Long-term benefit of implantable cardioverter/defibrillator therapy after elective device replacement: results of the INcidence free SUrvival after ICD REplacement (INSURE) trial—a prospective multicentre study

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Received 17 March 2012; revised 9 May 2012; accepted 22 May 2012; online publish-ahead-of-print 6 July 2012

Aims
Prevention of sudden cardiac death by means of the implantable cardioverter/defibrillator (ICD) is considered to be a lifelong therapy. However, it is still unresolved if patients who never experienced an appropriate ICD intervention during generator longevity really need to undergo device replacement.

Methods and results
The INSURE trial was a multicentre prospective observational cohort study that enrolled patients at the time of their first ICD replacement. Patients with and without previous appropriate ICD therapy were enrolled prospectively and were evaluated every 3–6 months after ICD replacement. Primary endpoint of the study was the first occurrence of appropriate ICD therapy after device replacement. Five hundred and ten patients (83% males, mean age 65 ± 10 years, mean ejection fraction 39 ± 16%) were enrolled between 2002 and 2007 in the study after an average lifespan of their first ICD generator of 62 ± 18 months. Three years after elective ICD replacement, the rates of appropriate ICD therapies in patients with (n = 245) and without (n = 265) former appropriate ICD intervention were 48.1 and 21.4% (adjusted hazard ratio 3.08, CI: 2.15–4.39, P < 0.001). Notably, no predictive factors for lower need of ICD therapy could be identified in patients without prior appropriate ICD intervention.

Conclusions
In this study, a significant number of ICD-indicated patients without the need for therapy by their first device received appropriate ICD intervention after generator replacement. There were no predictors for lower need of ICD therapy. Hence, ICD replacement appears still necessary in patients without prior appropriate ICD interventions.

Keywords
ICD • Replacement • Sudden cardiac death • Prevention • Appropriate ICD therapy

Introduction
The implantable cardioverter/defibrillator (ICD) has been proved to be one of the most efficacious therapeutic means for prevention of sudden cardiac death (SCD) due to ventricular tachyarrhythmias.1−7 As a consequence of randomized trials on the efficacy of ICD therapy for primary or secondary prevention of SCD, implantation rates have increased around the globe during the past two decades.8,9
Prevention of SCD through the ICD is generally considered to represent a therapy which is needed for the rest of a patient’s life. However, there is still considerable debate if patients without any appropriate ICD intervention during the lifespan of their index ICD really need further ICD protection. Therefore, the question whether or not to replace an ICD generator at the time of battery depletion is of paramount importance predominantly for the affected patients, but also for health care providers and payers.

The INSURE trial aimed to provide data on the need for ICD generator replacement in a large cohort of unselected ICD patients. Specifically, we addressed the question of how many patients with and without appropriate ICD intervention before battery depletion will utilize their device after generator replacement. In addition, we wanted to see if there are clinical patient characteristics which could help predict this.

Methods

This was a prospective, multicentre, observational study. The study protocol was approved by the International Ethics Committee Freiburg, Germany. All patients provided written informed consent prior to enrolment. Patient data were collected and stored in an anonymized fashion in compliance with applicable German data protection law requirements. The Institute for Clinical Cardiovascular Research (Munich, Germany), associated with the German Cardiovascular Society, managed the data collection and analysis.

Patient population

Study sites were requested to screen eligible patients in a consecutive manner. Patients with an indication for ICD therapy according to the contemporary guidelines were eligible if they met the following inclusion criteria: (i) age older than 18 years; (ii) elective replacement of a first ICD generator due to battery depletion or ICD generator replacement for other reasons at least 3 years after first ICD implantation (e.g. upgrade to dual or triple chamber devices); (iii) known status as to presence or absence of appropriate ICD therapies (shock or ATP) during the lifespan of the first ICD generator; (iv) implantation of a Boston Scientific ICD generator. Patients were excluded if their life expectancy was \( \leq \) 1 year, if the lack of compliance was expected, and if pregnancy could not be excluded.

