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Indications and management of implantable cardioverter-defibrillator therapy in childhood hypertrophic cardiomyopathy

A position statement from the AEPC Working Group on Basic Science, Genetics and Myocardial Disease and the AEPC Working Group on Cardiac Dysrhythmias and Electrophysiology

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Abstract

Sudden cardiac death is the most common mode of death during childhood and adolescence in hypertrophic cardiomyopathy, and identifying those individuals at highest risk is a major aspect of clinical care. The mainstay of preventative therapy is the implantable cardioverter-defibrillator, which has been shown to be effective at terminating malignant ventricular arrhythmias in children with hypertrophic cardiomyopathy but can be associated with substantial morbidity. Accurate identification of those children at highest risk who would benefit most from implantable cardioverter-defibrillator implantation while minimising the risk of complications is, therefore, essential. This position statement, on behalf of the Association for European Paediatric and Congenital Cardiology (AEPC), reviews the currently available data on established and proposed risk factors for sudden cardiac death in childhood-onset hypertrophic cardiomyopathy and current approaches for risk stratification in this population. It also provides guidance on identification of individuals at risk of sudden cardiac death and optimal management of implantable cardioverter-defibrillators in children and adolescents with hypertrophic cardiomyopathy.

Hypertrophic cardiomyopathy is defined as left ventricular hypertrophy in the absence of abnormal loading conditions.[1] Although it is the commonest genetic heart disease in adults, it is rare in the paediatric population, with an estimated population prevalence of approximately 3 per 100,000[2] and an annual incidence of less than 0.5/100,000[2-4] based on available registry and population-based studies; more contemporary prevalence data are not currently available, but it is likely that the true prevalence of hypertrophic cardiomyopathy in childhood is higher than this. The underlying aetiology of childhood-onset hypertrophic cardiomyopathy is heterogeneous, including malformation syndromes, inborn errors of metabolism and neuromuscular disease, but most cases, even in very young children, are caused by variants in one or more cardiac sarcomere protein genes.[5-9] Sudden cardiac death is the most common cause of death during childhood and adolescence[6,10,11] and identifying those individuals with hypertrophic cardiomyopathy at highest risk of sudden cardiac death is a major aspect of clinical care in childhood hypertrophic cardiomyopathy. Early studies in small, highly selected childhood cohorts reported an annual incidence of sudden cardiac death of up to 7%,[12,13] but more recent data from larger population-based studies have shown sudden cardiac death rates between 0.8 and 2% per year,[10,14–16] much lower than the initial reports but nevertheless substantially higher than those seen in adults with

hypertrophic cardiomyopathy.[17,18] Recent longitudinal datasets from the Sarcomeric Human Cardiomyopathy Registry (SHaRE) have demonstrated that in childhood-onset hypertrophic cardiomyopathy patients, arrhythmic events are responsible for more than 50% of adverse events occurring within 10 years of diagnosis, with a cumulative incidence of 8.8%, and that children with hypertrophic cardiomyopathy are 36% more likely to experience an arrhythmic event during follow-up compared to those diagnosed in adulthood.[10] The mainstay of preventative therapy is the implantable cardioverter-defibrillator, which has been shown to be effective at terminating malignant ventricular arrhythmias in both children and adults with hypertrophic cardiomyopathy[19] but can be associated with substantial morbidity.[20] Accurate identification of those children at highest risk who would benefit most from implantable cardioverter-defibrillator implantation, while minimising the risk of complications is, therefore, essential.

This position statement aims to review the currently available data on risk factors for sudden cardiac death in childhood-onset hypertrophic cardiomyopathy and provide guidance on identification of individuals at risk of sudden cardiac death and optimal management of implantable cardioverter-defibrillator in this population.

