Implantable Cardioverter Defibrillator Therapy
The Sickest Patients Benefit the Most

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At times, our clinical intuition may lead us down the wrong path, but the scientific method helps direct us back to the proper course. In 1970, Mirowski et al published their first experience with the standby automatic defibrillator in animals, but their innovative approach to prevent sudden cardiac death was not initially accepted by the cardiac community. Concerns about the practicality of the implanted defibrillator to save lives stimulated Mirowski and colleagues to perform additional investigations; this culminated in their 1980 publication documenting life-saving internal defibrillation with an implantable device in 3 patients. The era of the clinical use of the implantable cardioverter defibrillator (ICD) therapy began just 20 years ago, and progress in the field since that time has been astounding.

A series of randomized ICD trials began in the early 1990s. When my colleagues and I were designing the Multicenter Automatic Defibrillator Implantation Trial (MADIT), the general attitude was that the ICD might prolong life for only a short time in patients with advanced coronary disease. Although the ICD had already been shown to be effective in terminating acute ventricular fibrillation, it was assumed that defibrillation in patients with chronic coronary disease would only be a temporizing measure, with early occurrence of death due to heart failure. This was not the case. The results of MADIT were published in 1996, and those of the Multicenter UnSustained Tachycardia Trial (MUSTT) in 1999. These 2 primary prevention trials substantiated improved survival with ICD therapy in coronary patients with nonsustained ventricular tachycardia. Two secondary prevention trials that focused on patients with aborted cardiac arrest and life-threatening cardiac arrhythmias have also been completed; these are the Antiarrhythmics Versus Implantable Defibrillators (AVID) study and the Canadian Implantable Defibrillator Study (CIDS). A similar survival benefit was achieved with ICD therapy when compared with amiodarone in both of these trials.

When these 4 trials were planned, it was thought that ICD therapy would be less effective in patients with more advanced left ventricular dysfunction. It was reasoned that the competing risk from nonarrhythmic death (heart failure) would dominate the mortality mechanism in patients with low ejection fractions, thereby limiting the effectiveness of ICD therapy in the sickest group of patients. Once again, our intuition was wrong. These 4 randomized trials (MADIT, MUSTT, AVID, and CIDS) all showed an improved benefit with ICD therapy in those patients having the highest mortality risk. This point is nicely highlighted in the article from the CIDS group by Sheldon et al, which is presented in this issue of Circulation.

The CIDS investigators retrospectively stratified the 659 study patients into 4 risk quartiles on the basis of reduced ejection fraction, advanced age, and poor New York Heart Association (NYHA) functional class. In the highest risk quartile, a 50% relative risk reduction in death occurred with ICD therapy when compared with amiodarone, with no evident benefit from ICD treatment over amiodarone in the 3 lower risk quartiles. Patients with the highest mortality risk received the greatest benefit from the ICD, with lower risk patients receiving little, if any, benefit. The implications of these findings regarding the clinical selection of patients for ICD therapy and the cost-effectiveness of using expensive ICD therapy primarily in the group at highest risk are self-evident.

These findings from the CIDS group are in excellent alignment with the recent publication by Domanski et al from the AVID investigators. The AVID data indicate that patients with a relatively well-preserved ejection fraction (≥0.35) do not have better survival when treated with the ICD when compared with antiarrhythmic drugs (mostly amiodarone). However, in patients with a lower ejection fraction, the ICD was associated with improved survival when compared with antiarrhythmic drugs. Kaplan-Meier survival curves revealed improved survival with ICD therapy in patients with ejection fractions in the range of 0.20 to 0.34, as well as in those with ejection fractions <0.20. Thus, patients with moderate to very severe left ventricular dysfunction achieved the greatest benefit from ICD therapy.

These findings and the request for this editorial influenced me to review the clinical experience with ICD therapy by ejection fraction subsets in MADIT. The eligibility criterion for MADIT was an ejection fraction ≤0.35, and the median ejection fraction for the 196 enrolled patients was 0.26. When the ejection fraction was divided at the median value, the benefit from ICD therapy was concentrated almost exclusively in those with an ejection fraction <0.26 (Figure).
The findings from MADIT, AVID, MUSTT, and CIDS paint a very clear picture—it is the sickest patients who benefit the most from ICD therapy. In retrospect, these results are not surprising when effective therapy is used. Similar results have been found with \( \beta \)-blocker therapy in postinfarction patients, with a greater benefit achieved with \( \beta \)-blockers than with placebo in those with left ventricular dysfunction and frequent ventricular ectopic beats. In patients with chronic congestive heart failure (NYHA functional class II from Guidant Corp to the University of Rochester. Dr Moss holds no stock options or equity with Guidant Corp or any other implantable defibrillator manufacturer, and he is not a paid consultant or on any advisory board of companies that produce defibrillator devices.

## References


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