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REGULAR ARTICLE

Sudden cardiac death in childhood hypertrophic cardiomyopathy is best predicted by a combination of electrocardiogram risk-score and HCMRisk-Kids score

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Abstract

Aim: To compare risk algorithms (HCMRisk-Kids, ECG Risk-score) in hypertrophic cardiomyopathy (HCM) without syndrome association (ns-HCM) and with Noonan-like syndromes (RAS-HCM).

Methods: A national paediatric HCM cohort (n = 151), presenting <19 years of age, mean follow-up 13.3 years, from all Swedish centres of Paediatric Cardiology (presenting 1972–2015), with 41 RAS-HCM patients (61% males), and 110 ns-HCM patients (68% familial; 65% males). The end-point was a composite of sudden cardiac death and resuscitated cardiac arrest (SCD/CA). Risk-factors were studied with Cox-hazard regression, and receiver operating characteristic curve analysis (C-statistic).

Results: There were 33 SCD/CA, 27/110 in ns-HCM and 6/41 in RAS-HCM ($p = 0.27$). In ns-HCM HCMRisk-Kids ≥6% at diagnosis had C-statistic of 0.69 for predicting SCD/CA during first 5 years of follow-up and positive predictive value (PPV) of 22%. After 7 years of age (HCMRisk-Kids7plus), C-statistic was 0.76. ECG Risk-score ≥6 at diagnosis had C-statistic 0.87 and PPV of 31%. Independent risk factors for SCD/CA were HCMRisk-Kids7plus score ($p = 0.005$) and ECG risk-score ($p < 0.001$), whereas early beta-blocker dose ($p = 0.001$) and myectomy ($p = 0.004$) reduced risk. The sum of HCMRisk-Kids7yplus and ECG Risk-score7yplus ≥14 best predicted SCD/CA within

Abbreviations: AHA, American Heart Association; AHA2011, American Heart Association 2011 Guidelines for Hypertrophic Cardiomyopathy; Cs-value, C-statistic, Area under the curve in a ROC curve; ECG Risk-score, ECG-based risk score; ECG, electrocardiogram; ESC 2014, European Society of Cardiology Guidelines for hypertrophic cardiomyopathy; HCM, hypertrophic cardiomyopathy; HCMRisk-Kids, risk stratification algorithm; ICD, internal cardioverter-defibrillator; ns-HCM, Hypertrophic cardiomyopathy without associated syndrome; PRIMaCy-SCD, Risk stratification algorithm; RAS-HCM, Hypertrophic cardiomyopathy associated with Noonan syndrome, Leopard syndrome, cardio-facio-cutaneous syndrome and other RASopathies; ROC curve, Receiver operating characteristic curve; SCD, sudden cardiac death; SCD/CA, sudden cardiac death and resuscitated cardiac arrest.

5 years in ns-HCM with C-statistic of 0.90 [0.83–0.96], sensitivity 100% and PPV 38%.

Conclusion: Combining the ECG Risk-score with HCMRisk-Kids improves risk stratification in ns-HCM and shows promise in RAS-HCM.

KEYWORDS
beta-blocker, hypertrophic cardiomyopathy, Noonan syndrome, risk factors, sudden death

1 | INTRODUCTION

In childhood hypertrophic cardiomyopathy (HCM), sudden death due to arrhythmia has a significantly higher rate in 8–16 years-old HCM patients, 0.112 deaths per 100,000 age-specific population, than in the 17–30 years age range.[1,2] Tragically, it often occurs in children with no, or minimal, symptoms. The implantation of an internal cardioverter-defibrillator (ICD) offers an approach to protection of high-risk individuals.[3] Studies in paediatric HCM have not confirmed that some of the major risk criteria used in adult American Heart Association (AHA) 2011 and 2020 guidelines, in particular family history of sudden cardiac death (SCD), are predictive in childhood HCM.[4-8] In the section on 'Unmet Needs', the 2020 Guidelines also comments that existing risk stratification algorithms still have low positive predictive values and that new algorithms are needed, particularly in children.[9] Two paediatric risk stratification algorithms have recently been published. HCMRisk-Kids was proposed in 2019, but has not had external validation.[10] This was followed by PRIMaCy-SCD which included an external validation study-group.[11] However, neither HCMRisk-Kids nor PRIMaCy-SCD are validated in, nor recommended for use, in RASopathy-associated HCM.[10,11] The ECG-phenotype has also been explored for risk stratification creating an ECG Risk-score that appeared promising both in adult HCM patients,[12] and in childhood HCM, where a cut-off of ≥6 points had a sensitivity of 97% for the prediction of SCD or cardiac arrest in paediatric HCM patients in a national cohort including both non-syndrome- and RASopathy-HCM.[7]

One main objective of the current study is to provide an independent external validation of the HCMRisk-Kids algorithm with a correct calculation of positive predictive value, as this should only be calculated in complete geographical cohorts. Furthermore, we explored whether the ECG Risk-score might add value to the HCMRisk-Kids score in risk stratification as assessed by using C-statistic from receiver-operated characteristic (ROC) curves. HCM associated with Noonan group syndromes comprise an important proportion of HCM presenting in childhood, around 23% in geographical cohort studies,[7,13] also with a significant risk of suffering SCD,[14-16] but there are no published risk factors. An additional objective of this study is a pilot study to assess if the HCMRisk-Kids and/or ECG risk-score can be used for risk stratification in HCM associated with the Noonan group of RASopathy syndromes.

Key Notes

- We find that the major risk-factors are the same in non-syndrome associated hypertrophic cardiomyopathy and RASopathy-associated hypertrophic cardiomyopathy.
- Prediction of risk of sudden cardiac death within 5 years is obtained with high sensitivity, and positive predictive value of 38%, by adding the ECG Risk-score to the HCMRisk-Kids score.
- We show that other therapeutic interventions apart from implantation of internal cardioverter-defibrillator also reduce risk of sudden cardiac death.

2 | METHODS AND MATERIALS

A national cohort of Swedish paediatric HCM patients diagnosed <19 years of age has previously been assembled from 1972 from all six Swedish centres of Pediatric Cardiology[7,14,15] and was updated to include patients diagnosed up to December 2015 (for more details see Supporting Information e-Methods). 151 patients in the national cohort, follow-up 13.3 ± 9.3 years, had ECGs, cardiac ultrasound measurements and hospital records pre-SCD, out of whom there were 33 patients with sudden death or resuscitated malignant arrhythmia (21 sudden deaths, six resuscitated cardiac arrests and six appropriate ICD-interventions), referred to as SCD/CA-group. Detroit Z-score was used to relate ultrasound-measured maximal left ventricular wall thickness to body size.[17] Clinical characteristics of the cohort are shown in Table 1, and Supplementary Table S1.