Study design

At study inclusion, patient characteristics, comorbidities, and indication for ICD therapy were recorded. All ICDs were interrogated prior to replacement and episodes of ICD therapy were carefully assessed at the participating centres and stored on disk for subsequent review by an adjudication committee consisting of three experienced electrophysiologists. The same committee reviewed and adjudicated all arrhythmia episodes which occurred during the follow-up without the knowledge as to the presence or absence of arrhythmia episodes prior to ICD generator replacement in the same patient.

Based on the absence or presence of appropriate device therapy prior to ICD generator replacement, patients were assigned into two groups:

(i) Group A: patients with appropriate ICD interventions prior to ICD generator replacement;
(ii) Group B: patients without appropriate ICD interventions prior to ICD generator replacement.

Programming the new ICD generator was at the discretion of the investigator. From the time of ICD replacement, all patients were followed every 3–6 months (Figure 1). The follow-up was terminated after the first appropriate ICD therapy (ATP and/or shock-confirmed by the adjudication committee) or death of the patient (whatever occurred first). Patients without appropriate ICD therapy detected at regular follow-up intervals continued to be followed for subsequent appropriate ICD-treated VT/VF episodes, death, or subsequent ICD generator replacement. One year after enrolment of the last patient, the study was halted at a common termination point.
Statistical analysis

Baseline characteristics were compared between groups A and B by percentages and Chi-square test for categorical variables and by arithmetic mean, standard deviation, and t-test or, in case of skewed distributions, median, interquartile ranges, and Mann–Whitney U-test for continuous variables. Primary endpoint of the study was time to first occurrence of an appropriate ICD therapy. The primary analysis was a log-rank test of differences between groups A and B with respect to cumulative event rates which were visualized by Kaplan–Meier plots. Further, adjusted hazard ratios were calculated by applying Cox regression analysis to group A vs. group B with covariates coronary artery disease (CAD), NYHA II/III/IV when compared with NYHA I, left ventricular ejection fraction (LVEF), pacemaker rhythm, QRS width 120–149/150–179/180 vs. <120 ms, atrial fibrillation, amiodarone, beta-blocker, sotalol, and diuretics, all determined at study entry. The Cox analysis was repeated in group B to identify potential indicators of low risk. The results were visualized by use of forest plots. In each of the survival analyses, death was treated as censored.

With respect to the safety of the patients, the most important secondary endpoint was mortality, including causes of death. Mortality was analysed analogous to the primary endpoint. Further secondary endpoints were myocardial infarction, stroke, resuscitation, syncope, PTCA, coronary bypass, and valvular interventions. We report group-wise frequencies and results of Chi-square tests.

Statistical analyses were performed using SPSS 19.0. All statistical tests were two-sided. P-values < 0.05 were considered significant.

Results

Patient population

Between 2002 and 2007, a total of 510 patients were enrolled in 29 German study sites at the time of ICD generator replacement. Implantable cardioverter/defibrillator generators were replaced after an average lifespan of 62 ± 18 months. Of these patients, 245 (48%) had experienced at least one appropriate episode of ICD therapy for VT or VF prior to generator replacement (group A). In the remaining 265 patients (52%), the ICD generator had reached the end of its battery life without any appropriately treated arrhythmia episode (group B). After generator replacement, patients were subsequently followed for a mean of 22 ± 16 months.

Table 1  Patient characteristics at baseline (prior first implantable cardioverter/defibrillator replacement)

