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CHAPTER 3

Gender Specific Differences in Clinical Outcome of Primary Prevention Implantable Cardioverter Defibrillator Recipients

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CHAPTER 3

ABSTRACT

Objective
To assess differences in clinical outcome of implantable cardioverter-defibrillator (ICD) treatment in men and women.

Design
Prospective cohort study.

Setting
University Medical Centre.

Patients
1946 primary prevention ICD recipients (1528 (79%) men and 418 (21%) women). Patients with congenital heart disease were excluded for this analysis.
Main outcome measures: All-cause mortality, ICD therapy (antitachycardia pacing and shock) and ICD shock.

Results
During a median follow-up of 3.3 years (25th–75th percentile 1.4–5.4), 387 (25%) men and 76 (18%) women died. The estimated 5-year cumulative incidence for all-cause mortality was 20% (95% CI 18–23) for men and 14% (95% CI 9–19) for women (log rank p<0.01). After adjustment for potential confounding covariates all-cause mortality was lower in women (HR 0.65; 95% CI 0.49–0.84; p<0.01). The 5-year cumulative incidence for appropriate therapy in men was 24% (95% CI 21–28) as compared with 20% (95% CI 14–26) in women (log rank p=0.07). After adjustment a non-significant trend remained (HR 0.82; 95% CI 0.64–1.06; p=0.13).

Conclusion
In clinical practice, 21% of primary prevention ICD recipients are women. Women have lower mortality and tend to experience less appropriate ICD therapy as compared with their male peers.
INTRODUCTION

Sudden cardiac death (SCD) is a major cause of death in the western world, with annually 300,000 deaths in the USA alone.\(^1\) Randomized trials demonstrated the beneficial effect of an implantable cardioverter-defibrillator (ICD), initially in survivors of life-threatening arrhythmias (ie, secondary prevention); thereafter also in patients at high risk of SCD (ie. primary prevention).\(^3\) The number of ICD implantations for primary prevention has increased since implementation of these results in international guidelines.\(^9\)\(^10\)

The rate of SCD in women is approximately half that in men. Prevalence of coronary artery disease is lower, and in case of out-of-hospital cardiac arrest, women are less likely to present with ventricular tachycardia (VT) or ventricular fibrillation (VF), but more likely to have asystole or pulseless electrical activity, both rhythms in which an ICD is ineffective.\(^11\)\(^12\) As our knowledge of life-threatening arrhythmias increases, gender differences in epidemiology, aetiology, clinical presentation and prognosis become more apparent.\(^11\)\(^13\)\(^14\) In all landmark trials supporting ICD implantation, women are under-represented, and subgroup analyses regarding effectiveness show conflicting results.\(^15\)\(^20\) Data on effectiveness of ICD therapy in women is limited and additional studies show an increased risk of major and minor complications in female population.\(^21\) Nevertheless, in daily clinical practice, ICDs are routinely implanted in women, comprising 16–27% of all ICD recipients.\(^10\)^\(^22\)^\(^23\) Thus far, most studies were conducted in the setting of clinical trials and data on long-term follow-up in female population are scarce.

The present study aims to provide insight in long-term clinical outcome of ICD treatment in women as compared with men through analysing the mortality rate, occurrence of appropriate and inappropriate therapy in a large prospectively followed cohort of ICD recipients.

METHODS

Patients

Since 1996, details of all patients who underwent ICD implantation at the Leiden University Medical Centre, The Netherlands, are collected in the departmental Cardiology Information System (EPD-vision, Leiden University Medical Centre) and prospectively followed. Patient characteristics and implantation data were registered at baseline, and all follow-up visits were documented. For the current analysis, patients receiving a transvenous ICD system for primary prevention of SCD in the period 1996 to May 2012 were included. Patients with congenital or monogenetic heart disease were excluded from this analysis. Both patients with ischaemic and non-ischaemic heart disease were included in which ischaemic heart disease was defined as the presence of coronary artery disease (a diameter stenosis of at least 50% in at least one coronary artery).

