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EDITORIAL

Separating the Forest From the Trees: New Tools for a Personalized Sudden Cardiac Death Risk Stratification

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Sudden cardiac death (SCD) from ventricular arrhythmias accounts for up to 50% of all deaths from cardiovascular disease,[1,2] with ≈390 000 SCDs from out-of-hospital cardiac arrest in the United States annually. The implantable cardioverter-defibrillator (ICD) has been an effective intervention for the prevention of SCD in patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF). However, more recent data from ICD registries[3] show lower rates of appropriate ICD therapies in comparison with the 8% annualized rates of appropriate ICD therapies in randomized ICD trials on which the current guidelines are based.[4] In addition, the recent Danish ICD trial in patients with nonischemic cardiomyopathy showed an absence of mortality benefit of ICDs over standard medical care.[5] One major issue is that the criteria for primary prevention ICD implantation rely heavily on a single measurement of LVEF,[6] and are too broad to precisely identify subgroups with lower risk profiles who may not benefit from an ICD. To overcome this limitation, multivariate risk models have been developed to improve SCD risk stratification.[7–9] For example, the Seattle Heart Failure Model[7] incorporates multiple baseline clinical parameters, including HF class, comorbidities, medical therapy, and laboratory parameters, to improve prediction of all-cause mortality in a large cohort of patients with and without an ICD. However, it is more accurate at identifying patients at risk of non-SCD than SCD.[10] On the other hand, the Seattle Proportional Risk Model uses similar multivariable clinical parameters to estimate mortality attributable to ventricular arrhythmias.[8] When used together,[9] these models helped to identify both a low-risk quartile, whose survival was not altered by ICD implantation, and a high-risk quartile, where mortality risk reduction attributable to ICD was 40%. However, this leaves a significant proportion of patients in the middle, where existing risk models remain suboptimal at discriminating those who benefit from an ICD versus those who do not. Second, the existing models remain limited by the use of baseline clinical variables obtained at a single time point and do not account for the time-varying influence of HF exacerbations[11] or LVEF progression[12] on the underlying arrhythmic substrate.

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To address this, Wu et al[13] have conducted a pilot study using a well-known machine learning statistical method known as “Random Forest” to illustrate how fixed and time-varying factors interact to promote ventricular arrhythmias. In that sense, they have managed to statistically incorporate dynamic HF and LVEF progression at varying points, to one that includes multiple parameters in aggregate at a single time point, such as demographics, comorbidities, medications, electrophysiologic parameters, laboratory values, enrollment

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LVEF and cardiac magnetic resonance (CMR) imaging metrics, biomarkers of inflammation, neurohormonal activation, and myocardial injury. In other words, to "combine an ensemble of predictions from a collection ('forests') of individual trees," where each individual tree generates a prediction and the overall prediction is the average of all trees in the forest. This approach also reduces prediction error by averaging multiple predictions. They enrolled 382 patients across 3 institutions who met primary prevention criteria for ICD implantation based on LVEF ≤35%, as part of a prospective observational study of ICD outcomes.[14,15] They included patients with cardiac resynchronization devices who comprised 28% (n=107) of the cohort. Fifty-one percent of patients had an ischemic cause of cardiomyopathy. All patients underwent baseline CMR preimplant and were followed up biannually or after any ICD discharge for 8 years, after which event data were censored. The primary end point was appropriate ICD shock for ventricular tachycardia or ventricular fibrillation above the programmed rate cutoff, which was generally (although not uniformly) >180 beats per minute, or definite or suspected SCD. The primary end point was reached in 75 patients (19.6%), although only 2 of these (0.5%) were attributable to SCD. Of 382 patients, 140 had ≥1 HF hospitalizations.

The authors found significant interactions between dynamic factors, such as acute HF hospitalizations, and baseline factors, such as circulating markers of inflammation, including interleukin-6 and various CMR indexes of myocardial substrate. Specifically, HF hospitalizations were the strongest predictor of subsequent life-threatening ventricular arrhythmias following ICD insertion and accounted for two thirds of variation in the predicted risk of ventricular arrhythmias. Larger CMR-derived left ventricular and left atrial volumes, larger total scar and gray zone extents, and lower left atrial ejection fraction and serum interleukin-6 concentrations were the top baseline variables that contributed to risk prediction, particularly among patients without HF. Imaging metrics and interleukin-6 accounted for 27% and 2%, respectively, of variation of the predicted ventricular arrhythmia risk. In terms of absolute risk, ≥1 HF hospitalizations were associated with an increase of 10 events per 100 person-years (3.5-fold) and imaging metrics with an increase of 2 to 6 events/100 person-years (3-fold). Interestingly, when clinical HF events and baseline CMR metrics and interleukin-6 levels were already included as covariates, serial LVEFs did not add significantly to the prediction model and no LVEF threshold could be identified above which risk is reduced. This work is novel because it applies a valid statistical machine learning technique to illustrate the complex interactions between dynamic and fixed arrhythmogenic factors. Their results are intuitive pathophysiologically as HF exacerbations are known to precipitate ventricular arrhythmias in a vulnerable substrate through mechanisms that include myocardial stretch, hemodynamic labilities, autonomic imbalance, and electrolyte and biochemical abnormalities. Moreover, because of the highly variable individualized progression of cardiac disease and risk factors, they may become increasingly relevant in the transition from a broad, one-size fits all risk model to a more personalized risk prediction model for SCD. Third, their findings may inform decision-making about the risk/benefit of replacement of an ICD generator at the time of end-of-battery life.

Nevertheless, there are several important caveats before this method can be more broadly applied. First, this was a pilot study obtained from a small prospective observational cohort. The results require validation in much larger prospective cohorts or registries to identify patients at sufficiently low risk of SCD in whom ICD or ICD generator replacement could be deferred. Second, the clinical event rate was low and data were collected over a long enrollment period, reinforcing again the need for validation in larger prospective trials. For example, although the primary event rate was observed in 75 patients (19.6%), there were only 2 deaths (0.5%) from an arrhythmic cause. Third, the statistical method used is highly complex, more so than the Seattle models. This complexity may be a limitation to broader clinical application, even if it is subsequently proved to be more robust. However, the authors presented the data in the form of a decision tree or variable dependence plot (Figures 2 and 3 of their article, respectively), which is significantly easier to understand for the average clinician and could be incorporated as a telephone application, as an example of how it may be practically used by clinicians in the future. Fourth, to be useful, a significant lead-in period may be needed to capture a sufficient number of HF events. Therefore, the question remains how this would this work in the real-world setting where the time from diagnosis of cardiomyopathy to primary prevention ICD implant may be <1 year? Could ICD therapy be deferred long enough so that a longitudinal risk assessment be performed? In this report, HF hospitalizations beyond the first year did not further improve risk prediction, although notably 45% of patients who met the primary end point did not have a prior HF hospitalization. Until we see more data, which are sorely needed, our current imperfect practice guidelines remain. Thus, this study is a welcome and necessary new tool in our growing armamentarium for SCD risk prediction. The pathophysiologic factors that cause ventricular arrhythmias and SCD are numerous, complex, and time varying. Our experience with existing risk stratification models, based on either a single factor/measurement (LVEF) or multiple aggregated factors obtained at a single time point, has proved inadequate to date. This is why this elegant study by Wu et al[13] may provide a future road

map to navigate the complex, more personalized task of SCD risk stratification with more precision or, in their words, with more forests, not less trees.

ARTICLE INFORMATION

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Disclosures

None.

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