Long-term predictors of mortality in ICD patients with non-ischaemic cardiac disease: impact of renal function

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Background Randomized trials have demonstrated that implantable cardioverter defibrillator (ICD) therapy may reduce the risk of death in patients with non-ischaemic cardiomyopathy (CMP). In this study, we aimed at determining the long-term benefit of ICD therapy among patients with dilated CMP (DCM) and among those with other non-ischaemic cardiac diseases (NICDs). Methods and results We performed a single-centre longitudinal study to assess the outcomes of 176 patients with NICDs who were implanted with an ICD for primary or secondary prevention of cardiac death. The cumulative survival rate after 1, 2, 5, and 10 years was 91, 87, 78, and 65%, respectively. Mortality risk did not differ significantly between patients with DCM and those with other NICDs. Atrial fibrillation, recurrent ventricular arrhythmias requiring ICD therapy, and right ventricular pacing, but not delayed intrinsic ventricular conduction, were associated with higher risk. New York Heart Association (NYHA) functional class III was an independent predictor of adverse outcome among patients with DCM [hazard ratio (HR) 5.27, P = 0.01], whereas reduced left ventricular function with ejection fraction, ≤35% (HR 12.1, P < 0.001) and anti-arrhythmic drug use (HR 4.82, P = 0.03) were independent predictors among those with other NICDs. Impaired renal function (HR 5.9, P < 0.001) was a strong independent predictor of mortality among all patients with NICD, irrespective of underlying cardiac condition.

Conclusion In ICD patients with DCM, higher NYHA functional class is associated with adverse outcomes. Impaired left ventricular function and anti-arrhythmic drug use predict higher mortality among patients with non-dilated, NICDs. Impaired renal function is a strong predictor of mortality in all patients with NICD.

KEYWORDS Implantable cardioverter defibrillator; Non-ischaemic heart disease; Mortality; Sudden cardiac death; Renal insufficiency

Introduction Implantable cardioverter defibrillator (ICD) therapy has been adopted in current guidelines for use in patients with coronary artery disease and in those with non-ischaemic cardiomyopathy (CMP).1,2 Although randomized controlled trials provide the best evidence about the scientific value of medical interventions, they may not always reflect clinical reality. Patient selection and stringent follow-up schedules may compromise estimation of the benefit for patients, which may be achieved under everyday clinical conditions. Clinical registries can help overcome these limitations by providing long-term follow-up and supplemental data of patients who are generally not included in randomized controlled trials. In patients with ICDs, appropriate therapies and complications may occur even years after device implantation. Information derived from long-term studies may help the clinician to select which patients will benefit most and least from ICD treatment and may influence decisions about device replacement after battery depletion. Most randomized controlled trials of ICD recipients with non-ischaemic cardiac disease (NICD) have included primarily patients with dilated CMP (DCM) and have excluded patients with other NICDs, including valvular disease, hypertrophic and other non-dilated conditions.
CMCs, and primary electric disorders. The aim of the current study was to investigate the rate and to determine factors of mortality during long-term follow-up of patients with non-ischaemic DCM and with other NICDs, who had been implanted with an ICD for primary or secondary prevention of sudden cardiac death (SCD).

Methods

We performed a longitudinal study of consecutive patients with NICD, who underwent both ICD implantation and device follow-up at the University Hospital Zurich. The study was conducted according to the institutional and regional ethics guidelines. Patients were excluded from the study if they received post-implantation care at another institution or if they were lost to follow-up. Patients implanted with a device for cardiac resynchronization therapy with defibrillator (CRT-D) were not included in this study.

Baseline characteristics including patient history, clinical parameters, electrocardiogram, indication for ICD implantation, and device-related parameters of all patients were collected at the time of implantation and during follow-up visits. Comorbidities such as diabetes and hypertension were considered to be present if the diagnosis had been established previously by referring physicians or if disease-specific therapies were required. Renal function was determined by the estimation of the glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease equation. According to the definition of the National Kidney Foundation, reduced renal function was defined as eGFR < 60 mL/min/1.73 m² of the body surface area.

