Implantable cardioverter defibrillator following acute myocardial infarction: the ‘48-hour’ and ‘40-day’ rule

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Until recently, randomized studies of implantable cardioverter defibrillator (ICD) have only included patients with a remote history of myocardial infarction (MI). Two studies evaluated the use of ICDs early following MI, the DINAMIT and BEST−ICD studies, but failed to demonstrate significant reduction in mortality. Current guidelines therefore recommend deferring ICD implantation for at least 40 days following MI. This article highlights the limitations of these two studies and reviews the application of the ‘40-day’ rule to patients with acute MI.

KEYWORDS
Implantable cardioverter defibrillator; Acute myocardial infarction

Introduction
Ventricular arrhythmias are a major cause of death in the early phase of acute myocardial infarction (MI), even in the setting of normal ventricular function prior to the event. This is largely the basis for the success of coronary care units in reducing mortality from acute MI.1 During this early phase after MI, ventricular arrhythmias are provoked by myocardial ischaemia.2 Subsequent scar formation following the index MI may provide the substrate for intramyocardial re-entry, resulting in ventricular tachycardia, which, in turn, may precipitate cardiac arrest even in the absence of active ischaemia and may be temporally remote from the index ischaemic event.

Data from the major studies of the thrombolytic era on ‘high-risk’ patients, defined by either left ventricular dysfunction [left ventricular ejection fraction (LVEF) <40%] or frequent (more than 10/h) ventricular premature complexes (PVCs), indicate that the overall risk of arrhythmic death from the index event and up to day 45 after MI was persistently higher than that of non-arrhythmic death.3 The absolute risk of both arrhythmic and non-arrhythmic death was higher in the first 6 months after MI and decreases with time. This point is supported by a more recent analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT) study, which clearly demonstrates that the highest absolute risk of sudden death was in the first month after MI, particularly in patients with left ventricular dysfunction. The sudden death or cardiac arrest with resuscitation event rate fell from 1.4%/month [95% confidence interval (CI) 1.2–1.6] in the first month to 0.5%/month (95% CI 0.45–0.55) between 1 and 6 months.4

Assuming that these ventricular arrhythmias contribute directly to the total mortality in the early phase of the acute MI and do not simply represent an epiphenomenon linked to the initial ischaemic event, the benefit of an implantable cardioverter defibrillator (ICD) may be expected to be greatest in the early period, following an acute MI. However, this appears to be at odds with the current recommendations of deferring ICD implantation for at least 40 days following MI for the purpose of primary prevention against sudden cardiac death (Table 1).5 These recommendations are based on the entry criteria of well-publicized primary prevention studies, which included patients with a remote (at least 1 month) history of MI6,7 and perhaps more importantly data from randomized studies of ICDs in the early period following an acute MI (Table 2). In this article, we will review the use of ICD in patients with acute MI and, in particular, the two studies that evaluated the early use of ICD following acute MI.

The DINAMIT study
The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) compared ICD implantation within 6–40 days of an acute MI (average time from MI to randomization of 18 days) with conventional medical therapy.8 First and foremost, this is a study of primary prevention against sudden cardiac death and the investigators excluded patients with sustained ventricular tachycardia or fibrillation >48 h...
after the qualifying MI. The DINAMIT study included a measurement of heart rate variability (HRV), with an ejec-
tion fraction of $\frac{35}{100}$ as study inclusion criteria. The majority of patients had significant anterior MI and heart failure, but about one-third of the study patients did not receive any reperfusion therapy, either fibrinolysis or percu-
taneous coronary intervention (PCI). The DINAMIT study demonstrated a reduction in the arrhythmic death, which was largely balanced by an increase in the non-arrhythmic cardiac death in the ICD arm when compared with the control group, but there was no reduction in the total mor-
tality (Table 3).