2.1 | Calculation of HCMRisk-Kids

We were kindly provided an Excel sheet by Dr Norrish and Dr Kaski, programmed with the HCMRisk-Kids algorithm.[10] Within that calculation sheet, the modified Boston weight-only *Z*-score is displayed[10] and recorded for comparison with Detroit *Z*-scores. The algorithm is now also available via https://hcmriskkids.org.

TABLE 1 Baseline clinical characteristics of national cohort of non-syndrome childhood hypertrophic cardiomyopathy (median [interquartile range], or per cent of total) and some details of management

	Total cohort	With SCD/CA	No event	
	N = 110	(*n* = 27)	*N* = 83	*p*-value
Age at diagnosis, years	10.9 (4.0–15.3)	10.3 (5.2–13.8)	11.9 (3.4–15.3)	n.s.
Male sex	65%	63%	66%	n.s.
Duration of follow-up	11.6 (8.0–15.9)	5.3 (4.1–18.6)	12.0 (9.6–15.7)	0.001
FH of HCM	68%	48%	75%	0.016
FH of SCD	34%	26%	36%	n.s.
Unexplained syncope	15%	14%	16%	n.s.
NSVT early follow-up	11%	29%	3%	0.051
NSVT anytime	22%	71%	6%	<0.0001
VEBs on exercise	11%	36%	6%	0.029
Max wall thickness (mm) at D	15 (12–22)	21 (14–27)	15 (12–19)	0.005
Detroit *Z*-score (MWth)	4.3 (2.6–5.8)	5.8 (4.1–6.9)	3.5 (2.7–4.8)	<0.001
Boston wt only Z-score (MWT)	9.6 (5.9–16.5)	16.7 (11.9–20.8)	8.1 (5.7–12.9)	<0.001
SEPPER at D (%)	183 (126–211)	202 (180–174)	145 (120–191)	<0.001
LVPER at D (%)	106 (90–121)	112 92–133)	103 (88–118)	0.11
LA:ao ratio	1.3 (1.2–1.5)	1.4 (1.3–1.6)	1.3 (1.2–1.5)	0.11
LVOTO at rest at diagnosis	36%	63%	28%	0.0025
HCMRisk-Kids at diagnosis	4.8 (3.2–7.4)	6.9 (4.1–11.2)	4.0 (3.0–6.8)	0.010
HCMRisk-Kids age 7plus	4.7 (3.0–8.2)	7.3 (5.2–10.8)	3.8 (2.9–11.2)	<0.001
ECG Risk-score at diagnosis	3 (2–8)	8 (6–9)	2 (0–5)	<0.001
ECG Risk-score age 7plus	4 (2–8)	8 (6–10)	3 (1–5)	<0.001
HCMRiKi7pl+ECGrisk7pl	8.4 (4.7–14.1)	16.7 (14.1–20.8)	6.1 (4.1–17.0)	<0.001
Age at SCD	-	15.9 (11.8–23.0)	-	-
Medical management				
Early beta-blocker	68%	48%	74%	0.017
Early prop-eqv mg/kg cohort	-	0 (0–4)	4.5 (0–6.0)	0.005
Early prop-eqv mg/kg in treated	6.0 (3.4–9.2)	5.0 (1.5–6.0)	6.0 (4.2–7.0)	0.106
Calcium-channel blocker	5%	13%	2%	0.031
No therapy	15%	22%	13%	n.s.
Addition of disopyramide	30%	19%	33%	0.08
Addition of amiodarone	2%	13%	1%	0.045
Subsequent myectomy	10%	21%	7%	n.s.
Residual LVOT gradient late FU	-	12 (0–54)	0 (0–0)	<0.001
Late LVOTO >50 mm Hg	8%	32%	1%	<0.0001
Late LVOTO >30 mm Hg	9%	32%	2%	0.0002
Late prop-eqv mg/kg in treated	5.5 (3.4–9.2)	3.8 (1.7–8.3)	5.8 (3.8–9.5)	0.047

Note: p-value refers to Fishers exact test for proportions, and Mann-Whitney *U* test for measures. 'Early' is defined as within six months of diagnosis, 'Late' as dose/measurement at latest follow-up visit.

Abbreviations: at D, at diagnosis; ECG, electrocardiogram;FH, Family history; HCM, hypertrophic cardiomyopathy; LA:ao ratio, ratio between left atrial and aortic root diameter on long-axis M-mode measurement; LVOTO, left ventricular outflow-tract obstruction; MWth, maximal wall thickness; NSVT, non-sustained ventricular tachycardia; prop-eqv, beta-blocker dose measured in propranolol equivalents; wt, weight. SEPPER, septal thickness in per cent of 95th centile for age.

2.2 | Calculation of ECG risk-score

The score was calculated as previously described,[12,14] by scoring four morphological features, and three voltage and duration ECG measurements (see supplementary Table S2).

2.3 | Causes of death

All Swedes have a unique personal identification number, and no patients were lost to follow-up. Vital status was last ascertained in May 2021. All SCD/CA have been validated through

hospital records and, where necessary, postmortem records with histology.

2.4 | Statistics

Primary end-point was a composite of sudden deaths, resuscitated cardiac arrests and appropriate ICD-interventions (SCD/CA). Receiver operating characteristic (ROC) curve analysis with C-statistic and Cox-hazard uni- and multivariate analysis was performed using IBM SPSS Statistics (v.22). Risk prediction was verified by C-statistic being statistically significantly above 0.5. *p*-values <0.05 were considered significant, but in Cox-hazard regression parameters with $p < 0.010$ were left in the multivariate model (more details in Supplementary Information e-Statistics).

The study complies with the 2013 Helsinki declaration, and collection of the case note information had been approved of the local Ethics Committee, most recently EPN-Gbg Dnr783-15.