All patients attended regular follow-up visits at our ICD outpatient clinic, which were scheduled at 3–6 month intervals. Additional appointments were made if ICD shock delivery or in the presence of new symptoms, according to patients’ requirements. A full interrogation of the device’s memory, including programmed parameters, stored measurements and electrograms, pacing threshold and sensing tests, and evaluation of appropriate device programming, was performed at each visit. Device programming was individualized according to patients’ underlying cardiac disease and tachycardia characteristics. Bradycardia pacing parameters were programmed to allow for intrinsic rhythm whenever possible. Right ventricular pacing was considered to be present in patients with a proportion of ventricular pacing 50% or more. Anti-tachycardia therapies were enabled in all patients. Mortality data were collected from hospital charts, primary care physicians, and from patients’ families.

Statistical analysis was performed with SPSS Version 13 for Windows (SPSS Inc., Chicago, IL, USA). All analyses were performed for the overall group and for two subgroups: patients with DCM and those with other underlying cardiac conditions (non-dilated NICD group), including all diagnoses listed in Table 1. Descriptive statistics were performed for the analysis of baseline variables. Categorical data are presented as frequencies (%), whereas continuous variables are presented as mean (SD). Time to death was plotted using the Kaplan–Meier method, and differences between groups were compared by the log-rank statistic. Univariate Cox regression analysis was used to determine hazard ratios for various pre-specified clinical factors, including age, sex, blood pressure, heart rate, left ventricular function, electrocardiographic characteristics, underlying cardiac disease, family history of cardiac death, anti-arrhythmic drug use, proportion of right ventricular pacing, diabetes mellitus, and renal function. All clinical factors were assessed at the time of device implantation. Serial measurements during follow-up were not available. A multivariate Cox regression model was used to identify independent predictors of mortality. Forward stepwise regression was performed with a probability of 0.5 for entry and 0.1 for removal from the model. For the regression analysis, amiodarone and sotalol was combined in a single variable (anti-arrhythmic drugs). A two-sided P-value less than 0.05 was considered statistically significant.

Results

Between January 1995 and April 2006, 481 patients were implanted with an ICD in the University Hospital Zurich. Of those, 294 patients had coronary artery disease. Eleven patients moved away and were lost to follow-up. The remaining 176 patients (78% male, age 20–80 years) with NICD were included in the analysis. In 40 patients (23%), an ICD was implanted for the primary prevention of SCD without electrocardiographic documentation of sustained ventricular arrhythmia prior to device implantation. In 136 patients (77%), an ICD was implanted for a secondary prevention indication. Of those, 41 (30%) had survived SCD, 92 (68%) had experienced syncope or presyncope with spontaneous documented ventricular arrhythmia, 2 (2%) had no spontaneous VT, but inducible VT during electrophysiological study, and 1 patient with hypertrophic CMC had stress-induced syncope, but no documented ventricular arrhythmia. Baseline characteristics of the patients studied are presented in Tables 1 and 2.

During a mean follow-up time of 51 months (SD, 39; range 1–142), 76 patients (43%) experienced adequate ICD therapies and 32 patients (18%) died. The estimated mean survival time was 105 [standard error (SE), 5] months. The cumulative survival rate after 1 year was 91% (SE, 2%), after 2 years 87% (3%), after 4 years 84% (3%), and after 5 years 78% (4%), and after 10 years 65% (6%). Survival rates did not differ significantly among patients with DCM compared with those with non-dilated NICD [estimated mean survival time 93 (SE, 9) vs. 111 (6) months, P = 0.07].

The overall survival time did not differ significantly among patients who had received an ICD for secondary prophylaxis compared with those who had a primary prevention indication for ICD implantation [66 (SE, 10) vs. 110 (5) months; P = 0.1]. In the primary prevention group, a higher rate of deaths occurred during the first 2 years following ICD implantation when compared with the secondary prevention group. This could be observed among patients with DCM (Figure 1, left panel), as well as in those with other NICDs (right panel).

