Canadian Journal of Cardiology 35 (2019) 1626–1628

Editorial

The ESC Risk Score Is Less Reliable than ACC/AHA Risk Factors in Hypertrophic Cardiomyopathy: When Sensitivity Trumps Specificity

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See article by Wang et al., pages 1791–1799 of this issue.

Sudden cardiac death (SCD) remains the most visible and devastating consequence of hypertrophic cardiomyopathy (HCM).[1-3] The proven efficacy of the implantable cardioverter defibrillator (ICD) in aborting lethal ventricular tachyarrhythmias, changing clinical course, and saving young lives in patients with HCM has placed increasing weight on the importance of accurate selection of patients for device therapy.[3-9] Beginning in 2003, and most recently in 2017, North American expert consensus guidelines have recommended a strategy in which decisions for primary prevention ICDs are based on the presence of 1 or more risk markers regarded as major within the clinical profile of a patient with HCM.[1,2] Over this period of time, the American College of Cardiology/American Heart Association (ACC/AHA) risk-factor strategy has continued to evolve, incorporating novel markers for SCD including, most recently, extensive late gadolinium enhancement (LGE) and the left ventricular (LV) apical aneurysm.[10,11] This matured risk-stratification approach has now translated into a substantial reduction of sudden deaths in HCM, providing the opportunity for normal longevity for the majority of patients with this disease.[2]

More recently, the European Society of Cardiology (ESC) has promoted a different approach to risk stratification in HCM, developing a risk score based on a formula comprising 7 disease-related features that can be imputed into a smartphone after downloading the ESC Risk Score App, to calculate a 5-year risk of sudden death.[4,12-16] Management recommendations for primary prevention ICDs are provided after placing patients into 1 of 3 risk categories: low (<4%, ICD not indicated), intermediate (4% to 6%, ICD could be considered), or high (≥6%, ICD should be considered). Emergence of 2 distinctly different methods for risk stratifying patients with HCM for primary prevention ICDs raises the question of which is the optimal strategy for selecting individual high-risk patients for prevention of SCD.

In this regard, the meta-analysis by Wang et al.[17] in the current issue of the *Canadian Journal of Cardiology* is timely and provides important insights and clarity on the limitations inherent in the ESC risk-score model and its impact on selecting patients for potentially lifesaving therapy with the ICD. These authors have assembled into a meta-analysis 9 studies comprising 9651 patients with HCM followed for a mean of 5 years with the endpoint of sudden death events. The primary statistical metric employed to judge performance of the ESC risk score was concordance: that is, the C-statistic, measuring the area under the curve (AUC), which describes the strength of the model to discriminate patients with sudden death events compared with those without such events. A C-statistic with values of 0.5 is consistent with poor discriminatory power, whereas 1.0 is virtually perfect.

However, it should be underscored that judging performance of the ESC risk score solely by concordance statistics reveals only how the prediction model performs broadly on the cohort level. For example, although large and diverse studies were included in this meta-analysis, the ESC risk-prediction model demonstrated only modest discriminatory power in predicting patients with HCM who experienced sudden death events with a C-statistic of 0.75. Expressing performance this way, through the prism of *group statistics*, does *not* aid clinicians tasked with making often-challenging management decisions in individual patients with HCM; for example, how accurate is the SCD risk strategy I am using in predicting whether my *individual* patient with HCM is a candidate for an ICD?

In this regard, based on the data of Wang et al.,[17] these authors demonstrate a particularly low sensitivity (range: 41% to 71%) for the ESC risk score in predicting those individual patients with HCM who, over the follow-up period, experienced an SCD event. Indeed, as Wang et al.,[17] correctly state, the low sensitivity of the ESC score means that an important subset of patients with HCM at risk of an SCD event would likely have been excluded from an ICD implant recommendation.

Received for publication May 29, 2019. Accepted June 18, 2019.