Review of proposed risk factors for sudden cardiac death in childhood hypertrophic cardiomyopathy

Risk factors with good evidence of an association with sudden cardiac death risk in childhood hypertrophic cardiomyopathy

Unexplained syncope

The mechanisms of syncope in hypertrophic cardiomyopathy include left ventricular outflow tract obstruction, abnormal vascular reflexes, ventricular arrhythmia, and atrioventricular block secondary to conduction disease in specific aetiologies of hypertrophic cardiomyopathy (e.g., variants in the *PRKAG2* gene). A ventricular arrhythmic cause should be suspected following an unheralded episode, particularly if it occurs at rest or during minimal exertion, but can also occur during or just after exercise. Thorough investigation should be undertaken to determine the cause of syncope in a child with hypertrophic cardiomyopathy, including, where possible, exercise echocardiography to exclude provocable left ventricular outflow tract obstruction.[1,21]

Unexplained syncope, usually defined as transient non-neurocardiogenic loss of consciousness with no identifiable cause, has been assessed as a potential risk factor for sudden cardiac death in childhood hypertrophic cardiomyopathy in 10 studies.[12,15,22–29] A significant association with sudden cardiac death was reported in five univariate[12,14,15,24,29] and two multivariate analyses.[15,29] Unexplained syncope is also included in two multiparametric paediatric risk prediction models.[14,15] In adults, there are data to suggest that episodes occurring within 6 months of evaluation may be more predictive,[30] but the temporal association of syncope and events has not been assessed in childhood.

This writing group considers unexplained syncope to be a major risk factor for sudden cardiac death in childhood hypertrophic cardiomyopathy. Future studies to evaluate the temporal association of a syncopal episode with sudden cardiac death risk in the paediatric population are required.

Left ventricular hypertrophy

Left ventricular hypertrophy is the key diagnostic feature in hypertrophic cardiomyopathy.[1,21] In childhood non-syndromic disease, the distribution of left ventricular hypertrophy is most commonly seen at the ventricular septum (asymmetric septal hypertrophy), but increased wall thickness can occur in any myocardial segment. Although several indices of myocardial hypertrophy exist, from a diagnostic perspective, maximal left ventricular wall thickness in any single segment and at any level is the most important parameter.[1,21]

Measures of left ventricular hypertrophy are the most studied clinical risk factor for sudden cardiac death in childhood hypertrophic cardiomyopathy: 14 studies have investigated the association between left ventricular hypertrophy and sudden cardiac death in children with hypertrophic cardiomyopathy.[15,19,22–28,31–35] In these, the measure of left ventricular hypertrophy varied widely, including interventricular septal thickness, left ventricular posterior wall thickness, septal thickness in percent of 95th centile for age, and extreme left ventricular hypertrophy, variably defined (e.g., >30 mm, z > 6, z > 22, using different normative data). Eight studies reported a significant association between left ventricular hypertrophy and sudden cardiac death on univariable analysis.[19,24–26,31,32,34,35] Five studies reported a statistically significant association between left ventricular hypertrophy and sudden cardiac death on multivariable analysis,[14,15,25,31,35] generally with very strong significance levels. Measures of left ventricular hypertrophy are included in two multiparametric paediatric risk prediction models[14,15] and had the strongest significance level of all risk factors in one of these, the HCM Risk-Kids cohort.[14] The role of left ventricular hypertrophy as a risk factor for sudden cardiac death has been evaluated in a large multicentre cohort, and the data suggest that it should not be used in isolation or as a binary variable in children with hypertrophic cardiomyopathy.[36]

What is the paediatric definition of extreme hypertrophy?. The presence of a maximal wall thickness ≥30 mm has historically been the definition of severe hypertrophy in adult hypertrophic cardiomyopathy,[1,37] but proposals for a paediatric definition have varied from ≥20 mm,[24] a Z-score ≥6,[1,25,38] ≥ 190% of 95th centile for age,[35] or, in the new AHA2020 Guidelines, a Z-score "around 20."[21] Many of the publications referring to particular Z-score values have not defined which Z-score data have been used. This is problematic, as using different reference equations for the same wall thickness can yield vastly different Z-scores (Table 1). This highlights the importance, when using Z-scores for risk prediction, of using the same Z-score data for left ventricular hypertrophy as those on which the relevant risk prediction model used was developed.