Univariate predictors of mortality are presented in Table 3. Patients who were younger than 55 years had better survival when compared with those who were older at the time of ICD implantation. In contrast, advanced age was only weakly associated with increased mortality among those who were older than 55 years. Accordingly, there was no significant difference in survival time among patients older than 70 years compared with those aged 55–70 years (P = 0.4). Estimated survival time of patients younger than 55 years, 55–69 years, and those aged 70 years or older was 108 (SE, 13), 92 (14), and 56 (10) months in patients with DCM (P = 0.23) and 128 (5), 69 (9), and 65 (2) months in those with non-dilated NICD, respectively (P < 0.001).

New York Heart Association (NYHA) functional class III or IV and renal insufficiency were strong predictors of mortality in both patient groups. The cumulative proportion of patients with renal impairment surviving at 6 years after implantation was 38%, compared with 89% among those with
normal renal function ($P < 0.001$). The mean survival of patients with left ventricular ejection fraction 20% and below was 47 (SE, 8) months, compared with 92 (9) months of those with ejection fraction between 20 and 35% and 124 (5) months of those with ejection fraction >35%. However, left ventricular ejection fraction, angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor antagonist use, and anti-arrhythmic drug use were significantly associated with mortality risk only among patients with non-dilated NICD, but not in those with DCM. Moreover, atrial fibrillation and a percentage of right ventricular pacing of 50% or more were strong predictors of mortality solely among patients with non-dilated NICD. Patients with recurrent arrhythmias requiring ICD therapies were at higher risk of death than those who did not experience adequate ICD therapies.

### Table 1: Underlying cardiac disease according to primary or secondary prophylactic indication for ICD implantation

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Primary prevention</th>
<th>Secondary prevention</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated CMP (%)</td>
<td>26 (63)</td>
<td>48 (36)</td>
<td>74 (42)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertrophic CMP (%)</td>
<td>3 (7)</td>
<td>13 (10)</td>
<td>16 (9)</td>
<td>0.69</td>
</tr>
<tr>
<td>Arrhythmic right ventricular CMP</td>
<td>1 (2)</td>
<td>18 (13)</td>
<td>19 (11)</td>
<td>0.05</td>
</tr>
<tr>
<td>Non-compaction CMP (%)</td>
<td>4</td>
<td>6 (4)</td>
<td>10 (6)</td>
<td>0.18</td>
</tr>
<tr>
<td>Idiopathic ventricular tachycardia</td>
<td></td>
<td>8 (6)</td>
<td>8 (5)</td>
<td>0.12</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>1 (2)</td>
<td>4 (3)</td>
<td>5 (3)</td>
<td>0.89</td>
</tr>
<tr>
<td>Long QT syndrome (%)</td>
<td></td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0.59</td>
</tr>
<tr>
<td>Congenital heart disease (%)</td>
<td>1 (2)</td>
<td>9 (7)</td>
<td>10 (6)</td>
<td>0.08</td>
</tr>
<tr>
<td>Unclassified/other (%)</td>
<td>5 (12)</td>
<td>28 (21)</td>
<td>33 (19)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

CMP, cardiomyopathy.

### Table 2: Baseline characteristics of ICD patients with dilated CMP (DCM) and of those with other non-ischaemic cardiac diseases (other NICD)

