Sudden Cardiac Death in Hypertrophic Cardiomyopathy: Time to Change the Narrative

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"... we know what we are, but know not what we may be."

— William Shakespeare, Hamlet

Hypertrophic cardiomyopathy (HCM) is a heart muscle disorder, defined clinically as left ventricular hypertrophy unexplained solely by abnormal loading conditions [1]. The disease is frequently familial and is the commonest inherited heart condition affecting an estimated one million individuals in Europe. People with HCM develop limiting symptoms, often years after the first detection of electrocardiographic or echocardiographic evidence of left ventricular hypertrophy and as the disease progresses, become prone to heart failure, atrial fibrillation and stroke [2,3,4]. Sudden cardiac death (SCD) is the most common mode of death in younger patients, but death from heart failure or the need for heart transplantation is frequent in those with left ventricular dysfunction. Current management strategies for the disease focus on three aspects: identification of individuals who are potential beneficiaries of an ICD; relief of left ventricular outflow tract obstruction using drugs, surgery and alcohol septal ablation; and alleviation of limiting symptoms caused by systolic and diastolic ventricular dysfunction [1,5].

HCM is and always has been a controversial field, although the origins of some of the most rancorous disputes are often historical and have diminishing contemporary relevance. One of the foremost points of contention has been the identification and treatment of patients at high risk of SCD, a subject of particular sensitivity as it often occurs in young and otherwise healthy individuals and is potentially preventable through the use of an implantable cardioverter defibrillator (ICD).

In this edition of *the Journal*, Nauffal and colleagues [6] shine a light on one of the murkier points of contention; namely, perceived differences in the approach to risk stratification in the US and Europe. Their study uses retrospective data from the SHaRe consortium–a voluntary registry involving specialist cardiomyopathy centres in North America, Europe and several other countries–that have provided important insights into disease natural history [2,7]. This paper's focus is a comparison of primary prevention ICD implantation rates and associated clinical outcomes in US vs. non-US centres.

The basic premise of this paper is that differences in SCD risk stratification algorithms in US and European practice guidelines for HCM promote uncertainty about best practice. To better understand the impact of this discord on outcomes, the SHaRe investigators studied adult patients with HCM diagnosed in eight US and five non-US sites and used multivariable Cox proportional hazards models to compare outcomes between those sites: specifically, the time to primary prevention ICD insertion, the incidence of appropriate and inappropriate ICD therapy, and all cause mortality. In patients with and without an ICD, they examined two endpoints: an SCD composite (SCD or resuscitated cardiac arrest) and a non-SCD composite (non-sudden cardiac death or heart transplant/ventricular assist device implant). The main findings of the study were as follows: (1) primary prevention ICD insertion rates in US sites were 2-fold higher than non-US sites; (2) rates of appropriate ICD therapy were significantly lower in US vs. non-US sites; (3) there was no difference in the incidence of sudden cardiac death/resuscitated cardiac arrest among non-recipients of ICDs in US versus non-US centres; and (4) there were a large number of ICD recipients without risk factors or a low calculated European Society of Cardiology (ESC) HCM Risk-SCD score in the US and non-US cohorts.

In the past, debates on risk stratification in HCM were often based on eminence rather than evidence based medicine, but in recent years the emergence of analyses from large international consortia has promoted a convergence of views and a more scientific approach to risk estimation [8,9]. Nevertheless, echoes of past disagreements about the approach to risk management persist in the literature.

Different national rates of ICD implantation are well described and, while not fully explained, may be attributable to differences in risk perception and tolerance, patient/provider preferences as well as cultural, socioeconomic, and healthcare system factors such as the number of implanting centres [10,11]. While the results of the SHaRe study tempt one to conjecture on the relative merits of different healthcare models, the real lessons of this paper lie elsewhere.