Despite the use of different echocardiographic parameters to measure left ventricular hypertrophy, and the use of different normative data to normalise for body size (see below), this writing group considers left ventricular hypertrophy to be a major incremental risk factor for sudden cardiac death in childhood hypertrophic cardiomyopathy. The importance of normalising echocardiographic parameters of left ventricular hypertrophy to body size (ideally body surface area) or age is highlighted.

Non-sustained ventricular tachycardia

Non-sustained ventricular tachycardia is usually defined as three or more consecutive ventricular beats at a rate of greater than 120 beats per minute and lasting under 30 seconds detected on ambulatory electrocardiogram monitoring.[1] Its association with sudden cardiac death during follow-up in childhood hypertrophic cardiomyopathy has been investigated in nine studies.[14,15,19,22,24–27,31] Four studies reported a significant association with sudden cardiac death on

Table 1. Illustrating IVS Z-scores arrived at with different algorithms based on body size, compared with wall thickness related to 95th centile for age.

Subject	Height cm	Weight kg	MaxWall mm	Detroit Z-score[39]	Kampmann Z-score[40]	Boston-M-Mode Z-score[41]	Boston 2-D z-score[41]	HCM Risk-Kids Z-score (wt only)[14]	IVS% of 95th centile for age (SEPPER)[35]
Boys									
Average 18 years	180	71	30	5.83	16.6	13.3	19.8	19.58	271
			20	3.93	8.56	6.67	10.6	10.9	180
			11	1.15	1.36	0.74	2.28	3.09	99
			10	0.70	0.56	0.09	1.36	2.23	90
Average 16 years	177	64	30	6.11	18.3	14.0	21.0	20.3	284
			20	4.22	10.0	7.16	11.3	11.4	190
			10	0.99	1.67	0.31	1.65	2.48	95
Average 12 years	154	42	30	6.99	25.9	17.9	27.4	23.6	316
			20	5.10	14.8	9.66	15.4	13.6	211
			10	1.86	3.67	1.47	3.28	3.56	105
Average 6 years	119	22	20	5.94	16.00	13.9	23.2	17.4	254
			10	2.71	4.89	3.46	6.61	5.49	127
			8	1.67	2.67	1.37	3.29	3.10	102
Newborn	51	3.55	20	7.91	23.3	24.9	52.0	32.7	Not applicable
			10	4.68	9.00	8.86	20.0	13.2	
			5.5	1.89	2.57	1.64	5.54	4.33	
Girls									
Average 18 years	168	60	30	6.38	18.3	14.8	22.2	20.8	271
			20	4.49	10.0	7.65	12.1	11.7	180
			11	1.70	2.50	1.25	2.96	3.55	99
			10	1.26	1.67	1.1	1.95	2.64	90
Average 16 years	166.5	59	30	6.43	18.3	14.9	22.5	20.9	284
			20	4.54	10.0	7.76	12.2	11.8	190
			10	1.30	1.67	0.58	2.01	2.68	95
Average 12 years	154	42	30	6.99	25.9	17.9	27.4	23.6	316
			20	5.10	14.8	9.66	15.4	13.6	211
			10	1.86	3.67	1.47	3.28	3.56	105
Average 6 years	118	21	20	5.99	18.5	14.1	23.7	17.7	254
			10	2.76	6.00	3.57	6.81	5.63	127
			8	1.72	3.50	1.46	3.22	3.22	102
Newborn	50	3.5	20	7.93	23.3	25.2	53.1	32.9	Not applicable
			10	4.70	9.00	9.0	20.5	13.2	
			5.5	1.91	2.57	1.72	5.79	4.63	

univariable analysis.[14,19,25,27] Of three multivariable analyses with an end point of sudden cardiac death, one showed a significant association with sudden cardiac death[15] and another trended towards significance.[26] Moak et al.[24] found no association with non-sustained ventricular tachycardia on ambulatory electrocardiogram recordings, but a significant association with inducible ventricular tachycardia on electrophysiology study. Non-sustained ventricular tachycardia is included in two multiparametric paediatric risk prediction models.[14,15] No study has explored the importance of rate, duration, or frequency of non-sustained ventricular tachycardia on the risk of sudden cardiac death in childhood hypertrophic cardiomyopathy. Of note, the assessment of the role of non-sustained ventricular tachycardia in childhood hypertrophic cardiomyopathy sudden cardiac death risk is limited by the fact that there are often substantial missing data on Holter monitoring data in published studies,[14] but the data available suggest that, although a rare occurrence, non-sustained ventricular tachycardia is a marker with high relative risk when present.