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See page 1628 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.06.018

Notably, these observations are also consistent with the recent large (n = 2094 patients) Tufts HCM Institute study, with prospective ICD decision making, which demonstrates that the most efficacious strategy for identifying high-risk patients with HCM deserving primary prevention ICD therapy is an individual risk marker strategy enhanced from the 2011 ACC/AHA guidelines and incorporating more contemporary risk markers.[5]

In the Tufts study, 82 patients likely experienced life-saving device therapy terminating ventricular fibrillation (VT/VF) episodes, which exceeded by approximately 50-fold (Fig. 1A) the 5 HCM-related SCDs occurring in patients not implanted with ICDs, including 2 patients who declined device therapy despite our intention to treat.[5] Sensitivity of the ACC/AHA risk factor strategy was very high (95%), resulting in identification of nearly all at-risk patients with HCM (Fig. 1B) On the other hand, consistent with the observations in the Wang et al. meta-analysis,[17] sensitivity of the ESC risk score, when applied retrospectively to the same patients at Tufts, was particularly low (34%). Among the 82 patients with appropriate ICD interventions terminating VT/VF, almost 50% had low ESC risk scores inconsistent with an ICD recommendation and therefore with this strategy would not likely have been protected from SCD.[5]

The higher sensitivity associated with the enhanced ACC/AHA risk marker strategy is due, in part, to its inherent flexibility, which allows the opportunity to incorporate novel high-risk markers such as extensive LGE, systolic dysfunction with ejection fraction <50% and LV apical aneurysms, which account for a significant proportion (~25%) of appropriate

