Predicting the future is always hard, and no more so than in a common disease like hypertrophic cardiomyopathy (HCM), which is usually associated with few if any symptoms yet can be a rare cause of sudden death in young people. For decades, the approach to the identification of individuals at high risk has been based on a semiquantitative estimation of relative risk derived from the summation of a small number of clinical markers. There are no prospective data on which to judge the clinical efficacy of this approach, but retrospective analyses suggest that it is only modestly predictive of future events. Similar dilemmas in other areas of medicine have been addressed with sophisticated risk models designed to estimate absolute risks. Until recently, the approach in HCM has been very different. Most investigators have hunted for new and ever more sophisticated tools that provide a window into the complex substrate that causes ventricular arrhythmia. In this issue of Circulation, Chan et al present a study using cardiac magnetic resonance imaging (CMR) and suggest that it improves on current risk prediction methods. Specifically, they suggest that CMR assessment of late gadolinium enhancement (LGE) provides the following: a statistically stronger predictor of sudden cardiac death events than each of the individual conventional risk factors used in HCM; a "unique opportunity" to identify sudden cardiac death risk in asymptomatic HCM patients, previously thought to be at low risk for lethal ventricular tachyarrhythmias; and the ability to identify unrecognized high-risk patients who could potentially benefit from implantable cardioverter-defibrillator (ICD) therapy. Given the high stakes associated with the decision to implant an ICD in young and often otherwise healthy people, we must be sure that the data are robust enough to change clinical practice.

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Current American and joint American/European guidelines for sudden death prevention are based on 5 risk factors: syncope, family history of premature sudden death, nonsustained ventricular tachycardia during 24-hour ECG, severe left ventricular hypertrophy, and an abnormal blood pressure response during upright exercise. Patients without these features are at very low risk of lethal events, and their survival does not differ from that of matched non-HCM control populations. The challenge is to improve the predictive accuracy to maximize the benefit-to-risk ratio of an ICD. A step toward improved targeting of therapy is provided in a recent multicenter study of >3500 patients that uses a validated risk tool to calculate individualized 5-year estimates of sudden cardiac death risk. The model confirms the very low risk of death in patients without validated risk markers and provides a new benchmark against which other putative risk predictors can be measured.

CMR is evolving into an important diagnostic tool in myocardial disease. Evaluation of LGE and now native T1 mapping and extracellular volume quantification permit differentiation of amyloidosis, edema/inflammation, iron overload, and Fabry disease from HCM. The extent of LGE has been associated with HCM heart failure–related outcomes and in cross-sectional studies has been associated with established risk factors for sudden death. Previous outcome studies with fewer patients and events have failed to demonstrate the prognostic utility of LGE for the identification of patients with HCM at risk of sudden death. Two recent studies have evaluated LGE as a predictor of sudden death events in larger cohorts. Chan et al studied 1293 patients, of whom 20 died suddenly or survived a cardiac arrest (1.5%) and 17 had an appropriate ICD discharge (1.3%) during a median of 3.3 years. This was a prospective study in that follow-up was from the time CMR was performed, and all studies were rigorously assessed in a CMR core laboratory, a particular strength of the study given the recognized intercenter variability in LGE measurements. Risk evaluation, however, was retrospective, and a major weakness was the absence of 24-hour ECG in 24% of the apparently low-risk cohort who had no other risk factors; this was a consequence of the study design in which Holter was obtained “at the discretion of investigators at each institution.” In contrast to the work by Chan et al, a study by a group of European HCM investigators found the extent of LGE to be a strong univariate predictor of sudden cardiac death, which was not maintained after adjustment for left ventricular ejection fraction.

Perhaps the most important claim in the study by Chan et al is the ability of CMR to identify patients who would be classified as low risk with current methods who go on to develop events. The statistical analysis appears to support this statement (Tables 3–5 and Figures 2 and 3), but the raw data (Table 2) do not. Setting aside for a moment appropriate ICD discharge as an end point, 20 patients died suddenly or experienced a cardiac arrest. Of these, 1 had extensive LGE as a percentage of mass (40%) with impaired systolic function (ejection fraction, 31%), 3 had small amounts of LGE.
(7%, 10%, and 11%), and the remaining 16 patients had LGE ≤5% of mass, which the authors acknowledge “...is trivial and does not differ significantly from that of patients without LGE.” From these data, LGE appears to have very limited utility in the identification of the very small number of individuals without risk factors who subsequently die suddenly. Close scrutiny of the data shows that the predictive power of LGE is generated from the cohort in which an appropriate ICD discharge is considered a sudden death event. The inclusion of ICD discharge events as equivalent to sudden cardiac death may have led to an overestimation of the sudden death rate, as has been shown in coronary artery disease and congestive heart failure studies. This cohort numbers only 17 patients, 13 of whom (77%) had conventional risk factors (6 with ≥2 risk factors). This is not a low-risk cohort, the apparent target population of this prognostic CMR study. Only 4 patients had no conventional risk factors (However, the Holter data are not presented; only the fact that they received a Holter is mentioned). Of these 4 patients, 3 had extensive LGE, and LGE may be adding value. Similarly, the patients with a single risk factor may receive added value from evaluation of LGE, but study design and size preclude this conclusion. There were insufficient analogous patients to enable analysis of the potential role for CMR to refine risk.

A major limitation of being a “prospective retrospective” study is the inevitable exclusion from analysis of 376 patients (23%) because of prior ICD implantation. The resultant cohort is enriched for low-risk patients and new patients undergoing preliminary or repeat risk stratification. This led to a low annual sudden death rate (0.5%) and, within the cohort who subsequently received ICDs, a low ICD discharge rate (0.4%). The low number of events affects statistical analysis in which the number of events limits the number of risk markers that can legitimately be evaluated. In this study, 4 conventional risk markers (syncope, adverse family history, nonsustained ventricular tachycardia, severe left ventricular hypertrophy) were collapsed into the analysis as a single continuous variable. The use of this statistical approach highlights the need for more robust data sets with larger numbers of events.

The authors conclude their article with the following: “Extensive LGE measured by quantitative contrast-enhanced CMR provides additional information for assessing sudden cardiac death event risk among HCM patients, particularly patients otherwise judged to be at low risk.” The data presented in the low-risk cohort without risk factors who nonetheless had events do not substantiate a special role for CMR in such patients. We look to future collaborations such as the HCMR: Novel Markers of Prognosis in Hypertrophic Cardiomyopathy study (a 5-year, prospective 2750-patient study) for further answers.17

Disclosures
None.

References


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