This writing group considers that non-sustained ventricular tachycardia should be considered a major risk factor in childhood hypertrophic cardiomyopathy. The importance of routinely performing ambulatory electrocardiogram monitoring as part of clinical assessment in children with hypertrophic cardiomyopathy is emphasised.

Left atrial enlargement

The cause of left atrial dilatation in hypertrophic cardiomyopathy is multifactorial and includes mitral regurgitation secondary to systolic anterior motion of the mitral valve in children with obstructive hypertrophic cardiomyopathy and elevated left ventricular filling pressures related to left ventricular diastolic dysfunction.[42]

The relationship between left atrial size and sudden cardiac death in childhood hypertrophic cardiomyopathy has been evaluated in five studies.[14,15,26,33,34] Increased left atrium size was associated with an increased risk of sudden cardiac death in two studies on univariate analysis[26,33] and in two studies on multivariable analysis.[14,15] Left atrium diameter is included in two paediatric multiparametric hypertrophic cardiomyopathy risk prediction models.[14,15] The assessment of the relationship between left atrium size and sudden cardiac death in childhood is limited by the different methods of measuring left atrium size reported (e.g., antero-posterior diameter in the parasternal long-axis view, left atrium

area, or left atrium volume in the apical four-chamber view on echocardiography, or left atrium volumes on cardiac MRI), and by missing data on left atrium size in published paediatric studies.

This writing group considers that left atrial dilatation can be considered a major risk factor for sudden cardiac death in childhood hypertrophic cardiomyopathy. The importance of routinely measuring left atrium size and of achieving consensus on which imaging modality and measurement should be used is highlighted.

Additional risk factors with less conclusive or emerging evidence of an association with sudden cardiac death in childhood hypertrophic cardiomyopathy

Left ventricular outflow tract obstruction

Left ventricular outflow tract obstruction is a recognised risk factor for sudden cardiac death in adult hypertrophic cardiomyopathy.[1,43] In contrast, data in childhood hypertrophic cardiomyopathy are conflicting. Early studies with few sudden cardiac death end points found no evidence that left ventricular outflow tract obstruction was a significant predictor,[27,38] although Ziolkowska et al. found it to be a significant risk factor for combined arrhythmia and heart failure death end points.[26] Notably, however, in a multicentre study, patients who had suffered sudden cardiac death had a much higher prevalence of outflow tract obstruction (79%) compared with long-term survivors (46%), or the total combined group (55%).[44] A national cohort study with 32 end points found that an left ventricular outflow tract gradient >20 mmHg at diagnosis was a significant risk factor for sudden cardiac death on univariate Cox hazard (p = 0.009), and it remained a risk factor in the multivariate analysis.[25] If at last visit the left ventricular outflow tract gradient was >20 mmHg the relative risk for sudden cardiac death was 3.7, and if it was >50 mmHg it was 6.6 (p = 0.004 and p < 0.001, respectively).[25] In contrast, the large multicentre studies producing the HCM Risk-Kids, and PRIMaCY-sudden cardiac death algorithms, suggested that, although there was a higher prevalence of left ventricular outflow tract gradients >30 mmHg at diagnosis in patients with end-points (31.7%) than in patients without end points (20.7%), the presence of a gradient was associated with a slight reduction in sudden cardiac death risk.[14,15] This observation may be due to a confounding effect of patients with left ventricular outflow tract obstruction gradients being more commonly treated with beta-blockers, or with larger doses of beta-blockers, compared to non-obstructive patients, in keeping with a reported association of beta-blocker therapy with a dose-dependent reduction in sudden cardiac death and overall mortality.[25,45–47] This may also explain the finding that childhood implantable cardioverter-defibrillator recipients with left ventricular outflow tract obstruction appear to receive fewer appropriate shocks.[31] Additional possible confounders include duration of unrelieved left ventricular outflow tract obstruction to explain the different effects in adult and paediatric hypertrophic cardiomyopathy, and gradient reduction by surgical or interventional treatments during follow-up; surgical myectomy was associated with a significantly reduced risk of sudden cardiac death on multivariate analysis in one study.[47] The degree of left ventricular outflow tract obstruction has been shown to correlate with degree of delayed late enhancement on MRI in childhood hypertrophic cardiomyopathy, suggesting that it might accelerate myocardial fibrosis.[48] Finally, it is possible that left ventricular outflow tract obstruction may confer a longer-term risk than the 5-year risk assessed in HCM Risk-Kids[14] and PRIMaCY-sudden cardiac death[15] cohorts.[47]

