Mechanisms of Sudden Cardiac Death in Myocardial Infarction Survivors
Insights From the Randomized Trials of Implantable Cardioverter-Defibrillators

T. Jared Bunch, MD; Stefan H. Hohnloser, MD; Bernard J. Gersh, MB, ChB, DPhil, FRCP

Sudden death is a catastrophic but unpredictable complication of coronary artery disease and is frequently the consequence of an acute ischemic event.1–3 The efficacy of the implantable cardioverter-defibrillator (ICD) in reducing sudden cardiac death incidence is irrefutable and strongly supported by evidence from randomized trials of both primary and secondary prevention (Figure 1).4–8 Nonetheless, the 2 neutral trials9,10 raise intriguing and puzzling issues in regard to the temporal relationship between myocardial infarction (MI), coronary revascularization, residual myocardial ischemia, and severe left ventricular dysfunction and its impact on the mechanisms of presumed sudden cardiac death and the efficacy of the ICD. In this respect, this commentary addresses current knowledge regarding the mechanisms of death early and late after MI, limitations in our abilities to stratify risk, and analyses from the randomized trials in an attempt to reconcile the apparently paradoxical observation that the highest rate of sudden cardiac death occurs the first few weeks after MI and that the only ICD trial to address this population was neutral.10

Mechanisms of Death After MI
The causes of death after MI are multifactorial and depend in part on the duration of time that has elapsed since the initial MI. During the acute phase of the MI, sudden death is typically the result of ischemia that provokes lethal ventricular arrhythmias.11,12 Mechanical complications resulting in profound hemodynamic derangements such as ventricular or papillary muscle rupture, pericardial tamponade, septal defects, and ischemic valvular dysfunction also may mimic sudden arrhythmic death, even if the rhythm is not ventricular fibrillation. A similar sequence of events may occur in patients with cardiogenic shock as a result of extensive myocardial necrosis.

Over time, the origin of sudden cardiac death evolves as a consequence of structural remodeling of the left ventricle. Ventricular arrhythmias usually result from regional or intramural reentry circuits that incorporate regions of diseased myocardium and electrically unexcitable scars.13,14 A second process underlying mortality after MI occurs in patients who develop progressive ventricular remodeling and worsening left ventricular function as part of the grim cascade of progressive loss of cardiac output and the symptoms of congestive heart failure. In these patients, activation of the neurohumoral pathways underlies progressive vasculopathy, left ventricular dysfunction, fibrosis, and ultimate progression of the disease.15,16 Moreover, dilatation of the ventricle predisposes to electrical inhomogeneity characterized by a temporal dispersion of repolarization predisposing to reentry arrhythmias.17,18

Risk Stratification After MI
Historical data suggest that the most important risk factor for cardiac mortality and sudden death after MI is the extent of myocardial injury, characterized by a reduction in ejection fraction and increased end-systolic and end-diastolic volumes. These indexes of left ventricular function have been shown to be consistent, although nonspecific, predictors of mortality after MI.19,20 Other factors associated with risk of sudden cardiac death include the QRS width, ventricular arrhythmias at electrophysiological testing or during 24-hour ambulatory monitoring, T-wave alternans, exaggerated QT dispersion, heart rate variability, and persistently elevated neurohormone and troponin levels.21 However, because of inconsistency in the accurate prediction of subsequent clinical events, these factors are difficult to use alone and may theoretically be best applied in a multifactorial model, although such models have major limitations.22,23 Unfortunately, we have to accept that currently available techniques are unable to effectively risk stratify patients for sudden cardiac death, and although genetic approaches to the problem are intriguing and a promising focus of investigation, their utility in a clinical setting has yet to be defined. For these reasons, the major inclusion criterion in the large randomized trials has been a reduction in ejection fraction in combination with other risk factors (Table).