Eligibility for ICD implantation in this population was based on international guidelines which, due to evolving guidelines, might have changed over time. Patients received an ICD in the presence of a depressed left ventricular ejection fraction (LVEF) with or without non-sustained VT.\(^2\)^\(^9\)

Device implantation

Defibrillators used were manufactured by Biotronik (Berlin, Germany), Boston Scientific (Natick,
follow-up procedure, sensing and pacing thresholds were tested, and defibrillation threshold testing was performed. Except for the early years (1996–1998), devices were all programmed with three different therapy zones: a monitor zone in which no therapy was programmed (lower limit 150–155 beats per minute (b.p.m.); upper limit 185–190 b.p.m.); a VT zone where antitachycardia pacing (ATP) in two separate bursts initially attempt to terminate arrhythmia, followed by shock when arrhythmia continues (lower limit 185–190 b.p.m.; upper limit 205–210 b.p.m.); and in a fast VT or VF zone a defibrillator shock was the initial therapy (≥ 205–210 b.p.m.). Standard zone limits were adjusted according to patient characteristics. Moreover, supraventricular tachycardia discriminators were enabled and atrial arrhythmia detection was set to >170 b.p.m.

Follow-up
Patients were clinically assessed and devices were interrogated every 3–6 months or when clinically indicated. Due to geographic factors the follow-up of some patients was performed elsewhere. If periodical follow-up visit was not performed in the past 6 months a patient was considered lost to follow-up. During ICD interrogation, stored episodes were checked and therapy was classified. ICD therapy (ATP/shocks) was considered as appropriate when triggered by sustained VT or VF, and inappropriate when occurring in the response to sinus or supraventricular tachycardia, non-sustained ventricular arrhythmia, T-wave oversensing or lead dysfunction. Additionally, the survival status of patients was obtained from municipal civil registries. Cause of death was based on letters and follow-up reports from patients who died in the hospital or by the expertise of the contacted general practitioners. The modified Hinkle-Thaler method was used to categorise modes of death into cardiac death, non-cardiac death, and sudden death. The cardiac deaths were further classified as arrhythmic, heart failure, non-arrhythmic/non-heart failure and cardiac, but unable to classify further. Sudden death was defined as sudden death without clear alternative mode of death.

Endpoints
All-cause mortality, appropriate device therapy (appropriate ATP or appropriate shock) and appropriate shock were defined as primary endpoints. Secondary endpoints were all-cause mortality and appropriate device therapy as a combined endpoint, inappropriate shock and mode of death.

Statistical analysis
All statistical analyses are performed using the statistical software program SPSS V.20.0 (Chicago, Illinois, USA). Categorical variables are expressed as numbers and percentages. Continuous variables are presented as mean with SD, or when appropriate as median with IQR. Differences in baseline characteristics were assessed using the independent sample Mann–Whitney U test for continuous data, and \( \chi^2 \) test in combination with Mantel–Haenszel OR Estimate for categorical data. A value of \( p \leq 0.05 \) was considered significant. Kaplan Meier curves with log rank statistics were calculated to analyse time to events, stratified by gender.
Furthermore, in a Cox proportional hazard model the risk of mortality was assessed, the model subsequently adjusted for a predetermined set of covariates that were considered to effect the outcome of ICD recipients, including age, aetiology of heart failure, device type, LVEF, New York Heart Association (NYHA) functional class, history of atrial fibrillation/flutter, renal clearance and use of β-blockers. A similar model was used to analyse risk of appropriate therapies. Inappropriate shock was solely adjusted for history of atrial fibrillation/flutter which was considered as the most important predictor.

RESULTS

Patients
A total of 2192 patients underwent ICD implantation for primary prevention of SCD since 1996 of whom 77 (3.5%) were lost to follow-up and 169 (8%) patients with congenital or monogenetic heart disease were excluded. The remaining 1946 patients were included in the current analyses, comprising of 1528 (79%) men and 418 (21%) women. Clinical characteristics are summarized in table 1. Median age at implantation was 65 years (25th–75th percentile 57–72 years); majority of patients (66%) had ischaemic heart disease with a depressed LVEF (mean 29% ±12). Patients were followed for a median 3.3 years (25th–75th percentile 1.4–5.4 years).