Based on current evidence, this writing group considers that data on the role of left ventricular outflow tract obstruction at diagnosis in sudden cardiac death risk stratification in childhood hypertrophic cardiomyopathy are conflicting, and further work is needed to clarify this.

Late gadolinium enhancement on cardiovascular MRI

The prevalence of myocardial fibrosis assessed by late gadolinium enhancement is highly variable in childhood hypertrophic cardiomyopathy, ranging from 18 to 73% of patients.[49–55] The predictive value of late gadolinium enhancement on cardiac magnetic resonance imaging as a risk factor for sudden cardiac death in childhood hypertrophic cardiomyopathy has been investigated in seven studies. Four[49–52] reported an increased incidence of late gadolinium enhancement in patients with adverse outcomes, but this did not reach statistical significance. Spinner et al.[53] reported that the extent of late gadolinium enhancement was associated with 1.4-fold increased odds of non-sustained ventricular tachycardia, but these findings also did not reach statistical significance. In a study by Axelsson Raja et al.,[54] no statistical difference was found comparing children with hypertrophic cardiomyopathy who experienced an adverse event to those that did not with respect to either the presence or the extent of late gadolinium enhancement. The incorporation of late gadolinium enhancement (the estimated optimal cut-off point of the extent of late gadolinium enhancement using >6 SDs above the remote area was >0.7% of the left ventricular mass) significantly improved the performance of American College of Cardiology (ACC)/American Heart Association (AHA) strategy as well as HCM Risk-Kids algorithm with both cut-off points of ≥4% and ≥6%.[55]

This writing group considers that the association between sudden cardiac death risk and late gadolinium enhancement in children with hypertrophic cardiomyopathy is not yet well defined, and the extent of late gadolinium enhancement that constitutes high risk in children has not been established. Extensive late gadolinium enhancement may be an additional risk factor for sudden cardiac death risk in children, but further studies are required to confirm this.

Electrocardiogram phenotype and electrocardiogram risk score in risk stratification

Electrocardiogram features correlating with sudden cardiac death. McLeod et al.[56] reported that there were no sudden deaths in adult hypertrophic cardiomyopathy patients with a normal electrocardiogram. Conversely, large Sokolow–Lyon index voltages were associated with higher mortality in paediatric hypertrophic cardiomyopathy.[57] A subsequent study suggested the voltage sum of the six limb-leads (LLQRSS) >10 mV as a possible risk factor for sudden cardiac death, independent of echocardiographic measures of left ventricular hypertrophy, and that risk factors for sudden cardiac death were different from risk factors for heart-failure-related death in paediatric hypertrophic cardiomyopathy patients.[35] Electrocardiogram abnormalities that have been reported to correlate statistically with sudden cardiac death or malignant arrhythmia in children and adults with hypertrophic cardiomyopathy are shown in Table 2.

