Brief Rapid Communications

Time Dependence of Mortality Risk and Defibrillator Benefit After Myocardial Infarction

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Background—Prophylactic implantable defibrillators (ICDs) improve survival in patients with impaired ventricular function after myocardial infarction (MI), but it is uncertain whether mortality risk and survival benefit depend on the elapsed time from MI.

Methods and Results—The Multicenter Automatic Defibrillator Implantation Trial II examined the impact of ICDs on survival in post-MI patients with ejection fractions ≤30%. In 1159 patients, mean time from most recent MI to enrollment was 81 ± 78 months. Patients were randomized to an ICD (n = 699) or conventional care (n = 460) in a 3:2 ratio. Mortality rates (deaths per 100 person-years of follow-up) in both treatment groups were analyzed by time from MI divided into quartiles (<18, 18 to 59, 60 to 119, and ≥120 months). In conventional care patients, these rates increased as time from MI increased (7.8%, 8.4%, 11.6%, 14.0%; P = 0.03). Mortality rates in ICD patients were consistently lower in each quartile and showed minimal increase over time (7.2%, 4.9%, 8.2%, 9.0%; P = 0.19). Covariate-adjusted hazard ratios for risk of death associated with ICD therapy were 0.97 (95% CI, 0.51 to 1.81; P = 0.92) for recent MI (<18 months) and 0.55 (95% CI, 0.39 to 0.78; P = 0.001) for remote MI (≥18 months).

Conclusions—Mortality risk in patients with ejection fractions ≤30% increases as a function of time from MI. The survival benefit associated with ICDs appears to be greater for remote MI and remains substantial for up to ≥15 years after MI.

Key Words: defibrillation ▪ myocardial infarction ▪ survival

Arrhythmia-related sudden death remains a major cause of mortality after myocardial infarction (MI). Long-term follow-up of MI survivors conducted in the 1970s and 1980s indicated that the greatest risk of sudden death was in the initial 6 to 12 months after infarction, particularly in high-risk subgroups such as those with impaired ventricular function.1–4 However, therapeutic innovations of the past decade, including widespread use of coronary reperfusion and revascularization, β-adrenoceptor blockade, and angiotensin-converting enzyme inhibition, have improved survival in the initial phases of MI associated with diminished ventricular function.5–8 These efforts have contributed to a growing cohort of patients with chronic left ventricular dysfunction at risk for late death as a result of both arrhythmias and heart failure. Optimal timing of prophylactic defibrillator implantation in these patients remains unclear.

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The Multicenter Automatic Defibrillator Implantation Trial (MADIT II) examined survival in postinfarction patients with a left ventricular ejection fraction (LVEF) ≤30% who were enrolled between 1997 and 2001, providing an opportunity to reexamine the epidemiology of postinfarction sudden death in a contemporary population.9 The purpose of this study was to analyze the time dependence of mortality risk after MI in the MADIT II cohort and to evaluate whether long-term implantable defibrillator (ICD) survival benefit diminished as a function of elapsed time from infarction to device implantation.

Methods

The design and results of MADIT II have been reported elsewhere.9 Briefly, 1232 patients with documented prior MI and an LVEF ≤30% were randomized to receive a prophylactic ICD or conventional medical therapy in a 3:2 ratio. Screened patients were excluded from enrollment if they had class IV congestive heart failure, coronary revascularization within the previous 3 months, elapsed interval from most recent MI of <1 month, or advanced medical comorbidity. After a mean follow-up of 20 months, the study was terminated by the Data Safety and Monitoring Board. Unadjusted mortality was 19.8% in the conventional therapy group and 14.2% in the ICD group. The overall hazard ratio of 0.69 (95% CI, 0.51 to 0.93) reflected a 31% reduction in the risk of death associated with ICD therapy.

Time from most recent MI was unavailable in 73 patients who did not differ from the remaining population in any baseline demographic or clinical variables. The remaining 1159 patients were divided into quartiles based on elapsed time from infarction to device implantation.