Grouping by gender at implantation showed similar age and systolic function. Women had less ischaemic heart disease (71% vs. 48%; p<0.001), and statin usage was lower (68% vs. 55%; p<0.001). Women had more symptomatic heart failure (median NYHA class 2±1 vs 3±1; p<0.001), subsequently, usage of diuretics was higher (67% vs 73%; p=0.02), and they more often had a CRT-D (56% vs 66%; p<0.001). Furthermore, women had poorer renal function (creatinine clearance 81±37 vs 72±34; p<0.001) and lower body mass index (26.7 vs. 26.1 kg/m²; p=0.02). Patient characteristics by gender are summarized in table 1.

Mortality
During follow up, 463 (24%) patients died, 387 (25%) men and 76 (18%) women. The annual mortality rate was 6.8% in men and 5.3% in women. Five-year cumulative all-cause mortality was 20% (95% CI 18%–23%) in men and 14% (95% CI 9%–19%) in women (figure 1A). Mortality risk was significantly lower in women, also after adjustment for age, aetiology of heart failure, device type, LVEF, NYHA functional class, history of atrial fibrillation/flutter, creatinine clearance and use of β-blockers (adjusted HR 0.65; 95% CI 0.49–0.84; p<0.01; table 2).
Table 1. Gender differences at baseline

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>All patients (N=1946)</th>
<th>Male (N=1528)</th>
<th>Female (N=418)</th>
<th>Unadjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>65 ± 15</td>
<td>65 ± 15</td>
<td>65 ± 17</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Ischaemic heart disease</strong></td>
<td>1274 (66%)</td>
<td>1075 (71%)</td>
<td>199 (48%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Left ventricular ejection fraction, %</strong></td>
<td>29 (11.7)</td>
<td>29 (11.5)</td>
<td>29 (12.3)</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>NYHA functional class</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>I</td>
<td>357 (19%)</td>
<td>293 (20%)</td>
<td>64 (16%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>673 (35%)</td>
<td>563 (38%)</td>
<td>110 (27%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>795 (42%)</td>
<td>585 (39%)</td>
<td>210 (51%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>77 (4%)</td>
<td>50 (3%)</td>
<td>27 (7%)</td>
<td></td>
</tr>
<tr>
<td><strong>QRS duration, ms</strong></td>
<td>132 (35.9)</td>
<td>132 (35.8)</td>
<td>130 (36.2)</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>History of atrial fibrillation/flutter</strong></td>
<td>531 (27%)</td>
<td>439 (29%)</td>
<td>92 (22%)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Creatinine clearance, ml/min</strong></td>
<td>78.7 (36.4)</td>
<td>80.6 (36.8)</td>
<td>72.0 (34.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>26.6 (4.5)</td>
<td>26.7 (4.3)</td>
<td>26.1 (5.0)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>442 (23%)</td>
<td>347 (23%)</td>
<td>95 (23%)</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>History of smoking</strong></td>
<td>396 (22%)</td>
<td>310 (22%)</td>
<td>86 (22%)</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Device type</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Single chamber</td>
<td>80 (4%)</td>
<td>61 (4%)</td>
<td>19 (5%)</td>
<td></td>
</tr>
<tr>
<td>Dual chamber</td>
<td>743 (38%)</td>
<td>618 (41%)</td>
<td>125 (30%)</td>
<td></td>
</tr>
<tr>
<td>CRT-D</td>
<td>1122 (58%)</td>
<td>848 (56%)</td>
<td>274 (66%)</td>
<td></td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors/AT II antagonists</td>
<td>1675 (86%)</td>
<td>1323 (87%)</td>
<td>352 (84%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>1337 (69%)</td>
<td>1056 (69%)</td>
<td>281 (67%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>165 (9%)</td>
<td>135 (9%)</td>
<td>30 (7%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Diuretics</td>
<td>1336 (69%)</td>
<td>1040 (67%)</td>
<td>306 (73%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Statins</td>
<td>1263 (65%)</td>
<td>1034 (68%)</td>
<td>229 (55%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>237 (12%)</td>
<td>195 (13%)</td>
<td>42 (10%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Sotalol</td>
<td>190 (10%)</td>
<td>154 (10%)</td>
<td>36 (9%)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Categorical variables expressed by N (%), and continuous variables presented as mean (SD), or when appropriate median (IQR). ACE=angiotensin-converting enzyme; AT=angiotensin; CRT-D = cardiac resynchronization therapy-defibrillator; NYHA = New York Heart Association.
Table 2. Gender-specific outcome in implantable cardioverter-defibrillator recipients