Electrocardiogram risk score. A systematic study of the resting electrocardiogram in adult hypertrophic cardiomyopathy patients showed that the most discriminating electrocardiogram features were QRS axis deviation, LLQRSS, 12-lead amplitude duration product, QTc > 440 msecs, T-wave inversion, ST-depression, and dominant S-waves in V_4; these features were used to develop an electrocardiogram risk score (supplementary Table S1) which

Table 2. ECG features and measures with statistically significant correlation to malignant arrhythmia or sudden cardiac death in hypertrophic cardiomyopathy.

ECG measure	Paediatric HCM	Adult HCM
QRS axis deviation	25	58
QRS duration ≥120 ms		59
Precordial T-wave inversion	25	58
Dominant S-wave in V4	25	58
ST-depression at rest	25	58,60
ST-depression on exercise	25,61	
ST-segment "hump-elevation" rest or exercise		59,62
QTc prolongation	24,25,63	58,64,65
QTc dispersion	26,27	
Sokolow-Lyon index	35	
Limb-lead QRS amplitude sum (LLQRSS)	25,35,44	58
12-lead QRS amplitude*duration product	25	58

was found to correlate with risk for sudden cardiac death.[58] An electrocardiogram risk score of 5 points had a sensitivity in adult hypertrophic cardiomyopathy for cardiac arrest of 84%, and high specificity, particularly in younger patients <40 years of age.[58] In a national paediatric hypertrophic cardiomyopathy cohort, an electrocardiogram risk score >5 conferred a relative risk of sudden cardiac death of 46.5 [6.6-331], with sensitivity of 97% and specificity of 80%.[25] Restricting analysis to patients with non-syndromic hypertrophic cardiomyopathy and sudden cardiac death within 5 years sensitivity for electrocardiogram risk score >5 was 100% and positive predictive value was 31%,[47] and an external validation in a Canadian cohort with >5 years follow-up found a sensitivity of 95%, positive predictive value of 28% and C-statistic 0.76, although it overestimated sudden cardiac death risk.[66] In contrast, a large study of 356 children from the HCM Risk-Kids cohort with electrocardiograms archived found that a cut-off of >5 points was not predictive for freedom from major arrhythmia over a short follow-up of 3.9 years but found a hazard ratio of 1.11 per point when total point score was used.[67] One multicentre study suggested that adding the electrocardiogram risk score to the HCM Risk-Kids score with ≥14 as cut-off gave better specificity than either algorithm on its own, with a C-statistic of 0.90 [0.83-0.96] after 7 years of age. The strength of the electrocardiogram risk score is its high sensitivity in non-selected cohorts and a very high negative predictive value of 97–99%.[25,47,67] It is possible that an electrocardiogram score < 3 could be used to identify low-risk patients,[25,56] but this will need to be specifically assessed in future studies.

This writing group considers that the electrocardiogram phenotype is not specific enough to be used as a risk indicator on its own, but it may be an independent and complementary risk factor to the extent of left ventricular hypertrophy on echocardiography. Due to its widespread availability, it may be a good screening method for selecting cases that need to accelerate further investigations and to identify low-risk individuals.

Restrictive physiology. Three studies[26,33,34] have analysed the predictive value of echocardiographic markers of restrictive physiology for sudden cardiac death in children with hypertrophic

cardiomyopathy. The measurement of restrictive physiology varied and included early transmitral flow velocity (E)/septal and lateral mitral annulus velocity E' (E/E' ratio),[33,34] transmitral inflow Doppler E/A ratio[26,33], and left atrium enlargement in the absence of more than mild mitral regurgitation and without evidence of left ventricular dilatation.[26,33] McMahon et al.[34] reported that early transmitral left ventricular filling velocity (E)/early diastolic septal (E') tissue Doppler velocity (septal E/E' ratio) predicted major clinical events and risk of sudden cardiac death in childhood hypertrophic cardiomyopathy, although this did not reach statistical significance. In the study by Maskatia et al.,[33] echocardiographic features of restrictive physiology were associated with a 3.8-fold increase in the risk of sudden cardiac death. Left atrial enlargement, lateral mitral E/E' ratio ≥ 10, and septal E/E' ratio ≥ 13 correlated significantly with aborted sudden cardiac death. Increased left atrium size and decreased early transmitral E velocity were independent predictors for combined arrhythmic and heart failure death end points in a study published by Ziolkowska et al.[26]

This writing group considers that restrictive physiology parameters may be considered an additional risk factor for sudden cardiac death in childhood hypertrophic cardiomyopathy, but further studies are required to determine whether this is independent of other established risk factors.

