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Editorial

ICDs for Patients With Stable VT, Cardiomyopathy, and Relatively Preserved LVEF: Core Therapy, Precision Medicine, or Indication Creep?

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See article by Gula et al., page 1271–1276 of this issue.

Unexpected sudden cardiac death (SCD) remains one of the most common causes of mortality.[1] The majority of SCDs are caused by ventricular tachycardia (VT) or ventricular fibrillation (VF), with fewer related to asystole, electromechanical dissociation, or sudden hemodynamic catastrophes.[1] A normally functioning implantable cardioverter defibrillator (ICD) will terminate the vast majority of VT/VF episodes and will preclude asystole, thereby reducing the probability of SCD in high risk patients by ~50% and of all-cause mortality by ~25% in comparison with antiarrhythmic drug (AAD) therapy.[2] Nevertheless, the placement and subsequent presence of ICDs have risks including surgical complications, system infections, component failures, inappropriate therapies, and death.[3] Accordingly, ICDs are reserved for patients judged to have higher risks of SCD, a judgement that, at present, is neither sensitive nor specific.

Because most SCDs result from VT/VF, the strongest predictors of SCD are predictors of future episodes of VT/VF, the strongest of which is a past episode of VT/VF. Thus, early trials of ICDs focused on patients who had survived life-threatening VT/VF (secondary prevention). In these trials, the incidence of SCD in patients randomized to AAD therapy was 6.1% per year vs 2.8% per year in patients randomized to ICDs.[2] Subgroup analyses of these trials suggested that the mortality benefit of an ICD was limited to patients with advanced left ventricular systolic dysfunction.[2] Accordingly, subsequent ICD trials in patients without previous VT/VF (primary prevention) focused on patients with cardiomyopathies and left ventricular ejection fractions (LVEFs) $\leq$ 0.35, wherein the incidence of SCD in patients randomized to conventional therapy was 3.4% per year vs 1.2% per year in patients randomized to ICDs.[4]

Patients with hemodynamically stable VT were excluded from the secondary prevention ICD trials, as they were believed to have low probability of SCD, based on the conviction that, despite being likely to re-experience stable VT, they were not likely to experience life-threatening VT/VF. Observational reports of the probabilities of SCD or rapid, potentially life-threatening VT/VF in patients with hemodynamically stable VT are at odds; some report a low probability,[5,6] whereas others report a high probability of these events.[7-10] Patients in these studies were dominated by those with LVEFs $\leq$ 0.35. Two studies reported the probabilities of rapid (presumed hemodynamically unstable) VT/VF in patients with previous hemodynamically stable VT who had received ICDs.[9,10] Böcker et al.[9] studied 50 such patients (82% ischemic cardiomyopathy, mean LVEF 0.39 $\pm$ 0.16), who had received ICDs after failure to identify predicted effective AAD therapy. Their 2-year actuarial probability of any ICD-treated VT/VF was 77%. Their 2-year actuarial probability of unstable VT/VF (VF or VT with a cycle length both $<$ 250 ms and $>$ 50 ms less than the baseline VT) was 29%. Data specific to patients with relatively preserved LVEF was not provided. Glikson et al.[10] studied 82 such patients (89% ischemic cardiomyopathy, mean LVEF 0.32 $\pm$ 0.11) who had received ICDs. Their degree of AAD resistance was not specified, although 28% were receiving AADs at the time of their hemodynamically stable VT. Their 2-year actuarial probability of any ICD-treated VT/VF was 67%. Their 2-year actuarial probability of hemodynamically unstable VT/VF (VF or VT with a cycle length $>$ 100 ms less than the baseline VT or 50 ms less than the baseline VT if the resulting cycle length was $<$ 300 ms) was 12%. Seventeen patients had LVEFs $\geq$ 0.40. They had 4-year actuarial probabilities of any ICD-treated VT/VF of 80% and of hemodynamically unstable VT/VF of 11%. The 56 patients with LVEFs of $<$ 0.40 had 4-year actuarial probabilities of any ICD-treated VT/VF of 76% and of hemodynamically unstable VT/VF of 29%. The difference in rates of hemodynamically unstable VT/VF did not reach statistical significance (P = 0.29), "probably because of the small number of subjects."[10]

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Guidelines are relatively silent regarding patients with hemodynamically stable VT, ischemic or nonischemic cardiomyopathy, and LVEF $\geq$ 0.40. European Society of Cardiology (ESC)[11] guidelines provide a Class IIa/Level of Evidence C recommendation for ICDs in such patients, without specifically mentioning patients with hemodynamically stable VT; American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS)[12] guidelines provide a Class I/Level of Evidence B-NR recommendation for ICDs in such patients, without specifically mentioning patients with relatively preserved LVEF; and Canadian Cardiovascular Society (CCS)[13,14] guidelines provide a Strong Recommendation/Moderate-Quality Evidence guideline for ICDs in such patients, without specifically mentioning patients with either hemodynamically stable VT or patients with relatively preserved LVEF.