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Reconciling the “Neutral” ICD Trials

The efficacy of the ICD in patients with reduced left ventricular function with and without ischemic heart disease is strongly supported by evidence from many randomized trials.4–6 However, 2 neutral or negative trials, the Coronary Artery Bypass Graft (CABG) Patch trial6 and Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) trial,10 have generated interesting questions regarding mechanisms of sudden cardiac death and the role of the ICD in the primary prevention of sudden cardiac death (Figure 1).

First, the CABG Patch trial6 randomized 900 patients who were undergoing coronary bypass surgery to routine medical care or to an adjunctive epicardial ICD implant. The inclusion criteria for the CABG Patch trial included the presence of left ventricular dysfunction (ejection fraction <0.36) and an abnormal signal-averaged ECG. The trial did not exclude individuals who had a recent MI. In fact, >80% had a history of a MI (52% had Q-wave MI). During a follow-up period of 32±16 months, there were 71 cardiac deaths in the defibrillator group and 72 in the control group.

A pivotal aspect of this trial is that it draws attention to the impact of revascularization on sudden cardiac death in high-risk patients. In the CABG Patch trial, 45% of the patients had 1- or 2-vessel disease (36% had 2-vessel disease) and 55% had 3-vessel disease.9 Both the extent of coronary artery disease and its management will affect sudden cardiac death risk. In a prior analysis of the Coronary Artery Surgical Study (CASS), Holmes and colleagues24 evaluated the effect of revascularization on sudden death. Five-year survival free of sudden death for medically treated patients was 94% versus 98% in surgically treated patients (P<0.0001). In this study population, the sudden death rate after coronary artery bypass surgery was very low. Even in high-risk patients with a history of congestive heart failure, 5-year survival free of sudden death after coronary artery bypass surgery was 98% in patients with 2-vessel disease and 91% for those with 3-vessel disease. In retrospect, although all CABG Patch patients had significant left ventricular dysfunction, the expected sudden cardiac death rates based on their coronary anatomy were, in all likelihood, substantially reduced by the performance of coronary revascularization at the time of the ICD implantation, thus reducing the power of the study to demonstrate a difference in mortality.

A recent substudy of patients in Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) highlighted the temporal association between ICD impact and timing of revascularization.25 This analysis examined the 951 patients in MADIT-II who underwent coronary revascularization (either coronary artery bypass grafting or percutaneous coronary intervention) before ICD implantation. Of these patients, 14% had revascularization ≥6 months before enrollment; 44%, between 6 to 60 months; and 42%, >60 months. The impact of time from revascularization and sudden death was striking. In patients with recent revascularization (<6 months), there was no benefit for ICD implantation. However, in those with intermediate (6 to 60 months) or remote (>60 months) revascularization, ICD implantation greatly decreased sudden death (hazard ratio, 0.27 [95% CI, 0.11 to 0.66] and 0.40 [95% CI, 0.19 to 0.86], respectively). Nonetheless, it appeared that the significant protective impact of revascularization on mortality declined after ~2 years, perhaps because of the progression of coronary disease or left ventricular dysfunction. Unfortunately, the time from MI to revascularization was not reported in the CABG Patch trial, but these data, along with other studies, in aggregate highlight the profound beneficial effect of revascularization on sudden death and provide a mechanism underlying the apparent lack of benefit from the ICD in this trial.

Inclusion Criteria for ICD Trials That Involve Patients With Coronary Artery Disease

