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Sudden Cardiac Death Risk Prediction: Challenging the Status Quo

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There have been significant improvements in primary and secondary prevention of CHD resulting in substantial declines in CHD mortality over the last several decades(1, 2). Despite declining CHD mortality rates, the decline in sudden cardiac death (SCD) rates has not kept pace with that observed for other modes of CHD death(3, 4). The proportion of CHD deaths that are sudden appears to be increasing despite advances in therapies directed against CHD and the growing utilization of implantable cardioverter-defibrillators (ICDs). This unfavorable trend is both a consequence of our inability to accurately identify those who will die suddenly from a lethal ventricular arrhythmia and to develop and/or disseminate SCD preventive strategies for all populations at risk.

Presently, primary prevention of SCD relies on risk stratification based upon left ventricular ejection fraction (LVEF) and degree of congestive heart failure (CHF), followed by implantation of an ICD in patients with LVEF<35% and New York Heart Association Class II–III CHF. Although clinical trials have demonstrated clear survival benefits conferred by this strategy(5, 6), there are major limitations to utilizing this approach as the only method for SCD risk stratification. First, the majority of patients who suffer a cardiac arrest do not have a depressed LVEF documented prior to SCD(7), and over half do not have clinically recognized heart disease(8, 9). Therefore, this strategy will not impact the vast majority of individuals who will go on to suffer a SCD. Second, the mortality benefit and cost-effectiveness of the ICD is limited by other competing modes of cardiovascular death(10, 11). Patients with reduced LVEF and CHF are also at a substantially elevated risk of nonsudden cardiac death, a limitation which becomes particularly important when considering the appropriateness of a costly therapy such as the ICD, where the time horizon for cost-effectiveness is 5–7 years(12–14). Therefore, there is a clear need to move beyond the present risk stratification schema based solely on LVEF and to develop improved markers of arrhythmia risk and preventive strategies that can be applied to broader populations.

Unlike global CHD risk prediction, where there are widely accepted predictive models, there are no similar models for SCD risk prediction among the general population or even among patients with coronary disease without depressed LV function. The article by Dao et al(15) represent an initial step at examining risk prediction in a broader and understudied

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population, women with CHD and relatively preserved ejection fractions. The authors utilized competing risk and risk prediction modeling to identify predictors of SCD among 2763 postmenopausal women with CHD enrolled in the Hormone and Estrogen Replacement Study. As the authors point out, SCD appears to be less common among women(16, 17), and women are often under-represented in studies of this health outcome as a result. In addition, women who do suffer SCD are 50% less likely to have an LVEF <35% documented prior to SCD than men(18). Therefore, our current SCD prevention strategies are less likely to apply to women, and studies aimed at identifying novel methods of SCD risk stratification in this population are clearly needed

Over a mean follow-up of 6.8 years, the annual SCD event rate, defined as death within one hour of the onset of symptoms, was 0.79% in this population. The actual SCD rate is likely somewhat higher since unwitnessed deaths often do not have the information available to fulfill the accepted but rigorous one hour definition of SCD(19, 20). Nevertheless, over half of all deaths from cardiovascular disease were still classified as due to SCD utilizing this definition. This rate is approximately 10-fold greater than the estimated annual incidence of SCD in the general population(20), and is at a sufficiently high level that a risk prediction algorithm that might be able to elevate this risk 3- or 4- fold could have clinically important implications for SCD risk stratification.

The authors found that a risk score combining standard easily measurable clinical characteristics in combination with lifestyle factors stratified risk of SCD in this population. The final multivariable model included myocardial infarction, heart failure, renal dysfunction, atrial fibrillation, diabetes, physical activity and alcohol intake. These individual risk factors have been associated with ventricular arrhythmias and SCD in other populations. However, the authors went further and evaluated whether a combination of these risk factors could improve SCD risk prediction. Women with three or more of these risk factors at baseline (9% of the population) had an annualized SCD risk of 2.9%, as compared to only 0.34% in those without any risk factors (25% of the population). To put these numbers into perspective, the SCD rate in the highest category of the risk score is comparable to annual SCD rate observed in the placebo arm of the Sudden Cardiac Death In Heart Failure Trial (SCD-HeFT) (21), where ICDs reduced overall mortality by 24 percent(5). In comparison, the SCD rate in the lowest category is comparable to estimates for the general population(8, 20). Therefore, these risk categories if confirmed in validation populations may have potential clinical utility.

The authors then compared the predictive ability of the risk score to LVEF among a subset of 1773 patients (66%) who had echocardiograms available. The C-index, a measure of discrimination, was higher for the risk score alone (0.66) or in combination with LVEF (0.68) as compared to LVEF alone (0.60). However, a formal statistical test comparing the differences in the C-index was not reported, and therefore, it is unclear whether the clinical risk score significantly improved discrimination.(22) However, the clinical risk score did significantly improve net reclassification into clinical risk categories when added to LVEF alone, mostly due to reclassification of 24% of women into a higher risk category. Since women with LVEFs > 35% comprised 95% of the population, it is unclear whether these clinical markers would add to the information provided by LVEF in patients with greater degrees of systolic dysfunction. Unfortunately, the derived clinical risk score shares with LVEF the inability to discriminate risk for sudden versus nonsudden cardiac death. Indeed, most current clinical predictors, with the possible exception of invasive electrophysiologic testing(23), predict cardiovascular death in general rather than mode of death. The combination of clinical predictors assembled here is not an exception.

In summary, a combination of easily measured clinical risk variables stratified risk of SCD and appears to add predictive value beyond that provided by LVEF alone in this understudied population of women with CHD and preserved systolic dysfunction. Although these data in isolation have uncertain clinical implications, the study is an important step towards future research aimed at deriving and testing SCD risk prediction scores in broader populations. Once validated and compared to existing risk stratification approaches in independent populations, these prediction algorithms could then be tested in future randomized trials. However, to significantly improve the performance of prediction algorithms in identifying patients who will derive maximum benefit from the ICD, we will also need to identify and incorporate novel risk markers that specifically predict sudden cardiac death into risk prediction algorithms. The discovery of such novel markers may also serve to illuminate biologic pathways involved in the genesis of lethal ventricular arrhythmias, and could ultimately lead to new therapeutic approaches for SCD prevention beyond the ICD.

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