropriate shocks was observed (HR 1.0, $p=0.9$).

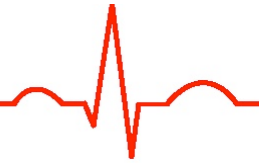
**Conclusion:** During long-term follow-up primary prevention patients exhibited a lower risk of appropriate therapy but comparable mortality rates were observed between both groups. Both groups showed similar occurrence of inappropriate shocks.



## Introduction

Sudden cardiac death, mainly caused by ventricular arrhythmias (VA) in a population with coronary artery disease, is a major cause of mortality in the Western world. In the United States, the annual incidence of sudden cardiac death varies from 200.000 to 450.000 subjects.[1-4] Initially, large trials proved the effectiveness of implantable cardioverter defibrillator (ICD) treatment in survivors of life-threatening VAs such as ventricular fibrillation or ventricular tachycardia (secondary prevention).[5-7] Since survival rates of VA, prior to ICD implantation, are low, focus shifted to the identification of patients at risk of VA (primary prevention).[1] Randomized trials tested the hypothesis that ICD treatment was beneficial in a population characterized by depressed left ventricular ejection fraction (LVEF) without prior cardiac arrest and demonstrated a reduction in all-cause mortality.[8-11] Not only did the implementation of these results in the international guidelines dramatically increase the number of implantations worldwide, it also changed the ICD-treated population from VA survivors to patients characterized by decreased LVEF and symptomatic or asymptomatic heart failure.[12] It is therefore important in follow-up studies to clearly describe the population currently receiving ICD treatment and to assess differences between secondary and primary prevention ICD recipients. Previous studies have clearly shown a higher occurrence of VA, causing appropriate device therapy, in secondary prevention ICD patients as compared to primary prevention ICD patients. However, data on potential differences in mortality and inappropriate ICD shocks during long-term follow-up are scarce.

Since 1996, all ICD recipients in the Leiden University Medical Center have been assessed and followed-up. This cohort allows the evaluation of the long-term outcome in these two groups of patients.



## Methods

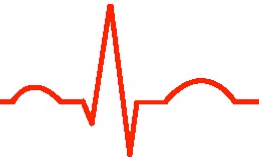
### *Patient population*

Since 1996, all patients who received an ICD in the Leiden University Medical Center have been registered in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center). Characteristics at baseline and data of all follow-up visits are recorded. Eligibility for ICD implantation is based on the international guidelines which, due to evolving guidelines, may have changed over time.[4, 12] For the current study all ICD treated patients up to January 2008 were included. Patients with congenital monogenetic cardiac disease, such as hypertrophic obstructive cardiomyopathy, long-QT syndrome, Brugada syndrome and idiopathic ventricular fibrillation, related to an increased risk of cardiac arrhythmia were excluded.[13]

The study population was grouped by type of prevention (secondary or primary) for sudden cardiac death. Prevention was defined secondary after survival of an episode of cardiac arrest, occurrence of VA with loss of consciousness or VA lasting longer than 30 seconds.[5, 6] Prevention was considered primary in case of depressed LVEF without prior sustained VA.[8, 9, 11, 12]

### *Device implantation and programming*

All implantations were carried out in the catheterization laboratory and all devices were implanted transvenously without thoracotomy. Ventricular and atrial (pacing and shock) leads were positioned conventionally. For implantation of a cardiac resynchronization therapy - defibrillator, a coronary sinus venogram was obtained using a balloon catheter, followed by insertion of the LV pacing lead into one of the posterolateral veins through an 8Fr guiding catheter. During implantation, sensing and pacing thresholds were tested and defibrillation threshold testing was performed. Implanted systems were manufactured by Biotronik (Berlin,



Germany), Medtronic (Minneapolis, MN, United States), Boston Scientific (Natick, MA, United States, formerly CPI, Guidant [St. Paul, MN, United States]) and St. Jude Medical/Ventritex (St. Paul, MN, United States). All devices were programmed with three consecutive zones: a monitor zone (150-188 bpm), an antitachycardia pacing (ATP) shock zone (188-210 bpm) and an initial shock zone (≥210 bpm). In the monitor zone, no therapy was programmed unless slow VA was detected during follow-up. In the ATP-shock zone, arrhythmias were initially attempted to be terminated by two bursts of ATP and, if arrhythmia continued, defibrillator shocks were used. In case of VA faster than 210 bpm, device shocks were the initial therapy. Furthermore, atrial arrhythmia detection was set to >170 bpm with supraventricular tachycardia discriminators enabled.

