Prophylactic Implantable Defibrillators for Hypertrophic Cardiomyopathy

Disarray in the Era of Precision Medicine

Andrew Grace, MB, PhD

Discussions with individuals and families affected by hypertrophic cardiomyopathy (HCM) concerning prophylactic implantable defibrillators (ICDs) will on occasion offer some new challenges. In a bold attempt to provide categorical answers, the European Society of Cardiology have incorporated a mathematical approach to risk prediction into their 2014 guidelines that includes some risk factors (RFs) that are not broadly agreed and without any prior independent testing. Furthermore, 2 groups have now examined how the guidance would have performed in their patients and arrived at essentially polar opposite conclusions on utility.

Why risk prediction remains so difficult has been extensively considered. Despite large patient cohorts, it is the exemplar monogenic cardiac disorder and study of the underlying genetics has enhanced understanding of disease pathophysiology opening up candidate therapeutic approaches. More complete follow-up along with multidisciplinary considerations of the range of treatment options has allowed better timing of surgical/nonsurgical interventions. Such progress has had a significant impact on improving patient outcomes, but there is the critical issue that we remain only modestly capable of identifying accurately the small subset that will benefit from an ICD.

Possible RFs have been the subject of long-standing dispute on both their definition and relative importance. These include syncope, ventricular wall thickness, exercise-associated blood pressure responses, nonsustained ventricular tachycardia, and left ventricular outflow tract (LVOT) obstruction. One point that is striking is that neither the nature nor the number of RFs predicts ICD discharge. Furthermore, factors previously not considered risk markers, eg, fractional shortening, have been associated with appropriate shocks thereby again questioning individual RF validity. Simply stacking up RFs has low predictive power strongly supported by observational, retrospective, cohort study of 1606 patients in whom 5 RFs were assessed in their capacity to predict risk. Although risk was seen to increase with multiple RFs, the C-statistic obtained from the receiver operating characteristic curve (in the range 0.61 to 0.64 at 5 years) indicated limited capacity to resolve risk. These data essentially recapitulate prior evidence provided from a prospective evaluation of the same RFs. The results taken together provide substantial support for the view that softer but nonetheless effective contributions such as physician experience are crucial to making the right decisions.

The HCM Risk-SCD algorithm has been presented with an aim “to develop and validate a new SCD prediction model that provides individualized risk estimates” and is the basis of the European Society of Cardiology 2014 risk guidance. The algorithm is based on a Cox proportional hazards model internally validated with boot strapping. The data populating the model was obtained from a retrospective, multicenter, longitudinal cohort study involving 3675 consecutively presenting patients. The model was developed across 5 sites (2082 patients) with validation at a further participating center (1593 patients). Seven continuous or binary RFs (age, maximal LV wall thickness, left atrial [LA] size, max. LVOT gradient, family history of SCD, nonsustained ventricular tachycardia, and unexplained syncope) derived from the literature and each independently associated with SCD in at least one multivariable survival analysis were then assessed in respect of the occurrence of SCD or appropriate ICD shocks. These events occurred in ≈5% of patients over a median follow-up of 5.7 years. Patients were then banded into one of 3 groups based on 5-year risks of SCD. If the 5-year risk was calculated at <4%, an ICD would not be recommended; if in the range 4% to 6%, it would be contingent; and if >6%, an...
was no significant influence on the risk of SCD. The problems raised by the inclusion of LVOT obstruction mainly relate to frequency of occurrence, variability, and modest impact. 

The predictor variables included in the HCM Risk-SCD algorithm that have probably attracted most comment are LA enlargement and LVOT obstruction. At first pass, LA enlargement is not the most intuitively obvious potential predictor of the risk of SCD. The incorporation in the algorithm has been justified by a single observation in which LA enlargement conferred a relative risk of 1.03 (confidence interval, 1.00–1.06; P<0.04). LA enlargement has been used, rather than the presence of atrial fibrillation, as we are told: “LA enlargement predisposes to atrial fibrillation and contained less missing data.” A further problem is that the association between atrial fibrillation and SCD in patients who has been never been robust and in a recent study of 3673 patients, although atrial fibrillation enhanced overall risk, there was no significant influence on the risk of SCD. The main conclusion was that application of HCM Risk-SCD would now get an ICD). This group also tested the algorithm in an online calculator (doc2do.com/hcm/webHCM.html) and a recommendation obtained as to whether to recommend or seek out ICD implantation.

The predictor variables included in the HCM Risk-SCD algorithm have now been assessed in an observational cohort design conducted in two tertiary referral centers. A total of 706 HCM patients who had been under consideration for a prophylactic ICD have been included, and the end points of SCD-equivalent event (SCD, appropriate ICD discharge) was observed in 5.9% of patients at follow-up. Interestingly, basal LVOT gradient was >30 mm in 53% patients, and >30% of patients underwent interventions that could have had a significant impact on key inputs into the algorithm (LVOT gradient, LA size). Of course, we already know that relief of LVOT obstruction with myectomy is associated with subsequent low rates of SCD. The research provides similar results to those in the first description of HCM Risk-SCD with an improved C-statistic (0.69) when compared with derivations based on the 2003 (C-statistic, 0.55) and 2011 guidance (C-statistic, 0.60). Using this approach still required the implantation of 17 ICDs to save one life at the end of 5 years.