<table>
<thead>
<tr>
<th></th>
<th>Patients with prior appropriate ICD therapy (n = 245)</th>
<th>Patients without prior appropriate ICD therapy (n = 265)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years] (mean ± SD)</td>
<td>65.2 ± 10.6</td>
<td>63.6 ± 11.3</td>
<td>0.095</td>
</tr>
<tr>
<td>Male gender (n, %)</td>
<td>210 (85.7)</td>
<td>214 (80.8)</td>
<td>0.135</td>
</tr>
<tr>
<td>Underlying heart disease (%)</td>
<td></td>
<td></td>
<td>0.151</td>
</tr>
<tr>
<td>Ischaemic CMP</td>
<td>40.8</td>
<td>33.6</td>
<td></td>
</tr>
<tr>
<td>Non-ischaemic CMP</td>
<td>20.8</td>
<td>18.9</td>
<td></td>
</tr>
<tr>
<td>Valvular CMP</td>
<td>3.7</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>No CMPa</td>
<td>34.7</td>
<td>41.1</td>
<td></td>
</tr>
<tr>
<td>Indication for ICD (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>6.5</td>
<td>18.1</td>
<td></td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>93.5</td>
<td>81.9</td>
<td></td>
</tr>
<tr>
<td>LVEF [%] (mean ± SD)</td>
<td>37.4 ± 16.3</td>
<td>41.1 ± 15.9</td>
<td>0.009</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td>0.018</td>
</tr>
<tr>
<td>I</td>
<td>22.0</td>
<td>27.9</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>55.9</td>
<td>57.7</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>20.8</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>1.2</td>
<td>0.0</td>
<td></td>
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<tr>
<td>Cardiac rhythm (%)</td>
<td></td>
<td></td>
<td>0.016</td>
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<tr>
<td>Sinus rhythm</td>
<td>69.8</td>
<td>80.4</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>14.7</td>
<td>10.9</td>
<td></td>
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<tr>
<td>Paced</td>
<td>15.5</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>QRS duration [ms] (median, interquartile range)</td>
<td>110 (90/130)</td>
<td>110 (94/130)</td>
<td>0.609</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>62.7</td>
<td>70.0</td>
<td>0.084</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>24.3</td>
<td>22.7</td>
<td>0.675</td>
</tr>
<tr>
<td>Renal dysfunction (%)</td>
<td>13.8</td>
<td>11.6</td>
<td>0.477</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>8.1</td>
<td>6.8</td>
<td>0.608</td>
</tr>
</tbody>
</table>

CMP, cardiac myopathy; HD, heart disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
P-values below 0.05 in bold.

*Secondary prevention patients with preserved ejection fraction but with coronary artery disease (with or without previous myocardial infarction), as well as patients with genetic diseases or unknown reasons for VT/VF.
Of 510 patients, 497 (97.5%) had at least one follow-up with ICD storage data available, while 13 (2.5%) dropped out early (12 due to an early change of the follow-up centre and 1 due to withdrawal of his study participation after ICD replacement without specifying a reason). Further, 76 patients (14.9%) stopped their participation later during the course of the trial (mostly due to a change of the follow-up centre) and were censored at that date, altogether resulting in a loss of 10.1% of the scheduled overall follow-up time.

Patient characteristics and cardiac medications are displayed in Tables 1 and 2. Patients in group A had more advanced heart failure (P = 0.018), had more left ventricular dysfunction (mean LVEF 37 vs. 41% in group B, P = 0.009), and presented more often with atrial fibrillation or a paced rhythm (14.7/15.5 vs. 10.9/8.7% in group B, P = 0.016). The vast majority of patients had been initially implanted for secondary prevention of sudden death (94% in group A and 82% in group B, P < 0.001). Patients in group A were more often treated with amiodarone and sotalol (Table 2) due to prior ventricular arrhythmias.

### Primary study endpoint

A total of 158 patients, 107 patients from group A and 51 from group B, had appropriate ICD therapies during the follow-up period. The cumulative rates of appropriate ICD interventions after 1, 2, and 3 years in group A were 32.4, 41.3, and 48.1% and in group B 10.6, 17.6, and 21.4%, respectively, log-rank P < 0.001 (Figure 2). The corresponding Cox regression model yielded an adjusted hazard ratio of 3.08 (95% CI: 2.12–4.32, P < 0.001). In group A, 51% of the episodes were terminated by ATP, while 49% required ICD shock therapy. In one case, external defibrillation was needed due to recurrent ineffective ICD shocks with 31 Joule. In group B, 60% of arrhythmia episodes were terminated by shock and 40% treated by ATP.

Regarding the overall study population, patients with coronary artery disease (HR: 1.79; CI: 1.18–2.71, P = 0.007), advanced NYHA functional classes (HR: 14.65; CI: 3.11–69.03, P = 0.001), and former appropriate ICD intervention (HR: 3.02; CI: 2.12–4.32, P < 0.001) were at significantly higher risk for appropriate ICD therapies (Figure 3A), whereas amiodarone therapy was associated with the lower risk (HR: 0.64; CI: 0.41–1.00, P = 0.049). In group B patients, only advanced NYHA stages were associated with the higher risk for appropriate ICD interventions (Figure 3B). Notably, no predictive factors for lower need of ICD therapy could be identified in group B.