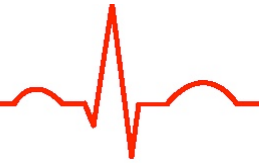
### *Follow-up and device interrogation*

ICD treated patients were periodically seen at the outpatient clinic every 3-6 months, which included device interrogation. Printouts were checked for appropriate and inappropriate therapy (ATP and shocks). Adjudication of the delivered therapy was performed by a trained electrophysiologist. Unscheduled device interrogations were performed in case of symptomatic episodes of arrhythmia and during unplanned hospitalization.

Last follow-up data was acquired in February, 2009. Patients with more than six months of missing data were considered lost to follow-up.

### *End-points*

All-cause mortality was considered the primary end-point. ICD therapies were classified appropriate when they occurred in response to ventricular tachycardia or ventricular fibrillation (secondary end-point) and inappropriate when triggered by sinus or supraventricular tachycardia, T-wave over sensing, or electrode dysfunction (tertiary end-point).



Furthermore the risk for subsequent VA after the first experienced VA was assessed and compared between both subgroups. By definition, secondary prevention patients have experienced a VA prior to ICD implantation and primary prevention patients have not. Therefore, to evaluate differences in the risk for subsequent VA, the risk of a first appropriate shock in secondary prevention patients was compared to the risk of a second appropriate shock in primary prevention patients.

### *Statistical analysis*

Continuous data are expressed as mean ± standard deviation; categorical data are presented as numbers and percentages. Differences at baseline were evaluated with the independent-sample t-test for continuous variables, and Chi-square test for categorical variables. Cumulative incidences were analyzed by method of Kaplan-Meier and compared using the log rank test. The 95% confidence intervals (CI) were calculated as 1.96 times the standard error in each direction. The relation between baseline characteristics and end-points was assessed by using Cox regression analysis and described with hazard ratios (HR) and 95% CI. In the multivariate Cox regression analysis for all-cause mortality, adjustments were made for age, gender, QRS-duration, New York Heart Association (NYHA) functional class, renal function, LVEF, history of atrial fibrillation.[14, 15] For all tests a p-value $<0.05$ was considered significant.

## Results

### *Baseline*

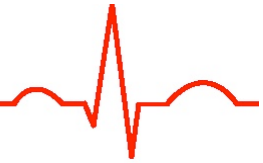
A total of 2471 patients received ICD treatment during the study period. Two-hundred-and-six (8%) patients were diagnosed with a congenital monogenetic cardiac disease. One-hundred-thirty-one (5%) patients were lost to follow-up, of whom 52 (40%) patients received an ICD for

secondary prevention and 79 (60%) patients for primary prevention. The remaining 2134 patients were considered the study population and had a mean follow-up duration of 3.4±2.8 years.

The study population was, as mentioned above, grouped by type of prevention (secondary or primary) for sudden cardiac death. Thirteen-hundred-and-two (61%) patients received an ICD for primary prevention and 832 (39%) patients for secondary prevention. Primary prevention patients had a mean follow-up duration of 2.5±2.0 years and secondary prevention patients a mean follow-up duration of 4.9±3.3 years. As can be seen in Table 1, comparison of the two groups revealed in the primary prevention group a higher NYHA functional class (mean NYHA: 2.3 ± 0.8 vs. 1.8 ± 0.8, p<0.001), a wider QRS complex (mean QRS: 130 ± 35 ms vs. 120 ± 32 ms, p<0.001) and a lower LVEF (mean LVEF: 29 ± 12% vs. 37 ± 15%, p<0.001).