To directly test the algorithm, a US group has also retrospectively examined the clinical prediction capabilities of HCM Risk-SCD in 1629 consecutive patients followed up for a median of 6.4 years of whom 460 received ICDs. Forty-six patients went on to receive appropriate ICD interventions, but 27 (59%) of this group had low HCM Risk-SCD scores that would have precluded an ICD recommendation. In addition, only 16 of the total of 81 (20%) who had an SCD-equivalent event had a high HCM Risk-SCD score along with a definite ICD recommendation. This group also tested the algorithm in a series of simulations providing examples of patients with large single RFs (who would not receive an ICD according to HCM Risk-SCD) and situations such as a combination of relative youth, LVOT obstruction, and increased LA size (who would not currently receive an ICD but in whom with uncritical application of HCM Risk-SCD would now get an ICD). The main conclusion was that application of HCM Risk-SCD might reduce the number of inappropriate ICDs but was thoroughly insensitive to the accurate identification of high-risk patients.

In view of these various continuing issues, it is likely that most of us will (for now) steer clear of an algorithmic approach that might obscure useful raw data. Some patients will undoubtedly access the HCM Risk-SCD algorithm, input their own data, and raise possibly challenging questions that will need to be addressed. To minimize such occurrences, a single, inclusive community effort in guideline formulation based on international cooperation should again be our aim. Most experienced physicians will continue to take a careful history probing difficult aspects (family history, syncope), review all the data in multidisciplinary discussion, and reach a measured conclusion to take back to the well-informed patient. Patients without manifest RFs will be reassured in the knowledge that their risk is low and not too far away from the general population mean. The question of risk will be revisited at future visits in the light of their further test results and accumulating research findings. In those in whom an ICD is thought likely to provide net benefit, the simplest device possible for that patient should be used to minimize adverse risks. This may be a single ventricular lead, single-coil transvenous unit but consideration should be made of the subcutaneous ICD, especially in young patients who will be especially prone to the issues emerging from both acute and progressive lead failure.

The variable performance of the HCM risk-SCD algorithm again highlights the need for new methods to identify those at risk of ventricular fibrillation. It is universally agreed that the source of risk is myocardial, and that the presence of myofibrillar disarray is a key determinant yet no current assessment method addresses this aspect directly. The use of late gadolinium enhancement as a possible means of risk stratification is of great interest, but it is unlikely to be sensitive to the presence of disarray. Gadolinium is taken up into expanded extracellular spaces and detects large areas of scar tissue during washout but smaller patches of collagen, interstitial fibrosis, and disarray may not be detected. Late gadolinium enhancement is, however, relevant to HCM-related heart failure outcomes, and although the relationship to SCD outcomes is not yet secure and probably again modest, it associates with potential surrogates of SCD (hypertrophy, nonsustained ventricular tachycardia). The American College of Cardiology/American Heart Association guidelines support a potential role of late gadolinium enhancement in decision making although whether the absence of late gadolinium enhancement predict those at low risk remains a point of much discussion.

Developments of cardiac MRI technology, eg, T1 mapping, will no doubt usefully input into phenotypic categorization. It would, however, appear that the architectural pattern not the density of fibrosis had the most impact on the electrophysiology of human cardiomyopathic hearts when studied ex vivo. So while diffuse, short-stand fibrosis had marginal effects on conduction delay, patchy fibrosis with long fibrotic strands substantially delayed conduction and such patterns are more likely to facilitate wavebreak and fibrillation.
direction of wavefront activation is also of relevance to the occurrence of nonuniform anisotropic conduction with effects being the most prominent with activation perpendicular to fiber direction.27 Clearly, some elements of this complex structural/functional milieu are going to be more amenable to non-invasive imaging than others.

Invasive electrophysiological assessment of patients with HCM is not usually recommended having fallen out of favor after disappointing, contentious responses to conventional ventricular stimulation.13 Nonetheless, evidence of regional voltage variation, increased latency, and delayed conduction has been consistently observed.30,31 In addition, the feasibility of invasive assessment of electrogams with the aim of addressing the functional significance of myofibrillar disarray without arrhythmia induction has been reported.14 The capacity of such approaches to enhance risk prediction was strongly supported in a prospective study of 179 patients followed up over 4 years. This investigation demonstrated that the electrophysiological approach predicted outcome with a high PPV (C-statistic, 0.88) although further validation is required.14

The ICD provides an effective means of protecting HCM patients from SCD but we must precisely target high-risk subcategories of the disease to gain most benefit.32 To make further significant progress, we require a focus on deep phenotyping (imaging/electrophysiology) directed to the heart muscle to address the prognostic consequences of myofibrillar disarray. In the interim, as Spiegelhalter has pointed out, we should be cautious in the use of large data sets as “precision will delude us if selection bias and overinterpretation of associations as causation are not properly taken into account.”33

**Sources of Funding**
The British Heart Foundation, the Medical Research Council, and the Biotechnology and Biological Research Council, UK, support Dr Grace’s research.

**Disclosures**
Dr Grace is a member of the Patient Safety Advisory Board of Boston Scientific Inc. He consults for Acutus Medical Inc, and is a former consultant and stockholder for Cameron Health Inc.

**References**
Late gadolinium enhancement on cardiac magnetic resonance represents the histologic basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy.


Key Words: Editorials | cardiomyopathy, hypertrophic | death, sudden, cardiac | defibrillators, implantable | guideline | ventricular fibrillation


Prophylactic Implantable Defibrillators for Hypertrophic Cardiomyopathy: Disarray in the Era of Precision Medicine

Andrew Grace

_Circ Arrhythm Electrophysiol_, 2015;8:763-766
doi: 10.1161/CIRCEP.115.003140

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/8/4/763

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Arrhythmia and Electrophysiology_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Arrhythmia and Electrophysiology_ is online at:
http://circep.ahajournals.org//subscriptions/