In 2021, there is much more to agree upon about HCM than to dispute. Specifically, (i) SCD (or its equivalent) is a rare event in the short to medium term, (ii) event rates are highest in patients with clinical risk markers that describe the vulnerability of the myocardium to ventricular arrhythmia, (iii) in individual patients ICDs are a life-saving therapy, and (iv) with aging, patients become prone to the competing risks of heart failure, stroke and non-cardiac diseases. The much vaunted differences in US versus European approaches to risk stratification are, I venture to suggest, based on a false premise. The heterogeneous nature of HCM necessitates the use of multiple variables reflecting different aspects of the disease to provide an accurate estimate of prognosis. In this respect the US and ESC guidelines are identical [1,5]. Aside from some narrow and somewhat obsessive debates about individual clinical risk markers, the major point of difference is the extent to which prediction models should be used to estimate absolute risk. Although risk tools are acknowledged as a useful

adjunct to decision making in the most recent US guidelines [5], advice on ICD implantation is still based mostly on the presence or absence of particular features (such as severe hypertrophy) rather than an estimated probability of an event. In contrast, the 2014 ESC guidelines start with an individualised five year risk derived from real patient data and then consider scenarios where there may be gaps in evidence [1]. As in the past, I continue to argue that it is the second approach that holds most promise for greater precision in risk estimation.

The SHaRE investigators emphasise the role of shared decision making when considering ICD implantation in people with HCM. As stated by the authors *"at the heart of both paradigms is shared decision-making with an adequately informed patient because real world decision making is nuanced and not uncommonly forced to deviate from strict adherence to guideline recommendations*" [6]. This important concept is increasingly seen as an essential component of routine clinical practice [12] and is emphasised strongly in the most recent US guidelines on HCM. However, the term *shared decision making* is sometimes no more than shorthand for the traditional physician-patient relationship rather than a deliberate and systematic collaborative process that supports a person and their doctor to work together to reach a joint decision. Shared decision making should, wherever possible, be evidence-based and take into account a person's individual preferences, beliefs, circumstances and values. Critically, it also requires assurance that the person understands the benefits, harms and possible consequences of different treatment options. This goal can be achieved through discussion and information sharing but is greatly enhanced by patient decision aids tailored specifically to receivers of care as well as more traditional decision support tools for healthcare practitioners. In this regard, there is still much work to be done for patients with HCM, but we already have tools that, with refinement, could form the basis of a more consistent approach to disease management (**figure**).

It is important to sound a few words of caution about the generalisability of the SHaRe study. Firstly, clinical practice is not static as shown by the substantial decrease in the number of primary prevention ICDs and the proportion of devices not meeting the *Centers for Medicare & Medicaid Services National Coverage Determination* (NCD) criteria following the announcement of a US Department of Justice investigation into ICD use in 2010 [13]. There are also some important limitations of the SHaRe registry itself including the risk of inclusion bias, missing data and a relatively short follow-up period. Nevertheless, this is an important paper because it confirms the major limitation of current approaches to SCD prevention in HCM to be overuse rather than underuse of ICDs. It also provides a much needed punctuation to a narrative on risk management that is now rather dated.

The quest to find new risk predictors in HCM will continue, but low event rates and disease heterogeneity will make prospective validation of prognostic biomarkers extremely challenging. In the short to medium term, the best we can expect is a recalibration of existing models with routinely collected data including left ventricular function and genotype, while recognising that overtreatment with ICDs will be the norm. This puts a huge onus on industry to redouble the effort to mitigate the downsides of ICD therapy. More optimistically, a plethora of emerging disease modifying strategies including small molecules and gene therapies create new horizons in patient care that–in the same way that drug therapies reduce arrhythmic and heart failure deaths in patients with left ventricular systolic dysfunction–offer new opportunities for the improvement of survival and quality of life of people with HCM.

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Figure Legend

A worked example of how individualised risk models combined with robust and validated patient decision aids might be used in shared decision making in the future. The left hand panel shows a simulated sudden death risk estimation using the 2014 European Society of Cardiology HCM RISK-SCD tool [1]. The middle and right panels are a visual representation of how an ICD is predicted to alter outcomes over a five year period together with the risks of ICD implantation [14]. Assuming 100% effectiveness, death from ventricular tachyarrhythmia would be prevented but the risk of other disease complications and non-cardiac deaths might increase. The visual representation of risk is inspired by http://understandinguncertainty.org/visualisation-information-nhs-breast-cancer-screening-leaflet

*www.http://www.doc2do.com/hcm/webHCM.html

Key: HCM=hypertrophic cardiomyopathy; ICD=implantable cardioverter defibrillator; LV=left ventricle; LVOTO=left ventricular outflow tract; mm=millimetres; mmHg= millimetres of mercury; NSVT=non sustained ventricular tachycardia; SCD=sudden cardiac death; VT=ventricular tachycardia.

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Conflicts of Interest

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Figure: A worked example of how patient decision aids might be used in shared decision making.