*All-cause mortality*

During follow-up, 423 (20%) patients died. Cumulative incidence for all-cause mortality was 6% (95%CI 5-7%) at 1 year, 16% (95%CI 14-17%) at 3 years and 25% (95%CI 22-28%) at 5 years. Comparison between the two groups demonstrated a higher, but not statistically significant cumulative incidence for all-cause mortality for primary prevention patients as compared to secondary prevention patients during follow-up (Figure 1); at 5 years of follow-up the incidence was respectively 25% (95%CI 21-29%) versus 23% (95%CI 20-26%). As can be seen in Figure 1, during the first 3 years of follow-up, differences in mortality rates between both groups increased, whereas after 3 years the differences in mortality rates remained stable. The risk for all-cause mortality was higher for primary prevention patients than for secondary prevention patients, but did not reach significance (HR 1.2 95%CI 1.0-1.5) after 5 years of follow-up (p=0.05). Moreover, multivariate Cox regression analysis demonstrated that after adjustment for age, gender, QRS duration, NYHA functional class, renal function, LVEF and history of atrial



fibrillation primary prevention patients exhibited similar risk for death as compared to secondary prevention patients. (HR 1.1 95%CI 0.8-1.4, p=0.6).

**Table 1.** Baseline characteristics of primary vs. secondary prevention ICD patients.

| | Primary (n=1302) | Secondary (n=832) | p-value |
|---|---|---|---|
| **Clinical parameters** | | | |
| Male gender | 1035 (80%) | 680 (82%) | 0.204 |
| Age (years) | 63 ± 11 | 63 ± 13 | 0.459 |
| Ischemic heart disease | 881 (68%) | 605 (73%) | 0.020 |
| NYHA functional class | | | <0.001 |
| I | 245 (19%) | 372 (45%) | |
| II | 486 (37%) | 288 (34%) | |
| III | 529 (41%) | 158 (19%) | |
| IV | 42 (3%) | 14 (2%) | |
| QRS duration (ms) | 130 ± 35 | 120 ± 32 | <0.001 |
| Renal clearance (ml/min)* | 78 ± 36 | 79 ± 38 | 0.791 |
| LVEF (%) | 29 ± 12 | 37 ± 15 | <0.001 |
| History of atrial fibrillation | 347 (27%) | 173 (21%) | 0.002 |
| **Type of device** | | | <0.001 |
| Single chamber | 36 (5%) | 219 (26%) | |
| Dual chamber | 517 (40%) | 487 (59%) | |
| CRT-D | 722 (55%) | 126 (15%) | |
| **Medication** | | | |
| Beta blockers | 830 (64%) | 337 (41%) | <0.001 |
| ACE inhibitor / AT antagonist | 1100 (85%) | 569 (68%) | <0.001 |
| Diuretics | 975 (75%) | 429 (52%) | <0.001 |
| Amiodarone | 117 (14%) | 226 (27%) | <0.001 |
| Statins | 864 (66%) | 436 (52%) | <0.001 |

**Renal clearance was determined with the formula of Cockcroft-Gault. ACE = angiotension-converting enzyme; AT = angiotensin; CRT-D = cardiac resynchronization therapy – defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.*

