EDITORIAL

MADIT-II and Implications for Noninvasive Electrophysiologic Testing

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The implanted cardioverter defibrillator (ICD) has now come of age. In 1980, Mirowski and associates reported the first three patients in whom the defibrillator was implanted to manage recurrent ventricular tachyarrhythmias refractory to medical therapy.[1] During the 1980s the clinical experience with ICDs progressively increased, but mostly involved patients who had been resuscitated from out-of-hospital cardiac arrest or who had documented episodes of recurrent, life-threatening ventricular tachycardias. The 1990s ushered in a number of randomized primary and secondary ICD trials. In 1996, the Multicenter Automatic Defibrillator Implantation Trial (MADIT) was published, and ICD therapy was associated with 54% reduction in all cause mortality when compared to conventional therapy in patients without prior cardiac arrest or syncope who had reduced ejection fraction (EF $\leq$ 0.35), nonsustained ventricular tachycardia, and inducible nonsuppressible ventricular tachycardia or fibrillation at electrophysiologic study.[2] A study reported in 1999 by the Multicenter Unsustained Tachycardia Trial (MUSTT) confirmed the MADIT findings.[3] Both the MADIT and MUSTT trials were primary prevention studies. During the same period of time, several secondary prevention trials were reported, including the Antiarrhythmics Versus Implantable Defibrillators (AVID) study,[4] the Canadian Implantable Defibrillator Study (CIDS),[5] and the Cardiac Arrest Study Hamburg (CASH).[6] In each of these studies, ICD therapy was associated with improved survival when compared to antiarrhythmic drug therapy.

The protocol used in most of the aforementioned studies suggested that electrophysiologic testing for inducibility should be used to identify patients who would benefit from ICD therapy, but this approach had never been substantiated. In subset analyses from the original MADIT study, we showed that the survival benefit from the ICD was directly related to the severity of the cardiac dysfunction. More specifically, the combinations of the presence of one, two, or three noninvasive factors (EF $<$ 0.26, QRS duration on ECG $\geq$ 0.12 seconds, history of heart failure requiring treatment) were associated with a progressively lower hazard ratios, indicating better survival in higher risk patients with ICD therapy.[7,8]

When we designed the MADIT-II trial in 1977, we reasoned that in patients with a prior myocardial infarction and advanced left ventricular dysfunction as manifest by an EF $\leq$ 0.30, the scarred myocardium would serve as a substrate for malignant ventricular arrhythmias and electrophysiologic testing would not be needed for risk stratification. The MADIT-II trial randomized 1232 patients to ICD or conventional therapy; the only criteria for eligibility was a prior myocardial infarction and EF $\leq$ 0.30. MADIT-II showed a 31% reduction in mortality with ICD therapy compared to conventional therapy, with both groups receiving equivalent and appropriate beta blocker, angiotensin converting enzyme (ACE) inhibitor, diuretic,

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digitalis, and aspirin therapy.[9] In subset analyses, the sicker patients received greater benefit from ICD therapy than those receiving conventional therapy. In an editorial that accompanied the MADIT-II publication, Bigger suggested that improved risk stratification with identification of higher risk subsets within the MADIT-II defined population might save almost as many lives as was observed in the overall MADIT-II population, and effective risk stratification might be more cost-effective.[10]

Thus, the MADIT-II trial substantiates that benefit of ICD therapy in high-risk coronary patients and raises important questions about methods to enhance risk stratification beyond simply a low EF. We have preliminary evidence from MADIT-II that patients who were inducibile at electrophysiologic testing (carried out at the time the ICD was implanted) did not identify those who subsequently experienced an ICD shock for ventricular tachycardia or fibrillation during follow-up. Thus, electrophysiologic testing with documentation of inducibility was not a good risk stratifier. However, the survival benefit from the ICD progressively increased in direct relationship to the manually measured QRS duration on the baseline 12-lead ECG. Patients with QRS duration > 0.12 seconds, and especially those with QRS duration > 0.15 seconds, seemed to receive the greatest benefit from the ICD. We believe these preliminary post-hoc MADIT-II noninvasive analyses have major implications for reinvigorating noninvasive electrophysiologic testing to better identify patients who will achieve maximum benefit from ICD and/or resynchronization therapy.

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