Expanding Risk-Profiling Strategies for Prediction and Prevention of Sudden Cardiac Death*

Robert J. Myerburg, MD, Robert C. Hendel, MD
Miami, Florida

Prediction and prevention of sudden cardiac death (SCD) in the individual patient remains a huge challenge for the clinician. Sudden cardiac death accounts for as many as 50% of all cardiovascular deaths, and most SCDs occur either as a first cardiac event or as an unexpected incident among patients in the large subgroup with recognized heart disease whose profiles do not suggest a high risk for SCD (1). To impact upon the population burden of SCD, in parallel with benefitting the individual patient, it is necessary to develop risk-profiling strategies that distinguish small subsets at much higher risk within the general population or among those with known disease currently classified at low risk.

Two major risk-profiling strategies dominate the application of our current knowledge on the subject. One focuses on high-risk subsets of patients with ischemic and nonischemic heart disease and some of the inherited disorders associated with SCD risk, largely for the purpose of identifying candidates for potentially lifesaving implantable cardioverter defibrillator (ICD) therapy. The other approach uses methodologies such as Framingham risk assessment and clinical markers of risk to encourage preventive and lifestyle-modification therapies among more general population sets. The efficiencies of both strategies have been disappointing. We have, in regard to the high-risk subgroups used in the design of the ICD trials, come to focus primarily on left ventricular ejection fractions (LVEFs)—usually dichotomized at 30% or 35%—as the major determinant of risk. The accuracy of the latter is limited by the absence of stratifying at various levels of LVEF in the trials (2). Moreover, the methods used for determining LVEF also introduce variability and inconsistence with regard to the risk threshold, and variations within categories of LVEF might be modulated by clinical, anatomic, electrophysiological, and autonomic factors that were not included in the studies. Therefore, the power of individual risk-profiling on the basis of left ventricular function is limited, especially when LVEFs are ≥30%. For the general population, we have identified some reasonably good population stratifiers for the question of prevention of SCD; but because the incidence is low within more general populations, individual risk prediction remains problematic, despite the large cumulative numbers.

In recent years, the need to identify new risk-profiling strategies and new technological approaches that are intended to yield better stratification have been discussed in a number of publications, for both the high-risk populations and the more general subpopulations from which large numbers of SCDs emerge (3–6). Anatomic, clinical, and electrophysiological components have been proposed or evaluated, but no 1 technique, or combination, seems to stand alone. The proposed targets include the magnitude and pattern of myocardial scarring (e.g., LVEF, heart failure, and contrast magnetic resonance imaging anatomy) and extent of coronary artery disease; electrophysiological and autonomic measurements such as QT and heart rate variability, T-wave alternans, and biomarkers such as BNP; and comorbidities such as chronic renal disease. One intriguing approach is the use of neurohumoral imaging with iodine-123 metaiodobenzylguanidine, which closely correlates with SCD, when myocardial activity or washout rates of this tracer are abnormal (5,6). Common to most of these discussions is the notion that there is not likely to be a single marker or 2 that will achieve effective individual risk-profiling; rather, more complex profiling strategies are needed. Even the hope that a few genetic markers of risk, standing alone, will lead to better individual profiling is giving way to the emerging recognition of the intricacies of the genetic underpinnings of complex diseases due to interactions with clinical and environmental factors (7).

The problem is further complicated by the inaccuracy and variability related to the measurement of left ventricular function due to geometric assumptions and hemodynamic conditions, including loading conditions. In addition, LVEF measurements at a point in time might not remain stable, as occurs with ventricular remodeling in post-
infarction patients. Furthermore, after acute coronary syndromes, LVEF might either improve or worsen over time, and we have yet to define the implications of such changes in the context of the underlying substrate or their effect on risk prediction over time. Insight is needed into the pathophysiological implications of dynamic changes in risk-profiling as the markers change over time (8). Therefore, risk stratification becomes a dynamic process, often with relative subjectivity of many parameters, rather than a static measure that provides consistent measures of risk that can reliably be extrapolated for the prediction of future events.

In this issue of the *Journal*, Piccini et al. (9) present the results of a study examining risk stratification of SCD risk in a cohort of 4,865 patients with angiographically documented coronary artery disease and LVEF > 35%, most of whom had normal global function (median value 51%). The study design was intended to determine retrospectively whether SPECT myocardial perfusion imaging score, alone and in combination with other measures, enabled identification of a subset within that population who are at a high risk for SCD. Their primary methodological measure was summed stress score, a combined measure of fixed and reversible perfusion defects, identified during stress imaging studies. The authors suggest that the magnitude of the perfusion defects on SPECT stress testing identifies increasing risk of SCD, particularly when combined with other markers in a risk nomogram that included the SPECT score, Charleison score, and LVEF.

It is interesting to note that the summed difference score was not predictive of SCD, suggesting that the presence of at least some scar tissue is required to place the patient within the high-risk group. This is supported by the observation within the paper (9) that the summed stress score remains predictive of SCD even when adjusted for revascularization. The pathophysiology underlying these findings is unknown, but scar tissue and/or transient ischemia might be involved in the initiation of cardiac arrest (10,11). Related to the summed score, it is unclear why the threshold value of 8 was selected; additional validation of this cut-point is warranted either by a validation set of subjects or another trial, so as to demonstrate the ability to apply this value in other cohorts.

The meritorious goal of risk-profiling within a large low-risk population, to identify a small high-risk subset, reflects the need for new strategies for SCD prediction. However, the intriguing fact that the subset defined as high-risk (>10% at 3 years) was concentrated in only 0.5% of the total cohort is modulated by the observation that only 2 of 79 SCDs occurred in that subset, with the remaining 77 SCDs occurring in the low-risk subgroup. Although the crude 3-year incidence of SCD in the high-risk group (2 of 26; 7.7%) was more than 4-fold greater than the incidence in the low-risk group (77 of 4,839; 1.6%), this risk-profiling strategy still limits our ability to achieve high-risk resolution within a low-risk subset. Stated another way, only 2.5% of all SCDs were identified as high-risk by the SPECT nomogram. Most SCDs emerged from the subgroup with low summed SPECT scores. Whether the nomogram has more predictive power than evident in this study will require prospective testing, likely in conjunction with additional markers.

A strategy employing SPECT imaging might also have application to higher-risk post-myocardial infarction populations. Because ejection fraction alone does not discriminate ICD benefit as accurately as desired, especially among those with ejection fractions > 30%, it would be intriguing to know whether this strategy would be useful for discriminating risk in that important albeit smaller population. In contrast, for the estimated 30% to 50% of all SCDs that occur as first cardiac events, most of whom will have coronary heart disease at postmortem examination, this strategy will not contribute to prediction and prevention.

The current study should be viewed primarily as hypothesis-generating, given its cross-sectional nature and susceptibility to unintended bias. As the authors themselves recognize, these observations cannot be used for risk-profiling of the subset with coronary artery disease and normal ejection fractions at this time. Future prospective studies might identify a value that would be useful in large clinical trials. In the long run, the added costs of larger trials with additional stratifiers are justified because they may translate into improved economy of therapeutics (8).

**Reprint requests and correspondence:** Dr. Robert J. Myerburg, Division of Cardiology (D-39), University of Miami Miller School of Medicine, P.O. Box 016960, Miami, Florida 33101. E-mail: rmyerbur@med.miami.edu.

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