Myocardial deformation. Strain, a measure of myocardial deformation, is an increasingly used assessment of global and regional left ventricular function. In adult patients with hypertrophic cardiomyopathy, decreased strain by two-dimensional (2-D) speckle-tracking echocardiography has been associated with areas of hypertrophy and myocardial fibrosis and with adverse cardiac events.[68–70] Only one paediatric study[71] has shown an association between myocardial systolic activation delay assessed by echocardiographic strain and strain rate and increased risk for ventricular arrhythmias (sustained ventricular tachycardia and/or non-sustained ventricular tachycardia) in children with hypertrophic cardiomyopathy.

Recently, cardiac magnetic resonance imaging myocardial feature tracking, a technique similar to echocardiographic speckle tracking, has been introduced for the evaluation of global and regional myocardial mechanics and strain. Smith et al. demonstrated a significant relationship between reduced global longitudinal and radial strain and increased risk of sudden cardiac death in children and young adults with hypertrophic cardiomyopathy.[72] The results of a study in 55 hypertrophic cardiomyopathy children of whom 7 reached the arrhythmic end points (4 sudden deaths and 3 appropriate implantable cardioverter-defibrillator discharge) demonstrated a strong trend towards better arrhythmic end point identification performance of baseline HCM Risk-Kids model (AUC = 0.724, 95% CI – 0.569–0.824) compared to ACC/AHA strategy (AUC = 0.638, 95% CI – 0.496–0.765). Adding left atrial strain parameters such as conduit function component assessed by cardiac magnetic resonance imaging myocardial feature tracking significantly increased prediction performance of both approaches, suggesting that the inclusion of atrial strain indices may improve sudden cardiac death risk stratification strategies in children with hypertrophic cardiomyopathy.[73]

This writing group considers that ventricular and atrial myocardial strain parameters may be an additional risk factor for sudden cardiac death in children with hypertrophic cardiomyopathy, but further paediatric studies are required.

Exercise-induced ischaemia. Assessment of myocardial ischaemia during exercise is usually performed with exercise testing. Yetman et al. reported that childhood hypertrophic cardiomyopathy patients with myocardial bridging on angiography had greater ST-depression on exercise testing and a significantly higher proportion of cardiac arrest or sudden cardiac death than patients without myocardial bridging.[61] Few paediatric hypertrophic cardiomyopathy patients are investigated with angiography in the current era, but in a subsequent study ST-segment depression during exercise testing had a hazard ratio of 2.45 for sudden cardiac death that just missed statistical significance (p = 0.06).[27] A more recent and larger study of paediatric hypertrophic cardiomyopathy patients showed that ST depression at rest was present in 43.5% of patients with sudden cardiac death or cardiac arrest, and only in 8.4% of patients without arrhythmia events (p < 0.0001), and that ST-depression during exercise conferred a relative risk of 5.7 [95% CI 1.9–17.4; p = 0.0035] of sudden death or cardiac arrest, with a positive predictive value of 56% and a specificity of 83%.[25] For children too young for formal exercise testing, a Holter recording during prescribed physical exercise may also reveal ST-depression during high heart rates, but there are no studies exploring whether this feature is predictive.

This writing group considers that, although paediatric studies of myocardial ischaemia are limited, there is some evidence to suggest that ST-segment depression during exercise testing may be an additional risk factor for sudden cardiac death in childhood hypertrophic cardiomyopathy.

