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Editorial

The ST2-SCD score and the conundrum of sudden death prediction in heart failure

Giuseppe Vergaro [a,b,*], Alberto Aimo [c], Wojciech Zareba [d], Michele Emdin [a,b]

[a] Institute of Life Sciences, Scuola Superiore Sant'Anna, Pisa, Italy
[b] Cardiology Department, Fondazione Toscana Gabriele Monasterio, Pisa, Italy
[c] Cardiology Division, University Hospital of Pisa, Italy
[d] Heart Research Follow-Up Program, Cardiology Division, University of Rochester Medical Center, NY, United States of America

Sudden cardiac death (SCD) represents a relevant cause of mortality in patients with heart failure (HF) [1]. Although the occurrence of life-threatening arrhythmias likely derives from a complex interplay of different factors, including disease severity and etiology, comorbidities, neurohormonal activation, myocardial structural substrate, and non-cardiac triggers (e.g. abnormal thyroid function, infections, electrolyte disturbances), current guideline recommendations rely on the simple left ventricular ejection fraction (LVEF) criterion (i.e., ≤35% after ≥3 months of optimal medical therapy) [2]. As a result, the prediction of SCD is largely suboptimal, leading on one hand to a significant number of futile, potentially harmful device implantations, on the other hand to deadly events in patients not fulfilling current criteria for primary prevention by implantable cardioverter defibrillator (ICD) therapy. The refinement of SCD prediction models is, therefore, a true unmet need in the clinical management of HF patients.

Concerning the established predictors, the ischemic etiology of LV dysfunction is acknowledged as a risk factor for the development of ventricular arrhythmias [3,4], whereas no randomized trial of ICD vs. no-ICD treatment has ever reported a survival benefit in non-ischemic HF [5,6]. Late gadolinium enhancement (LGE) at cardiac magnetic resonance has been extensively searched as a potential tool for risk stratification, as myocardial fibrosis represents a substrate for reentrant ventricular arrhythmias and/or indicates persistent activation of mechanisms of myocardial damage. Among patients with non-ischemic HF and LVEF ≤ 35%, LGE predicted a composite endpoint, including sustained ventricular arrhythmias, appropriate ICD discharge or SCD. Nonetheless, the issues still remain to be addressed, whether patients with LGE could benefit from primary prevention with ICD regardless of LV systolic function, and whether patients without LGE might not need preventive ICDs despite a severe LV dysfunction [7].

Among other potential predictors of risk, circulating biomarkers have been also evaluated, particularly soluble suppression of tumorigenesis-2 (sST2), a biomarker related to the activation of inflammatory and profibrotic pathways [8]. In a nested case-control study performed on 36 cases of SCD and 63 matched controls, without ICD at study entry, nor undergoing ICD implantation during follow-up, circulating sST2 levels were significantly higher among cases, and the combination of sST2 ≥ 15 ng/mL and N-terminal fraction of pro-B-type natriuretic peptide ≥2000 ng/L predicted SCD, regardless of baseline characteristics including ischemic etiology [8].

In the present issue of the Journal, Lupón and Colleagues extend these findings by deriving and validating a prediction score including sST2 [9]. The Authors performed a retrospective evaluation of patients with "HF […] irrespective of etiology, at least one HF hospitalization, and/or reduced LVEF", excluding patients with ICD at baseline or receiving ICD implantation during follow-up. The derivation cohort included 744 consecutive outpatients, with LVEF 37 ± 14%. Forty SCD (i.e. 5.4% of the whole population) occurred over 5 years. HF duration, estimated glomerular filtration rate (eGFR), LVEF < 45%, and sST2 were identified as independent predictors of SCD. A predictive score (ST2-SCD) including dichotomous variables (ST2 > 45 ng/mL, LVEF < 45%, HF duration > 3 years, eGFR < 55 mL/min/1.73 m^2, age ≥ 60 years, and male sex) was defined, yielding an area under the curve = 0.81 in the derivation cohort and =0.87 in the validation cohort (n = 149) [9].

The score developed by the Authors is biologically plausible, as it encompasses the individual patient characteristics, disease duration and severity, comorbidities, and biohumoral indices of ongoing cardiac damage. Moreover, the study results support the use of prediction models that are less focused on systolic dysfunction and take into account other possible mechanisms leading to life-threatening arrhythmias. Still, while of great interest, the evidence reported should be viewed in the light of an ICD implantation rate in this series seemingly lower than expected. Indeed, the mean baseline LVEF in the derivation cohort was as low as 37%, but none of these patients had ICD at baseline nor received an ICD over a 5-year follow-up [9]. To address this point, the Authors repeated their analysis considering also patients with ICD at baseline or receiving an ICD. Nonetheless, the fact that only 93

* Corresponding author at: Scuola Superiore Sant'Anna and Fondazione Toscana Gabriele Monasterio, Italy.
E-mail address: vergaro@ftgm.it (G. Vergaro).

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patients from the derivation population underwent ICD implantation over a 5-year period [9] points out an ICD underuse. On the whole, these issues, which relate to the study design, may limit the clinical applicability of these findings to patients managed according to guideline recommendations. Patients receiving ICD based on the LVEF ≤ 35% criterion might even display a lower rate of SCD than the already low rate observed in the derivation cohort (40 out of 744, 5%) [6]. Such a low incidence of SCD might be related to the small size of the validation cohort, and involves a risk of model overfitting when running the multivariable analysis, as acknowledged by the Authors themselves.

With regards to the ST2-SCD score, the continuous variables were dichotomized according to the best cut-offs at the receiver operating characteristics curve, and adding age and sex to the independent predictors [9]. The identification of the 45% LVEF cut-off, higher than the guideline-recommended 35% value, was possibly influenced by the exclusion of patients with ICD, who were likely those with most severely depressed systolic function. Additionally, the inclusion of male sex as a risk factor for SCD is also in agreement with a meta-analysis of trials on ICD for primary prevention, showing that only men displayed a significant survival benefit from ICD implantation [10]. Notably, ischemic HF etiology did not emerge as a predictor of SCD even at univariate analysis, although the uncertain benefit of ICD implantation in patients with non-ischemic HF would suggest a greater risk of SCD among patients with ischemic etiology.

The possibility to predict SCD, thus refining the referral to ICD implantation in primary prevention, is appealing. The ST2-SCD score scales down the assessment of systolic function in the risk prediction of SCD and emphasizes the value of other mechanistically plausible variables. Still, several methodological issues should be carefully examined before the ST2-SCD score could be proposed for clinical use. Furthermore, the place of the ST2-SCD score in the decisional algorithm for ICD implantation should be clearly defined, and the additive value of this score to the guideline-based decision should be formally assessed by a dedicated trial.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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