### The BEST + ICD study

The second study, the Beta-Blocker Strategy plus ICD (BEST + ICD) trial, compared a strategy of early ICD implantation (5–30 days of an acute MI) guided by electrophysiological testing with conventional medical therapy. This study was limited by significant recruitment difficulties. The study investigators screened 15 507 patients, identified 10 724 patients with documented left ventricular function measurement, and found only 1190 patients with an LVEF of $\frac{35}{100}$ (eligible for the study). However, only 143 patients were eventually recruited from these 1190 eligible patients. In addition to a reduced LVEF, the study population needed to be on metoprolol of at least 25 mg/day and had at least one additional risk factor: at least 10 PVCs/h, reduced HRV, or an abnormal signal-averaged ECG. As in the DINAMIT study, the BEST + ICD trial excluded patients with sustained ventricular arrhythmia associated with the acute MI ($\frac{35}{100}$), and a large proportion of patients in the BEST + ICD trial had anterior MI but did not receive either fibrinolysis or PCI. There was no significant difference in the overall mortality (Table 3). However, the limited external validity of this study (majority of the patients who were screened were excluded) and the small number of events (26 deaths in

### ACC/AHA/ESC Class I recommendations

(i) Aggressive attempts should be made to treat heart failure that may be present in some patients with LV dysfunction due to prior MI and ventricular tachyarrhythmias.

(ii) Aggressive attempts should be made to treat myocardial ischaemia that may be present in some patients with ventricular tachyarrhythmias.

(iii) Coronary revascularization is indicated to reduce the risk of SCD in patients with VF when direct, clear evidence of acute myocardial ischaemia is documented to immediately precede the onset of VF.

(iv) If coronary revascularization cannot be carried out and there is evidence of prior MI and significant LV dysfunction, the primary therapy of patients resuscitated from VF should be ICD in patients who are receiving chronic optimal medical therapy and those who have reasonable expectation of survival with a good functional status for $\frac{1}{2}$ year.

(v) ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF $\leq\frac{30}{100}$–$\frac{40}{100}$, are NYHA functional class II or III, are receiving chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for $\frac{1}{2}$ year.

(vi) The ICD is effective therapy to reduce mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who present with haemodynamically unstable sustained VT, are receiving chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for $\frac{1}{2}$ year.

### Randomised studies of early use of implantable defibrillator in acute MI

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Time from MI (days)</th>
<th>LVEF (%)</th>
<th>Additional factors</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>DINAMIT</td>
<td>674</td>
<td>6–40</td>
<td>$\leq\frac{35}{100}$</td>
<td>Heart rate variability</td>
<td>Sustained VT/VF $\geq \frac{48}{100}$ h after MI</td>
</tr>
<tr>
<td>BEST + ICD</td>
<td>143</td>
<td>5–30</td>
<td>$\leq\frac{35}{100}$</td>
<td>PVCs $\geq\frac{10}{100}$/h</td>
<td>Sustained ventricular arrhythmia (except ‘primary VF’), NSVT</td>
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<td></td>
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<td>Heart rate variability</td>
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<td>Signal-averaged ECG</td>
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<td>Metoprolol therapy $\geq\frac{25}{100}$ mg/day</td>
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</tbody>
</table>

Table 1: ACC/AHA/ESC Class I recommendations

Table 2: Randomised studies of early use of implantable defibrillator in acute MI

Table 3: Clinical outcome in DINAMIT and BEST + ICD
total) render the conclusions of this study almost impossible to interpret.

**Study limitations**

Both these studies included only patients without evidence of sustained ventricular arrhythmia >48 h following the index MI, as sustained ventricular tachycardia or fibrillation >48 h was believed to be unrelated to the index acute MI and deemed a requirement for ICD therapy by the study investigators for secondary prevention against sudden cardiac death. Sustained ventricular arrhythmia early post-MI has been shown to be associated with significantly higher risk of early mortality.10,11 This exclusion of high-risk patients may introduce potential selection bias, which may favour a lower risk cohort of patients.

