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.

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Key Words: defibrillation • myocardial infarction • survival

A rrhythmia-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. 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. 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. 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. 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
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 β-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 2. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Recent MI (&lt;18 mo) (n=300), %</th>
<th>Remote MI (≥18 mo) (n=859), %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 y</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>β-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.
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. 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.

The findings of the present study have important clinical implications. Despite comprehensive therapy with revascularization, blockade of the renin-angiotensin system, and β-adrenoceptor antagonism, the presence of extensive myocardial scar after infarction, as reflected by an LVEF ≤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. 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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