Mechanisms of Death in the CABG Patch Trial

A Randomized Trial of Implantable Cardiac Defibrillator Prophylaxis in Patients at High Risk of Death After Coronary Artery Bypass Graft Surgery

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Background—The CABG Patch trial compared prophylactic implantable cardiac-defibrillator (ICD) implantation with no antiarrhythmic therapy in coronary bypass surgery patients who had a left ventricular ejection fraction <0.36 and an abnormal signal-averaged ECG. There were 102 deaths among the 446 ICD group patients and 96 deaths among the 454 control group patients, a hazard ratio of 1.07 (P=0.63). The mechanisms of death were classified, and hypotheses were tested about the effects of ICD therapy on arrhythmic and nonarrhythmic cardiac deaths in the CABG Patch Trial and the Multicenter Automatic Defibrillator Implantation Trial (MADIT).

Methods and Results—The 198 deaths in the trial were reviewed by an independent Events Committee and classified by the method of Hinkle and Thaler. Only 54 deaths (27%) occurred out of hospital; 145 deaths (73%) were witnessed. Seventy-nine (82%) of the 96 deaths in the control group and 76 (75%) of the 102 deaths in the ICD group were due to cardiac causes. Cumulative arrhythmic mortality at 42 months was 6.9% in the control group and 4.0% in the ICD group (P=0.057). Cumulative nonarrhythmic cardiac mortality at 42 months was 12.4% in the control group and 13.0% in the ICD group (P=0.275). Death due to pump failure was significantly associated with death >1 hour from the onset of symptoms, dyspnea within 7 days of death, and overt heart failure within 7 days of death.

Conclusions—In the CABG Patch Trial, ICD therapy reduced arrhythmic death 45% without significant effect on nonarrhythmic deaths. Because 71% of the deaths were nonarrhythmic, total mortality was not significantly reduced. (Circulation. 1999;99:1416-1421.)

Key Words: trials ■ heart-assist device ■ bypass

During 1996–1997, 2 randomized trials of implantable cardiac-defibrillator (ICD) prophylaxis published strikingly different results. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) found substantial benefit for prophylactic ICD therapy, whereas the CABG Patch Trial found none. MADIT compared ICD prophylaxis with conventional antiarrhythmic therapy consisting primarily of amiodarone in patients with coronary heart disease, left ventricular ejection fraction <0.36, spontaneous unsustained ventricular tachycardia, and sustained ventricular tachycardia induced during electrophysiological study.1 During an average follow-up of 27 months, 15 deaths occurred among the 95 patients assigned to the ICD group and 39 deaths occurred among the 101 patients assigned to the conventional therapy group, a hazard ratio of 0.46 (P=0.009). The CABG Patch Trial compared prophylactic implantation of an ICD with no antiarrhythmic therapy in patients scheduled for coronary artery bypass surgery who had a left ventricular ejection fraction <0.36 and an abnormal signal-averaged ECG.2 During an average follow-up of 32±16 months, 102 deaths occurred among the 446 patients in the ICD group and 96 deaths occurred among the 454 patients in the control group, a hazard ratio of 1.07 (P=0.63). The overall crude mortality rate was 27.6% in MADIT and 22.0% in the CABG Patch Trial.

The disparity in the average results of therapy between the 2 trials may reflect the different arrhythmia indicators used to qualify patients.2 Inducible sustained ventricular tachyarrhythmias, the indicator used by MADIT, may predict ICD-preventable deaths more accurately than an abnormal signal-averaged ECG, the indicator used in the CABG Patch Trial. If so, the CABG Patch Trial should find a lower fraction of arrhythmic deaths than MADIT.

Both MADIT and the CABG Patch Trial had external Events Committees classify causes of death with the Hinkle-Thaler classification,1 permitting comparison of mechanisms of death in...
the 2 studies. Before deaths were classified in the CABG Patch Trial, 2 hypotheses were formulated: (1) ICD therapy would significantly reduce the arrhythmic death rate in the CABG Patch Trial and (2) a smaller percentage of all deaths would be arrhythmic in the CABG Patch Trial than in MADIT.