3 | RESULTS

There were 110 patients without syndrome association (ns-HCM); Table 1. In the ns-HCM group, 27 SCD/CA occurred, during a mean follow-up of 13.4 years (±8.5SD). Seventeen patients had SCD/CA during first 10 years of follow-up (15.7%) and 11 during the first 5 years. There are many significant differences in known risk-factors between the patients with, and without, SCD/CA but a notable finding is that persistence of a significant left ventricular outflow-tract (LVOT) gradient on late follow-up is strongly over-represented in patients with SCD/CA, ($p < 0.0001$). Forty-one patients (27%) had stigmata of Noonan, Leopard or Cranio-Facial-Cutaneous syndrome and were grouped as RASopathy-HCM (RAS-HCM). The patients with RAS-HCM had six SCD during follow-up ($p = 0.27$ vs. ns-HCM; Fisher´s exact test), no SCD occurring below eight years of age and with median age at SCD 14.4 years [95%CI 12.3–42]. Median age at diagnosis was significantly lower than ns-HCM, 0.2 years [0.1–1.2]; ($p < 0.00001$). However, eight RAS-HCM patients died from heart failure already in infancy and did not reach the age range at highest risk for sudden death, and comparing proportion of SCD after age eight, and excluding patients presenting with SCD, the proportions of subsequent SCD, 24/106 (23%) in ns-HCM and 6/27 (22%) in RAS-HCM, were essentially equal ($p = 1.0$). The mean follow-up in RAS-HCM group was 12.7 years (±10.6). For further clinical details in RAS-HCM, see supplementary Table S1.

Table 2 illustrates the results of Cox-hazard regression analysis in ns-HCM. HCMRisk-Kids and ECG Risk-score are both strong risk factors at diagnosis and eliminated Detroit-Z-score from the multivariate model. However, HCMRisk-Kids value after 7 years of age (HCMRisk-Kids7plus) was stronger than HCMRisk-Kids at diagnosis on bi-variate analysis and was retained in the multivariate model, as was ECG risk-score at diagnosis, together with decreasing age at diagnosis, that is in ns-HCM the younger the age at diagnosis, the higher the risk of subsequent SCD. In addition, two therapeutic measures used to treat left ventricular outflow-tract obstruction were associated with significant reduction in risk, both surgical myectomy and early beta-blocker therapy. The beta-blocker effect was dose-dependent, as is shown by the *B*-value for early propranolol-equivalent dose being significantly negative. Patients with outflow-tract obstruction at diagnosis had significantly better freedom from SCD/CA if treated with maintenance beta-blocker dose of >4.5 mg/kg of propranolol equivalents, ($p = 0.003$, see Figure S1). Interestingly, as beta-blocker dose and lastly myectomy were added, the significance levels of the other parameters in the model became stronger. Posterior left ventricular wall thickness was not a significant risk factor either in univariate or multivariate models in our ns-HCM cohort, which contains a high proportion of familial HCM.

3.1 | Estimate of predictors for 5-year risk (Table 3)

The assessment of 5-year risk has been proposed as a decision-instrument for considering prophylactic ICD implantation. However, there are particular problems about applying this concept in patients diagnosed in infancy as the highest risk of SCD is after 8 years of age,[1] and clinical findings might have altered substantially by then. Thus, we illustrate two key risk predictors both at diagnosis and as values recorded nearest 7th birthday, useful for cases with infant diagnosis (ECG Risk-score7plus and HCMRisk-Kids7plus). For 7plus values, subsequent follow-up for 5-year and 10-year risk was calculated from 8th birthday in cases with infant diagnosis. HCMRisk-Kids values were calculated as validated, only on patients below 17 years of age at diagnosis, but for HCMRisk-Kids7plus values we included values also in patients diagnosed in 17–18 years age range to have complete cohort data.

3.2 | Non-syndrome HCM

As a continuous function HCMRisk-Kids at diagnosis (0.77) is not obviously superior to either Detroit Z-score or the weight only Z-score as discriminator of early risk. HCMRisk-Kids7plus has a higher Cs-value (0.83) however, and this is true even with the proposed 6% high-risk cut-off applied (Cs-value 0.76, compared to 0.69 at diagnosis). The ECG risk-score is a powerful predictor of early SCD/CA events both as continuous function, but also with a ≥6 point cut-off, where it has a Cs-value of 0.87. Since the ECG risk-score is independent of HCMRisk-Kids on multivariate analysis, and both have increased risk with increasing value, we did an explorative ROC analysis with the sum of ECG Risk-score and HCMRisk-Kids per cent score. This lead to higher Cs-values than either variable alone (Table 3; Supplementary Figure S2). Best discrimination is achieved by the sum of HCMRisk-Kids7plus score and the ECG Risk-score7plus which had a Cs-value of 0.91 as continuous variable and with a cut-off of ≥14 a Cs-value of 0.90.

TABLE 2 Univariate and multivariate Cox proportional hazard analysis in ns-HCM of significant early risk factors for sudden cardiac death and resuscitated cardiac arrest

Measure	*B*	SE	Exp (*B*)	*p*-value
Univariate Cox-hazard regression (n = 110, SCD/CA =27)				
HCMRisk-Kids (per cent)	0.162	0.042	1.135	**0.003**
HCMRisk-Kids 7yplus (per cent)	0.141	0.042	1.151	**0.001**
Total ECG Risk-score at diagnosis	0.313	0.065	1.367	**<0.001**
Total ECG Risk-score 7 years	0.325	0.071	1.384	**<0.001**
Age at diagnosis (years)	0.009	0.031	1.009	0.77
LVPER at diagnosis	0.007	0.007	1.007	0.32
LA:Ao ratio at diagnosis	1.246	0.568	3.468	0.160
LVOTO at rest at diagnosis	0.641	0.419	1.899	0.117
Latest LVOT gradient (mm Hg)	0.023	0.007	1.023	0.001
Early prop equiv Bbl-dose mg/kg	−0.132	0.075	0.877	0.080
Calcium-channel blocker therapy	−0.004	0.685	0.996	1.00
Disopyramide	−0.970	0.533	0.379	0.069
Multivariate model with HCM Risk-Kids and ECG risk-score excluding cases presenting with cardiac arrest (n = 107, SCD/CA =24) (17.6% of cases had a missing value)				
Total ECG Risk-score at diagnosis	**0.473**	**0.116**	**1.605**	**<0.001**
HCMRisk-Kids7plus per cent	**0.223**	**0.079**	**1.250**	**0.005**
Early prop equiv Bbl-dose mg/kg	**−0.359**	**0.104**	**0.699**	**0.001**
Myectomy	**−2.372**	**0.814**	**0.795**	**0.004**
Age at diagnosis	**−0.229**	**0.064**	**0.795**	**<0.001**

Abbreviations: B, regression coefficient; ECG, electrocardiogram; Exp(*B*), change in odds from unit change of predictor; HCM, hypertrophic cardiomyopathy; LA:Ao, left atrial diametre:aortic root diameter; LVOT, left ventricular outflow-tract; LVOTO, left ventricular outflow-tract obstruction; LVPER, LV posterior wall thickness in per cent of 95th centile for age[14]; prop equiv Bbl-dose, Beta-blocker dose expressed as propranolol-equivalent dose in mg/kg/day[7]; SCD/CA, sudden cardiac death and resuscitated cardiac arrest; SE, standard error of *B*.