<table>
<thead>
<tr>
<th></th>
<th>All (N=1946)</th>
<th>Male (N=1528)</th>
<th>Female (N=418)</th>
<th>Unadjusted HR (95% CI)</th>
<th>P value</th>
<th>Adjusted* HR (95% CI)</th>
<th>P value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>463 (24%)</td>
<td>387 (25%)</td>
<td>76 (18%)</td>
<td>0.73 (0.57 – 0.93)</td>
<td>0.01</td>
<td>0.64 (0.49 – 0.85)</td>
<td>0.002</td>
</tr>
<tr>
<td>Appropriate therapy</td>
<td>494 (25%)</td>
<td>401 (26%)</td>
<td>93 (23%)</td>
<td>0.82 (0.65 – 1.02)</td>
<td>0.08</td>
<td>0.82 (0.64 – 1.06)</td>
<td>0.15</td>
</tr>
<tr>
<td>Appropriate shock</td>
<td>267 (14%)</td>
<td>220 (14%)</td>
<td>47 (11%)</td>
<td>0.78 (0.57 – 1.07)</td>
<td>0.12</td>
<td>0.80 (0.66 – 1.13)</td>
<td>0.19</td>
</tr>
<tr>
<td>All-cause mortality +</td>
<td>814 (42%)</td>
<td>667 (44%)</td>
<td>147 (35%)</td>
<td>0.78 (0.65 – 0.92)</td>
<td>0.005</td>
<td>0.73 (0.60 – 0.89)</td>
<td>0.002</td>
</tr>
<tr>
<td>Appropriate therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inappropriate shock</td>
<td>195 (10%)</td>
<td>158 (10%)</td>
<td>37 (9%)</td>
<td>0.87 (0.61 – 1.25)</td>
<td>0.46</td>
<td>0.91 (0.64 – 1.31)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

* HR adjusted for age, aetiology of heart failure, device type, left ventricular ejection fraction, NYHA class, history of atrial fibrillation / flutter, creatinine clearance, and usage of beta-blockers, HR of inappropriate device therapy adjusted for atrial fibrillation/flutter.
**Appropriate device therapy**

In total, 494 (25%) patients (401 [26%] men, 93 [22%] women) received appropriate device therapy. The 5-year cumulative event rate of appropriate therapy was 24% (95% CI 21%–28%) in men, compared with 20% (95% CI 14%–26%) in women (figure 1B). A trend was observed that appropriate device therapy was lower in women (HR 0.82; 95% CI 0.65–1.02; p=0.07).

Additionally, at least one device shock was observed in 267 (14%) ICD recipients, consisting of 220 (14%) men and 47 (11%) women. Five-year cumulative event rates were, respectively, 13% (95% CI 10%–16%) and 10% (95% CI 5%–15%) in men and women (figure 1C). Women tended to experience less appropriate shocks (HR 0.78; 95% CI 0.57–1.07; p=0.12).

Furthermore, after adjustment (age, aetiology of heart failure, device type, LVEF, NYHA functional class, history of atrial fibrillation/flutter, creatinine clearance and use of β-blockers), a non-significant trend remained in both device therapy (HR 0.82; 95% CI 0.64–1.06; p=0.13; table 2) and device shock (HR 0.79; 95% CI 0.56–1.13; p=0.19; table 2).

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**Figure 1.** Gender differences in outcome of primary prevention ICD treatment.

Inappropriate device shocks
Inappropriate shocks were experienced by 195 (10%) patients, 158 (10%) men and 37 (9%) women. Cumulative event rates of inappropriate shock at 5 years were 9% (95% CI 7%–11%) in men and 8% (95% CI 3%–12%) in women (figure 1D). There was no difference between genders in the rate of inappropriate shock (HR 0.87; 95% CI 0.61–1.25; p=0.46; table 2).