Methods

Mortality Review
A detailed form and a structured narrative description were used to collect information about each death. These documents were submitted to the Data Coordinating Center by the clinical centers within 30 days of a death. The Quality Control Subcommittee reviewed each death form for completeness and consistency. Then, a 3-member external Events Committee reviewed each death to ascertain its location, underlying cause, probable mechanism (in patients who died of cardiac causes), and associated acute cardiac symptoms.

Location of Death
The location of death was classified as out-of-hospital, emergency department, in-hospital, other, or unknown. “Emergency department” referred to death in which the patient arrived with the potential for resuscitation but died in the emergency room. “In-hospital” referred to deaths that occurred at any time after admission to a hospital. “Out-of-hospital” deaths were subclassified by whether or not they occurred in “hospital-equivalent” settings, such as nursing homes or skilled nursing facilities, hospices, or home hospice care.

Underlying Cause of Death
Each death was classified as due to atherosclerotic coronary heart disease, atherosclerotic vascular disease excluding atherosclerotic coronary heart disease, nonatherosclerotic cardiovascular disease, noncardiovascular disease, unknown/uncertain cause, and other causes.3

Mechanisms of Cardiac Death
The classification of Hinkle and Thaler3 was used to assign mechanisms to cardiac deaths. Problems of classification discussed by Epstein et al4 were taken into account. Primary arrhythmic death was defined as sudden and unexpected death within 5 minutes of acute cardiac symptoms in patients in New York Heart Association functional class I, II, or III without preceding active symptoms and/or signs of cardiac failure. Also, deaths in patients who were previously well and died during sleep were classified as primary arrhythmic deaths. Secondary arrhythmic/mechanical death was defined as death with preceding active or acute symptoms and/or signs of heart failure but without evidence of myocardial pump failure before death. For testing the 2 hypotheses, primary and secondary arrhythmic death were combined and called arrhythmic death. Death due to myocardial pump failure was defined as circulatory collapse in the form of hypotension or symptoms and/or signs of cardiac failure. The category of death due to a cardiac procedure included complications from coronary bypass graft surgery, cardiac catheterization, percutaneous transluminal coronary angioplasty, or cardiac pacemaker/defibrillator implantation.

Suddenness of Death
The time interval between onset of acute cardiac symptoms and cardiac death was estimated for patients who died of atherosclerotic coronary artery disease. In the event of a cardiac arrest with resuscitation but irretrievable brain death, the estimated interval between onset of symptoms and cardiac arrest was recorded.

Statistical Analyses
Frequency distributions were used to summarize the characteristics of deaths in terms of location and mechanism. The strength of association between the characteristics of death and randomization groups was estimated by odds ratios and associated asymptotic confidence intervals.5 The null hypothesis that the proportion of all deaths that were from arrhythmic causes was the same among CAGB Patch control patients as for MADIT conventional therapy patients was tested by a \( \chi^2 \) test with a correction for continuity.3

The Kaplan-Meier method was used to estimate cause-specific survival distributions, and the log-rank test was used to test for differences between distributions.6

The extent to which ICD therapy produced a different effect on cardiac deaths due to arrhythmic causes than on cardiac deaths due to nonarrhythmic causes (ie, a formal test for interaction between these 2 causes of death and randomization groups) was determined by use of a multiple cause of death proportional hazards regression model.7,8 Proportional cause-specific hazard ratios were estimated on the basis of the partial likelihood for a discrete time proportional hazards model with 2 competing causes of death.9 The hazard estimates for each cardiac cause of death, their standard errors, and the covariance between them were used to construct a Wald statistic for testing the hypothesis of equal hazard ratios for the 2 causes of death.9

All hypothesis tests were 2-tailed and conducted at the 0.05 level.