In the column for *p*-values we have high-lighted those parameters which were statistically significant risk factors by setting those *p*-values in bold.

The weight-only *Z*-score utilised in HCMRisk-Kids algorithm had numerical values strikingly higher, more than double, compared to Detroit *Z*-score on within-patient comparison ($p = 0.00001$; Table 1), and thus, optimal cut-off values would be very different with these two *Z*-scores. The effect of residual left ventricular outflow- gradient after therapy appears to increase risk with duration of follow-up: in our ns-HCM cohort the Cs-value for latest left ventricular outflow-tract obstruction gradient for SCD/CA within 5 years is 0.65 (not significant), for SCD/CA within 10 years 0.70 and for whole duration of follow-up 0.79 [0.68–0.92], ($p < 0.001$).

3.3 | RASopathy HCM

Amongst 27 subjects surviving past their 8th birthday, there were only three SCD during the subsequent 5 years so statistical power is poor, but Cs-values for the strongest risk factors in ns-HCM had similar Cs-values in RAS-HCM, with the sum of HCMRisk-Kids7plus and ECG risk-score7plus being significant ($p = 0.022$; Table 3); and predictive also over subsequent 10 years of follow-up (Figure 1).

3.4 | Implications of various cut-offs to designate ICD candidates (Table 4; Figure 1)

For comparison of efficacy as indications for ICD implantation, we have calculated the 5- and 10-year risk of SCD/CA in test-positive individuals for different proposed risk-stratification strategies. For suggested cut-offs for the combined ECG Risk-score with HCMRisk-Kids, we used the Youden index to maximise specificity without losing much sensitivity. Sensitivity, specificity, positive predictive value and negative predictive value were calculated from individuals designated at diagnosis by the test, using survivors that had completed 5 years of follow-up. For 7plus values, subsequent follow-up for 5-year and 10-year risk was calculated from 8th birthday in cases with infant diagnosis. Lastly, also using the Kaplan-Meier survival curve we calculated the proportion of 'true positives' (i.e. SCD/CA) amongst test-positive individuals that had completed 10 years of follow-up. The ECG Risk-score ≥6 points is the only single criterion in this cohort that combines highest sensitivity and a high positive predictive value (27% 5-year risk) with 0% false negatives amongst those below the cut-off, but it is not specific enough on its own. HCMRisk-Kids has 73% sensitivity, 22% positive predictive value and similar specificity

TABLE 3 Prediction of SCD/CA during first 5 years*: C-statistic for proposed risk factors

Non-syndrome HCM $n = 107$			
Clinical measures at diagnosis as continuous functions			
Variable	**C-stat**	**95% CI**	***p*-value**
ECG Risk-score	0.91	0.85–0.97	**<0.001**
ECG Risksc+Risk-Kids	0.91	0.83–0.98	**<0.001**
ECG Risksc7pl+Risk-Kids7pl	0.91	0.85–0.97	**<0.001**
HCMRisk-Kids 7plus	0.86	0.75–0.92	**<0.001**
ECG Risk-score7plus	0.83	0.75–0.92	**<0.001**
MaxWDetroit Z-score	0.79	0.65–0.92	**0.003**
HCMRisk-Kids	0.77	0.62–0.93	**0.003**
MaxWHRK Z-score	0.76	0.60–0.93	**0.005**
Number AHA2011RF	0.55	0.36–0.74	0.59
Potential cut-offs and binary risk factors			
ECG-Risksc7+Risk-Kids7≥14	0.90	0.83–0.96	**<0.001**
ECG Risk-score >5	0.87	0.80–0.94	**<0.001**
ECG risksc+Risk-Kids ≥14	0.82	0.68–0.96	**<0.001**
ECG Risk-score7y >5	0.81	0.70–0.91	**<0.001**
Detroit Z-score ≥4.5	0.79	0.66–0.92	**0.003**
Detroit Z-score ≥6	0.72	0.54–0.91	**0.021**
HCMRisk-Kids7y ≥6%	0.76	0.64–0.89	**0.002**
HCMRisk-Kids ≥6%	0.69	**0.52–0.85**	**0.045**
HCMRiskKids ≥4%	0.68	0.54–0.82	0.053
MaxWHRK Z-score ≥12.5	0.69	0.53–0.85	**0.042**
ESC2014 ≥2RF	0.66	0.47–0.85	0.087
oneAHA2020RF	0.55	0.37–0.73	0.59
RASopathy HCM (n = 27 survivors to age 8 years)			
ECG Risksc7pl+Risk-Kids7pl	0.91	0.79–1.00	**0.022**
ECG-Risksc7+Risk-Kids7≥14	0.83	0.67–1.00	0.064
ECG Risk-score >5	0.81	0.62–0.99	0.087
HCMRisk-Kids7y ≥6%	0.80	0.62–0.99	0.092

Abbreviations: CI, Confidence interval; C-stat, C-statistic; ECG Risksc+Risk-Kids, sum of ECG Risk-score at diagnosis and HCMRisk-Kids at diagnosis calculated per cent figure; ECG-Risksc7+Risk-Kids7≥14, calculated as ECG Risk-score age 7 years plus HCMRisk-Kds age 7 years plus; HCM, hypertrophic cardiomyopathy; MaxWDetroit Z-score at diagnosis, Maximal wall thickness expressed as Detroit Z-score; MaxWHRK, Maximal wall thickness at diagnosis using HCMRisk-Kids Z-score (Boston, wt only) RF, risk factor.

