

# Should patients with severely impaired left ventricular function following myocardial infarction receive an implantable defibrillator?

*Trial: Moss AJ, Zereba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002; 346: 877-883.*

## Question

Will implantation of defibrillators improve survival in patients with prior myocardial infarction and severely impaired left ventricular function?

## Trial details

**Design:** A prospective, randomised, non-blinded, multicentre, controlled trial of medical therapy versus implanted cardiac defibrillators (ICDs) in patients with severely impaired ventricular function resulting from prior myocardial infarction.

**Background:** Patients with severely impaired left ventricular function are at high risk of sudden death from ventricular arrhythmias. The presence of spontaneous arrhythmias or arrhythmias induced at cardiac electrophysiological (EP) study identifies a high-risk group, but even in the absence of spontaneous or induced arrhythmias the risk of sudden death is considerable. The ICD is known to be effective in treating malignant ventricular arrhythmias. The MADIT-II trial was designed to evaluate the effect of an ICD on survival in patients with severe left ventricular dysfunction caused by previous infarction.

**Methods:** 1232 patients from 76 sites were enrolled over 4 years. All had prior myocardial infarction and a left ventricular ejection fraction of 0.30 or less, and were randomly assigned in a 3:2 ratio to receive a defibrillator (742 patients) or conventional medical therapy (490 patients). Spontaneous ventricular arrhythmias or EP testing were not required for entry into the trial. The primary endpoint was death from any cause.

**Results:** The two treatment groups were similar at baseline with respect to clinical characteristics and medication use at the last follow-up. During a mean follow-up of 20 months, the mortality rate was 19.8% in the conventional therapy group and 14.2% in the ICD group. The hazard ratio for the risk of death from any cause in the defibrillator group compared with the conventional therapy group was 0.69 (95% CI, 0.51–0.93;  $P=0.016$ ). Subgroup analysis showed that defibrillator therapy improved survival regardless of age, sex, ejection fraction, New York Heart Association class or QRS interval.

**Conclusion:** In patients with a prior myocardial infarction and advanced left ventricular impairment, prophylactic implantation of a defibrillator improves survival.

impaired ventricular function, and to implant ICDs in all would place a considerable burden on the health budget. A possible solution is to identify those at highest risk using cardiac EP testing. The MADIT<sup>1</sup> and MUSTT<sup>2</sup> trials reported that ICDs improved survival in patients with coronary artery disease, reduced left ventricular function, non-sustained ventricular tachycardia, and inducible ventricular tachycardia at EP testing. Recent research, however, suggests that the EP study may be a relatively insensitive method of identifying those at highest risk.<sup>3</sup> Moreover, it appears that the lower the left ventricular ejection fraction, the less sensitive the EP study becomes. The MADIT-II study was designed to investigate the potential survival benefit of ICDs in those without spontaneous arrhythmias and without performing EP testing.<sup>4</sup>

## Trial methods

The trial methods were relatively sound. The sample size (1232 patients from 76 sites in the United States and Europe) was adequate. Random allocation of patients resulted in well-matched treatment groups with similar baseline characteristics and similar medical therapy at last follow-up. Treating physicians were encouraged to prescribe effective drug therapy for heart failure and to minimise the use of conventional antiarrhythmics. Similar proportions in both groups received angiotensin-converting enzyme inhibitors,  $\beta$ -blockers and statins. Attendance rates at follow-up were 94% in the conventional therapy group and 97% in the defibrillator group. The trial was open label because blinding was not practical, but the primary end-point was unequivocal — death from any cause. However, a criticism is that mean follow-up was only 20 months, and this may impair assessment of cost-effectiveness. Another criticism is that when the trial commenced in 1997, a selection criterion was that patients have frequent spontaneous or repetitive ventricular premature contractions. This requirement was removed 6 months later, but only 23 of the 1232 patients were enrolled in those first 6 months.

## New information

The trial showed that ICDs improve survival in patients with severely impaired left ventricular function caused by previous myocardial infarction, even in the absence of spontaneous arrhythmias or inducible arrhythmias at EP testing. A disturbing finding was that new or worsening heart failure requiring hospitalisation was more frequent in the ICD group. The cause of this is uncertain. One possible explanation is that the patients in the ICD group lived longer and therefore had more time to develop cardiac

## Commentary

### Rationale for the trial

For several years, it has been routine clinical practice to implant ICDs in survivors of cardiac arrest or malignant ventricular arrhythmia. The prophylactic use of ICDs in high-risk patients who have not yet had a ventricular arrhythmia is more controversial. Patients with impaired left ventricular function are at high risk of malignant ventricular arrhythmias, but the implantation of a defibrillator is relatively expensive. There are large numbers of patients with

failure. Another is that the cardiac failure was caused by asynchronous ventricular contraction caused by ventricular pacing. The results of the recent DAVID<sup>5</sup> trial tend to support the latter hypothesis. If this is indeed the case, the cardiac failure can probably be reduced by judicious programming of the pacing function of the ICD.



### Implications for clinical practice

The routine use of ICDs in patients with an ejection fraction of 0.30 would have profound implications for healthcare spending. Routine use of ICDs for this indication would potentially increase the number of implants by a factor of between 10 and 30 per annum. Currently, about 950–1000 ICDs are implanted annually in Australia and New Zealand, at a total cost for hardware alone of about A\$30 million (my estimates based on information obtained from device manufacturers). A 15-fold increase in the implantation rate would result in an increase in the annual cost for the hardware alone of about A\$420 million. This is about twice the annual budget of a large Australian teaching hospital. This figure does not take into account the increase in hospital and professional fees. Moreover, it is uncertain that there are enough trained cardiac electrophysiologists to implant defibrillators in and follow up such a large number of patients. By comparison, Australian national spending on the lipid-lowering “statin” drugs in the 2001–2002 financial year was about A\$670 million.<sup>6</sup>

Australian cardiologists have not yet embraced the findings of MADIT-II. This is probably because of the cost implications, preferring to wait until the findings are confirmed in other large trials. However, preliminary reports of the COMPANION<sup>7</sup> trial appear to confirm the MADIT-II findings (the study populations of these two trials are not strictly comparable). The findings of another large trial of prophylactic ICD use, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), will soon be reported, and might shed additional light on this question.

The true cost of implementing the MADIT-II findings awaits a detailed cost-benefit analysis. The cost of ICD hardware has been falling for several years, but it is difficult to predict the magnitude of future cost reductions. It may be possible to identify a low-risk cohort which will not benefit from ICD implantation, but the preliminary results are not

encouraging. Recently, in the United States, the Centers for Medicare and Medicaid Services approved the use of ICDs in Medicare patients meeting the MADIT-II inclusion criteria and having a QRS duration of more than 120 ms. This decision was based, in part, on a subsequent analysis of the MADIT-II data, which showed that the benefit was greatest in this group of patients.<sup>8</sup>

The MADIT-II trial is likely to provoke vigorous debate over the best use of healthcare spending for some time to come.

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### Competing interests

None identified.

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