Results

Location of Death
During an average follow-up of 32 ± 16 months, 198 (22%) of the 900 randomized patients died, 102 in the ICD group and 96 in the control group. For both groups combined, 130 (66%) of the deaths occurred in hospital and 54 (27%) occurred out of hospital (Table 1). Of the 54 out-of-hospital deaths, 25 (46%) occurred in home hospice services, nursing home or skilled nursing facility care, or hospice care, and 29 deaths (54%) occurred in settings without hospital-equivalent care. There was no difference between ICD and control groups for location of death.

Overall, 73% of the deaths were witnessed, and there was no difference in the percent of witnessed deaths between ICD and control groups (Table 2). The lowest percentage of witnessed deaths was found in the arrhythmic deaths (60%), and the highest percentage was found in the procedure deaths (92%). Among 119 in-hospital deaths for which witness status was known, 107 deaths (90%) were witnessed, and among 63 deaths that were not in hospital and for which the witness status was known, 38 deaths (60%) were witnessed. The odds were 5.9 times as great that an in-hospital death was witnessed status was known, 38 deaths (60%) were witnessed. The odds were 5.9 times as great that an in-hospital death was witnessed.

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**TABLE 1. Location of Death by Treatment Group**

<table>
<thead>
<tr>
<th></th>
<th>Control (n=454)</th>
<th>ICD (n=446)</th>
<th>Total (n=900)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Out of hospital</td>
<td>28 (0.292)</td>
<td>26 (0.255)</td>
<td>54 (0.273)</td>
</tr>
<tr>
<td>Home/car/outside</td>
<td>18 (0.188)</td>
<td>11 (0.108)</td>
<td>29 (0.146)</td>
</tr>
<tr>
<td>Home, under hospice care</td>
<td>5 (0.052)</td>
<td>3 (0.029)</td>
<td>8 (0.040)</td>
</tr>
<tr>
<td>Nursing home/skilled nursing facility</td>
<td>2 (0.021)</td>
<td>7 (0.069)</td>
<td>9 (0.045)</td>
</tr>
<tr>
<td>Hospice</td>
<td>3 (0.031)</td>
<td>5 (0.049)</td>
<td>8 (0.040)</td>
</tr>
<tr>
<td>Emergency department</td>
<td>7 (0.073)</td>
<td>6 (0.059)</td>
<td>13 (0.066)</td>
</tr>
<tr>
<td>In hospital</td>
<td>60 (0.625)</td>
<td>70 (0.686)</td>
<td>130 (0.657)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.010)</td>
<td>0 (0.000)</td>
<td>1 (0.005)</td>
</tr>
<tr>
<td>Total</td>
<td>96 (1.000)</td>
<td>102 (1.000)</td>
<td>198 (1.000)</td>
</tr>
</tbody>
</table>

*The rows represent numbers (proportions) of deaths at a given location for each column (treatment group). For example, 60 (63%) of the 96 deaths in the control group occurred in hospital.
witnessed than an out-of-hospital death (95% CI, 2.7 to 12.8; \( P < 0.001 \)).

In 46 (48%) of the control group and 52 (51%) of the ICD group, an ECG was recorded in the terminal event. Autopsies were performed in 21 patients (11%).

### Cause and Mechanism of Death

Seventy-nine (82%) of the deaths in the control group and 76 (75%) of the deaths in the ICD group were due to cardiac causes (Table 3). Five noncardiac deaths (29%) in the control group and 8 (32%) in the ICD group were due to cancer, and 3 noncardiac deaths (18%) in the control group and 5 (20%) in the ICD group resulted from strokes. Seventy-seven deaths (80%) in the control group and 74 deaths (73%) in the ICD group were attributed to atherosclerotic coronary heart disease.