<table>
<thead>
<tr>
<th>Trial</th>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>MUSTT</td>
<td>EF &lt;0.40; asymptomatic, unsustained ventricular tachycardia (&gt;3 beats to a maximum of 30 s); patients with the above criteria were included if &gt;4 d had passed since the most recent MI or revascularization procedure</td>
</tr>
<tr>
<td>MADIT-I</td>
<td>EF ≤0.35; unsustained ventricular tachycardia (3–30 ventricular ectopic beats at a rate &gt;120 bpm); New York Heart Association functional class I, II, or III; Q-wave or enzyme-positive MI ≥3 wk before trial entry</td>
</tr>
<tr>
<td>MADIT-II</td>
<td>EF ≤0.30; MI ≥1 mo before trial entry</td>
</tr>
<tr>
<td>CABG Patch</td>
<td>EF &lt;0.36; abnormalities on a signal-averaged ECG (&gt;80% had an MI, 52% had Q-wave MI)</td>
</tr>
<tr>
<td>DINAMIT</td>
<td>EF ≤0.35; recent MI (6–40 d) before trial entry; SD of normal-to-normal RR intervals of ≤70 ms or a mean RR interval of ≤750 ms (heart rate ≥80 bpm) over a 24-h period</td>
</tr>
<tr>
<td>SCD HeFT</td>
<td>EF ≤0.35; New York Heart Association functional class II or III; chronic, stable congestive heart failure resulting from ischemic or nonischemic causes</td>
</tr>
</tbody>
</table>

MUSTT indicates Multicenter Unsustained Tachycardia Trial; MADIT, Multicenter Automatic Defibrillator Implantation Trial; CABG, Coronary Artery Bypass Graft; DINAMIT, Defibrillator in Acute Myocardial Infarction Trial; SCD HeFT, Sudden Cardiac Death in Heart Failure Trial; and EF, ejection fraction.
The DINAMIT trial\textsuperscript{10} randomized 675 to receive an ICD or standard medical therapy 4 to 40 days after MI. Inclusion criteria consisted of left ventricular dysfunction (ejection fraction $<0.35$) and abnormal heart rate variability. During a mean follow-up period of 30±13 months, there was no difference in overall mortality between the 2 treatment groups (62 in the ICD group versus 58 in the control group). This trial underscores the importance of the relationship between recent MI and early mechanisms of sudden cardiac death. In contrast to the majority of prior ICD trial patients, including patients with a remote MI (average time from myocardial to enrollment for the Multicenter Unsustained Tachycardia Trial [MUSTT] was 39 months and for MADIT-II was 81 months), the DINAMIT trial examined the impact of an ICD relatively early after MI. Hypothetically, the ICD should have a profound benefit in improving mortality early after MI because ventricular arrhythmias are very common in this time period. Even in the modern era with aggressive use of revascularization and pharmacological therapies, sudden cardiac death rates remain high early after MI (2.3% per month in those with left ventricular dysfunction), although rates have declined quite substantially in patients undergoing successful early reperfusion therapy.\textsuperscript{26,27} In a large community-based study of 2317 persons with an incident MI, 7.5% experienced ventricular arrhythmias. Of note, 5.7% of the patients had ventricular fibrillation, and these arrhythmias were associated with subsequent mortality (relative risk, 5.36; 95% CI, 3.71 to 7.72; $P<0.001$).\textsuperscript{28} Nonetheless, these data from DINAMIT have been substantiated in part by a substudy of MADIT-II. In this analysis, Wilber et al\textsuperscript{29} found that only those who received an ICD with a remote MI (≥18 months) benefited (hazard ratio, 0.55; 95% CI, 0.39 to 0.78; $P=0.001$) versus those with a relatively recent MI (<18 months; hazard ratio, 0.97; 95% CI, 0.51 to 1.81; $P=0.92$).

