Refining Patient Selection for Primary Prevention Implantable Cardioverter-Defibrillator Therapy
Reeling in a Net Cast Too Widely

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The Multicenter Automatic Defibrillator Implantation Trial (MADIT) II and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) prospectively tested the hypothesis that implantable cardioverter-defibrillators (ICDs) could reduce mortality in patients at increased risk for sudden death from ventricular tachycardia (VT) or ventricular fibrillation (VF). These trials, which demonstrated 5% to 7% absolute mortality reductions over 2 to 4 years, established ICDs as a standard of care for primary prevention of sudden cardiac death. However, the significant risks and high cost of ICD therapy, combined with the high number needed to treat to save 1 life in these populations, have led some to ask whether we have cast the net of sudden death prevention too widely. In this issue, Levy et al provide cautionary evidence that ICD therapy is futile in an identifiable subgroup of SCD-HeFT patients because their heart failure is too advanced.

Most risk stratification efforts to identify candidates for primary prevention ICDs have been based on the hypothesis that patients are likely to benefit if their risk of sudden death is high enough. Various electric measures of arrhythmic risk, such as T-wave alternans, signal-averaged ECG, and electrophysiological study, have not demonstrated adequate or consistent discriminatory power. Paradoxically, the mortality reduction benefit of primary prevention ICDs was established only when risk stratification was based on measures of left ventricular dysfunction and functional class (left ventricular ejection fraction <30% after myocardial infarction in MADIT II or left ventricular ejection fraction <35% with New York Heart Association class II to III in SCD-HeFT) rather than direct measures of arrhythmic risk.

Presently, the number needed to treat to save 1 life for primary prevention ICDs is 15 to 20. Analysis of SCD-HeFT demonstrated an incremental cost-effectiveness ratio <$100 000 only by extrapolating 3 years beyond the end of trial follow-up ($127 503 per life-year saved at 5 years and $88 657 at 8 years). Analysis of MADIT II estimated a less favorable incremental cost-effectiveness ratio of $235 000 per life-year saved at 3.5 years. These cost-effectiveness figures are particularly concerning for a therapy that has significant morbidity both at implantation and during long-term follow-up.

Four distinct approaches may enhance the therapeutic efficiency of primary prevention ICDs: improved risk stratification, improved ICD programming, improved ICD technology, and improved therapy for heart failure. Improved risk stratification may identify either those presently indicated patients whose risk of VT/VF is too low to benefit or those whose risk of death from competing comorbidities is too high to benefit.

On the basis of a proportional hazards regression analysis in MADIT II, Goldenberg et al reported a U-shaped curve for efficacy of primary prevention ICDs, in which patients with the lowest and highest risk scores were less likely to benefit. Much attention has been focused on the lowest-risk patients comprising the left arm of this U-shaped curve. It has been motivated by the dual observations that only ~20% of patients receive ICD shocks for VT/VF at 3 to 5 years and that this rate of shocks is approximately twice the mortality rate in control groups. Thus, only 10% of primary prevention ICD patients receive life-saving therapy, exposing the remaining 90% to all of the risks of ICD implantation and therapy without benefit. However, examination of the mode of death in the low-risk group does not support the concept of patients “too healthy” to benefit from ICD therapy: ICDs reduced the risk of sudden death in this group, but there was a counterbalancing increase in nonarrhythmic death, similar to the findings in the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) of primary prevention ICDs in patients early after myocardial infarction.

Several cohort analyses have evaluated the right limb of the U-shaped curve of Goldenberg et al, comprising the sickest patients. Investigators have reported that patients with advanced age and chronic renal failure do not benefit from primary prevention ICDs because of imminent, competing causes of death. Both the risk-benefit and cost-benefit ratios of primary prevention ICD therapy would be improved by strategies to exclude presently indicated patients who are unlikely to benefit, if they could be identified accurately.

In this context, Levy et al modify a previously validated, risk-prediction model (Seattle Heart Failure Model) to examine the relationship between baseline, predicted mortality rate, and survival benefit from ICD therapy in SCD-HeFT. The model incorporates readily available clinical variables including age, sex, systolic blood pressure, ischemic etiology, ejection fraction, New York Heart Association class, serum
sodium, and creatinine, as well as dosages of heart failure medications. Patients were partitioned into 5 equal-sized groups by mortality risk ranging from 12% to 50% at 4 years. Those in the highest quintile had more advanced age, higher creatinine, and worse clinical heart failure; they had lower left ventricular ejection fraction and blood pressure; and they were less likely to utilize standard medical therapy.

