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EDITORIAL COMMENT

Sudden cardiac death in heart failure: more than meets the eye

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This article refers to 'Dynamic changes in cardiovascular and systemic parameters prior to sudden cardiac death in heart failure with reduced ejection fraction: a PARADIGM-HF analysis' by L.E. Rohde *et al.*, published in this issue on pages 1346–1356.

Sudden cardiac death (SCD) remains an important mode of death for patients with heart failure (HF).[1] Many deaths are unwitnessed, and without rhythm monitoring at the time of the event a definitive mode of death is difficult to establish. Major distinction that should be addressed is whether a death occurred suddenly (within minutes), i.e. due to an arrhythmia, or whether death occurred over a longer period of time due to progression of HF (or other causes, leading to an unwitnessed death such as stroke, pulmonary embolism, and ruptured aneurysm).[2] Several arrhythmias may lead to SCD, in particular, ventricular tachycardia/fibrillation, but bradyarrhythmias may also be the final arrhythmia.[3,4] However, this requires a form of rhythm monitoring at the time of death to confirm an arrhythmic cause. Prevention of SCD is based on left ventricular ejection fraction (LVEF) with only a primary prevention indication for implantable cardioverter defibrillator (ICD) in those with a reduced LVEF.[1,5] Of note, SCD is also common in HF with preserved ejection (HFpEF, 11–28% of all deaths), although this is lower than in HF with reduced ejection fraction (HFrEF, 24–42%).[6] Therefore many HFpEF patients may suffer from SCD since an ICD is usually not implanted for primary prevention. On the other hand, HFrEF patients with an ICD may never receive appropriate ICD therapy and still suffer from SCD. The question is therefore, why are we unable to identify HF patients at high risk for SCD and what do we know about SCD in HF?

Two definitions are of relevance with regard to SCD. According to the European Society of Cardiology guidelines for ventricular arrhythmias and SCD, the definition of sudden death is a non-traumatic, unexpected fatal event occurring within 1 h of the onset of symptoms in an apparently healthy person. If death is not witnessed, the definition applies when the victim was in good health 24 h before the event.[1] SCD is defined in the same guidelines as a potentially fatal cardiac condition (e.g. HF) that was known to be present during life; or autopsy has a cardiac or vascular anomaly as the probable cause of the event; or no obvious extra-cardiac causes have been identified by post-mortem examination and therefore an arrhythmic event is a likely cause of death.[1]

Prediction of who is at risk for SCD has been an active area of research.[1] Several indicators for SCD have been described in HFrEF, including QRS prolongation or fragmentation, heart rate turbulence, heart rate variability, or T-wave alternans and many others.[1,2] The same holds true for patients with HFpEF where indicators such as heart rate turbulence, deceleration capacity and non-sustained ventricular tachycardia have been associated with SCD.[1,7] Remarkably some of the variables are also, and sometimes even stronger, predictors for non-SCD.[7] Also, many of these indicators are not routinely used in clinical practice.[1]

One way to comprehend the development of arrhythmias (or SCD) is by using the classic triangle of Coumel.[8] A complex interplay of vulnerable substrate, modulating factors and critical triggers contribute to the arrhythmogenesis for a 'perfect storm' leading to a fatal event. In HF, for example, a vulnerable substrate for arrhythmogenesis can be created as a consequence of acute myocardial infarction, i.e. myocardial scar.[1] Although modern revascularization techniques and secondary prevention have led to preservation of LVEF after myocardial infarction, myocardial scar as a consequence of acute myocardial infarction may also be present in HFpEF.[9] Furthermore, a scar may also be observed in patients with non-ischaemic cardiomyopathy.[1] Certainly, many other variables may additionally contribute to a vulnerable substrate.[1] Triggers that may lead to a critical event are, for example, interim hospitalization for HF (haemodynamic alteration) or coronary events (ischaemia).[10] In view of Coumel's triangle, there are probably additional unknown 'modulating factors' or 'critical triggers' contributing to the risk for SCD in HF.

In this issue of the Journal, Rodhe *et al.*[11] describe some novel contributing factors as they investigated predictors of SCD in patients with HF (LVEF <40% on optimal medical therapy) who were enrolled in the PARADIGM-HF trial. SCD was defined as

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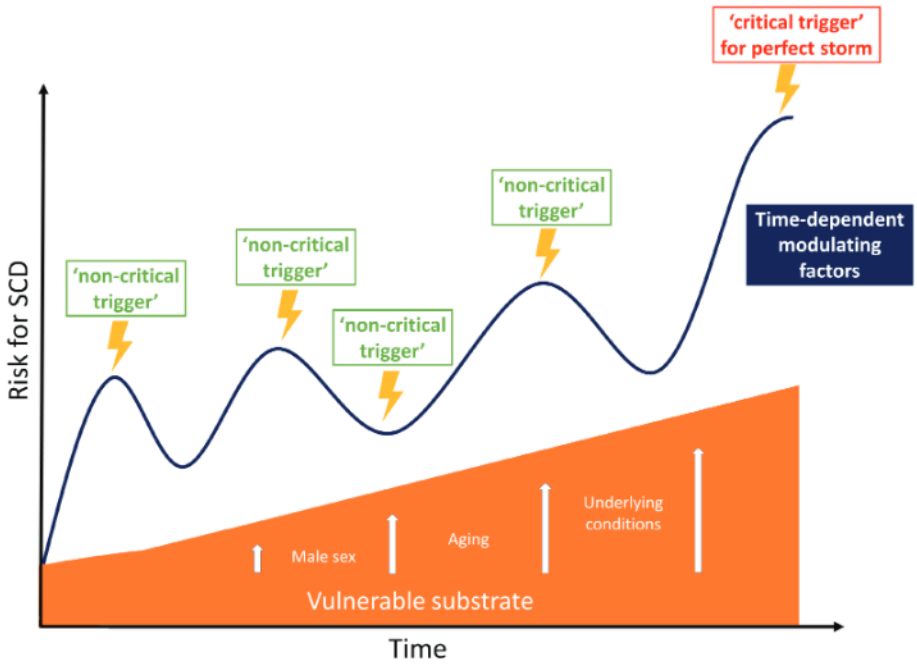