<table>
<thead>
<tr>
<th></th>
<th>DCM ($n = 74$)</th>
<th>Other NICD ($n = 102$)</th>
<th>Total ($n = 176$)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59 (13)</td>
<td>48 (14)</td>
<td>53 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>58 (78)</td>
<td>80 (78)</td>
<td>138 (78)</td>
<td>0.57</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>28 (9)</td>
<td>49 (18)</td>
<td>40 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV EF &lt;35% (%)</td>
<td>63 (85)</td>
<td>31 (31)</td>
<td>94 (54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA I (%)</td>
<td>3 (4)</td>
<td>22 (22)</td>
<td>25 (14)</td>
<td></td>
</tr>
<tr>
<td>NYHA II (%)</td>
<td>43 (58)</td>
<td>62 (61)</td>
<td>105 (60)</td>
<td></td>
</tr>
<tr>
<td>NYHA III (%)</td>
<td>27 (37)</td>
<td>16 (16)</td>
<td>43 (24)</td>
<td></td>
</tr>
<tr>
<td>NYHA IV (%)</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats x min$^{-1}$)</td>
<td>73 (17)</td>
<td>71 (18)</td>
<td>72 (18)</td>
<td>0.47</td>
</tr>
<tr>
<td>Heart Rhythm</td>
<td></td>
<td></td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>Sinus rhythm (%)</td>
<td>55 (74)</td>
<td>80 (78)</td>
<td>135 (77)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>10 (14)</td>
<td>12 (12)</td>
<td>22 (13)</td>
<td></td>
</tr>
<tr>
<td>Right ventricular pacing</td>
<td>9 (13)</td>
<td>10 (10)</td>
<td>19 (11)</td>
<td>0.62</td>
</tr>
<tr>
<td>ECG ventricular conduction</td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Right bundle branch block (%)</td>
<td>3 (4)</td>
<td>8 (8)</td>
<td>11 (6)</td>
<td></td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>27 (35)</td>
<td>13 (13)</td>
<td>40 (23)</td>
<td></td>
</tr>
<tr>
<td>Left anterior fascicular block (%)</td>
<td>6 (8)</td>
<td>7 (7)</td>
<td>13 (8)</td>
<td></td>
</tr>
<tr>
<td>bifascicular block (%)</td>
<td></td>
<td>3 (3)</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>QRS &gt;120 ms (%)</td>
<td>39 (53)</td>
<td>31 (30)</td>
<td>70 (40)</td>
<td>0.003</td>
</tr>
<tr>
<td>Arterial hypertension (%)</td>
<td>15 (20)</td>
<td>15 (15)</td>
<td>30 (17)</td>
<td>0.33</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>115 (23)</td>
<td>119 (20)</td>
<td>117 (21)</td>
<td>0.26</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>70 (12)</td>
<td>74 (13)</td>
<td>73 (13)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypotension (systolic BP &lt;100 mmHg) (%)</td>
<td>27 (38)</td>
<td>16 (17)</td>
<td>43 (24)</td>
<td>0.02</td>
</tr>
<tr>
<td>Family history of SCD (%)</td>
<td>9 (12)</td>
<td>16 (16)</td>
<td>25 (14)</td>
<td>0.66</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>14 (19)</td>
<td>3 (3)</td>
<td>17 (10)</td>
<td>0.001</td>
</tr>
<tr>
<td>Clinical diagnosis of chronic renal disease (%)</td>
<td>24 (32)</td>
<td>19 (19)</td>
<td>43 (24)</td>
<td>0.04</td>
</tr>
<tr>
<td>Estimated GFR (mL x min$^{-1}$ x 1.73 m$^{-2}$)</td>
<td>61 (18)</td>
<td>76 (18)</td>
<td>70 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>60 (81)</td>
<td>58 (58)</td>
<td>118 (67)</td>
<td>0.001</td>
</tr>
<tr>
<td>Amiodarone (%)</td>
<td>23 (31)</td>
<td>22 (22)</td>
<td>45 (26)</td>
<td>0.22</td>
</tr>
<tr>
<td>Sotalol (%)</td>
<td></td>
<td>4 (4)</td>
<td>4 (2)</td>
<td>0.14</td>
</tr>
<tr>
<td>ACEI/ARB (%)</td>
<td>70 (95)</td>
<td>44 (43)</td>
<td>114 (65)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SCD, sudden cardiac death; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
Estimated survival of subgroups according to indication for device implantation, age, renal function, left ventricular ejection fraction, NYHA functional class, occurrence of adequate ICD therapy, and underlying cardiac condition is presented in Table 4, along with the life expectancy of age-matched Swiss population. The multivariate Cox regression analysis was performed to identify factors that were independent predictors of mortality (Table 5). Reduced left ventricular ejection fraction and anti-arrhythmic drug use (among patients with non-dilated NICD) and higher NYHA functional class (among those with DCM) were independently associated with an
increased risk of death. Angiotensin-converting enzyme inhibitor/angiotensin receptor antagonist use (among patients with DCM) and occurrence of inappropriate ICD therapies (among those with non-dilated NICD) were associated with better outcome. Impaired renal function with eGFR below 60 mL/min/1.73 m² was associated with higher risk in both patient groups and was the strongest independent predictor of mortality in the overall patient group (Figure 2). Adequate ICD therapy, the use of beta-blockers, atrial fibrillation, and ventricular pacing were not significantly associated with higher mortality in the multivariate model.