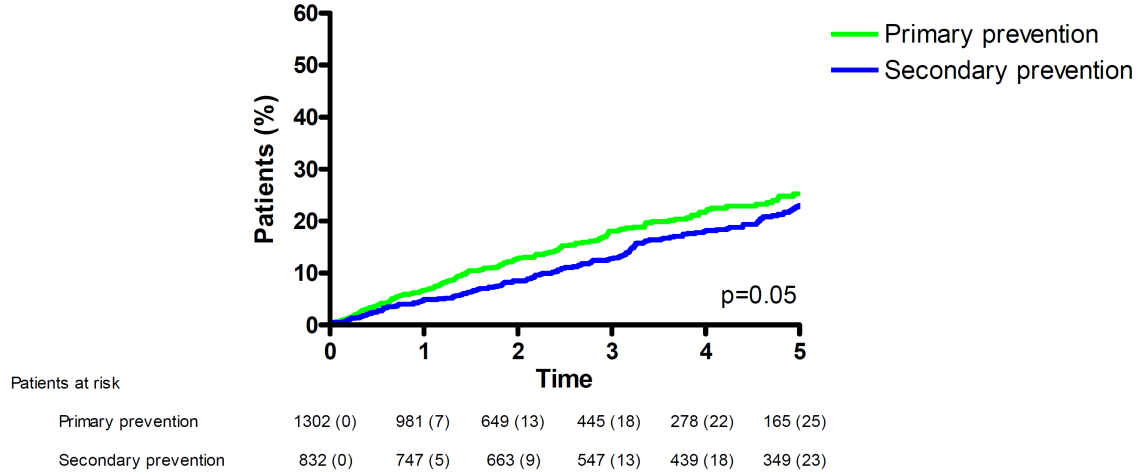



**Figure 1: All-cause mortality.** Kaplan-Meier curves of all-cause mortality for primary and secondary prevention ICD recipients. In the parenthesis, next to patients at risk, the yearly incidences (%) per corresponding time point are noted.

*Appropriate therapy*

Ventricular arrhythmia triggered appropriate therapy (ATP or shock) in 674 (32%) patients. A total of 1529 episodes of VA were terminated by ICD shocks in 423 (20%) patients. Appropriate ATP ended VA in 14006 episodes in 466 (22%) patients. Cumulative incidence for appropriate therapy was 18% (95%CI 16-19%) at 1 year, 33% (95%CI 31-35%) at 3 years and 43% (95%CI 40-46%) at 5 years. Comparison between the two study groups demonstrated a cumulative 5-year incidence for appropriate therapy of 37% (95%CI 33-42%) for primary prevention patients and 51% (95%CI 47-55%) for secondary prevention patients (Figure 2). Cox regression analysis demonstrated a 74% increased risk of appropriate therapy in the secondary prevention group as compared with the primary prevention group (HR 1.7, 95%CI 1.5-2.0, p<0.001).

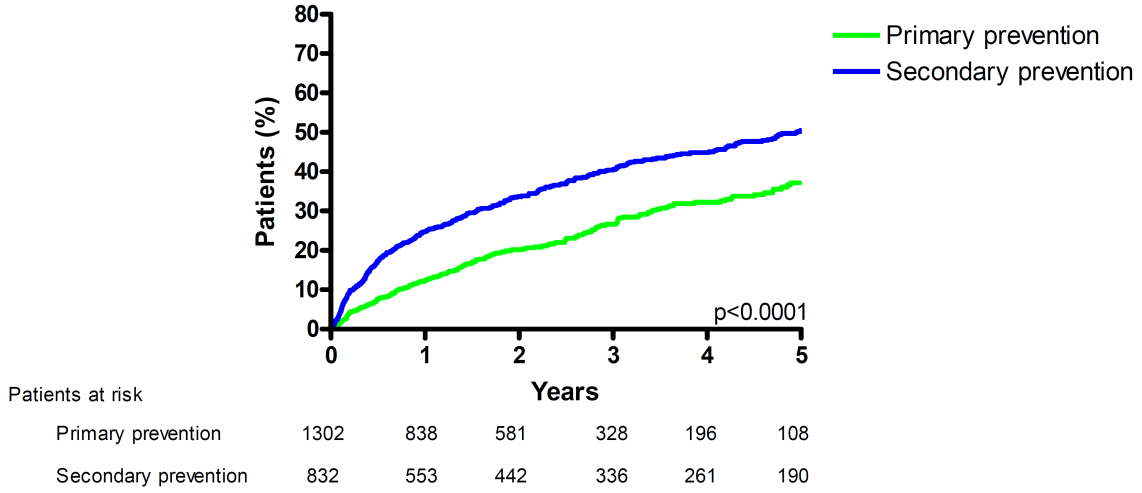



**Figure 2: Appropriate therapy.** Kaplan-Meier curves of appropriate therapy for primary and secondary prevention ICD recipients.

Cumulative incidence for appropriate shock only was 28% (95%CI 25 - 31%) at 5 years. For primary prevention patients, the 5-year cumulative incidence for appropriate shocks was 20% (95%CI 16 - 23%) as compared to 37% (95%CI 33 - 41%) for secondary prevention patients (Figure 3). Secondary prevention patients exhibited more than double the risk for appropriate shocks during long-term follow-up (HR 2.3, 95%CI 1.9 – 2.9, p<0.001).