Because the DINAMIT trial was neutral despite a high expected incidence of ventricular arrhythmias, it raises the question of whether these arrhythmias are an independent risk factor of mortality or merely a risk marker manifest from other underlying disease. To evaluate this question, the mode of death early after MI needs to be clarified. In a pathological analysis of the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL), which randomized 5477 patients with heart failure or evidence of left ventricular dysfunction after acute MI to losartan or captopril, Orn et al\textsuperscript{30} found that the majority of deaths (57%) were related to recurrent infarction and that only 14% were classified as sudden cardiac death. Similar findings also were reported in a subanalysis of the Assessment of Treatment With Lisinopril and Survival (ATLAS) trial,\textsuperscript{31} which assessed the use of low- or high-dose lisinopril in patients with congestive heart failure.\textsuperscript{32} In this study, 54% of those with known ischemic cardiomyopathy had acute coronary findings at autopsy. Finally, in a large community-based study, Jokhador and colleagues\textsuperscript{33} examined time-dependent morbidity and mortality after an index MI. In this study of 2277 patients with MI, 589 had recurrent ischemic events. Recurrent MI was independently associated with a 44% increase in the risk of sudden cardiac death (relative risk, 1.44; 95% CI, 1.12 to 1.86; $P=0.005$). These data suggest that recurrent myocardial ischemia results in a substantial number of cases of sudden death after an index MI. Moreover the DINAMIT trial provided additional evidence to support this hypothesis. In this study, the annual mortality rates were high, 7.5% in the ICD group and 6.9% in the control group, despite optimization of medical therapy. In a subset analysis of the mortality rates, arrhythmia-related death rates were lower in the ICD group (1.5% per year) compared with control (3.5% per year). Therefore, the high rates of cardiac mortality in the ICD group were from mechanisms other than tachyarrhythmia. This conclusion is supported by an observational study of 324 consecutive MI survivors studied with 24-hour Holter monitoring for an average of 10 days after the event. The authors found that nonsustained ventricular tachycardia was not associated with future arrhythmic events but rather a composite all-cause cardiac mortality.\textsuperscript{34} Furthermore, in patients with chronic coronary artery disease and left ventricular dysfunction, sudden cardiac death may also be the consequence of bradyarrhythmias and electric-mechanical dissociation.\textsuperscript{35,36}

If ventricular arrhythmias are mainly risk markers or surrogates of recurrent ventricular injury after MI, then those patients with ICD shocks should have higher rates of mortality and morbidity from progressive left ventricular dysfunction or recurrent infarctions. In other words, the ICD may merely change the mode of death from arrhythmia to heart failure or death as a result of recurrent MI (“conversion hypothesis”). The DINAMIT trial provides evidence behind this hypothesis. In a study by Dorian et al,\textsuperscript{37} the 55 patients of the DINAMIT trial who had an appropriate ICD shock were examined for long-term outcomes. Within the cohort of the ICD population that received shocks, 40% had died within 1 year, and this was independent of age, ejection fraction, and low heart rate variability. In addition, data from the MADIT-II trial showed that patients who received appropriate ICD therapies had an increased risk for first (hazard ratio, 1.90; $P=0.01$) and recurrent (hazard ratio, 1.74; $P<0.001$) congestive heart failure events within a relatively short period after the shock. These heart failure events were independently associated with increased mortality.\textsuperscript{38} These findings suggest that the ICD transformed the risk of arrhythmic sudden death to that of heart failure–mediated death.

Finally, these data from the DINAMIT trial raise an important question regarding a potential “survivorship bias” with prior ICD trials. This bias stems from the possibility that those patients with recurrent MIs and severe congestive heart failure included in the DINAMIT trial would have died before enrollment in some of other trials in which the duration of time between prior MI and randomization was far longer, leading to a selection bias toward early MI survivors with the development of compensated left ventricular dysfunction with remodeling and a vulnerability to arrhythmias.

Unresolved Issues

These studies support the conclusion that myocardial ischemia is an important trigger for the development of ventricular tachyarrhythmias, particularly in the early phase after MI, and coronary revascularization reduces sudden death risk. This
assumption is further strengthened by recent findings of Elhendy et al., who studied 90 ICD recipients by means of stress echocardiography to assess residual myocardial ischemia and by electrophysiological testing. Ischemia during stress echocardiography was an independent predictor of death or ICD therapy. In addition, when both the echocardiographic and electrophysiological studies were positive, the subsequent risk of events was very high. In some patients, myocardial dysfunction may be due to dysfunctional but viable myocardium and/or hibernating myocardium. Independently of other risk factors, hibernating myocardium is associated with risk of sudden death.\(^{40,41}\) Left untreated in an animal model, hibernating myocardium in the left anterior artery distribution was associated with a sudden death incidence of nearly 50% over a 5-month period.\(^{42}\)

