Mechanisms Underlying the Lack of Effect of Implantable Cardioverter-Defibrillator Therapy on Mortality in High-Risk Patients With Recent Myocardial Infarction Insights from the Defibrillation in Acute Myocardial Infarction Trial (DINAMIT)

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Background—Although implantable cardioverter-defibrillators (ICDs) lower mortality in stable patients with low ejection fraction late after myocardial infarction, randomized trials of ICD versus control subjects implanted early after myocardial infarction do not show mortality benefit. Our objective was to investigate possible mechanisms underlying the lack of mortality benefit in the Defibrillation in Acute Myocardial Infarction Trial (DINAMIT).

Methods and Results—This is a secondary analysis of the prospective randomized clinical trial. Outpatients with recent (6 to 40 days) acute myocardial infarction, left ventricular dysfunction (ejection fraction <35%), and low heart rate variability were randomized to ICD (n=311) or to standard medical therapy (n=342). In a competing-risks analysis, those factors that increased the risk of arrhythmic death also increased the risk of nonarrhythmic deaths. After adjustment for these factors, receiving an ICD was associated with a decreased risk of arrhythmic death (hazard ratio, 0.33; 95% confidence interval, 0.15 to 0.71) but an increase in nonarrhythmic death (hazard ratio, 1.70; 95% confidence interval, 1.00 to 2.80). In an adjusted time-dependent analysis, patients receiving an ICD and having appropriate ICD therapy had a 15.1% yearly hazard of mortality compared with 5.2% in ICD patients with no appropriate therapy (P<0.001). The reduction in sudden death in ICD patients was completely offset by increased nonarrhythmic deaths, which were greatest in patients receiving ICD shock therapy (hazard ratio, 6.0; 95% confidence interval, 2.8 to 12.7).

Conclusions—In patients receiving ICDs early after myocardial infarction, those factors that are associated with arrhythmia requiring ICD therapy are also associated with a high risk of nonsudden death, negating the benefit of ICDs in this setting. (Circulation. 2010;122:2645-2652.)

Key Words: death, sudden ■ defibrillation ■ implantable cardioverter-defibrillators ■ myocardial infarction
seen in the recent Immediate Risk Stratification Improves Survival (IRIS) study of ICD implantation in high risk past MI survivors.9

Editorial see p 2638 Clinical Perspective on p 2652

The objective of this substudy of DINAMIT was to assess in detail the risk factors for arrhythmic and nonarrhythmic death in patients enrolled in the trial in an attempt to explain the lack of an effect of ICD therapy on all-cause mortality. Our hypothesis was that ICD therapy did not reduce death because the patients destined to receive ICD therapy were also at high baseline risk of nonsudden death and because arrhythmic events treated by an ICD in patients with recent MI are often associated with intercurrent cardiac events such as heart failure or ischemic events, resulting in poor prognosis after ICD therapy.

Methods

Patient Population

The methods and the main results of the DINAMIT study have been described in detail.8 In brief, patients 18 to 80 years of age were eligible for enrollment if they had had an MI 6 to 40 days before randomization, a left ventricular ejection fraction (LVEF) of ≤35%, and evidence of impaired cardiac autonomic function (SD of N-N intervals ≤70 ms or average heart rate >80 bpm on a 24-hour Holter monitor performed ≥3 days after the index MI).

Patients were excluded if they had New York Heart Association class IV heart failure symptoms at the time of randomization, coronary bypass grafting, 3-vessel percutaneous coronary intervention immediately after the acute MI (or planned at the time of randomization), or prior ICD therapy.

Three hundred thirty-two patients were randomized to the ICD group and 342 to a control group at an average of 18 days after MI. Follow-up ranged from 15 months to 4 years (and averaged 30±13 months). Because this analysis is primarily mechanistic, patients who were randomized to receive an ICD but were not implanted within 3 months were excluded. Among those randomized to ICD, 20 never received an implant, and 1 patient received the implant at 1293 days. Control patients (assigned to no ICD) who went on to receive an ICD were censored at the date of implantation.