In the column for *p*-values we have high-lighted those parameters which were statistically significant risk factors by setting those *p*-values in bold.

*Patients presenting with resuscited cardiac arrest excluded.

as the ECG Risk-score. Combining the two measures as a sum with a low cut-off of ≥10 still gives too high a number of ICD candidates to be ideal. A higher cut-off of ≥14 increases positive predictive value to 38% and reduces ICD-candidates to 26% but reduces sensitivity to 82%. However, if HCMRisk-Kids7plus and ECG Risk-score7plus scores are combined, both sensitivity and negative predictive value reached 100%, but ICD-candidates also increase to 32%. All of these risk stratification strategies were superior to ≥2 ESC2014 risk factors (sensitivity 45%) and at least one AHA2011/2020 major risk-factor at diagnosis (sensitivity 55% and specificity only 56%). It should, however, be noted that at diagnosis, a Detroit *Z*-score ≥4.5 (validated up to 19 years of age) tend to have a higher sensitivity and at least as good specificity as either HCMRisk-Kids ≥6% at diagnosis (only validated up to age 16 years), or weight-only Boston-2D Z-score.

3.5 | Five-year risk of SCD/CA in RAS-HCM

Calculating the hazard after the 8th birthday, 4/27 (15%) suffered SCD/CA in the first 10 years of follow-up, a similar proportion as in ns-HCM. Three SCD/CA occurred within first 5 years. As the best performing cut-offs were sum of ECG risk-score7plus and HCMRisk-Kids7plus ≥14, with Cs-value of 0.83, similar to the same measure in ns-HCM, we have assessed the performance of these measures also in a combined cohort (Table 4).

4 | DISCUSSION

4.1 | Independent validation of HCMRisk-Kids

The HCMRisk-Kids algorithm is an attempt at improving prediction in childhood HCM with a similar approach to the ESC2014 risk calculator,[18] including maximal wall thickness *Z*-score, left atrial diameter *Z*-score and peak left ventricular outflow-tract gradient as continuous functions, and non-sustained ventricular tachycardia and unexplained syncope as binary functions in the algorithm.[10] That study was handicapped by a lot of missing data (48.5%), but the authors did an internal validation on 527 patients with complete data sets resulting in a Cs-value of 0.69 [95%CI 0.66–0.72].[10] Applying the algorithm at a ≥6% risk level had a sensitivity of 76.5% for detecting a SCD/CA event during first 5 years. However, that cut-off would also suggest ICD implantation in 47.2% of the total patient-group amongst Norrish et al.'s[10] tertiary centre patients, which seems excessive when only 6.5% had an event during the first 5 years.

Our study supplies the first independent validation of the HCMRisk-Kids algorithm and provides almost identical results in our geographical cohort, a Cs-value of 0.69 and a sensitivity of 73% with a cut-off ≥6% for the detection of SCD/CA in the first 5 years. In our national cohort, 39% of ns-HCM would be ICD candidates which is also too high a proportion. Petryka-Mazurkiewicz et al.[19] suggested that a cut-off >4% might be better than 6%, but we cannot confirm that as false-positive rate is very high in our cohort (Tables 3, 4). Repeating HCMRisk-Kids calculations after 7th birthday in individuals with infant diagnosis (HCMRisk-Kids7plus), and including also patients 17–18 years at diagnosis, increases sensitivity to 83% but also proportion of ICD-candidates to 41%. Nevertheless, HCMRisk-Kids at diagnosis performs clearly better than AHA2011 and paediatric ESC2014 risk-stratification guidelines. Petryka-Mazurkiewicz et al. also suggested