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recruitment.10 Bias toward higher-risk patients associated with in-hospital enrollment took place in an outpatient setting, minimizing potential

0.03 for group to 14.0 in the most remote MI group (H11005 MADIT II from 7.8 (per 100 person-years) in the recent MI examination by dividing times from most recent MI to enrollment into approximate quartiles (<18, 18 to 59, 60 to 119, ≥120 months). To adjust for differences in follow-up time, mortality was converted to number of deaths per 100 person-years of follow-up. Mortality trends across quartiles were evaluated by weighted linear regression. The groups were compared with regard to potential differences in baseline variables that could affect observed differences in mortality. Significant variables affecting outcome were incorporated into a Cox proportional-hazards regression model, stratified by enrollment center, to determine covariate-adjusted hazard ratios for ICD survival benefit in each time-related quartile. Survival curves were constructed by the Kaplan-Meier method. All probability values were 2 sided, and a value of \( P=0.05 \) was considered significant.

Results

Mortality rates in conventionally treated patients increased as a function of time from most recent MI to enrollment in MADIT II from 7.8 (per 100 person-years) in the recent MI group to 14.0 in the most remote MI group (\( P=0.03 \) for mortality trend across quartiles; Figure 1). In contrast, mortality in ICD-treated patients was consistently lower in each quartile and demonstrated minimal time-dependent changes in mortality (from 7.2 to 9.0, \( P=0.19 \)). As a result, there appeared to be a trend toward increasing survival benefit associated with ICD therapy as time from MI increased.

Hazard ratios for the effect of ICDs on survival in each quartile were calculated from Cox proportional-hazard models adjusted for differences in baseline characteristics potentially influencing mortality (Table 1). The ICD appeared to provide the least survival benefit in patients with recent MI (<18 months; hazard ratio, 0.98) but provided substantial and similar reductions in the hazard ratios for the 3 groups with more remote MI (≥18 months). For the final analysis, these groups were combined.

![Figure 1.](image)

**Figure 1.** Mortality rates (per 100 person-years of follow-up) in conventionally (CONV) treated patients (black bars) and ICD patients grouped by time from MI in quartiles (Q).

Patients with recent MI differed significantly from those with remote MI with regard to several baseline variables (Table 2). Patients with recent MI were younger, had better ventricular function, were less likely to have a wide QRS, and were more likely to have received \( \beta \)-blockers before study entry. After adjustment for these differences, the trend toward increased ICD benefit with remote MI (hazard ratio, 0.55; 95% CI, 0.39 to 0.78; \( P=0.001 \)) compared with recent MI (hazard ratio, 0.97; 95% CI, 0.51 to 1.81; \( P=0.92 \)) persisted (Figure 2), although the difference between the 2 hazard ratios did not reach statistical significance (\( P=0.27 \)). Similar findings were obtained when time from MI to study enrollment was dichotomized at 6 months.

**Discussion**

The major new finding of the present study was that in contrast to early clinical reports, mortality risk in the MADIT II cohort did not diminish as a function of time from MI; instead, it actually increased. Correspondingly, in this population with impaired ventricular function, reduction in mortality with the ICD remained substantial for up to ≥15 years after MI. A trend toward increasing device benefit with remote MI was found but did not reach statistical significance.

**Table 1. Effect of the ICD by Elapsed Time From MI**

<table>
<thead>
<tr>
<th>MI Time, mo</th>
<th>HR</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>0.98</td>
<td>0.52–1.84</td>
<td>0.95</td>
</tr>
<tr>
<td>18–59</td>
<td>0.52</td>
<td>0.26–1.05</td>
<td>0.07</td>
</tr>
<tr>
<td>60–119</td>
<td>0.50</td>
<td>0.28–0.91</td>
<td>0.02</td>
</tr>
<tr>
<td>≥120</td>
<td>0.62</td>
<td>0.36–1.08</td>
<td>0.09</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio for ICD vs conventional therapy.