Substudy Outcomes

The primary outcome in DINAMIT was death resulting from any cause. Deaths resulting from cardiac arrhythmia and cardiac causes were classified by a blinded (with respect to therapy assignment) central validation committee using criteria developed by Hinkle and Thaler and validated in the Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II) trial.11 Defibrillator therapies were assessed at regular follow-up visits in each center by interrogation of the ICD data logs. All ICD therapies were adjudicated by 1 of 3 central validation committees using criteria developed by Hinkle and Thaler and validated in the MADIT-II trial.11

For the purpose of this analysis, patients were classified into 3 groups: patients not receiving an ICD (control), patients randomized to and receiving an ICD and not receiving appropriate ICD therapy at any time (no appropriate ICD therapy), and patients randomized to and receiving an ICD and receiving appropriate ICD therapy (antiarrhythmic pacing [ATP], high-energy shocks, or both; appropriate ICD therapy).

Statistical Analysis

The relationships between clinical factors at baseline and outcomes and between postrandomization events and outcomes were analyzed in 2 sequential steps. The relationship between baseline clinical factors and presumed arrhythmic deaths and nonarrhythmic deaths was investigated with the use of “competing-risks” proportional hazards analysis and displayed as cumulative incidence over time (otherwise known as actual probability).12,13

As a second step, outcomes were analyzed with a time-dependent analysis, which incorporates postrandomization events (appropriate ICD therapy in this case) into the model and seeks to assess whether such events alter subsequent risk of death, controlling for those baseline factors identified to alter risk in the first step.

Competing-Risks Analysis

Death resulting from an arrhythmia excludes the possibility of death resulting from another cause. This results in competing risks if interest is on cause-specific mortality. Although it is possible that the ICD reduces the risk of arrhythmic death and thus allows “more opportunity” for patients to be at risk of nonsudden death (the conversion hypothesis),14 it is also possible that patients with an ICD who are saved from arrhythmic death (and thus have longer time period at risk for nonarrhythmic death) have clinical characteristics different from patients having nonarrhythmic deaths in the absence of an ICD. Proportional hazards models can be extended to accommodate this competing-risk framework.15 The analysis adjusted for treatment effect by taking into account potentially differential effects of the risk factors for the different causes of death. The analysis uses all patients but excludes the randomized treatment allocation from the model. A backward elimination variable selection method was bootstrapped to identify those variables that were consistently identified as important predictors. Baseline variables considered for the model are given in Table 1. A final multivariable competing-risks model was fit, incorporating the variables identified as potentially important and treatment allocation.

Time-Dependent Analysis

As a subsequent step, the contribution of defibrillator therapy (any device therapy, appropriate therapy, and shock therapy) to mortality was analyzed with a time-dependent Cox proportional hazards model after adjustment for those baseline prognostic factors identified in the competing-risks model. In the time-dependent analysis, the outcome is considered to belong to the no therapy group until one of the therapy events occurred, after which the outcome is assigned to the therapy group.16 Cumulative probability of mortality after the first appropriate therapy for ventricular tachycardia (VT) and VF was calculated, as well as mortality in patients not having any appropriate therapy during follow-up. To illustrate the time-dependent effect of defibrillator therapy, the final Cox model was used to estimate survival curves for hypothetical low-risk (having none of the risk factors associated with mortality) and high-risk (having all the risk factors associated with mortality) patients. Survival curves were generated from the Cox model supposing that a therapy was delivered at 30 days, 6 months, 1 year, or never.

Results

Patient Characteristics

There were 674 patients in the DINAMIT study; 332 were randomized to an ICD. Among the 21 patients excluded because they did not receive an ICD within 90 days, 8 died, including 2 patients with arrhythmic deaths. Among 342 patients randomized to no ICD, 17 received an ICD at some time during follow-up and were censored at that time. Four of these patients died subsequently, all of nonarrhythmic causes. Of the ICD patients, 18% (n=59) received appropriate ICD therapy.
All patients received a single-chamber ICD. Approximately 99% of the patients were programmed according to protocol before the index infarct, more likely to have nonsustained VT on Holter, % 15 34 14

Baseline LVEF, % (% patients)*

29 (5) 28 (6) 28 (5)

Threshold Testing

Approximately 2-fold increase in all-cause mortality compared with either the control or the
Table 3. Mortality in the 59 Patients With Implantable Cardioverter-Defibrillator Therapy, With and Without Intercurrent Events*

<table>
<thead>
<tr>
<th>Event before ICD Rx (n=18)</th>
<th>Event occurrence</th>
<th>Mortality (50.0%)</th>
<th>Event after ICD Rx (n=11)</th>
<th>Event occurrence</th>
<th>Mortality (45.5%)</th>
<th>Event with ICD Rx† (n=3)</th>
<th>Event occurrence</th>
<th>Mortality (45.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>345±334 d before Rx</td>
<td>230±262 d after Rx</td>
<td></td>
<td>272±297 d after Rx</td>
<td>285±193 d after Rx</td>
<td></td>
<td>0±0 d before/after Rx</td>
<td>62±88 d after Rx</td>
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<td>Mortality (50.0%)</td>
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<td>Mortality (45.5%)</td>
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</tbody>
</table>

