Primary Prevention of Sudden Cardiac Death
The Time of Your Life

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The trouble with sudden cardiac death (SCD) is just that—it is sudden and individually unpredictable. Recent data from the Centers for Disease Control showed that SCD accounted for >460,000 deaths, or about 63% of deaths due to cardiac disease, in 1999. Typically, a cardiac arrest results from sustained ventricular tachycardia (VT) or ventricular fibrillation that progresses to death if effective resuscitative efforts are not started within several minutes of the arrest. It is not surprising that the overall survival rate of patients with out-of-hospital cardiac arrest in the United States is low, estimated to be <5%. Although more widespread use of automated external defibrillators could lead to a reduction in SCD, it is unrealistic to expect too much from this technology, especially because most cardiac arrests either are unobserved or occur in a location without ready access to an automated external defibrillator. The epidemic proportions of SCD have led to decades of research and randomized clinical trials designed to predict which individuals are at risk of SCD and to determine what methods prevent it.

Historical Milestones to Prevent SCD
Coronary artery disease (CAD) causes ~70% of SCD, and most clinical trials have evaluated this patient population. The emphasis of this Focused Perspective is on antiarrhythmic drug and device trials, but the reader should remember that selective use of β-adrenergic-blockers and angiotensin-converting enzyme inhibitors has reduced SCD. It has been known for decades that patients at highest risk for SCD after myocardial infarction (MI) have substantial left ventricular dysfunction, frequent premature ventricular complexes (PVCs) or nonsustained VT, or both conditions. Early efforts to prevent SCD employed the PVC suppression method. The Cardiac Arrhythmia Suppression Trial (CAST) was a randomized, placebo-controlled trial that tested the hypothesis that PVC suppression after MI would reduce arrhythmic death. Even though the drugs used (encainide, flecainide, and moricizine) successfully suppressed PVCs, arrhythmic death was more common in patients treated with drugs versus placebo. Furthermore, total mortality rate was greater with encainide or flecainide compared with placebo. The second Cardiac Arrhythmia Suppression Trial (CAST-II) showed an increased rate of mortality in patients given moricizine versus placebo in the early post-MI phase, as well as no long-term survival benefit of moricizine. CAST and CAST-II were the death knell for the PVC suppression hypothesis, but they ushered in the era of empirical amiodarone therapy to prevent SCD.

Two trials compared the survival benefit of empirical amiodarone therapy versus placebo after MI. The European Myocardial Infarction Amiodarone Trial (EMIAT) randomized patients with left ventricular ejection fraction (LVEF) <0.40, and the Canadian Myocardial Infarction Amiodarone Trial (CAMIAT) included patients with >10 PVCs per hour. Neither EMIAT nor CAMIAT showed a survival advantage with amiodarone, but unlike CAST, amiodarone did not worsen survival. The hopes for a treatment for primary prevention of SCD in patients with CAD now rested solely with the implantable cardioverter defibrillator (ICD). Three trials investigated this hypothesis: the Multicenter Automatic Defibrillator Implantation Trial (MADIT), the Multicenter Unsustained Tachycardia Trial (MUSTT), and the Coronary Artery Bypass Graft (CABG) Patch Trial. MUSTT enrolled patients with CAD, nonsustained VT, and LVEF ≤0.40 who had sustained VT induced at electrophysiology study. Seven hundred and four patients were randomized to receive an ICD or to a control group. During follow-up, there was no difference in mortality compared with patients not receiving an ICD. In fact, the survival curves for MUSTT and MADIT are almost superimposable. MUSTT included 196 patients with a previous MI who had LVEF ≤0.35, nonsustained VT, and sustained VT initiated at electrophysiology study that was not suppressed by intravenous procainamide. Patients were randomized to receive an ICD or conventional therapy, with amiodarone being given to many in the conventional treatment group. The ICD-treated group had a significant survival advantage, with a 56% reduction in mortality compared with patients not receiving an ICD. In fact, the survival curves for MUSTT and MADIT are almost superimposable.

The CABG Patch Trial did not show a survival advantage for the ICD. A total of 900 patients with LVEF <0.36 and an abnormal signal-averaged ECG were randomized in the operating room after CABG to receive an ICD or to a control group. During follow-up, there was no difference in mortality rate between patient groups.
Multicenter Automatic Defibrillator Implantation Trial II

MADIT-II is the latest published ICD primary prevention trial in patients with CAD. The design was quite simple, randomizing 1232 patients with a previous MI and LVEF ≤0.30 to receive an ICD or conventional medical therapy. The ICD resulted in a significant 31% reduction in risk of death compared with conventional therapy. Figure 3 from Moss et al shows hazard ratios for selected clinical characteristics, including various QRS duration interval cutoff values. There appeared to be a trend for patients in the widest QRS interval (>0.15 second) subgroup to derive the greatest survival benefit from an ICD. However, overall there was no significant difference in the effect of ICD on survival stratified to the QRS interval. Furthermore, and germane to the study by Wilber et al published in the present issue of Circulation, the authors state there were “no significant differences in the effect of defibrillator therapy on survival in...the interval since the most recent MI (six months or less versus more than six months).” A related finding from MUSTT shows that inducible sustained VT, a risk factor for mortality, occurs with a similar frequency in patients <1 month compared with >36 months after MI.