Discussion

This long-term observational study of patients with NICD implanted with an ICD demonstrated similar mortality rates (13, 16, and 22% at 2, 4, and 5 years) as those of published randomized ICD trials of patients with non-ischaemic heart disease. The Cardiomyopathy Trial (CAT), which was a randomized ICD trial of patients with DCM with left ventricular ejection fraction below 30% that was terminated prematurely, showed a 2-year mortality rate of 8% in the ICD arm and a 4-year mortality rate of 20%.3 In the DEFINITE trial, which included patients with non-ischaemic CMP, left ventricular ejection fraction below 36%, and frequent premature ventricular complexes or non-sustained ventricular tachycardia, the 2-year mortality rate was 7.9% in the ICD arm and 14.1% in the standard-therapy arm.4 Among patients with non-ischaemic chronic heart failure in the SCD-HeFT trial, 5-year mortality was 21% in the ICD-group and 28% in the placebo group.5

Among patients who had been implanted with an ICD for primary prevention of SCD, mortality was higher during the first 2 years after device implantation when compared with those with a secondary prevention indication, irrespective of underlying cardiac condition. This likely reflects the high risk associated with more reduced left ventricular ejection fraction, higher NYHA functional class, and worse renal function in the primary prevention group. However, long-term mortality was similar after 6 years among both patient groups. Interestingly, a similar survival curve with high initial mortality during the first year after device implantation has been recently demonstrated by Parkash et al.9 in ICD patients, who were classified as being at high risk by use of a clinical risk score.

Advanced age was associated with shorter survival time. Although patients younger than 55 years had significantly better survival compared with those who were older than 55 years, age was only weakly associated with adverse outcome in patients older than 55 years. Most randomized

Table 4 Survival of ICD patients subgroups estimated with the Kaplan–Meier method, compared with the life expectancy of the age-matched general Swiss population

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>ICD patients estimated survival, months (SE)</th>
<th>Age-matched general population life expectancy (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication for ICD implantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>66 (10)</td>
<td>319</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>106 (5)</td>
<td>341</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>123 (5)</td>
<td>462</td>
</tr>
<tr>
<td>55–70</td>
<td>85 (9)</td>
<td>239</td>
</tr>
<tr>
<td>&gt;70</td>
<td>56 (8)</td>
<td>134</td>
</tr>
<tr>
<td>Appropriate ICD therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>94 (7)</td>
<td>319</td>
</tr>
<tr>
<td>No</td>
<td>116 (6)</td>
<td>330</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>38 (8)</td>
<td>258</td>
</tr>
<tr>
<td>45–60</td>
<td>59 (11)</td>
<td>248</td>
</tr>
<tr>
<td>60–75</td>
<td>116 (9)</td>
<td>308</td>
</tr>
<tr>
<td>&gt;75</td>
<td>124 (5)</td>
<td>395</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>47 (8)</td>
<td>268</td>
</tr>
<tr>
<td>20–35</td>
<td>92 (9)</td>
<td>308</td>
</tr>
<tr>
<td>&gt;35</td>
<td>124 (5)</td>
<td>372</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA I</td>
<td>117 (10)</td>
<td>450</td>
</tr>
<tr>
<td>NYHA II</td>
<td>100 (9)</td>
<td>319</td>
</tr>
<tr>
<td>NYHA III–IV</td>
<td>46 (6)</td>
<td>267</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilated CMP</td>
<td>93 (9)</td>
<td>268</td>
</tr>
<tr>
<td>Hypertrophic CMP</td>
<td>98 (11)</td>
<td>406</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td>120 (9)</td>
<td>416</td>
</tr>
<tr>
<td>Non-compaction CMP</td>
<td>68 (13)</td>
<td>416</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>107 (9)</td>
<td>416</td>
</tr>
<tr>
<td>Unclassified/other</td>
<td>87 (12)</td>
<td>330</td>
</tr>
</tbody>
</table>