*Risk for subsequent appropriate shock*

In the primary prevention group, 141 (11%) patients received appropriate shocks. Of these 141 patients, 49 (35%) patients experienced a second appropriate device shock 275±455 days after the first episode. As can be seen in Figure 4, the 5-year cumulative incidence of a second appropriate device shock in primary prevention patients was 50% (95%CI 38-62%) and the cumulative incidence of a first appropriate shock in secondary prevention patients was 37% (95%CI 33-41%). Comparison of these groups demonstrated that primary prevention ICD recipients have

twice the risk for a subsequent appropriate shock as compared to a first appropriate shock in the secondary prevention group (HR 2.0, 95%CI 1.5-2.7, p<0.001).

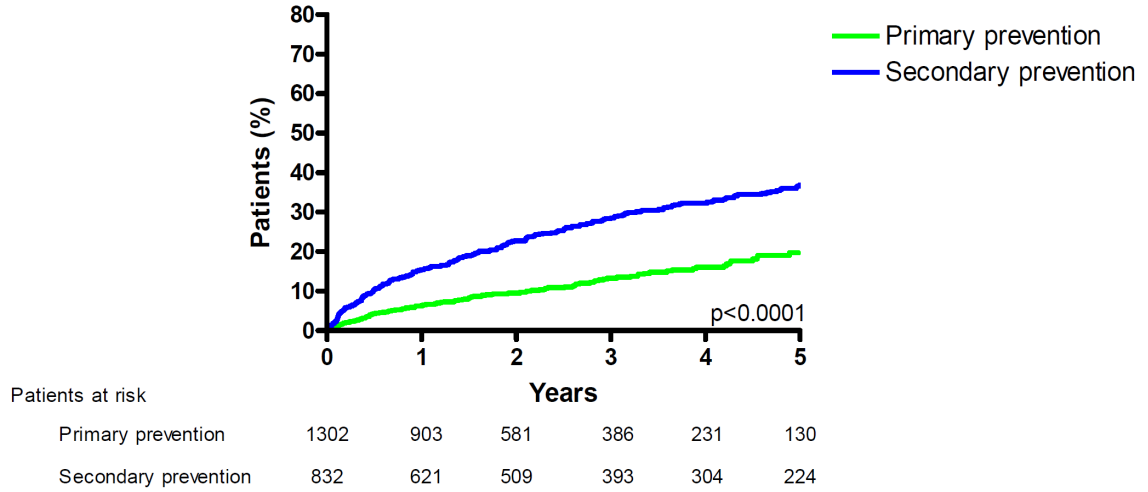



**Figure 3: Appropriate shocks.** Kaplan-Meier curves of appropriate shocks for primary and secondary prevention ICD recipients.

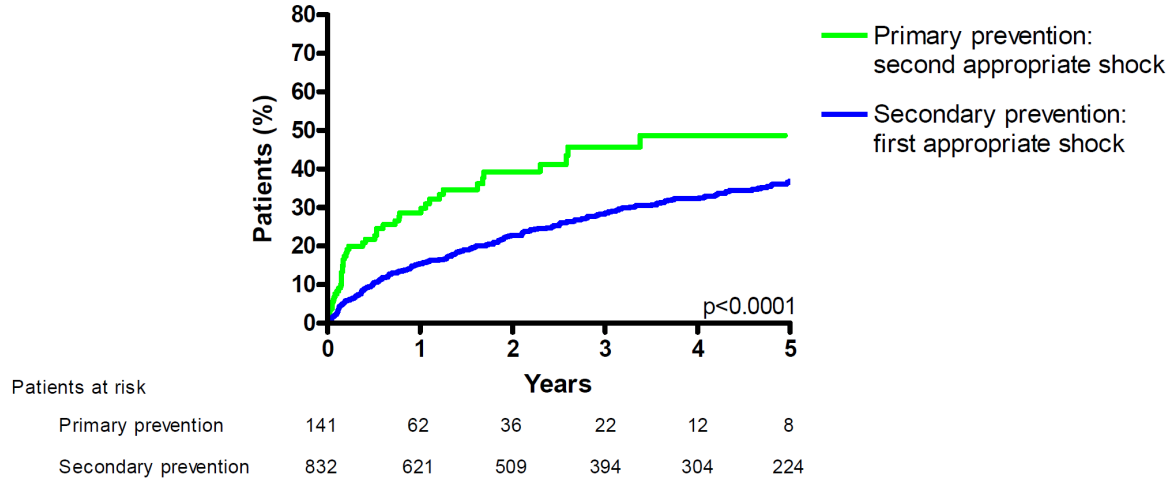



**Figure 4: Subsequent risk for appropriate shock.** Kaplan-Meier curves of appropriate shock for the second appropriate shock in primary prevention ICD recipients and the first appropriate shock in secondary prevention ICD recipients.

