Implantable Cardioverter Defibrillator Therapy
The Sickest Patients Benefit the Most

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A t 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.

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).
tion entry criterion for MADIT-II is ≤0.30, whereas SCD-HeFT is using an ejection fraction ≥0.35. Whether this minor difference in ejection fraction eligibility is important will be determined when the results of these studies become available in a few years. At this time, both studies have enrolled ≈50% of the target population, with an accumulation of only ≈25% of the anticipated patient-months of risk exposure for ICD and non-ICD therapy.

The ICD is not stand-alone therapy for the prevention of sudden cardiac death. The reduction of sudden death with β-blockers and angiotensin-converting enzyme inhibitors in patients with heart failure is well substantiated, and hypolipidemic therapy may also contribute additional benefit in patients with heart failure due to coronary disease. These results are in sharp contrast to the increased mortality found with antiarrhythmic drug therapy in the Cardiac Arrhythmias Suppression Trial.

The consistency of the ejection fraction/heart failure-ICD findings has several important clinical implications. In the future, ICD therapy will become increasingly targeted for patients with more severe heart disease. It is likely that ICD therapy will become an important adjunct to β-blocker and afterload-reduction drug therapy to improve survival in patients with advanced left ventricular dysfunction and congestive heart failure. At this time, insufficient data exist to determine if there is a lower limit of the ejection fraction below which ICD therapy is not helpful. Many patients with ejection fractions of ≤0.10 function at a level of NYHA class II to III for many years, and I suspect these patients will also benefit from ICD therapy. Improved cooperation is needed between the arrhythmologists and the heart failure specialists to answer these unresolved questions. Finally, better risk stratification will be required to identify arrhythmically-prone patients with good ventricular function who might benefit from ICD therapy.

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References

5. The Antiarrhythmics Versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic drug therapy with implantable

Probability of survival with defibrillator versus conventional therapy in MADIT patients subdivided at the median left ventricular ejection fraction. Top, Ejection fraction (EF) ≤26% (defibrillator, n = 46; conventional, n = 56; P < 0.01). Bottom, Ejection fraction of 26% to 35% (defibrillator, n = 49; conventional, n = 45; P = 0.11). The survival benefit of ICD therapy was significantly greater than conventional therapy only in the subgroup with an ejection fraction ≤26%.

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 β-blocker therapy in postinfarction patients, with a greater benefit achieved with β-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 to IV and an ejection fraction ≤0.40), controlled/extended release metoprolol was associated with a significant reduction in all-cause mortality, cardiovascular mortality, and sudden death. In a similar vein, coronary artery bypass graft surgery is associated with a better survival benefit in those with severe coronary artery disease (ie, those with left main coronary stenosis and those with 2 or 3-vessel coronary disease plus associated left ventricular dysfunction) than in those with milder forms of coronary disease.

The ejection fraction–ICD findings that have surfaced in recent publications were known to the investigators during the data analysis and manuscript preparation phase of these studies, and these preliminary findings were the backbone for the design decisions that were made in planning the recently initiated MADIT-II and Sudden Cardiac Death–Heart Failure Trial (SCD-HeFT) ICD studies. These 2 randomized trials will be evaluating the survival benefit of ICD therapy in patients with left ventricular dysfunction. The ejection fraction–ICD therapy

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