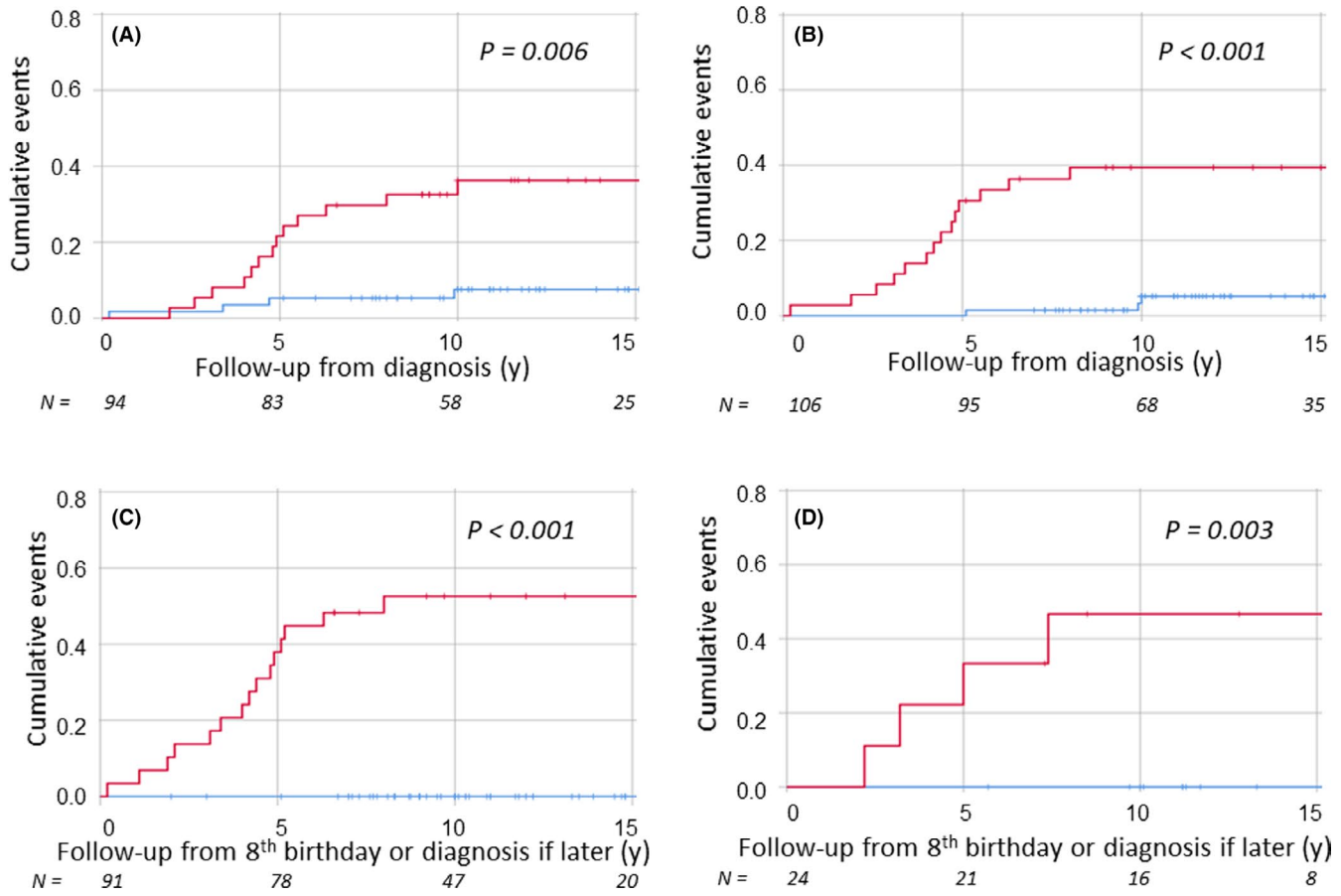

FIGURE 1 Illustrates Kaplan-Meier plots of 1 minus proportion free from sudden cardiac death and resuscitated cardiac arrest (SCD/CA), that is shows the proportion experiencing SCD/CA events. Survival curves start at diagnosis in A and B and after 8th birthday or at diagnosis whichever the latest in C and D. Kaplan-Meier plots are compared with log-rank test. Number of subjects remaining in curves is shown below the *X*-axis at the bottom of the figure, separately for ns-HCM (A-C) and RAS-HCM (D). (A) Shows survival plots in ns-HCM with red line showing subjects with HCMRisk-Kids score ≥6% at diagnosis, and blue line subjects <6%. (B) Shows survival plots in ns-HCM with red line showing subjects with ECG Risk-score ≥6 points at diagnosis, and blue line subjects with ECG Risk-score <6 points. (C) Shows survival plots in ns-HCM with red lines showing subjects with sum of HCMRisk-Kids7plus score and ECG Risk-score 7plus being ≥14, and blue line subjects with sum <14. (D) Shows survival plots in RAS-HCM with red lines showing subjects with sum of HCMRisk-Kids7plus score and ECG Risk-score 7plus being ≥14, and blue line subjects with sum <14

that combining HCMRisk-Kids with late gadolinium enhancement >4% of myocardial mass on magnetic resonance imaging (MRI) would improve Cs-values.[19] This is noteworthy, as Wålinder Österberg et al.[20] found a significant correlation between ECG Risk-score and per cent late gadolinium enhancement on MRI ($p < 0.001$), and that all individuals with >4% late gadolinium enhancement had ECG Risk-score ≥3.

4.2 | Comparison with PRIMaCY-SCD

Recently, a new risk stratification model has been published, developed from the PRIMaCY study, including two additional risk factors in the clinical algorithm, age at diagnosis and posterior left ventricular-wall *Z*-score.[11] However, the mathematical details of the algorithm have not been published, so we were unable to include this algorithm in our comparison. Their publication also provided no numbers that allows comparable calculation of, for example, sensitivity or positive predictive value, but did provide a Cs-value of 0.71 (no confidence intervals given) from validation as a continuous function in a 285-patient external validation cohort.[11] When using HCMRisk-Kids as a continuous function in our cohort we achieve a Cs-value of 0.77 (Table 3), so PRIMaCY-SCD cannot be considered to be superior to HCM-Risk-Kids. The PRIMaCY-SCD study suggested a non-linear relationship of risk with age, with the risk low below 5 years of age.[11] Our findings fit with the data of Maurizi et al.[2] who demonstrated a higher event-rate in childhood HCM patients diagnosed ≤12 years of age as compared with those diagnosed >12 years, and with the particularly high population-based SCD-rate between 8 and 16 years of age found on death certificates.[1]

4.3 | Role of left ventricular outflow obstruction for risk of SCD

Outflow obstruction is a recognised risk factor for SCD in adult HCM,[21] however, in HCMRisk-Kids and similarly in PRIMaCY-SCD

TABLE 4 Comparison of risk assessment strategies in non-syndrome-associated HCM for prediction of sudden cardiac death and resuscitated cardiac arrest during first 5 years of follow-up

Parameter	Sensitivity, per cent (95%CI)	Specificity, per cent (95%CI)	PPV, per cent (95%CI)	NPV, per cent (95%CI)	Per cent test-positive	10 years True positive (per cent)
Non-syndrome associated HCM						
HCMRisk-Kids≥6	73 (43–90)	65 (54–74)	22 (11–37)	95 (86–99)	39	43
HCMRisk-Kids≥4	91 (62–100)	46 (35–56)	18 (10–30)	97 (87–100)	59	36
HCMRiKids7pls≥6	83 (55–97)	65 (54–77)	27 (13–38)	96 (87–99)	41	45
Risk-KidZ-sc≥12.5	73 (43–90)	66 (55–75)	21 (11–36)	95 (86–99)	59	24
Detroit Z-score ≥4.5	90 (60–99)	68 (58–77)	24 (13–39)	98 (91–100)	38	39
HRK+ECGri≥10	91 (62–100)	68 (58–77)	28 (16–44)	98 (91–100)	39	50
HRK+ECGri≥14	82 (52–97)	82 (72–89)	38 (21–57)	97 (90–99)	26	62
HRK7ECGri7pl≥14	100 (74–100)	77 (69–85)	38 (27–56)	100 (94–100)	32	63
ECG Risk-score ≥6	100 (74–100)	73 (57–77)	31 (18–47)	100 (95–100)	40	44
ESC2014≥2RF	45 (21–72)	86 (80–92)	28 (13–51)	93 (86–97)	17	44
AHA2020≥1RF	55 (28–79)	56 (46–65)	13 (6–25)	91 (81–96)	45	21
Combined non-syndrome and RASopathy HCM						
HCMRiKids7pl ≥6	86 (62–98)	64 (54–73)	27 (17–41)	97 (89–99)	43	44
ECG Risk-score ≥6	100 (78–100)	73 (64–81)	31 (18–47)	100 (95–100)	35	45
ECGR7HRK7pl≥14	100 (78–100)	76 (68–83)	37 (23–53)	100 (95–100)	33	55