Figure 1 Conceptual figure using the basis of Coumel's triangle in relation to susceptibility for sudden cardiac death (SCD).

death occurring unexpectedly in an otherwise stable patient. Events classified as SCD could be further classified if the patient was last seen alive <1 h or >1 h and <24 h. The findings were based on 8399 enrolled patients for which the authors used time-updated multivariable-adjusted Cox models, classification and regression tree (CART), and logistic regression to assess independent predictors of SCD. CART is a set of techniques used for classification and prediction. The technique is aimed at creating a model that predicts the value of a target (outcome) based on the values of several variables. By using CART, they were able to identify changes over time of common clinical characteristics and laboratory measurements. The authors report several interesting findings. First, 36% (561/1546 of all patients who died) of deaths were classified as SCD. Of the total population, this implies that 6.7% of patients died due to SCD during a median follow-up of 27 months, indicating that even today, with contemporary HF therapy, including ICD therapy, SCD is still prevalent and is a serious problem. As a result, many risk factors are yet to be identified. Second, by using CART, the authors integrated baseline co-variables and time-updated co-variables to enable the identification of subgroups of patients who have an increment in SCD risk. Furthermore, changes over time in heart rate, New York Heart Association functional class, blood urea nitrogen, and albumin levels were associated with SCD. As the authors state, the process underlying SCD is probably dynamic and slowly evolving over time. *Figure 1* illustrates this phenomenon where through the years many (dynamic) factors rise and fall and could contribute to SCD. A phenomenon comparable to the increase in the substrate underlying the severity and complexity of atrial fibrillation.[12]

As with any post-hoc analysis, there are several limitations, most of which are pointed out by the authors. The most relevant limitation is the issue of determining the cause of SCD. All endpoints were adjudicated by two members of the endpoint committee independently, but relied on the completeness of data collected at the moment of death. Determination of the mode of death of those classified as SCD is in absence of data largely based on experience, assumptions and translation of findings from similar cases. Many of SCD are presumed to be due to an arrhythmic cause.[3,4] However, data from implantable loop recorders suggest that for patients with HFpEF and HFrEF an arrhythmic event could not be correlated with the mode of death.[3,13] This implies that many HF patients die from other causes than SCD (e.g. pump failure, but may be due to aforementioned other unwitnessed causes as well). The present study underscores this, as several time-updated variables (e.g. functional class, heart rate, albumin, right ventricular function, estimated glomerular filtration rate, etc.) were also important for patients with non-SCD (therefore the time-updated variables may be considered as non-specific for SCD).

The authors should be congratulated for their important contribution in this field. They confirm that HF prognostication is difficult, relies on many variables, timing and underlying conditions. *Figure 1* illustrates that the vulnerability for a perfect storm is dependent on substrate, (time-dependent) modulators and a critical trigger. The remaining question is whether the identified characteristics can indeed improve prediction for SCD and reclassification of an individual HF patient. In addition, do they need different (medical) management? There is no simple answer to this question, however, based on the present study supplementary data, this is not to be expected. Numerous variables associated with SCD are also

associated with non-SCD, indicating that although identification of a generally increased risk of dying is possible, specific identification of SCD remains difficult if not often impossible. Also, ICD efficacy may even be reduced due to advancement of HF and non-arrhythmic mechanism of death, e.g. worsening of right-sided HF, indicated in the present analysis by hyperbilirubinaemia and hypoalbuminaemia.

What should be the next steps in SCD risk prediction? Beyond doubt there is a need for better validated and calibrated risk prediction models for SCD in HF.[14] Based on the present post-hoc analysis, future studies should not only focus on LVEF but right ventricular function as well. It is critical to understand which (time-dependent) clinical factors are contributing to fast progression of vulnerability, and that re-assessment of these potential contributing dynamic factors should be performed on a regular basis. Are there additional indicators of underlying substrate which could be more aggressively treated, for example whether premature ventricular contractions and may be a sign of increased vulnerability?[15] Lastly, the chronology of events may be of importance in the days to months before an event. Answers to these questions are needed to complete the picture on the mode of death in HF, otherwise there remains more than meets the eye.

In conclusion, identification of who is at risk for SCD is difficult. Rohde *et al.* illustrate that many of the variables are time-dependent implying a dynamic risk for SCD in HF. Therefore, regular re-assessment of these variables might refine identification of HF patients at high risk for SCD.

Conflict of interest: none declared.

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