Prediction of Sudden Cardiac Death in Patients With Coronary Heart Disease
The Challenge Ahead
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Despite widespread advances in coronary heart disease (CHD) treatment and the growing use of implantable cardioverter-defibrillators (ICDs), sudden cardiac death (SCD) remains a major cause of CHD death in the United States, and identification of patients at risk for SCD remains a challenge. Left ventricular ejection fraction (LVEF) has been found to be the strongest independent predictor of SCD among traditional clinical markers, and risk of SCD exponentially increases as LVEF decreases. Based on data from observational studies, clinical trials were designed to test the hypothesis that ICD therapy would prolong life in patients with clinically recognized left ventricular dysfunction. Although these trials have demonstrated convincing survival benefits, there continues to be great debate regarding the overall effectiveness, and in particular cost-effectiveness, of the current strategy of allocating ICD therapy on the basis of LVEF.

LVEF alone (0.70), the C-statistic will always increase when LVEF (0.72) as compared with the multivariable model with a statistically significant 16% increase in the risk of SCD even after controlling for LVEF and other clinical factors. This association has important pathophysiologic implications, and provides further support for the important role that myocardial ischemia and overall scar burden play in determining propensity toward recurrent ventricular arrhythmias and SCD in patients with CHD. These data also indirectly lend support to the use of interventions directed at reducing ischemia and scar formation as preventive modalities for SCD in CHD. However, the authors take the clinical implications of these data a step further suggesting that the SSS may provide a new more effective SCD risk stratification tool to be used either in combination with LVEF, or perhaps even replacing LVEF. Based on these data, the authors call for prospective trials to test this hypothesis. To make this assertion and justify the investment in large-scale prospective trials, there should be evidence in the present data that the SSS has the power to advance SCD risk stratification and preventive modalities for SCD in CHD. However, the authors state that the SSS improved discrimination for SCD as compared with LVEF, there are no data presented in the manuscript to clearly support this claim. Although the C-statistic, a measure of discrimination, is higher for the multivariable model that includes SSS and LVEF (0.72) as compared with the multivariable model with LVEF alone (0.70), the C-statistic will always increase when

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additional variables are entered into the model. To conclude that the variable improves discrimination, the differences in the C-statistic between models needs to be subjected to formal statistical testing, or a validation study in a separate data set would need to be performed. Neither was performed, and the widely overlapping confidence intervals for the C-statistics suggest that the difference between models may not have been significant if subjected to statistical testing. In addition, the C-statistic for the model with SSS and clinical factors (0.69) was actually lower than that for LVEF and clinical factors (0.70), suggesting that LVEF may be a better discriminator than SSS. However, again, no statistical comparisons are made and confidence intervals widely overlap. The significant change in the global $\chi^2$, or likelihood ratio test, presented in Figure 3 is a sensitive measure of model fit and establishes the association between SSS and SCD, but does not provide information regarding discrimination or clinical use.

There are well-recognized limitations of relying solely on the C-statistic for risk prediction, and therefore the apparently null results here do not negate the possibility that the association between SSS and SCD may be clinically useful. Techniques such as risk-reclassification would provide more useful information as to whether the addition of SSS to LVEF more accurately stratifies individuals into higher or lower risk categories of clinical importance. Although these important analyses were not performed, the article does provide some crude information on this topic. Table 4 displays the SCD event rates over 3, 5, and 10 years of follow-up stratified by LVEF and SSS. Given that the median follow-up of the population was 6.1 years, the results at 5 years should be estimated with a reasonable degree of confidence. Also, given the time horizon of ICD therapy, these results are likely the most clinically meaningful as well.

Among patients with an LVEF $\geq$35%, those with a SSS $\geq$6 had a SCD rate of 3.5% as compared with 1.9% among the low SSS group at 5 years of follow-up. Such an elevation in risk, although statistically significant, would likely not provide justification for prospective trials testing the ICD in this new population. The rate in the high SSS/high LVEF group is actually quite similar to the overall risk of SCD in the total CHD population (3.4% over median of 6.1 years of follow-up). Therefore, a trial in this population might be equivalent to one among unselected CHD patients, which would be difficult to justify. With respect to the much smaller low LVEF population, the data here are quite limited prohibiting any firm conclusions. The number of patients with low SSS and low LVEF were extremely small (70 patients, <2% of population) and minimal information on SCD free survival was available after approximately 2 years of follow-up (Figure 2).

Finally, as the authors acknowledge, SSS like LVEF does not specifically predict risk of SCD as compared with other modes of cardiovascular death. The unadjusted hazard ratio for SCD was similar to that for total CVD death, and therefore the SSS as a risk predictor would suffer from all the limitations outlined above for LVEF. Information on competing risks needs to be taken into account when examining risk predictors for SCD, especially when deciding how to allocate expensive and invasive therapies. This has been a major challenge in the CHD population as exemplified by the comparative incidence of sudden (3.4%) versus nonsudden causes of death (31.2%) in the present study. Although the true rate of SCD may have been underestimated to some degree given the inherent difficulties in confirming SCD in population-based studies, this CHD population is clearly at high risk for dying from other causes.

So should we just declare defeat and retreat? I would say the answer to that question is definitely “no.” Studies such as the one by Piccini et al examining risk factors for SCD should be encouraged because these can provide important insights regarding the underlying biology and mechanism of SCD, and may point to novel causal pathways or new targets for intervention even if they do not immediately advance risk prediction. However, before a risk factor or series of risk factors can be established as a risk stratification tool, a clinically meaningful improvement in risk prediction needs to be demonstrated and replicated using state-of-the-art statistical methods taking into account the issue of competing risks. As is the case for global CHD prediction, SCD prediction will likely involve multiple risk markers including those identified through advances in cardiovascular imaging as well as through advances in our understanding of the electrophysiology, genetics, and biology underlying SCD. We must not lose sight that the goal of such investigations is to not only identify new criteria that will result in more efficient utilization of ICDs, but to also make progress toward the ultimate goal of finding new therapeutic options for the SCD prevention.

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None.

References


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