Combined: mortality and appropriate device therapy
During follow-up, 814 (42%) patients either received appropriate ICD therapy and/or died. This was the case in 667 (44%) men and 147 (35%) women. The combined endpoint was significantly different between genders (HR 0.78; 95% CI 0.65–0.92; p=0.005). After adjustment for covariates (for age, aetiology of heart failure, device type, LVEF, NYHA functional class, history of atrial fibrillation/flutter, creatinine clearance and use of β-blockers) the difference remained (HR 0.74; 95% CI 0.61–0.90; p=0.003).
Of 657 patients with non-ischaemic heart disease, 267 (41%) experienced appropriate ICD therapy or died. Significantly more male patients (189 [43%]) reached the combined endpoint than female patients (78 [36%]; HR 0.76; 95% CI 0.58–0.98; p=0.03; figure 2A). In ischaemic heart disease patients (N=1274), although a trend towards a lower combined endpoint was observed in female compared with male patients, this difference was not significant. Respectively, 477 (44%) male vs 69 (34%) female patients reached the combined endpoint (HR 0.80; 95% CI 0.62–1.03: p=0.08).
As illustrated in figure 2B, a subanalysis stratified for device type yielded the following results: of the 823 ICD recipients 316 (38%) reached the combined endpoint, here of were 263 (39%) men and 53 (37%) women, this was similar between the genders (HR 0.93; 95% CI 0.69–1.3; p=0.63).
On the contrary, of the 1121 CRT-D recipients 498 (44%) reached the combined endpoint (404 [48%] men vs 94 [34%] women), which was significantly different between genders (HR 0.67; 95% CI 0.54–0.84; p=0.001).

Mode of death
Of all deceased ICD recipients, 216 (47%) suffered a cardiac death; 179 (46%) men and 37 (49%) women (table 3). An arrhythmic death was observed in 17 (4%) cases, 15 (4%) men and 2 (3%) women. Heart failure was the cause of death in 169 (37%) of all deceased, 141 (37%) men and 28 (37%) women. Twenty-two (5%) suffered a sudden death which could not be qualified further, and in 77 patients (17%) the mode of death remained unknown.
Figure 2. Gender differences in either ICD therapy and/or mortality by aetiology of heart failure and device type.

Panel A: mortality and ICD therapy in patients with ischaemic heart disease and patients with non-ischaemic heart disease.
Panel B: mortality and ICD therapy in ICD and CRT patients.

DISCUSSION

The main findings of the present study on gender differences in outcome in primary prevention ICD patients can be summarised as follows: 1) in routine clinical practice, 21% of primary prevention ICD patients is female; 2) mortality is 27% lower in women; 3) the risk of appropriate device therapy for VT of VF tends to be 18% lower in women; 4) the risk of either death or appropriate device therapy (combined endpoint) is 26% lower in women, 5) even though the occurrence of atrial fibrillation/flutter is lower in women, the risk for inappropriate ICD shocks is similar.

The current analysis provides insight in the long-term outcome in male and female primary prevention ICD recipients. This study adds to the growing evidence that gender differences regarding outcome in ICD treatment exist.

Mortality

Previous studies report conflicting results regarding mortality in female ICD recipients. In the present study, female gender was associated with 27% lower mortality. Trials on primary prevention were consistent with this finding. The SCD-HeFT investigators showed a similar (32%) lower mortality in women. Additionally, the COMPANION trial only published unadjusted analyses in which risk of mortality was 44% lower for women. In a posthoc analysis of the INTRINSIC...
RV trial, outcome of ICD treatment by gender was similar. However, data regarding LVEF were not available, and women were more likely to have congestive heart failure and diabetes at enrolment. Furthermore, the MUSTT and MADIT II trials did not observe gender differences in ICD effectiveness, but the small number of women enrolled in these trials significantly limit the power of each individual trial. Additionally, women were somewhat sicker at enrolment, MADIT II observed more frequent NYHA>II, diabetes, hypertension and LBBB in women. In MUSTT, women were older, more likely to have congestive heart failure and myocardial infarction within 6 months prior to enrolment.

On the contrary, recently MacFadden and co-workers observed no difference in mortality rate between genders. However, the study population consisted of 30% secondary prevention patients; data for primary prevention patients only were not reported.