A More Focused Reassessment

In this issue of the *Canadian Journal of Cardiology*, Gula et al.[15] provide additional data relative to recurrence of VT/VF from 64 patients with cardiomyopathy and LVEF 0.36 to 0.49 who had received ICDs after hemodynamically stable VT. The primary outcome variable was the first occurrence of ICD-treated VT/VF following a 7-day blanking period after ICD placement. Their major findings were that such patients have high probability of ICD-treated VT/VF (2-year actuarial probability of 55%); such patients have high probability of shock-treated VT/VF (2-year actuarial probability of 20%); the mean rate of recurrent VT/VF (199 $\pm$ 37 beats per minute [bpm]) in the 37 patients with VT/VF recurrence was statistically significantly faster ($P = 0.048$) than their baseline VT (183 $\pm$ 27 bpm); and no clinical variables were identified that independently predicted recurrent VT/VF.

Comparison to Existing Literature

Frequent recurrence of VT in the patients of Gula et al.[15] is expected, as the arrhythmogenic substrate for hemodynamically stable VT in most patients with cardiomyopathy includes a continuously present re-entrant circuit that will sustain VT when initiated by a trigger. The 2-year actuarial incidence of any ICD-treated VT/VF reported by Gula et al.[15] (55%) appears to be less than previously reported by Böcker et al.[9] (77%) and by Glikson et al.[10] (67%). This may reflect either interim improvement in patient prognosis and ICD technology or that Gula et al.[15] restricted their study to patients with relatively preserved LVEF. The only previous comparable study of patients with both stable VT and relatively preserved LVEF, comprising 17 patients, reported a 4-year actuarial incidence of any ICD-treated VT/VF of 80% (if linearity is assumed, 40% after 2 years).[10] Note that the study of Gula et al.[15] shares bias of previous studies of having included many patients with demonstrated resistance to AAD. Whether or not these recurrence rates are representative of drug-naïve patients with hemodynamically stable VT and relatively preserved LVEF cannot be determined from available data. Nevertheless, the study of Gula et al.[15] nearly triples the number of published patients with hemodynamically stable VT, cardiomyopathy, and relatively preserved LVEF addressing the natural history of VT/VF recurrence.

The presence of a continuously present re-entrant circuit capable of supporting stable VT predicts that recurrent VTs should have the same rate as the baseline VT in the absence of therapy changes. Indeed, in patients with LVEF $\geq$ 0.40 and VT/VF, more than 90% of recurrent VT/VF have a cycle length within 30 msec of the baseline VT/VF.[16] Nevertheless, there remains a worrisome possibility of a recurrent VT/VF with a faster rate that could be life threatening. As discussed earlier, based on 17 patients, the 4-year actuarial probability of hemodynamically unstable ICD-treated VT/VF was 11% in patients with stable VT, cardiomyopathy, and LVEF $\geq$ 0.40.[10] Three patients (4.7%) in the study of Gula et al.[15] had unstable VT/VF as defined by Böcker et al.[9] over a median follow-up of 827 days, translating into a 5-year probability of potentially life-threatening VT/VF of approximately 8.5% (likely an underestimate, as Gula et al.[15] only considered first recurrences of VT/VF). This rate is greater than the $\geq$ 6% estimated 5-year rate of SCD used by ESC[11] guidelines to recommend a Class IIa/Level of Evidence B recommendation for an ICD when considering precision medicine in individualized patients. Nevertheless, we must recognize the dangers of equating presumed life-threatening ICD-treated VT/VF with SCD.

Gula et al.[15] also provide novel evidence of a statistically significant increase in the rate of VT/VF over time in patients with stable VT, cardiomyopathy, and relatively preserved LVEF. Nevertheless, the extent to which changes in ADD therapy contributed to this observation cannot be determined from available data.

Future Research and Practice Implications

The study of Gula et al.[15] provides weak support for placement of ICDs in patients with stable VT, cardiomyopathy, and relatively preserved LVEF, particularly in patients with demonstrated resistance to AAD. Nevertheless, further research is clearly required, including prospective observational studies focused on patients early in their course before demonstrated AAD resistance that consider all recurrences of VT/VF following guidelines for high-quality observational trials.[17] Nevertheless, whether or not such patients truly benefit from ICD placement can only be determined by an appropriately designed randomized clinical trial, if, indeed, such a trial is feasible. Meanwhile, other approaches to reducing the risk of SCD in patients with cardiomyopathy and relatively preserved LVEF are focusing on identifying markers of increased SCD risk other than previous hemodynamically stable VT/VF and randomizing the population, so chosen, in a clinical trial of ICD therapy. One such ongoing study, the **R**isk **E**stimation **F**ollowing **I**nfarction **N**oninvasive **E**valuation-**ICD** (REFINE-ICD) trial (NCT00673842) is randomizing patients with myocardial infarction (MI) and LVEF 0.36 to 0.49 to usual care vs usual care plus ICDs. Study patients are selected based on both abnormal Holter-based T-wave alternans and abnormal Holter-based heart-rate turbulence, predicting ~9-fold higher risk of mortality. Enrollment in Refine-ICD is anticipated to be complete in the next 12 months, and it

will provide much needed evidence on the optimal care for these patients.

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