Mortality in patients with intercurrent events (n=32)

- Event before ICD Rx (n=18): 345±334 d before Rx
- Event occurrence: 230±262 d after Rx
- Mortality (50.0%)

- Event after ICD Rx (n=11): 272±297 d after Rx
- Event occurrence: 285±193 d after Rx
- Mortality (45.5%)

- Event with ICD Rx† (n=3): 0±0 d before/after Rx
- Event occurrence: 62±88 d after Rx
- Mortality (45.5%)

Mortality in patients with no intercurrent events (n=27)

- Event occurrence: 204±137 d after Rx
- Mortality (18.5%)

ICD indicates implantable cardioverter-defibrillator; Rx, therapy. 
*Events include myocardial infarction, unstable angina, and heart failure. 
†Event with ICD Rx is an event that occurs on the same day as ICD therapy.

Table 4. Death

<table>
<thead>
<tr>
<th>ICD Group* (n=311)</th>
<th>Control Group (n=342)</th>
<th>Appropriate ICD Therapy (n=59)</th>
<th>No Appropriate ICD Therapy (n=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths, n (%)</td>
<td>54 (16)†</td>
<td>21 (36)</td>
<td>33 (13)</td>
</tr>
<tr>
<td>Crude hazard of mortality, (%‡)</td>
<td>6.7</td>
<td>15.1</td>
<td>5.2</td>
</tr>
<tr>
<td>Type of deaths, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudden, presumed arrhythmic</td>
<td>29 (54)</td>
<td>5 (24)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Cardiac, nonarrhythmic</td>
<td>17 (31)</td>
<td>14 (67)</td>
<td>16 (48)</td>
</tr>
<tr>
<td>Noncardiac</td>
<td>8 (15)</td>
<td>2 (9)</td>
<td>12 (36)</td>
</tr>
</tbody>
</table>

ICD indicates implantable cardioverter-defibrillator. 
*After adjustment for the other covariates included in the model, there was a time-dependent effect of appropriate therapy on mortality (P=0.000005). 
†On-treatment analysis (ie, includes only patients with no ICD). 
‡Crude hazard of mortality is the number of events per patient-year of follow-up expressed as a percentage.

Figure 1 illustrates outcomes in the 3 groups of patients: those who were assigned to no ICD therapy (Figure 1A), those who received an ICD but received no appropriate therapy (Figure 1B), and those who received an ICD and appropriate ICD therapy (Figure 1C). In patients receiving an ICD, the cumulative incidence of arrhythmic mortality was low, whereas nonarrhythmic mortality was high in ICD recipients receiving appropriate therapy.

Figure 2 illustrates outcomes after the first appropriate therapy (ie, time 0 is the day of the first appropriate therapy, whenever it occurs). All-cause mortality is high in the period after the first appropriate therapy, with an ≈30% mortality at
1 year and 40% mortality at 2 years after appropriate therapy administered for VT or VF. Outcomes after therapy for VF appear worse than after therapy for VT.

**Competing-Risk Analysis**

All baseline clinical factors associated with increased risk of death from any cause except for diabetes mellitus had a similar effect (increase in risk) for both presumed arrhythmic death and nonarrhythmic death. The risk associated with these factors is thus considered for all-cause mortality.

Factors associated with significant risk from any cause (both arrhythmic and nonarrhythmic) included age >60 years (HR, 1.7; 95% CI, 1.0 to 2.9), QRS duration ≥120 ms on the baseline ECG (HR, 1.5; 95% CI, 1.0 to 2.5), nonsustained VT on the baseline Holter monitor (HR, 1.9; 95% CI, 1.2 to 3.0), treatment for hypertension (HR, 1.9; 95% CI, 1.2 to 2.9), and MI preceding the index MI (HR, 1.7; 95% CI, 1.1 to 2.5). Higher LVEF (LVEF, 30% to 35% versus 25%; HR, 0.42; 95% CI, 0.24 to 0.75) and β-blocker therapy (HR, 0.6; 95% CI, 0.4 to 1.0) were associated with a lower risk of death. Treated diabetes mellitus was associated with an increase in risk of arrhythmic death (HR, 2.6; 95% CI, 1.3 to 5.2) but not nonarrhythmic death (HR, 1.1; 95% CI, 0.7 to 1.8). After adjustment for these factors, assignment to an ICD was associated with a decreased risk of arrhythmic death (HR, 1.70; 95% CI, 1.00 to 2.80).