### Secondary endpoints

During the mean study period, 28 patients in group A died (11.4%) compared with 22 in group B (8.3%; log-rank P = 0.051, adjusted 0.049).
hazard ratio 1.23, 95% CI: 0.67 – 2.26, \( P = 0.509 \)). Regarding the overall study population causes of death as reported by investigators were cardiac in origin in 16 patients (3%), non-cardiac in 17 patients (3%), and were unknown in 17 patients (3%) without relevant differences between the groups. Incidences for the other secondary endpoints were (groups A/B in %): myocardial infarction 0.8/0.0, stroke
Discussion

To the best of our knowledge, this is the first prospective study to assess the long-term benefit of ICD therapy after elective ICD generator replacement in patients with and, more importantly, without prior appropriate ICD therapy. This trial shows that $\sim20\%$ of the patients without prior appropriate ICD therapy needed ICD intervention within 3 years after their elective device replacement. Notably, there were no predictors for lower need of ICD therapy.

Van Welsenes et al. reported a cumulative 5-year incidence for appropriate ICD therapy of 37% for primary prevention and 51% for secondary prevention during the lifespan of their first ICD generator. After elective device replacement (mean follow-up 25 ± 21 months), event rates for appropriate therapy of 7% at 1 year and 14% at 3 years were reported for ICD recipients without prior appropriate therapies. These data were based on a single-centre registry of 114 patients with primary prevention. Koller et al. reported in 2008 that patients with mainly secondary prevention and without prior adequate ICD intervention within 6 years after the first ICD implantation had a risk of only 6% for appropriate ICD therapies in the following 2 years. This finding was based on data from a single-centre ICD register of 442 patients with a mean follow-up of 3.6 years. Moreover, only 35 of these patients had follow-up of longer than 6 years. In contrast to these data, our findings demonstrate that the cumulative risk for appropriate ICD therapy is 10.6% after 1 year and 21.4% after 3 years after the first device replacement. The different results may be due to differences in clinical patient characteristics, shorter and perhaps less complete follow-up as well the low number of patients at the end of Koller’s study. In contrast to the data of van Welsenes, the increased incidence of appropriate ICD therapies in our study is most likely due to the patients with secondary prevention.

The extended follow-up of the Multicenter Automatic Defibrillator Implantation Trial II (MADIT) showed for the first time the long-term benefit of ICD therapy in primary prevention patients. In the MADIT II trial, only approximately one-third of ICD-treated patients received appropriate device therapy during the in-trial phase (mean follow-up of 1.5 years), suggesting that a substantial proportion of study patients did not derive benefit from device implantation during the trial. Acquiring post-trial mortality data for all study participants (median follow-up of 7.6 years), a significant reduction in the risk of death at 34% could be shown compared with non-ICD patients. However, complete information of ICD interrogation during long-term follow-up was only available in 109 of 1020 patients, with a cumulative probability of first appropriate ICD therapy of 68%. On the contrary, our reported incidence of appropriate ICD therapy during the long-term follow-up after elective ICD replacement was based on prospectively evaluated and complete data from a large number of ICD recipients.

As expected, the occurrence of appropriate ICD therapy after ICD generator replacement was considerably higher for patients with previous ICD interventions. Notably, in the presence of class III antiarrhythmics, this group experienced more often VT/VF episodes with subsequent appropriate ICD interventions. Significant disparities in the patients’ cardiac history and medication suggest that patients with prior appropriate ICD therapy presented sicker at time of enrolment which potentially has led to worse outcome of this group during the course of the follow-up. For the overall patient population, amiodarone therapy was associated with lower risk for appropriate ICD intervention, suggesting that some patients with less heart failure might derive therapeutic benefit.