Abbreviations: AHA2011≥1RF, presence of at least one of the major risk factors defined in American Heart Association 2011 guidelines[30]; ECG Risk-score denotes score at diagnosis; ESC2014≥2RF, at least two of paediatric risk factors as defined in European Society of Cardiology Guidelines2014[21]; HCM, hypertrophic cardiomyopathy; HCMRiKids7pl, HCMRisk-Kids score after, and closest to, 7th birthday; HRK+ECGri, sum of HCMRisk-kids score at diagnosis and ECG risk-score at diagnosis; HRK7ECGri7pl, sum of HCMRisk-Kids after 7 years of age plus ECG Risk-score after 7 years of age (nearest to 7th birthday); NPV, negative predictive value; PPV, positive predictive value; Risk-Kid Zsc, weight only Boston 2-D Z-score.

the presence of a gradient paradoxically seemed 'protective' and consequently reduces algorithm-calculated risk.[10,11] Larger initial outflow gradients were also associated with fewer appropriate shocks in childhood ICD recipients.[22] It seems unlikely that presence of an outflow gradient should be protective in early life, only to become a risk factor after the age of 16 years.[18] The apparent protection could be due to a confounding effect of patients with outflow gradients being more commonly treated with beta-blockers, or with larger doses of beta-blockers, compared to non-obstructive patients,[23] as increasing beta-blocker dose reduced risk for SCD in the total geographical HCM cohort[7] and in the multivariate Cox-hazard analysis in ns-HCM in this study. Patients with outflow-tract obstruction at diagnosis demonstrably had superior survival if treated with >4.5 mg/kg of propranolol equivalents ($p = 0.003$; Supplementary Figure S1). Studies in adult HCM patients have also found beta-blocker therapy associated with reduced mortality in a dose-dependent way.[24,25] Thus, in patients with high-risk scores and persisting outflow gradients, but as yet untreated, consideration of instituting effective beta-blockade should be given. Other treatments reducing outflow gradient, such as myectomy and addition of disopyramide (Table 2), may also potentially act as protective confounders if not taken account of in risk factor studies. Lastly, that duration of unrelieved left ventricular outflow obstruction is important is indicated by the comparison of the late gradients in Table 1 and might explain the different effects in adult and paediatric HCM, as supported by gradual increase with duration of follow-up of the Cs-value for residual gradient found in our cohort.

4.4 | Value of the ECG Risk-score in risk stratification

HCM patients with a normal ECG do not suffer SCD.[26] It makes etiological sense that patients that die from a malignant arrhythmia might show some signs of abnormality on the surface-ECG to indicate a greater arrhythmia susceptibility.[27] The ECG Risk-score was first validated in adult HCM, with the optimal cut-off for a high-risk status validated by boot-strapping analysis.[12] Subsequently, we found in a national paediatric cohort study that the same cut-off (≥6 points) appeared optimal even in childhood HCM with a sensitivity of 97%, and was as risk factor independent of maximal wall thickness.[7] We demonstrate in this study a Cs-value of 0.87 for this cut-off and that ECG Risk-score also is an independent risk factor to the HCMRisk-Kids7plus score in our multivariate Cox-hazard model (Table 2). That ECG Risk-score ≥6 points has high sensitivity for SCD/CA in paediatric patients has now been independently confirmed in a Japanese study of childhood HCM diagnosed by school ECG-screening, where sensitivity was also 100% for 'life-threatening events'.[28] However, that study also had a high rate of false positives amongst patients without events, who all had been diagnosed specifically because of ECG abnormalities. They constituted a high-risk group, confirmed