**Time-Dependent Analysis of the Effect of ICD Therapy on Subsequent Outcome**

Table 5 illustrates the adjusted HRs (adjusted for baseline risk and time from the therapy to death) for mortality associated with receiving ICD therapy (shock and/or ATP versus no ICD therapy). Appropriate shocks alone, any appropriate therapy, and any shock therapy were all associated with an increase in risk of ≥5-fold for mortality from both all-cause and nonarrhythmic death.

**Antiarrhythmic Drugs**

Of the 59 patients who received appropriate ICD therapy, 23 were placed on an antiarrhythmic (primarily amiodarone), and 11 of these 23 died. Among the 252 patients who received an ICD and had no appropriate therapy, 27 received an antiarrhythmic drug, and 6 of them died. Among the 342 patients with no ICD, 75 patients received an antiarrhythmic drug, and 14 of them died.

**Discussion**

Main Study Findings

The results of this substudy of the DINAMIT trial show that patients expected to be at high risk of sudden death after an acute MI who receive an ICD by random assignment and

**Figure 2.** Cumulative probability of all-cause death after the first appropriate therapy (day 0) according to type of arrhythmia treated by the implantable cardioverter-defibrillator (ICD). VF indicates ventricular fibrillation; VT, ventricular tachycardia.
subsequently receive appropriate ICD therapy have a high risk of death in the 6 months to 1 year after such appropriate therapy. Most of these deaths are cardiac nonarrhythmic in nature, presumably resulting from heart failure, recurrent ischemia, or both. Given the relatively small proportion of patients with an ICD who receive appropriate therapy (19% of ICD recipients after a follow-up of 14 months), this high mortality (40% at 2 years by the Kaplan-Meier method) completely offsets the observed sudden death reduction in the ICD group as a whole. The competing-risks analysis shows that even after adjustment for high-risk clinical features, patients with an ICD are at lower risk of arrhythmic but are at higher risk of nonarrhythmic death than patients without an ICD. Second, the time-dependent proportional hazards analysis shows that after adjustment for baseline clinical differences, patients who receive appropriate ICD therapy have a greater risk of death after therapy than they did before the therapy. In other words, although the device probably saved their lives at the time of therapy, it simply postponed their deaths for a short period of time.14

Both the competing-risks model and the time-dependent analysis suggest that defibrillators do not reduce all-cause mortality early after MI because patients “saved” by their defibrillator have a relatively high burden of ischemic and heart failure risk, both at baseline and during follow-up, and have a high likelihood of dying in the weeks to months after such effective ICD therapy.

For patients implanted with an ICD soon after MI, these observations suggest a fundamental limitation of the treatment paradigm: The patients at highest risk of receiving appropriate therapy (who might most “need” the ICD) are the ones at highest risk of dying of nonarrhythmic causes soon after the therapy; those at lowest risk of nonarrhythmic death (in whom the device can “do the most good”) are the ones at much lower risk of ever receiving appropriate therapy in the first instance. Figure 3 illustrates this conundrum: “Lower-risk” patients have a low likelihood of receiving ICD shocks, and their mortality is low whether they receive ICD shocks or not, and higher-risk patients have a greater chance of receiving ICD shocks, but their subsequent mortality rate is very high, offsetting the potential benefit from the ICD therapy.

It also merits emphasis that 38% of the events treated by the ICD were VF, a proportion that is higher than in prior trials of ICDs for primary prevention of sudden death. Having VF, in contrast to VT alone, may be a further risk marker for a poor outcome, particularly since it always requires a shock for successful treatment.