*Inappropriate shocks*

During follow-up, 241 (14%) patients experienced inappropriate device discharges with a mean number of 2.9 ± 4.5 shocks. Cumulative incidence for inappropriate shocks was 7% (95%CI 6-8%) at 1 year, 13% (95%CI 11-14%) at 3 years and 17% (95%CI 15-19%) at 5 years. As can be seen in Figure 5, the comparison between the two study groups demonstrated a cumulative 5-year incidence for inappropriate shocks of 18% (95%CI 14-21%) for primary prevention patients and 17% (95%CI 14-20%) for secondary prevention ICD patients. Cox regression analysis showed comparable risk of experiencing an inappropriate shock between the two groups (HR 1.0, 95%CI 0.8-1.3, p=0.9).

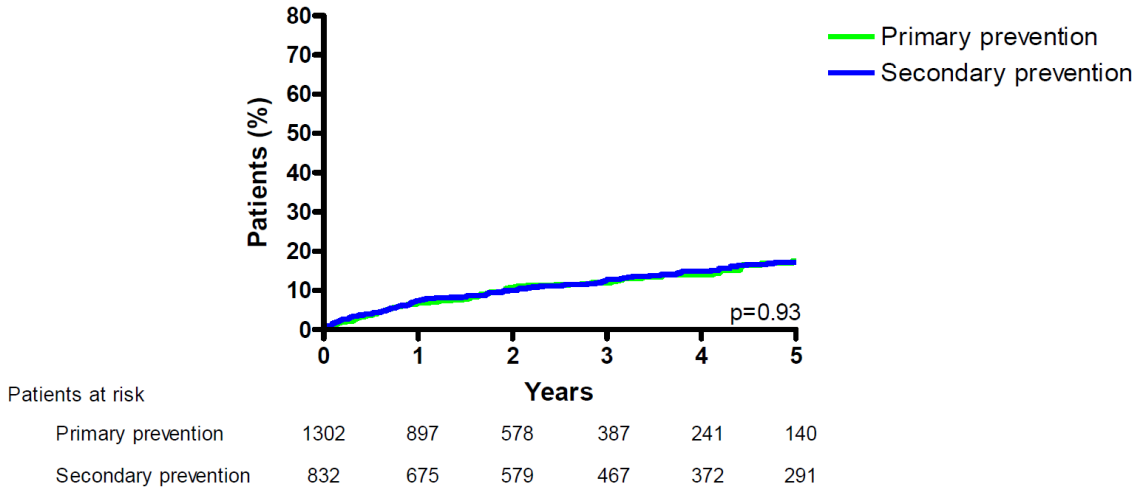
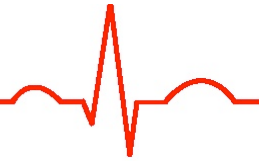



**Figure 5: Inappropriate shocks.** Kaplan-Meier curves of inappropriate shocks in primary and secondary prevention ICD recipients.

## Discussion

The main findings of the current study on the 5 years outcome of primary and secondary prevention ICD patients can be summarized as follows: 1) Patients treated for secondary prevention experienced appropriate therapy more often; 2) The long-term risk for all-cause

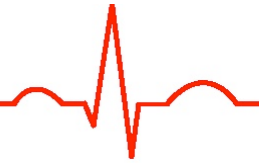


mortality was comparable for both groups; 3) Risk for subsequent VA was higher in primary prevention patients than in secondary prevention patients; 4) No differences were demonstrated in the incidence of inappropriate shocks.