Table 5 Multivariate Cox regression analysis of factors predicting mortality in patients with dilated cardiomyopathy (DCM), other non-ischaemic cardiac disease (NICD), and in the overall study group

<table>
<thead>
<tr>
<th>Predictor</th>
<th>DCM</th>
<th>Other NICD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class ≥3</td>
<td>5.27 (1.27–15.50)</td>
<td>0.01</td>
<td>—</td>
</tr>
<tr>
<td>LVEF &lt;35%</td>
<td>—</td>
<td>—</td>
<td>2.52 (1.08–5.84)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>4.44 (1.27–15.5)</td>
<td>0.02</td>
<td>12.08 (3.10–47.15)</td>
</tr>
<tr>
<td>Anti-arrhythmic drug use</td>
<td>—</td>
<td>—</td>
<td>8.66 (2.20–34.06)</td>
</tr>
<tr>
<td>ACEI/ARB use</td>
<td>0.16 (0.029–0.93)</td>
<td>0.04</td>
<td>4.82 (1.22–19.03)</td>
</tr>
<tr>
<td>Inadequate ICD therapy</td>
<td>—</td>
<td>—</td>
<td>0.097 (0.017–0.552)</td>
</tr>
</tbody>
</table>

CMP, cardiomyopathy.
trials have not specifically addressed the elderly. In the CIDS study, which included patients with ejection fraction < 35%, age ≥ 70 was an indicator of high risk, and patients at highest risk of death benefited the most from ICD therapy. Our data suggest that these patients may benefit from an ICD, unless device implantation is contraindicated based on the life-limiting comorbidities. Accordingly, a recent study of elderly patients, of which 20% had NICD, demonstrated a median survival greater than 4 years among octogenarian ICD recipients. These results indicate the importance of individualized decisions to implant an ICD, which must take into account the overall quality of life and expected life span after implant.

We found several clinical factors to be related with long-term mortality after implantation of an ICD. Both atrial fibrillation and right ventricular pacing were associated with higher risk among patients with non-dilated NICD. The incidence of atrial fibrillation is increased in patients with advanced age and structural heart disease. Adverse prognosis with atrial fibrillation may result from multiple factors, including heart failure, stroke, and drug toxicity. Additionally, atrial fibrillation may increase the risk of ventricular tachyarrhythmias. Left bundle branch block or a QRS width > 120 ms, which are frequently used as surrogate markers of ventricular dys synchrony, was not associated with an increased mortality risk. Electrical or mechanical ventricular dyssynchrony has been shown to be associated with adverse outcome and serves as a pathophysiological basis for CRT. However, in our current study, these surrogate markers did not reliably identify patients with higher risk, irrespective of the underlying cardiac condition. In contrast, the mortality risk of patients who were chronically paced from the right ventricle was increased, although this effect was not statistically significant among patients with DCM. Correspondingly, right ventricular pacing has been quantitatively associated with decreased survival in the DAVID trial. Experiencing appropriate ICD therapies was an indicator of an increased mortality risk, whereas risk was low among patients who received inappropriate ICD therapies only.