### Effect of ICD Therapy on Mechanism of Death

Table 3 shows that 29% of all deaths in the control group were arrhythmic versus 15% in the ICD group (\( \chi^2 = 5.10, P = 0.024 \)). Myocardial pump failure deaths composed 24% of all deaths in the control group and 29% of deaths in the ICD group (\( \chi^2 = 0.75, P = 0.358 \)).

The Figure shows Kaplan-Meier curves for arrhythmic and nonarrhythmic cardiac deaths cross-classified by treatment assignment. The difference in arrhythmic mortality rates between the ICD and control groups increased with duration of follow-up. At 42 months, the cumulative arrhythmic mortality rate was 4.0% in the ICD group and 6.9% in the control group (\( P = 0.057; \) log-rank test). At 42 months, the cumulative nonarrhythmic cardiac mortality rate was 12.4% in the control group and 13.0% in the ICD group (\( P = 0.275; \) log-rank test).

A Cox regression model revealed a significant interaction between treatment group and mechanism of cardiac death (\( P < 0.03 \) (Table 4). For arrhythmic deaths, the hazard ratio (ICD versus control) was 0.55 (95% CI, 0.3 to 1.0), ie, patients randomized to ICD therapy enjoyed a 45% decrease in the risk of arrhythmic death during 42 months of follow-up. For nonarrhythmic cardiac deaths, the hazard ratio was 1.2 (95% CI, 0.8 to 1.8); ie, there was no significant ICD effect on nonarrhythmic cardiac deaths.

### ICD Therapy in the Terminal Event

There were 15 arrhythmic deaths in the ICD group. Six arrhythmic deaths (40%) occurred in patients without a functioning ICD: the ICD was explanted before death (n=4), inactivated before death (n=1), or never had been implanted (n=1). The ICD was working normally at the time of death in the 9 remaining ICD group patients who died arrhythmic deaths. ICD discharges had occurred before death (median, 159 days) in 5 (56%) of these 9 patients.
Contrary to our second hypothesis, the proportion of all deaths that were arrhythmic was similar for the control groups of the 2 trials (29% for the CABG Patch Trial versus 33% for MADIT). In the CABG Patch Trial, 15% of all deaths were arrhythmic in the ICD group, compared with 20% in MADIT. However, the absolute arrhythmic death rate was 6.2% in the CABG Patch Trial control group compared with 12.9% in the MADIT control group. The ICD effect on nonarrhythmic cardiac deaths and noncardiac deaths was strikingly different between the 2 trials. In MADIT, nonarrhythmic cardiac and noncardiac deaths were substantially reduced in the ICD group, whereas in the CABG Patch Trial, mortality rates in these categories were slightly higher in the ICD group.

Discussion

Death of any cause was the primary end point for both MADIT and the CABG Patch Trial. In the CABG Patch Trial, there was no significant difference between the ICD and control groups for overall mortality or for cardiac mortality, whereas MADIT showed a substantial benefit for ICD therapy. The purpose of this article was to describe the causes of death in the CABG Patch Trial and to explain the greater ICD benefit found in MADIT. It should be noted at the outset that classifying the causes of death is a matter of judgment and subject to error. Although deaths can be classified as cardiac or noncardiac with considerable interrater consistency, classifying cardiac deaths as arrhythmic or nonarrhythmic is much more difficult. For both the CABG Patch Trial and MADIT, deaths were classified by an experienced Events Committee that was independent of the trial investigators.

Factors that affect the probability of finding a benefit of ICD therapy include the all-cause mortality rate in the control group, the percentage of control group deaths that are arrhythmic, and the CABG Patch Trial.
Deaths in the CABG Patch Trial