Previously executed large randomized trials have proven the beneficial effect of ICD treatment for primary and secondary prevention of sudden cardiac death. These trials, however, required specific patient criteria for inclusion and might therefore not be representative for the overall population presently considered for ICD treatment. The current study is of additive value to current literature since it assesses long-term follow-up in a large population of primary and secondary prevention ICD recipients in general practice, outside the setting of a clinical trial.

*Survival in ICD recipients*

Large randomized clinical trials for primary and secondary prevention have demonstrated improved survival in patients treated with ICD therapy.[8-11, 16] The first trials on the secondary prevention of sudden cardiac death reported all-cause mortality rates ranging from 16% to 36% over 18 to 57 months, respectively.[5-7] Primary prevention trials, on the other hand, demonstrated mortality incidences ranging from 14% to 23% over 20 to 39 months follow-up, respectively.[8-11, 17] In the current study comparable mortality rates were observed. During long-term follow-up of 5 years, 23% of secondary prevention patients died as compared to 25% of primary prevention patients. Considering the different clinical characteristics at baseline, one should expect higher mortality rates for primary prevention ICD patients. After all, primary prevention ICD patients have more advanced heart disease and more coexisting comorbidity which is in line with previous clinical trials.[5, 7, 9-11, 16, 17] Undisputedly, these characteristics are related to an increased risk for nonarrhythmic death. In contrast, secondary prevention ICD recipients exhibited a higher risk of experiencing life-threatening arrhythmic events than primary prevention patients, as can be concluded from higher incidences of appropriate device therapy.[18] Since ICDs extend survival

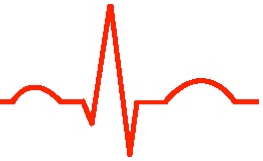


only in case of VA and not in case of nonarrhythmic events, one might expect higher all-cause mortality rates in primary prevention patients. It is therefore interesting that in the current study this thesis was not confirmed. Inaccuracy due to the smaller number of primary prevention patients with long-term follow-up could be an explanation, since initially the mortality curves were divergent (up to 3 years of follow-up). Another explanation could be the supposed negative impact of appropriate shocks on mortality (HR 2.2, $p<0.001$).[19] As demonstrated, secondary prevention patients exhibit a 74% increased risk for appropriate therapy and accordingly this might affect the mortality curve of the secondary prevention group more than it affects the curve of the primary prevention group.

*Occurrence of appropriate and inappropriate ICD therapy*

Germano and co-workers evaluated the incidence of appropriate therapy in 7 major primary and secondary prevention ICD trials and reported appropriate ICD therapy rates ranging from 54% during 45 months of follow-up to 64% during 36 months of follow-up in secondary prevention trials.[18] In primary prevention trials, lower incidences were reported ranging from 17% over 29 months of follow-up to 31% over 24 months of follow-up in primary prevention trials.[18] These results were in line with the observed cumulative incidences in the current study. As expected, the prevalence of appropriate ICD therapy was highest in survivors of life-threatening arrhythmias.

In the current study, inappropriate shocks were relatively common in both groups of ICD recipients, occurring in 18% of primary prevention patients and in 17% of secondary prevention patients after 5 years of follow-up. Comparable findings were observed in the review by Germano et al.[18] It should be noted that both groups had similar risk for experiencing inappropriate shocks. Previously reported studies in literature characterize patients who experience inappropriate shocks as younger patients with non-ischemic heart disease, and a history of atrial fibrillation and smoking.[20-23] Unlike with the occurrence of VA, for which poor cardiac function predicts well,



inappropriate shocks occur mainly due to erroneous discrimination of supraventricular arrhythmias or abnormal sensing by the algorithms within the ICD.[24, 25] Therefore, criteria for the classification of primary and secondary prevention (i.e. depressed LVEF or prior life-threatening VA) do not predispose for the occurrence of inappropriate shocks.

## Limitations

This was a prospective observational study, performed to assess differences between primary and secondary prevention ICD patients. Since patients were collected over a long period of time, evolving guidelines could have created a heterogeneous population.

## Conclusion

During long-term follow-up, compared to secondary prevention ICD patients, primary prevention ICD recipients exhibited a lower risk of VA which triggered appropriate ICD therapy but demonstrated comparable mortality rates. Both groups showed a similar occurrence of inappropriate shocks.

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