**Table 2. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Recent MI ((&lt;18) mo)</th>
<th>Remote MI (≥18 mo)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 y (n=300), %</td>
<td>47</td>
<td>55</td>
<td>0.01</td>
</tr>
<tr>
<td>Female gender</td>
<td>18</td>
<td>14</td>
<td>0.10</td>
</tr>
<tr>
<td>LVEF &lt;25%</td>
<td>41</td>
<td>49</td>
<td>0.02</td>
</tr>
<tr>
<td>CHF (FC II–IV)</td>
<td>65</td>
<td>62</td>
<td>0.43</td>
</tr>
<tr>
<td>QRS width &gt;0.12</td>
<td>25</td>
<td>40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7</td>
<td>9</td>
<td>0.22</td>
</tr>
<tr>
<td>Diabetes</td>
<td>34</td>
<td>35</td>
<td>0.84</td>
</tr>
<tr>
<td>Hypertension</td>
<td>56</td>
<td>51</td>
<td>0.14</td>
</tr>
<tr>
<td>BUN &gt;25</td>
<td>29</td>
<td>30</td>
<td>0.71</td>
</tr>
<tr>
<td>( \beta )-Blocker</td>
<td>72</td>
<td>59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>79</td>
<td>76</td>
<td>0.31</td>
</tr>
<tr>
<td>Statin</td>
<td>62</td>
<td>65</td>
<td>0.32</td>
</tr>
<tr>
<td>ICD therapy</td>
<td>58</td>
<td>61</td>
<td>0.42</td>
</tr>
<tr>
<td>Nonsurgical revascularization</td>
<td>51</td>
<td>44</td>
<td>0.03</td>
</tr>
<tr>
<td>Coronary bypass surgery</td>
<td>46</td>
<td>63</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure; FC, functional class; BUN, blood urea nitrogen; and ACE, angiotensin-converting enzyme.
The finding of persistent and substantial arrhythmia-related and all-cause mortality risk late after MI in patients with reduced LVEF is consistent with the results of other recently published trials. In the European Myocardial Infarction Amiodarone Trial, which examined survival in post-MI patients with LVEF \( \leq 40\% \), the slopes of both total and arrhythmic mortality curves were linear and increasing between 2 and 24 months after enrollment.\textsuperscript{11} Similar trends for total mortality and sudden death were reported in post-MI patients (mean LVEF, 33\%) enrolled in the placebo arm of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study.\textsuperscript{12} Data with respect to the time dependence of mortality risk \( > 2 \) years after MI in contemporary populations are limited.

The observed trend toward lesser ICD survival benefit in patients with recent MI may be partially explained by a somewhat lower prevalence of high-risk markers (older age, low LVEF, intraventricular conduction defects) in this subgroup compared with those enrolled \( \geq 18 \) months after MI. However, it is possible that the survival benefit of ICDs implanted early after MI would be considerably greater if follow-up were extended longer than the mean of 20 months at termination of this study, as the impact of progressive coronary disease and adverse ventricular remodeling becomes more apparent. This hypothesis is consistent with the overall study finding of greater mortality risk with increasing time from MI. Whether it is appropriate to defer implantation of an ICD in patients with recent MI and LVEF \( \leq 30 \) cannot be addressed definitively by this study and merits additional investigation.

Issues with regard to ICD implantation in the very early phase of MI are complex. Recent data suggest a brief period of accelerated risk for both total and arrhythmia-related death in the initial 1 to 2 months after MI before stabilization at a somewhat lower and constant risk over the next several years.\textsuperscript{7,11,12} The potential for substantial remodeling and improvement in ejection fraction in the initial weeks after MI renders decisions based on the first ejection fraction obtained in the early hospital phase problematic.\textsuperscript{5}

The findings of the present study have important clinical implications. Despite comprehensive therapy with revascularization, blockade of the renin-angiotensin system, and \( \beta \)-adrenoreceptor antagonism, the presence of extensive myocardial scar after infarction, as reflected by an LVEF \( \leq 30\% \), remains a consistent marker for lethal ventricular arrhythmias, with no clear lessening (and potentially increasing) of risk over time. Concerns have been raised about the role of ICD therapy in apparently stable patients with severe left ventricular dysfunction several years after MI.\textsuperscript{13} The present study suggests that the survival benefit of prophylactic ICDs does not diminish with time and that such patients should be considered for ICD therapy.

Acknowledgments

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References


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