The use of anti-arrhythmic drugs, ACE inhibitors, or angiotensin receptor blockers, was associated with increased mortality among patients with non-dilated NICD, whereas beta-blocker use was not. Various effects of medical therapy on outcomes have been reported in ICD recipients. However, in the current study, medical therapy was administered in an individualized manner according to the nature and severity of underlying diseases and was adapted to the clinical needs of the patients throughout the follow-up period. Further analysis of association with mortality risk may, therefore, not be warranted.

Many of the clinical factors that were associated with adverse outcome were highly intercorrelated. The multivariate analysis identified six independent predictors of mortality, i.e. left ventricular ejection fraction, NYHA functional class, ACE inhibitor/angiotensin receptor antagonist and anti-arrhythmic drug use, and renal function. Reduced left ventricular ejection fraction has been recognized as an indicator of adverse prognosis for several years. NYHA functional class, which is subjective and may be influenced by non-cardiac factors, including body weight, overall fitness, and comorbidities, adds independent prognostic information. In the current study, renal insufficiency was
the strongest independent predictor of mortality in the overall group and was the only factor predicting mortality in both subgroups. This finding is in line with the recent studies of mortality among ICD patients with renal insufficiency, which included primarily patients with ischaemic CMP.\textsuperscript{17–19} Impairment of renal function has been associated with increased risk of cardiovascular mortality in various studies. Although, in some of those, associations lost significance after correction for traditional cardiovascular risk factors, Henry et al.\textsuperscript{20} demonstrated in a population-based study of 632 Caucasian individuals aged 50–75 years that mild-to-moderate reduction in renal function is associated with increased cardiovascular mortality without involving common risk factors such as hypertension, diabetes, or hyperhomocysteinaemia. In patients with coronary disease and renal impairment, accelerated atherosclerosis, adverse left ventricular remodelling associated with erythropoietin deficiency and anaemia, and hyperactivation of the renin-angiotensin system may contribute to increased mortality. In patients with NICD, other factors may be more important. Sympathetic overactivity and a higher propensity to cardiac arrhythmias that may be refractory to ICD treatment have been observed in chronic kidney disease, and elevated defibrillation thresholds may be found in these patients.\textsuperscript{21–23} Furthermore, underuse of proven beneficial therapies as well as drug toxicity from therapies used may increase morbidity and mortality.

**Limitations**

This is a retrospective single-centre study that suffers from limitations typically associated with this type of trial design. Data were collected retrospectively from the implantation reports and medical charts and were therefore dependent on the accuracy of clinical documentation. Renal function and medical treatment were assessed at the time point of inclusion of the patient in the study. Serial reassessment throughout the study period, would give more detailed information, was not available. The results of this single-centre study might not be generalizable to other centres with different patient characteristics. However, our hospital not only serves as a tertiary referral centre but also provides primary medical services to the population of Zurich, which may reduce referral bias. It should be kept in mind that NICD is not a homogeneous entity. Outcomes are likely to vary according to underlying disease mechanisms and patient characteristics. The number of patients included in our study did not provide sufficient statistical power to allow for detailed subgroup analysis of patients with non-dilated NICD by underlying cardiac disease. However, the distinction between ischaemic cardiac disease and NICD is frequently used in clinical practice. Therefore, the results of this study may be helpful to the clinician to estimate the benefit of ICD therapy in patients with DCM and in those with other non-dilated NICD.

**Conclusion**

During long-term follow-up of ICD patients with DCM, higher NYHA functional class is associated with adverse outcomes, whereas in patients with non-dilated NICD, reduced left ventricular ejection fraction and anti-arrhythmic drug use predict higher mortality. Renal insufficiency is a strong predictor of mortality among all patients with NICD, irrespective of underlying heart disease. Additional studies are warranted to determine the impact of underlying cardiac disease on prognosis in this clinically important but heterogeneous patient group.

**Conflict of interest:** none declared.

**References**