ICD Studies in Coronary Patients

Prior studies of the ICD in post-MI patients have randomized patients late after MI.3,4 In a substudy of the MADIT II study, the mortality benefit of the ICD after MI seemed to be confined to the subgroup with a >18-month window between the index MI and ICD implantation.17

The Coronary Artery Bypass Graft Patch study randomized patients immediately after bypass graft surgery. A Cox regression model revealed a significant interaction between treatment group and mechanism of cardiac death (P=0.03).
For arrhythmic deaths, the HR (ICD versus control) was 0.55 (95% CI, 0.3 to 1.0). However, for nonarrhythmic cardiac deaths, the HR was 1.2 (95% CI, 0.8, 1.8). As a consequence, the overall mortality was very similar in patients randomized to ICD and no ICD.16

Moss et al,19 in their subanalysis of the MADIT-II study, showed an ~3-fold increased risk of death in patients with appropriate ICD therapy compared with those with no therapy and a 90% increase in the risk of a first HF hospitalization after appropriate ICD shocks.20 In the Sudden Cardiac Death in Heart Failure (SCD-HeFT) study, Poole et al,16 using a time-dependent analysis similar to that in the present study, showed that appropriate shock (versus no appropriate shock) was associated with an HR for all-cause death of 5.7 (95% CI, 4.0 to 8.1; P<0.001). These observations suggest that increased mortality after ICD therapy may not entirely explain the lack of ICD benefit in the DINAMIT study because both the MADIT and SCD-HeFT studies were able to show a reduction in mortality with ICD treatment.

In the recent IRIS study,17 patients within 5 to 31 days of a MI were enrolled if they had both an LVEF ≤40% and heart rate ≥90 bpm or nonsustained VT at ≥150 bpm during Holter monitoring. Randomization to therapy with an ICD (or no ICD) on top of optimal medical therapy had no significant overall impact on survival at 12, 24, or 36 months. Similar to the DINAMIT study, assignment to an ICD was associated with a significant reduction in sudden death (P=0.049) and a significant increase in nonsudden death (P=0.001) compared with the optimal medical therapy only group.

Cause-Specific Mortality After Appropriate ICD Therapy

In patients receiving appropriate device therapy in DINAMIT, several baseline clinical features were associated with a high risk of nonarrhythmic death. In these patients (compared with the no ICD therapy group and the control group), there was a higher incidence of an MI preceding the index infarct, heart failure before randomization, and absence of percutaneous coronary intervention with the index infarct. The same baseline factors that were associated with sudden death (except for diabetes mellitus) were also associated with an increased risk of nonarrhythmic death. Even after adjustment for baseline clinical features observed to be associated with increased mortality, being assigned to the ICD was still associated with a greater risk of nonarrhythmic death.

The adjusted time-dependent analysis suggests that the excess of nonsudden deaths in the ICD group receiving therapy is not due entirely to a higher burden of disease at the baseline evaluation. There were substantially more episodes of heart failure, MI, and unstable angina during follow-up in the group with ICD therapy compared with the group without therapy. However, this study is not able to distinguish between ventricular arrhythmias themselves causing cardiac deterioration and then an increased risk of death; an intercurrent cardiac event causing cardiac arrhythmia, treatment, and a subsequent increase in mortality rates; or the therapy (shocks) themselves directly or indirectly leading to increased mortality. The small number of deaths in the subgroups limits the inferences that can be drawn from these secondary analyses. The increase in risk of death soon after receiving ICD shocks suggests that VT or VF in these patients is associated with a “step” change in the course of the underlying cardiac disease and thus the prognosis for nonarrhythmic mortality.

Although the mechanisms responsible for the excess nonarrhythmic deaths in the ICD appropriate therapy group cannot be established with certainty, this study highlights the fact that appropriate ICD therapies in some patient populations do not necessarily lead to a meaningful overall mortality reduction, and it is not appropriate to equate ICD therapies with “deaths averted.”

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References


CLINICAL PERSPECTIVE

In the Defibrillation in Acute Myocardial Infarction Trial (DINAMIT) study, implanted defibrillators did not reduce mortality in high-risk patients if implanted early after myocardial infarction. In patients randomized to an implantable cardioverter-defibrillator (ICD), sudden deaths were reduced but nonarrhythmic mortality was increased. In an analysis of the potential causes of this finding, patients who are destined to receive therapy from their ICD (compared with those destined not to receive therapy) have clinical features that also increase their risk of nonsudden death, including risks related to heart failure and recurrent ischemic events. During follow-up, patients who receive therapy from their ICD are more likely to have intercurrent cardiac clinical adverse events both before and after ICD therapy compared with patients who receive no therapy or do not have an ICD. In an early post–myocardial infarction setting, the same clinical circumstances that increase the risk of ventricular arrhythmias also increase the risk of nonsudden death; in addition, ICD therapies themselves may increase the risk of subsequent death. These findings underscore the limitations of a strategy of ICD implantation in certain high-risk groups, especially early after acute myocardial infarction.

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