TABLE 6. Mechanisms of Death in MADIT and in the CABG Patch Trial*

<table>
<thead>
<tr>
<th></th>
<th>CABG Patch Trial</th>
<th>MADIT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n=454)</td>
<td>ICD (n=446)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>79 (0.823)</td>
<td>76 (0.745)</td>
</tr>
<tr>
<td></td>
<td>27 (0.692)</td>
<td>11 (0.733)</td>
</tr>
<tr>
<td>Primary arrhythmic</td>
<td>22 (0.229)</td>
<td>13 (0.127)</td>
</tr>
<tr>
<td></td>
<td>13 (0.333)</td>
<td>3 (0.200)</td>
</tr>
<tr>
<td>Secondary arrhythmic</td>
<td>6 (0.063)</td>
<td>2 (0.020)</td>
</tr>
<tr>
<td></td>
<td>0 (0.000)</td>
<td>0 (0.000)</td>
</tr>
<tr>
<td>Nonarrhythmic, cardiac</td>
<td>46 (0.479)</td>
<td>57 (0.559)</td>
</tr>
<tr>
<td></td>
<td>13 (0.333)</td>
<td>7 (0.467)</td>
</tr>
<tr>
<td>Myocardial pump failure</td>
<td>23 (0.240)</td>
<td>30 (0.294)</td>
</tr>
<tr>
<td></td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Cardiac procedure</td>
<td>23 (0.240)</td>
<td>27 (0.265)</td>
</tr>
<tr>
<td></td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Unwitnessed, cardiac</td>
<td>2 (0.021)</td>
<td>0 (0.000)</td>
</tr>
<tr>
<td></td>
<td>0 (0.000)</td>
<td>0 (0.000)</td>
</tr>
<tr>
<td>Uncertain, cardiac</td>
<td>3 (0.031)</td>
<td>4 (0.039)</td>
</tr>
<tr>
<td></td>
<td>1 (0.026)</td>
<td>1 (0.066)</td>
</tr>
<tr>
<td>Noncardiac</td>
<td>17 (0.177)</td>
<td>25 (0.245)</td>
</tr>
<tr>
<td></td>
<td>6 (0.154)</td>
<td>4 (0.267)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0.000)</td>
<td>1 (0.010)</td>
</tr>
<tr>
<td></td>
<td>6 (0.154)</td>
<td>0 (0.000)</td>
</tr>
<tr>
<td>Total</td>
<td>96 (1.000)</td>
<td>102 (1.000)</td>
</tr>
<tr>
<td></td>
<td>39 (1.000)</td>
<td>15 (1.000)</td>
</tr>
</tbody>
</table>

*The Hinkle-Thaler\(^3\) classification was used to categorize causes of death.

arrhythmic, the magnitude of decrease in arrhythmic deaths by ICD therapy, the magnitude of decrease in nonarrhythmic deaths by ICD therapy, and effects of other therapies on mortality rates. Factors that contributed importantly to the greater ICD benefit in MADIT than in the CABG Patch Trial are a higher all-cause mortality rate in the control group, a larger reduction in arrhythmic death by ICD therapy, and a reduction in nonarrhythmic deaths. The control group all-cause mortality rate in MADIT (39%) was substantially higher than in the CABG Patch Trial (21%), as was the 12.9% absolute arrhythmic death rate for MADIT compared with 6.2% for the CABG Patch Trial. With all other factors held constant, the higher absolute arrhythmic death rate for MADIT made it more likely that a benefit would be found for ICD therapy. The magnitude of reduction in arrhythmic death was somewhat greater in MADIT (76%) than in the CABG Patch Trial (45%). There was a substantial reduction in nonarrhythmic death (54%) in MADIT but an increase (30%) in the CABG Patch Trial. This difference between the 2 trials could be due to differences in non-ICD therapies or due to chance; our data do not permit us to distinguish. The ICD group in MADIT benefited from more frequent use of \(\beta\)-adrenergic blocking drugs and less frequent use of antiarrhythmic drugs. A longer duration of CABG surgery and a higher incidence of infections disadvantaged the ICD group in the CABG Patch Trial.\(^15\)

The CABG Patch Trial tested 2 hypotheses about causes of death. The first hypothesis, that ICD prophylaxis reduces cumulative probability of arrhythmic death, was confirmed in the CABG Patch Trial and in MADIT. A consistent decrease in arrhythmic death attributable to ICD therapy is consistent with the ability of ICDs to effectively treat sustained ventricular tachyarrrhythmias, thereby preventing arrhythmic deaths.