**Appropriate device therapy**

In this cohort, there was a non-significant trend in which women were 18% less likely to receive appropriate therapy for ventricular arrhythmias which is consistent with previous data. In the DEFINITE trial, the risk of ICD shock is 2.56 times lower in women, and MADIT-II showed that risk of ICD therapy was 40% lower in women. Additionally, the unadjusted analyses of COMPANION trial also pointed out that women experience less ICD shocks. Santangeli et al. supported our findings in a meta-analysis including more than 7200 ICD recipients (1600 women), in which women were 37% less likely to experience appropriate ICD therapy. Lastly, these data were recently confirmed by MacFadden et al. in a large cohort of both primary and secondary prevention ICD recipients.

One might hypothesise that, since women in the general population experience less ventricular arrhythmias and SCD, they will automatically experience less appropriate device therapy after implantation, possibly resulting in decreased ICD effectiveness. The exact reason for this lower incidence of ventricular arrhythmias and SCD remains unclear. Differences in arrhythmogenic

<table>
<thead>
<tr>
<th>Table 3. Mode of death specified by gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (N=1946)</td>
</tr>
<tr>
<td>Cardiac</td>
</tr>
<tr>
<td>Arrhythmic</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Non-arhythmic, non-heart failure</td>
</tr>
<tr>
<td>Cardiac but unable to classify</td>
</tr>
<tr>
<td>Further</td>
</tr>
<tr>
<td>Non-cardiac</td>
</tr>
<tr>
<td>Sudden death: unable to classify</td>
</tr>
<tr>
<td>Total death</td>
</tr>
</tbody>
</table>
substrate could be a possible cause. Non-ischaemic heart disease, observed more frequently in female ICD patients, might be less likely to trigger arrhythmias than ischaemic cardiomyopathy. This is illustrated by the annual rate of device shocks of 30% in the ischaemic MADIT II population compared with only 7% in the non-ischaemic DEFINITE population. Lampert et al. reported that women were less likely to experience ventricular arrhythmias, despite a similar rate of inducibility during ventricular stimulation, in a post-infarction population. These findings suggest differences in susceptibility of arrhythmias. Gender differences in cardiac repolarisation or hormonal differences have been suggested to cause this difference in susceptibility, however, the relation with risk of arrhythmia has not been clearly established.

**Inappropriate ICD shocks**

Few trials determined the difference of inappropriate shock by gender. In this study, a similar risk of inappropriate therapy in both men and women was observed, which is consistent with previously published data. It is, however, notable that atrial fibrillation/flutter, being the most frequent cause of inappropriate device shock, is less common in female ICD recipients. For this study, we did not determine the triggers for inappropriate therapy and, therefore, reasons for this similar rate of inappropriate therapy remain unclear.

**Effectiveness of ICD treatment**

This study was not designed to determine whether ICD treatment in women is effective, however when taking into consideration that ICD therapy mainly benefits survival by preventing death due to ventricular arrhythmias, a lower rate of appropriate device therapy in women, as suggested by the non-significant trend that has been observed, implicates a smaller beneficial effect of ICD treatment in women. According to current guidelines, ICD implantation is solely based on poor LVEF. In female patients, LVEF is less strongly correlated to ventricular arrhythmia than in male recipients. These results suggest that criteria for appropriate ICD implantation may differ between men and women. However, evidence remains controversial, and more research is necessary to identify men and women at risk for life-threatening arrhythmias and optimise ICD allocation.

**Limitations**

This was an observational cohort study to assess the effect of gender on long-term follow-up of ICD recipients outside the settings of a clinical trial. Patients were collected over a long period of time, and evolving guidelines could have created a heterogeneous population. Since most patients died outside the hospital, the role of general practitioners in retrieving the mode of death was crucial. To correct for possible errors, the mode of death was estimated on the basis of the modified Hinkle–Thaler method through analysing all anamnestic and clinical data available. By using this method, we aimed to be as accurate as possible. CRT-D devices were more frequently implanted in women which could have influenced the all-cause mortality, as well as the occurrence of ICD therapy.
CONCLUSION

In routine clinical practice, 21% of primary prevention ICD recipients are women. Mortality is 27% lower in female ICD recipients, and women tend to be 18% less likely to experience potentially life-saving appropriate device therapy for ventricular arrhythmia. The rate of inappropriate shocks is similar in both genders.
REFERENCES


22. Gauri AJ, Davis A, Hong T, Burke MC, Knight BP. Disparities