Experimentally, hibernating myocardium is characterized by a marked vulnerability for fatal ventricular arrhythmias via a variety of potential mechanisms, including regional myocyte hypertrophy, altered calcium uptake in the sarcoplasmic reticulum, an increase in interstitial connective tissue, inhomogeneity in sympathetic activation, and recurrent ischemic insults.\(^{40}\) Although revascularization of dysfunctional hibernating myocardium results in improvement of both survival and left ventricular function, the impact on long-term sudden death rates has not been established.\(^{43–46}\) Recently, the Occluded Artery Trial (OAT) provided no evidence that early revascularization (3 to 28 days) in asymptomatic MI survivors would improve prognosis and reduce sudden cardiac death.\(^{47}\) Nonetheless, patients who experience a significant recovery of left ventricular function may no longer meet previously met criteria for ICD implantation. However, it remains undetermined whether ICDs should be implanted in patients who are considered ICD candidates according to the trial criteria from MADIT-II or Sudden Cardiac Death in Heart Failure Trial I (SCD HEFT)\(^{48,49}\) and who are subsequently revascularized with some recovery of systolic function.

Finally, another issue to consider in interpreting the ICD trials in patients with both ischemic and nonischemic cardiomyopathy is the uniform inclusion criterion of a reduced ejection fraction (the Table). Left ventricular dysfunction is a powerful risk factor in determining mortality. Nevertheless, the use of specific values of ejection fraction as a criterion for implanting an ICD highlights the limitations in regard to the accuracy and reproducibility of current techniques for these measurements (Figure 2).

Regarding the assessment of ventricular function, a previous study assessed operator variability with the echocardiographic determination of ejection fraction. The authors found a 7% disparity (5% to 95% confidence limits) between consecutive measurements that were poorer in subjects who were technically difficult to image.\(^{48}\) Nonetheless, the echocardiographic assessment of ejection fraction may be more accurate and reproducible when an intravenous contrast agent is added.\(^{49}\) A similar discrepancy in measurement results has been reported with nuclear assessment of ejection fraction with evidence of accuracy improvement with software and technique advances.\(^{50–52}\) Regarding intratechnique variability, a study of 52 patients compared echocardiography (M mode, 2-dimensional Simpson’s method), radionuclide ventriculography, and cardiovascular magnetic resonance assessment of ejection fraction—identified marked variability in the calculated value (echocardiography, 0.31 ± 0.10; radionuclide ventriculography, 0.24 ± 0.9; cardiovascular magnetic resonance, 0.30 ± 0.11; \(P < 0.001\)).\(^{53}\) A similar variability was found in assessments of 3-dimensional echocardiography, computed tomography, and magnetic resonance reference, with the greatest correlation between echocardiography and computed tomography.\(^{54}\) Although these different modalities provide reasonable accuracy and reproducibility, we need to question our strict reliance on these values to definitively include or exclude patients for ICD implantation.

Moreover, ejection fraction has not been shown to distinguish between the risk of sudden and nonsudden cardiac death. In a study of ventricular fibrillation cardiac arrest survivors, the minority of patients had prior left ventricular dysfunction.\(^{55}\) Second, in a subanalysis of MUSTT, arrhythmic sudden death rates were similar between patients who had ejection fractions <30% versus those with ejection fractions of 30% to 40%.\(^{56}\) To circumvent the limitations of using the ejection fraction as a sole means to risk stratify patients for an ICD, the trials discussed here typically relied on other factors of high risk such as symptomatic heart failure, ECG changes, or preexisting arrhythmias, in addition to left ventricular dysfunction, to determine candidacy. Nonetheless, the incremental value of these other risk factors in identifying patients who are likely to benefit from an ICD is uncertain and unproved. Models of simple and complex risk factors have been suggested for use in combination with ejection fraction to truly identify those who will experience an arrhythmic sudden death.\(^{5}\) However, multifactorial predictive models require confirmation in a prospective study in patients with and without structural heart disease.