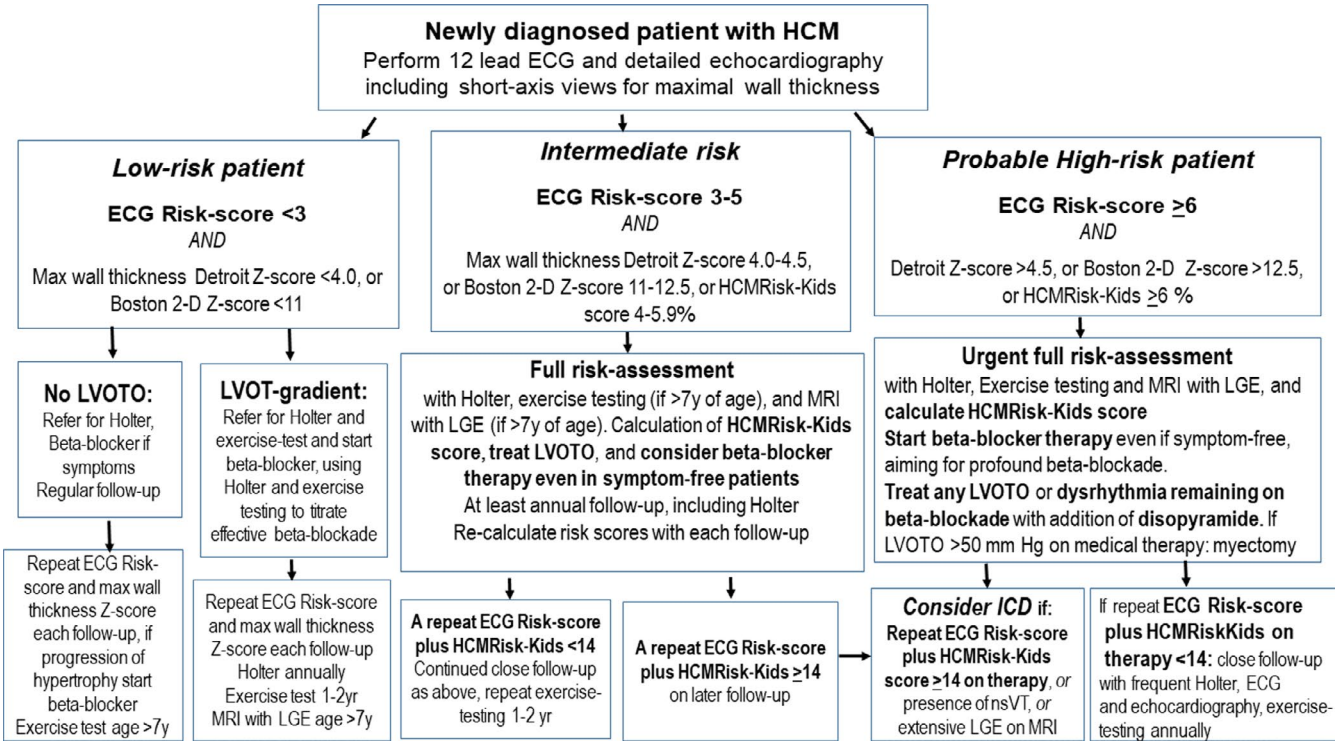

FIGURE 2 Illustrates a flow chart for suggested clinical management following initial risk assessment with 12-lead ECG and detailed echocardiography at the time of diagnosis. It is important to remember to measure also apical wall thickness as it can be area of maximal wall thickness. If repeat ECG risk-score and maximal wall thickness Z-scores in an initial low-risk patient increases on follow-up to fit intermediate- or high-risk definitions, further follow-up should be according to new risk-category path. Abbreviations: ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow-tract; LVOTO, left ventricular outflow-tract obstruction; MRI, magnetic resonance imaging; LGE, late gadolinium enhancement; ICD, internal cardioverter-defibrillator; nsVT, non-sustained ventricular tachycardia

by the high event-rate: 25% had events with a median interval of 3.7 years from diagnosis.[28] In a sub-set of the HCMRisk-Kids study patients with ECG-tracings archived, and a median follow-up of only 3.9 years, ECG Risk-score ≥6 was present in 44.7% of tertiary-centre patients that did not suffer a major arrhythmic event.[29] This is obviously uncomfortably high, but still a lower false-positive proportion than the 45.2% that were false positives on the HCMRisk-Kids ≥6% criterion.[10] That the short follow-up of this study gave insufficient statistical power is shown by some parameters currently included in their HCMRisk-Kids algorithm such as left atrial-diameter *Z*-score ($p = 0.788$), non-sustained ventricular tachycardia ($p = 0.120$) unexplained syncope ($p = 0.140$) and left ventricular outflow- gradient ($p = 0.519$) all failed to reach significance.[29] On univariate Cox regression analysis with this short follow-up the *p*-value of the total ECG Risk-score (0.114) was actually better than the parameters above, and negatve predictive value for ECG Risk-score ≥6 was 96.7% (29). The ECG Risk-score with a value ≥6 points had a positive predictive value of SCD/CA within 5 years of 31% in our geographical cohort, with negative predictive value 100%, both in ns-HCM, and in total cohort including RAS-HCM (Table 4). It is not sufficiently specific to use as only risk assessment, but will need to be combined with other risk assessment algorithms. Easy accessibility in district general hospitals, high sensitivity and extremely low risk for patients with risk-scores <3 points makes it a very good screening test to help general paediatricians in prioritising those patients that need urgent further investigations.[7,20]

4.5 | Combining HCMRisk-Kids and ECG Risk-score

As these two scores are both associated with cumulative risk and also independent of each other (Table 2), we explored a simple approach by adding the scores to each other. This approach looks promising as shown by a Cs-value of 0.91 as a continuous score-sum, and Cs-value of 0.82 for a preliminary cut-off value of combined scores of ≥14, and a Cs-value of 0.90 for the same cut-off for the sum of HCMRisk-Kids7plus and ECG Risk-score7plus. Further studies in larger and more ethnically diverse patient groups will establish if this is an optimal cut-off, and if the two scores could be combined in a more sophisticated way.

4.6 | Risk stratification for syndrome-associated HCM

The number of end-points in this group is limited, only six, here reported as a pilot study, and a much larger international collaboration would be required to collect enough data to contemplate having a

separate risk stratification algorithm for RAS-HCM. However, both ECG Risk-score7plus, HCMRisk-Kids7plus and the sum of the two scores perform very similarly in ns-HCM and RAS-HCM (Table 4), so until more specific algorithms are available, all those are reasonable to use in risk stratification for RAS-HCM.

4.7 | How should risk-scores influence treatment?

From our data, and earlier findings,[7,20] we would suggest to initially categorise patients as low-risk, intermediate-risk or probable high-risk depending on ECG and echocardiographic findings at first visit according to criteria in Figure 2, and then proceed with further investigations and treatment according to this flow chart. Any symptoms should of course be treated appropriately. There are no official guidelines for specific medical therapy in high-risk patients. Our data suggest that it is worth establishing effective medical therapy with beta-blocker dose sufficient to achieve good beta-blockade on exercise testing in all high-risk patients, even if asymptomatic, because of the risk-modifying effects seen in our multivariate analysis, and recently reported beneficial effects on all-cause cardiac mortality.[24,25] Similarly, complete control of outflow-tract obstruction, if necessary by addition of disopyramide (or myectomy if medical therapy insufficient), should be attempted (see above). It is our experience that high ECG Risk-scores may fall when the patient is on effective therapy, particularly in patients who present with large outflow gradients (Östman-Smith, Fernlund unpublished observations). In consideration, if a primary prevention ICD is warranted, additional risk-factors not in the flow chart such as severe diastolic dysfunction, or ventricular arrhythmias or ST-depression on exercise testing,[7] should also be considered. Genetic information indicating increased risk, for example the patient being compound heterozygote or homozygote for pathogenic mutations, should also be considered.

4.8 | Limitations of the study

The ECG Risk-score was initially constructed from data in Swedish adult HCM patients, and as shown here performs excellently in Swedish children with HCM (96.9% Caucasian; Supporting Information e-Methods). In Sweden, like in most of Northern Europe, *MBPC3* and *MYH7*-mutations are the most commonly encountered mutations causing HCM, but it is clearly desirable to test the ECG Risk-score in separate populations with a different ethnic and genetic mix. Likewise proposed cut-offs between risk categories in Figure 2 should be considered provisional until confirmed in further studies.

5 | CONCLUSION

The ECG Risk-score is an ideal screening method usable in district general hospitals. Our external validation in a geographical cohort shows the HCMRisk-Kids algorithm to have very similar performance to that reported in the original publication. Combining the ECG Risk-score with HCMRisk-Kids score provides improved risk-stratification in paediatric non-syndromic HCM and appears promising in RAS-HCM, with further improvement if values ≥7 years of age are used for scoring. Thus, including scoring of the ECG-phenotype in risk assessment algorithms seems likely to improve both sensitivity and specificity of risk assessment.

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CONFLICTS OF INTEREST

The authors have no financial or proprietary interests in any material discussed in this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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