Nonischemic dilated cardiomyopathy (NIDCM) is the second leading cause of sudden cardiac death (SCD) in the United States. As with coronary artery disease, large-scale clinical trials evaluating implantable cardioverter defibrillator (ICD) therapy based on noninvasive risk markers have focused largely on left ventricular ejection fraction (LVEF). These studies demonstrate that ICD use in selected patients with NIDCM and depressed LVEF is associated with improved survival. The broader question is whether ICD use based on LVEF (and New York Heart Association class) as currently listed in the guidelines represents optimal deployment of this valuable but costly resource. As with ischemic cardiomyopathy, this question is easily answered by the observations that many SCD cases occur in patients whose LVEF is not within the guideline criteria for ICD implantation and that the majority of patients whose LVEF does fall within the guideline criteria do not experience appropriate shocks from their ICD. Although ICD shocks may overestimate the benefit of ICDs to reduce SCD, ICD shocks were reported in only 33 of 229 patients in Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE). This underscores the need for improved risk stratification to better deploy ICD use for SCD prevention. In addition to providing improved clinical outcomes, better ICD deployment via improved risk stratification could dramatically enhance the cost-effectiveness of this treatment. However, the question of how to achieve improved risk stratification endures.

The limited predictive value of LVEF, in particular, is well demonstrated in the report by Pezawas et al. They report that 22% of patients with an LVEF ≥30% had fatal ventricular arrhythmias as their first event. It is therefore clear that a refreshed approach to risk stratification is required, one that does not anchor on LVEF. An American Heart Association scientific statement identified the steps needed to establish markers of risk. This approach represents an ascent on the pyramid of knowledge, using the broad knowledge base developed on individual risk predictors to develop practical approaches that can be implemented and evaluated for clinical use. The initial steps include proof-of-concept testing, prospective validation, and assessment of incremental value for the risk predictor. There are ample data that have addressed these issues for SCD risk stratification in NIDCM. The next hurdle is demonstration of clinical utility, does the predictor change predicted risk enough that it alters recommended therapy. Although a plethora of data exists to establish the predictive value of the parameters described in the previous paragraph, there are no data to establish that any of these parameters change risk sufficiently to alter therapy and improve outcomes. Although LVEF is helpful, its limitations are well recognized. At this point, the research focus for risk stratification must therefore shift to focus on identifying
whether any existing or novel risk factor can be used singly or in combination to provide clinically meaningful information that can be acted on to alter therapy and improve outcomes.9

The long duration of follow-up and the change in predictive value of the tests when repeated at 3 years raise the critical issue of the durability of risk assessment.10 Both heart rate variability and baroreflex sensitivity were significantly lower on initial evaluation among those who experienced arrhythmic death/resuscitated cardiac arrest and cardiac death than those who remained alive, but there was no difference when re-evaluated at 3 years. There is certainly a survival bias as patients with abnormal values had events and died between the 2 evaluations. Although testing was repeated at 3 years in survivors, there is no information whether this newer information provided updated information on arrhythmic risk. This is a critical question that will need to be further addressed, as well as the other aspects of dynamic risk, that is, activity and diurnal, weekly, and seasonal variations on SCD risk.11

In considering how to address the problem of risk stratification for SCD in patients with NIDCM, it is important to consider the multifactorial nature of the problem. Although nonarrhythmic causes of SCD are not likely to be addressed in the same fashion as arrhythmic causes, there remains a diverse set of causes for arrhythmic SCD that may require different tools for risk assessment: ventricular tachycardia, ventricular fibrillation, and bradyarrhythmias. Given the multifactorial nature of the problem, it is unlikely that a single test will be able to have adequate predictive power on its own. Although multicomponent risk evaluations are more complex, this may be necessary to advance this field. Focusing on the substrate for these arrhythmias and their triggers will likely provide a robust combination of risk predictors. In this regard, identification of fibrosis by cardiac MRI could be an important predictor of arrhythmic events, even moreso than in ischemic heart disease.12 In ischemic heart disease, there is a moderate negative relationship between infarct size and LVEF, as well as other aspects of dynamic risk, that is, activity and diurnal, weekly, and seasonal variations on SCD risk.11

Another important finding reported by Pezawas et al13 is the occurrence of electrical storm in 4 of 60 (7%) patients that resulted in arrhythmic death despite an ICD. Although the ICD is highly effective in terminating ventricular tachycardia/fibrillation, alternative approaches to prevent these arrhythmias are necessary. Although standard antiarrhythmic agents do not seem to be effective in this regard, other agents, such as statins,15,16 or nonpharmacologic therapies, such as biventricular pacing in appropriate patients,17 may be effective. A renewed focus on developing alternative device therapies or novel pharmacological agents to prevent rather than respond to fatal ventricular tachyarrhythmias is needed.

Pezawas et al13 highlight both the opportunity and the daunting task facing the medical community to improve risk stratification. As we ponder how to accomplish this, it is instructive to consider what may be the most significant barrier to climbing the pyramid of knowledge to hone a risk stratification approach that better identifies patients at risk for arrhythmic SCD, one that can be used to make robust clinical decisions leading to improved outcomes: availability of funding. Comparative effectiveness studies of new risk stratification approaches will require large studies. Traditionally, large-scale studies in this area have been supported by industry and the National Institutes of Health. Further efforts at risk stratification are high-risk propositions as it is not clear which approaches/algorithms are likely to provide sufficient incremental value. The diminishing availability of research funds from traditional sources poses a real challenge in advancing this research agenda. As the next step needed in this pyramid of knowledge is the demonstration of the clinical use of a risk marker or a risk stratification algorithm, large, simple clinical trials will be needed.18 The optimal method to streamline clinical trials of risk stratification for SCD needs to be delineated and alternative sources of support for these trials need to be considered. Some of the main beneficiaries of risk stratification research are patients themselves and payers. Yet, patient advocacy groups and the Center for Medicare and Medicaid Services (CMS), an important stakeholder in the appropriate use of ICDs to achieve improved survival, have not played an eminent role in funding this type of research. Currently, Center for Medicare and Medicaid Services is not empowered to conduct the necessary studies.

In conclusion, studies such as that of Pezawas et al13 have convincingly demonstrated that risk stratification for SCD in patients with NIDCM is possible. A new paradigm is required to render this a useful reality.

References


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Sudden Cardiac Death Risk Stratification in Dilated Cardiomyopathy: Climbing the Pyramid of Knowledge
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