**Clinical Approach**

The early management of high-risk patient survivors of an acute MI with left ventricular dysfunction remains a challenge. Current recommendations from the American Heart Association/American College of Cardiology recommend waiting 40 days before implanting an ICD unless other high-risk features of sudden death are present.\(^{57}\) Currently, no available data support ICD implantation at an early time (DINAMIT).\(^{10}\) However, many patients show significant
improvement in left ventricular function over the first 6 to 8 weeks after an acute MI. During this time period, aggressive attempts are needed to treat underlying heart failure and residual ischemia. For example, carvedilol improved left ventricular ejection fraction over a 6-month period by directly affecting the function of hibernating myocardium through reducing oxygen consumption while increasing diastolic perfusion.\(^8\) As to an aggressive approach to revascularization, complete revascularization with coronary artery bypass grafting of hibernating myocardium early after MI has shown an improvement in ejection fraction from 28±9% to 40±12% over a 9- to 12-month period.\(^9\) In patients with a relatively preserved left ventricular function, percutaneous coronary intervention in viable MI also improves ejection fraction,\(^60\) but there is a paucity of data regarding this approach in patients with severe LV dysfunction. Furthermore, it is unclear whether multivessel percutaneous coronary intervention for complete coronary revascularization will approximate the left ventricular function recovery results seen after surgery. Regarding mortality, in a post hoc analysis of the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) trial, in which 94 of 454 subjects had an ejection fraction <0.35, there was no difference between coronary artery bypass grafting and percutaneous coronary intervention.\(^61\) However, the extent to which complete revascularization provides a long-term protective effect against sudden cardiac death is unknown, and further studies are required. For now, left ventricular function should be reassessed after 6 to 8 weeks after the acute MI. If the function has not improved above the range of 30% to 35%, preventive ICD therapy should be strongly considered. It remains to be seen whether additional risk stratification measures will be helpful during this period of time.

**Conclusions**

Coronary artery disease is the most common cause of left ventricular dysfunction and heart failure in industrialized countries. Trials have shown that in patients with ischemic cardiomyopathy and a remote MI, ICD implantation on average reduces the incidence of sudden cardiac death. However, for patients with a recent MI and left ventricular dysfunction, there is no apparent benefit from ICD implantation. We conclude that these observations stem from 2 mechanisms (Figure 3). First, coronary revascularization reduces sudden death rates in these patients, thereby minimizing the impact of an ICD. Second, ventricular arrhythmias early after MI often are risk markers of underlying recurrent ischemic events that drive progression of the underlying cardiac disease rather than independent risk factors. ICDs provide us with an effective tool to prevent arrhythmic sudden cardiac death, but the risks of inappropriate discharges and device and procedural complications, plus the societal economic impact of widespread implantation for the primary prevention of all patients at risk, mandate further efforts to better our understanding of which patients are at risk of sudden arrhythmic cardiac death that could be prevented by the device.

**Lack of ICD Benefit After Recent MI Potential Explanations**

![Figure 3. Proposed potential explanations to explain the lack of ICD benefit in patients after a recent MI and persistent left ventricular dysfunction. CHF indicates congestive heart failure.](image)

**Disclosures**

Dr Hohnloser has been a consultant to and investigator of St Jude Medical Inc (St Paul, Minn) and Sanofi Aventis (Paris, France). Dr Gersh has served as a consultant to AstraZeneca, as a consultant to and on the advisory board of Cardiovascular Therapeutics, and as a consultant to Boston Scientific. Dr Bunch reports no conflicts.

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