In the DINAMIT study, less than half of the patients were treated with percutaneous coronary angioplasty. Previous studies have shown that recurrent myocardial ischaemia contributes to the majority of sudden death after acute MI.12,13 Indeed, the benefit of PCI is dominated by a reduction in re-infarction.14 Revascularization may also result in the recovery of cardiac function, particularly in the presence of viable myocardium. In a study using dobutamine stress echocardiography in patients with depressed LV function due to ischaemic heart disease, the presence of at least four dysfunctional but viable segments (25% of the LV) predicted improvement in the global LV function, heart failure symptoms, and had a significantly lower event rate during 2 years of follow-up (when compared with patients with less than four viable segments).15 In addition, patients with acute anterior MI, which formed the majority of the patients in both studies, have been shown to have a higher incidence of re-infarction, heart failure, and mortality.16,17 Hence, the exclusion of patients with sustained ventricular arrhythmia >48 h post-MI and the limited use of revascularization therapy in patients with significant anterior MI may have inadvertently resulted in a selected group of patients at relatively lower risk of sudden arrhythmic death and perhaps proportionately at a higher risk of death from re-infarction and heart failure.

Finally, the DINAMIT study employed HRV in conjunction with LV dysfunction as an inclusion criterion on the basis of previous studies.18,19 Heart rate variability has only limited sensitivity and specificity when used in isolation for predicting the risk of arrhythmic events,20 but the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI)18 study evaluated the use of HRV (and baroreflex sensitivity) with LVEF and found significantly increased mortality in patients with both low HRV and ejection fraction. However, the clinical endpoint of this and other previous studies of HRV21 consisted of not only arrhythmic but also non-arrhythmic deaths; the latter cannot be prevented by the implantation of an ICD. Furthermore, the use of β-blockers may have diminished the predictive value of HRV21 (~87% of the patients in the DINAMIT study were treated with β-blockers when compared with 20% in the ATRAMI study). The non-specific nature of HRV for arrhythmic death and the potentially diminished predictive value with widespread use of β-blockers question the value of HRV (in addition to LVEF) in identifying patients at high risk for ventricular arrhythmias in the DINAMIT study.

**Conclusion**

Two clinical scenarios may emerge following an acute MI (Figure 1). First, in patients with sustained ventricular arrhythmias only in the early period (arbitrarily defined as 48 h) following the index ischaemic event, the arrhythmic events may be regarded as epiphenomena related to myocardial ischaemia or the related mechanical complications. Aggressive treatment of myocardial ischaemia, including revascularization, is the main treatment in these patients, and early implantation of ICD does not reduce overall mortality (the DINAMIT study). Implantation of ICD should be deferred in these cases as is currently recommended, with re-assessment of left ventricular function after ‘40 days’ to determine whether ICD is still required for primary prevention of sudden cardiac death (if the LVEF <35%).

Secondly, in patients with sustained ventricular arrhythmias >48 h after the index MI in the absence of further ischaemia, deferring ICD implantation for ‘40 days’ cannot be justified, as these patients were implanted with ICDs and excluded from the both the DINAMIT and BEST-ICD studies (on the basis of secondary prevention against sudden arrhythmic death). Hence, the implantation of ICD is recommended on the basis of secondary prevention.

Clearly, risk stratification tools are required to identify these patients at risk of sustained ventricular arrhythmia >48 h following acute MI and potentially discharged from hospital. In the absence of robust risk stratification tools, wearable defibrillator may have a role in the prevention of sudden cardiac death, particularly in patients with depressed left ventricular function, but such a strategy will need to be evaluated in a randomized study.22

Finally, in patients without sustained ventricular arrhythmia for at least 40 days, ICD implantation may be indicated on the basis of primary prevention against sudden cardiac death.

**Figure 1** Current 48-hour and 40-day rule.
death based on the established survival benefit demonstrated in previous studies. This distinction between primary and secondary prevention in the setting of acute MI should be explicitly highlighted in national and international guidelines.

Conflict of interest: none declared.

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