Subgroup analysis is an hypothesis-generating exercise that may yield results requiring further investigation. One has to exercise caution when tossing out a large fishing net, for one may not like what one finds. Although it is pleasant to sort through a bountiful catch of fresh fish, the old tares are certainly a nuisance. For whatever their reason, the Centers for Medicare and Medicaid Services reevaluated the MADIT-II data and concluded that they would only reimburse for ICD therapy given to a MADIT-II patient with a QRS duration >0.12 second. Unfortunately, this is in conflict with the Class IIa recommendation reported in the ACC/AHA/NASPE Practice Guidelines for implantable devices. The practicing physician was left with a classic double bind: Instead of “wash your hands, but don’t get them wet,” we have, “you need an ICD, but it may not be reimbursed.”

In the present issue of Circulation, Wilber et al report a new MADIT-II subgroup analysis of the time dependence of mortality risk and ICD benefit after MI. Patients were entered into MADIT-II 81±78 months after MI, and in 89% of the patients, enrollment was in an outpatient setting, which should lessen the bias of higher-risk inpatients. ICD survival benefit was compared among 4 post-MI subgroups: <18 months; 18 to 59 months; 60 to 119 months; and ≥120 months. Mortality rates of conventionally treated patients increased significantly over time, whereas there were minimal time-dependent mortality changes in ICD-treated patients. Overall, the hazard ratio for ICD benefit was similar and substantial for quartiles 2 to 4 but was only 0.98 for patients <18 months after MI, suggesting little if any benefit for these patients. The patients <18 months after MI were younger, had better ventricular function, more often received β-blocker therapy, and less frequently had QRS duration >0.12 second, but adjusting for these variables continued to show a difference in ICD benefit between quartile 1 and the combined quartiles 2 to 4.

How to Handle Unexpected and Unwanted Data

The subgroup fishing net contents on ICD benefit over time yielded both bountiful fish (patients, even many years after MI, had a survival advantage with an ICD) and an old, unwanted tire (minimal ICD benefit to patients <18 months after MI). I suspect that the authors were satisfied with the observation of ICD benefit years after MI because one of their goals was “to evaluate whether long-term ICD survival benefit diminished as a function of elapsed time from infarction to device implantation.” This is not a surprising finding because about half of patients enrolled in MUSTT were >3 years after MI. Even still, this subgroup analysis only supports but does not prove the long-term ICD survival benefit.

More troublesome is the unexpected observation of minimal ICD benefit in quartile 1 patients <18 months after MI, especially because the initial trial results stated there was no difference in ICD benefit in patients ≤6 months versus >6 months after MI. This is the problem with trying to answer a prospective question with retrospective data analysis. In addition to selecting arbitrary time cutoffs for analysis, there are several other potential reasons that might explain the observed minimal ICD survival benefit in quartile 1 patients in this study. These include very low mortality rates 1 year after MI with advances in nonarrhythmic therapy; elimination of highest-risk patients by selection bias; need for additional risk factors, eg, electrophysiological testing in patients <18 months after MI; and simply just bad luck.

Recent data from thrombolytic-treated patients with acute MI show an approximately 90% survival rate at 1 year, and this remains a high-risk group of patients. There may have been some investigator selection bias, as evidenced by exclusion of patients who had an approved indication for an ICD. Thus, patients with nonsustained VT might have undergone electrophysiological testing and received an ICD if sustained VT was induced. Elimination of this high-risk patient population, especially if skewed to patients <18 months after MI, could reduce overall mortality in control patients and the likelihood of a survival benefit of the ICD. Furthermore, the high mortality rate in the first month after MI could eliminate another potential high-risk group because patients <1 month after MI were excluded from MADIT-II. It is noteworthy that the 1-year survival rate of patients without an ICD was 0.90 in MADIT-II but only 0.85 and 0.77 in MUSTT and MADIT, respectively. The value of risk stratifiers in addition to LVEF ≤0.30 (eg, electrophysiology testing, nonsustained VT, signal-averaged ECG, T-wave alternans) remains to be tested. It is possible that their prognostic value varies as a function of time from MI. Lastly, the results of this retrospective subgroup time-dependent analysis may have been due to just bad luck. By this, I mean that by not evaluating this question prospectively, multiple factors may have led to an answer that would most likely not be reproducible or would even be the opposite if the question were prospectively studied in a randomized clinical trial.

What Should the Clinician Do?

In my opinion, one cannot have it both ways, that is, accept the ICD survival benefit in patients late after MI as valid but...
disregard the lack of ICD benefit early after MI as a “fluke.” The acceptable answer to this important question will require a prospective randomized clinical trial. For the present time, clinicians should be guided in the care of their patients by the primary results from MUSTT, MADIT, and MADIT-II. MUSTT taught us that patients with nonsustained VT and LVEF ≤0.40 four days or more after MI or revascularization should undergo electrophysiological testing and receive an ICD if sustained VT is induced. MADIT-II showed the ICD survival value for patients with a LVEF ≤0.30 one month or more after MI and >3 months after coronary revascularization. The reimbursement based on QRS duration is government directed and will need to be addressed on an individual patient basis. Refinement of this simple approach awaits prospective data from randomized clinical trials. Until then, for those worrisome patients who don’t “fit the rules,” I often apply the concept of family-based medicine—what would I do for my parents, siblings, or spouse? This usually keeps me out of trouble.

References

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