This type of prediction model complements models commonly used in cardiology. Those models estimate risk of a primary treatable condition to identify patients who are at highest risk and thus most likely to benefit from therapy (eg, Thrombolysis in Myocardial Infarction [TIMI]15 and Framingham risk scores16). In contrast, the model of Levy et al calculates the risk of a competing comorbidity. The resultant “competing-risk futility score” defines the clinical context for the decision regarding treatment of the primary risk condition.

The present study corroborates previous reports of the competing roles of arrhythmic and heart failure deaths in patients with heart failure17: Patients with more advanced heart failure have lower proportions of arrhythmic death. Those in the lowest-risk quintile experienced the most life extension from ICD therapy (6.3 years) but also had the lowest absolute mortality reduction (6.6%). With increasing risk, life extension diminished to 1.9 years in the fourth quintile despite the largest absolute mortality reduction (14%) and the lowest number needed to treat to save 1 life (7.1). In the fifth and highest-risk quintile, ICD therapy was associated with an insignificant increase in absolute mortality (~4.9% benefit) despite the fact that ICD utilization for VT/VF was highest in this quintile: 33% of these patients had shocks for VT/VF in comparison with 16% to 22% for the lower 4 quintiles.

Several lines of evidence raise a troubling question: Does the nonsignificant increase in mortality associated with ICD therapy in the highest-risk quintile represent a weak signal of a true adverse effect? In their analysis of MADIT II, Goldberg et al also found that the highest-risk patients had higher mortality rates in the ICD arm than in the control arm (51% ICD versus 43% control at 2 years). Ventricular pacing may be proarrhythmic in ICD patients, even when programmed to demand pacing at 40 beats per minute, as in SCD-HeFT.18 ICD shocks have been associated with increased mortality in both SCD-HeFT and MADIT II, although neither analysis could determine whether the shocks were causal antecedents to death. Sweeney et al reported higher mortality in patients treated with shocks for VT/VF than those treated with antiarrhythmia pacing (ATP) in the PACING Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx II) study, after controlling for confounding variables. Furthermore, pulseless electric activity after shocks for VT/VF is an important cause of sudden death in ICD patients, and those with advanced heart failure are at highest risk.22 Shocks delivered during tachyarrhythmias have additional, less dramatic adverse effects on contractile function, which might increase mortality in patients with advanced heart failure.

These data focus attention on optimizing present ICD programming and therapy. ATP can terminate 60% to 70% of ventricular arrhythmias detected as VF. However, because ATP requires no delay for capacitor charging after detection of VT/VF, it treats even more self-terminating VT/VF than shocks. Thus, programming a sufficiently long time for detection of VT/VF is especially important in primary prevention ICDs when ATP is used. When one considers both the efficacy of ATP and the incidence of self-terminating VT/VF, it is likely that more than half of “appropriate” shocks for VT/VF in SCD-HeFT were unnecessary.

Because primary prevention ICDs usually require only 70% to 80% of ventricular intervals to be shorter than the programmed detection interval, rapidly conducted atrial fibrillation can be detected inappropriately as VT/VF even if the average ventricular cycle length exceeds the detection interval. The dual facts that the most common cause of “inappropriate” shocks in primary prevention patients is rapidly conducted atrial fibrillation and the increased risk of death associated with such shocks support routine programming of ICD algorithms to discriminate VT from supraventricular tachycardia. Before a strategy such as the one proposed by Levy et al is adopted, it should be verified prospectively in a primary prevention population with ICDs programmed to minimize unnecessary shocks.

Long-term goals include both improved ICD technology and improved heart failure therapy. Future ICDs may further reduce both appropriate and inappropriate shocks with the use of pacing algorithms for prevention of VT/VF, more reliable leads, improved supraventricular tachycardia–VT discrimination, including active pacing methods, and substantial delays in therapy to permit spontaneous termination of VT/VF if estimated arterial pressure remains normal. Improved heart failure therapy may permit patients who are resuscitated from VT/VF by ICDs to achieve survival benefit. Conversely, improved heart failure therapy may indirectly increase the survival benefit of ICD therapy: Fewer heart failure deaths may increase the incidence of VT/VF, which can be terminated by ICD therapy.

The unrealized goal of optimizing primary prevention ICD therapy is shared by physicians, payors, and patients. To reach this goal, we must both maximize benefit from existing ICDs and improve ICD technology. However, we must also cast the net of sudden death prevention more selectively by identifying those patients in whom present ICD therapy is futile or harmful, even though their risk of VT/VF may be substantial.

Disclosures
None.

References
Tung and Swerdlow Patient Selection for Primary Prevention ICDs


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