Our second hypothesis, that the CABG Patch Trial had a significantly lower proportion of arrhythmic deaths in its control group than found in MADIT, was rejected.\(^2\) The difference in ICD effect on nonarrhythmic cardiac deaths and noncardiac deaths between MADIT and the CABG Patch Trial contributed importantly to the different effect of ICD therapy on total mortality in the 2 trials. In the CABG Patch Trial, there was no significant effect of ICD therapy on nonarrhythmic cardiac deaths, noncardiac deaths, or deaths of unknown cause. In fact, there was a trend for these causes of death to increase. In MADIT, the reduction in nonarrhythmic cardiac deaths and noncardiac/unknown deaths in the ICD group was almost as great as the reduction in arrhythmic deaths (Table 6). ICD therapy could reduce nonarrhythmic cardiac death rate; controlling ventricular tachyarrrhythmias might prevent worsening of heart failure and prevent some nonarrhythmic cardiac deaths.\(^16\) This benefit of ICD therapy on nonarrhythmic deaths may have been counterbalanced in the CABG Patch Trial by prolongation of cardiopulmonary bypass to implant the ICD system.\(^13\)

The prevalence of ischemia in the terminal event was 13% in the CABG Patch Trial, compared with 60% in the Multicenter Post Infarction Program.\(^13\) This striking difference probably reflects substantial enduring efficacy for CABG surgery as a treatment for ischemia, a benefit enjoyed by the ICD and control groups alike.

In MADIT and in the CABG Patch Trial, ICD therapy substantially reduced arrhythmic deaths without a consistent effect on nonarrhythmic deaths, indicating that patients with substantial risk of arrhythmic death should be selected for ICD prophylaxis. Fogoros\(^17\) argued that ICD benefit for total mortality is purely a function of the ratio of arrhythmic to nonarrhythmic deaths in a population under study. Our results suggest that this ratio is not the only important factor. MADIT and the CABG Patch Trial had similar fractions of arrhythmic deaths, but other factors, including the absolute arrhythmic death rate, accounted for differences in ICD effect on total mortality.

At face value, electrophysiological testing, used in MADIT, selected a group of patients who benefited substantially from ICD therapy, whereas the signal-averaged ECG used in the CABG Patch Trial did not. We hypothesized previously that the primary reason for the low incidence of arrhythmic death in the CABG Patch Trial was recruitment of a small proportion of patients with inducible, sustained
ventricular tachycardia. MADIT showed that patients with previous myocardial infarction and inducible ventricular tachycardia had a death rate that was 4 times that found in similar patients who were not inducible. Also, MADIT showed that ICD prophylaxis reduced total mortality 54%. The electrophysiological substudy of the CABG Patch Trial will test the hypothesis that programmed ventricular stimulation is the key test for identifying coronary heart disease patients who benefit from prophylactic ICD therapy. If a low prevalence of inducible ventricular tachycardia is the explanation for the low prevalence of arrhythmic death in the CABG Patch Trial, then we calculate that fewer than 22% of the patients in the trial would have been inducible at the time of randomization, assuming that inducible patients would have a relative risk similar to that found in MADIT.

Acknowledgments

The authors express their gratitude for the indispensable efforts of the Events Committee: Bertram Pitt, MD, chair; H. Leon Green, MD; and Morrison Hodges, MD. This study was supported by grants HL-48210 and HL-48159 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md, and a grant from Guidant/CPI Corporation, Inc, St Paul, Minn. We used data from version 2.0 of the CABG Patch Trial database.

References

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Circulation. 1999;99:1416-1421
doi: 10.1161/01.CIR.99.11.1416

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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