The overall mortality rate of 9.8% in our study is lower than that reported in previous ICD studies, but was not substantially reduced in the patients without prior ICD therapy. Furthermore, regarding the other secondary endpoints in our study as causes of death, no significant difference between the both groups could be observed despite the difference in appropriate ICD shocks. These data are in contrast to some primary prevention trials, which suggested that ICD shock therapy itself is linked with poor clinical outcome due to, for example, direct myocardial injury. However, our study population consisted of mainly secondary prevention ICD patients pre-treated with heart failure drugs in a long-term follow-up with only a moderately limited ejection fraction at study inclusion (mean LVEF 37% in group A vs. 41% in group B) which might explain the better outcome of these patients. Moreover, patients included in this study have survived the first 6 years with ICD, which has perhaps caused pre-selection of some less critical cases.

Limitations

Our trial started enrolment of patients receiving their second ICD generator in 2002, so the majority of the evaluated population had been initially implanted for secondary prevention in the 1990s. Therefore, our data show the long-term outcome of patients with mainly secondary prevention after receiving their second device. The results in patients with a primary prevention cannot be extrapolated from the present results and need further investigation.

Patients were grouped by treatment indication, not by randomization (indicating that both groups are not homogeneous), unknown bias (e.g. confounding by indication/selection bias) cannot be ruled out.

Significant disparities in the patients’ cardiac history and medication suggest that patients in group A presented sicker at time of enrolment, which potentially has led to worse outcome of this group during the course of the follow-up. Nevertheless the worse clinical status at inclusion may also have been associated with the more severe initial status at first ICD implantation, which could not be explicitly assessed in this trial.

Since subgroup B of patients without appropriate therapy during the first ICD phase was only about half of the total group, the power may have been too low to identify further predictors for lower need of ICD.

It should be taken into consideration that there is no one to one relation between appropriate ICD-therapy and potential death, so...
that the real life saving potential of replacing an ICD in group B might be smaller than the numbers suggest.

In this trial the role of VT ablation as treatment option for patients with ventricular tachycardia was not evaluated.

**Conclusion**

In this study patients without need for therapy by their first ICD—mainly with a secondary prevention indication—were evaluated. A significant portion of these patients received appropriate ICD intervention within 3 years after generator replacement. Notably, there were no predictors for lower occurrence of ventricular tachyarrhythmias. Hence, ICD replacement appears still necessary in patients without prior ICD interventions.

**Acknowledgements**


**Funding**

The support by the IKKF team members Birgit Hirthhammer, Petra Kremer and Thomas Fetsch, MD, was much appreciated, as well as the cooperation within statistical analyses with Klaus Balzer, co-worker of Professor Wegscheider. Scientific and logistic support was provided by Klaus Contzen, PhD, Andreas Succiu, PhD, Sven Treusch, MD, and Andrea Ungefehr (all Boston Scientific).

**Conflict of interest:** none declared.

**References**


Optical coherence tomography (OCT) is a novel high-resolution intravascular imaging technique allowing characterization of coronary artery plaques and evaluation of stent strut coverage. As a new application, OCT can be also used in allograft vasculopathy as demonstrated by the following images.

Comparison of OCT and coronary angiography in a cardiac transplant recipient vs. a patient with coronary artery disease: OCT image of the left anterior descending coronary artery in a 72-year-old patient 14 years after heart transplantation and current immunosuppressive treatment with tacrolimus, azathioprine, and prednisone shows a well-defined signal-rich layer indicating concentric intimal hyperproliferation, which is pathognomonic for allograft vasculopathy (Panel A; see Supplementary material online, Video S1).

Optical coherence tomography image in a 70-year-old patient with coronary artery disease demonstrates a lipid-rich plaque with a large, homogeneous, poorly delineated and signal-poor region with alternating signal-rich spots reflecting single calcifications (Panel B). A signal-rich band mirrors a thin fibrous cap extending from 6 to 9 o’clock. Moreover, non-covered stent struts are well visualized (Panel B; see Supplementary material online, Video S2).

Sole coronary angiography does not allow assessing intraluminal tissue morphology such as allograft vasculopathy (Panel C) and plaque characterization (Panel D) which both may have important prognostic implication on patient outcome.

Supplementary material is available at European Heart Journal online.