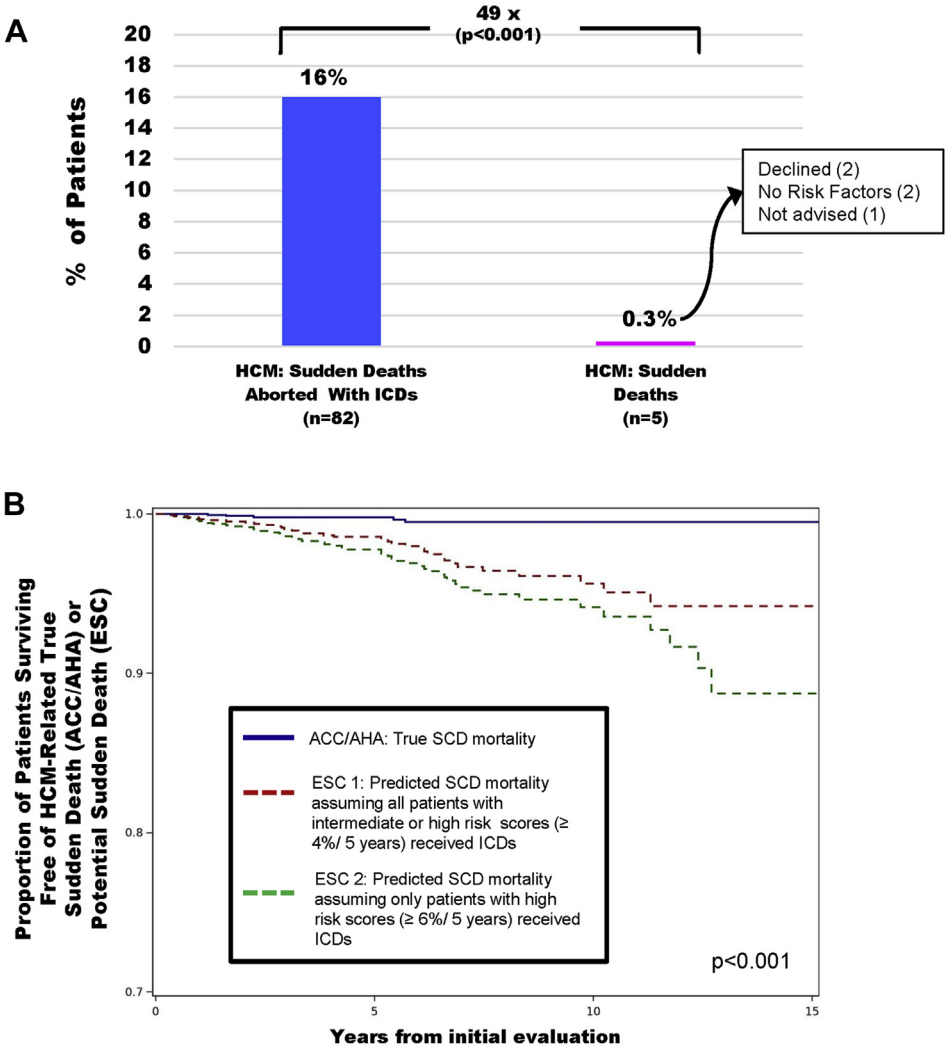

Figure 1. Superior sensitivity of enhanced American College of Cardiology/American Heart Association (ACC/AHA) risk-factor strategy compared with European Society of Cardiology (ESC) risk score in identifying high-risk patients with hypertrophic cardiomyopathy (HCM) for prevention of sudden cardiac death (SCD). **A**, Prospective implantable cardioverter defibrillator (ICD) decision making by risk stratification in 2094 consecutive patients with HCM. Clinical outcome in patients for whom potentially lethal ventricular tachyarrhythmias were terminated by primary prevention ICDs (n = 82) compared with sudden deaths occurring in patients without ICD implants (n = 5). **B,** Kaplan-Meier curves comparing true SCDs using enhanced 2011 ACC-AHA guidelines vs potential SCDs, applying the ESC risk-score model. ESC 1: Assumes that all patients with either high or intermediate risk scores (≥ 4% per 5 years) were implanted with primary-prevention ICDs. ESC 2: Assumes that only patients with the highest risk scores (≥ 6% per 5 years) were implanted with primary prevention ICDs. Reproduced with permission from Maron et al.[5]

ICD therapies among patients with HCM[5] but are excluded from the ESC risk-score algorithm. The ACC/AHA risk marker strategy also permits a greater measure of physician judgement and reasoning within the narrative of shared decision-making discussion, which is so important in a heterogenous disease such as HCM. Unfortunately, it is not possible to somehow combine both prediction approaches as a strategy to more reliably assess risk level in individual patients with HCM.

On the other hand, the ESC risk score is accompanied by relatively high specificity, suggesting that it could theoretically reduce the number of implants in low-risk patients and limit ICD overuse,[5,17] although the number of ICDs needed to treat 1 patient appropriately for VT/VF is only 6:1, with either the ESC or ACC/AHA strategies, a ratio not different from randomized clinical trials of ICDs in non-HCM diseases.[5] Therefore, the cost of preventing SCD events in patients with HCM may be only a modest number of ICDs placed in low-risk patients.

Unexpected SCD has been the scourge of HCM for more than 50 years, but we wish to underscore to those clinical cardiologists charged with the care of patients with HCM that it is now possible to identify with very high reliability (sensitivity 95%) those patients at unacceptably increased risk of SCD who could be candidates for potentially life-saving treatment with primary-prevention ICDs. The most effective strategy for achieving this aspiration is the clear and concise method using ≥ 1 of the established individual risk factors considered major within the clinical profile of the patient with HCM.[5] We do acknowledge the tendency to navigate instinctually to data that are new, but in this case of HCM risk stratification and SCD prevention, it is now evident that the new ESC risk score is less reliable than the established ACC/AHA risk-factor strategy for identifying candidates for ICD in a heterogenous disease such as HCM and does not represent an improvement over the older but enhanced guideline strategy predicated on individual risk markers. For these reasons, the ACC/AHA major risk factors should remain as the primary strategy in risk stratifying individual patients with HCM for primary prevention-device therapy.

Disclosures

The authors have no conflicts of interest to disclose.

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