Aetiology. The aetiology of hypertrophic cardiomyopathy in children is heterogeneous and includes malformation syndromes, neuromuscular disorders and inborn errors of metabolism.[5,6,8,16,74,75] In the North American Pediatric Cardiomyopathy Registry cohort,[8] survival rates from the time of hypertrophic cardiomyopathy diagnosis were poorer in patients with inborn errors of metabolism and malformation syndrome compared to neuromuscular disorder or non-syndromic hypertrophic cardiomyopathy patients, with the worst outcome in patients diagnosed before 1 year of age, mostly caused by heart failure-related death. Sudden cardiac death, however, was more frequent in those patients with non-syndromic hypertrophic cardiomyopathy than in patients with malformation syndrome or inborn errors of metabolism.[16] These data were also confirmed by Norrish et al.,[6] who evaluated a cohort of 687 hypertrophic cardiomyopathy patients (age range 0–16 years), showing that children diagnosed during infancy or with an inborn errors of metabolism had a worse prognosis. A major arrhythmic event (i.e., sudden cardiac death, resuscitated cardiac arrest, sustained ventricular tachycardia, or appropriated implantable cardioverter-defibrillator shock) occurred in 58 (8.4%) patients: 51 with non-syndromic hypertrophic cardiomyopathy; 5 with a RASopathy; 2 with an inborn errors of metabolism, 1 of these with Danon disease. Interestingly, no arrhythmic events occurred in 78 children with Friedreich's ataxia-related hypertrophic cardiomyopathy, suggesting that these patients may be at lower risk of ventricular arrhythmias.[76] Among the RASopathies, patients with Noonan syndrome with multiple lentigines (previously known as LEOPARD syndrome) appear to carry a higher risk. Limongelli et al.[77] evaluated 26 patients with Noonan syndrome with multiple lentigines (age range 0–63 years) and found that hypertrophic cardiomyopathy was present in 19 (73%) patients. Among these, four patients had sudden cardiac death or resuscitated cardiac arrest and two of these events occurred in the paediatric age. There has been no systematic

assessment of aetiology as a sudden cardiac death risk factor in childhood hypertrophic cardiomyopathy.

This writing group considers that, although the risk of sudden cardiac death appears to be higher in patients with non-syndromic hypertrophic cardiomyopathy and with RASopathies (particularly NSML), aetiology is not an independent risk factor for sudden cardiac death in children with hypertrophic cardiomyopathy.

Risk factors for sudden death in Noonan syndrome and other RASopathies. The hypertrophic cardiomyopathy associated with Noonan syndrome is histologically indistinguishable from hypertrophic cardiomyopathy associated with sarcomere mutations, including features such as myocardial disarray.[78] One early study of cardiac involvement in Noonan syndrome reported absence of sudden cardiac deaths, but subsequent studies with larger groups of Noonan-associated hypertrophic cardiomyopathy have reported significant numbers of sudden cardiac deaths, a few occurring during first 2 years of life, but the majority after a late hazard period starting around 10 years of age.[79,80] Several studies exploring risk factors for sudden cardiac death specifically in paediatric hypertrophic cardiomyopathy have also included Noonan-associated hypertrophic cardiomyopathy[25,27,35] and have suggested that the degree of left ventricular hypertrophy is a major risk factor for sudden cardiac death. One study has suggested that a limb-lead QRS amplitude sum >10 mV, maximal wall thickness Z-score >6 (using the Detroit Z-score values),[39] and an electrocardiogram risk score >5 were indicators of increased risk.[25] Only two studies so far have attempted to compare risk factors in non-syndromic hypertrophic cardiomyopathy and Noonan syndrome-related hypertrophic cardiomyopathy. In the first study, higher electrocardiogram voltage amplitudes in the limb leads were a significant risk factor in both Noonan-associated and non-syndromic hypertrophic cardiomyopathy, and severity of septal hypertrophy had a B-value on Cox hazard analysis of 0.015, p = 0.001 in non-syndromic hypertrophic cardiomyopathy, and virtually identical B-value of 0.014 in the smaller group with Noonan-associated hypertrophic cardiomyopathy.[35] The second study found that a sum of electrocardiogram risk score and HCM Risk-Kids score ≥14 after the age of 7 years was a significant predictor of sudden cardiac death both short and long term also in Noonan syndrome.[47]

This writing group considers that hypertrophic cardiomyopathy patients with RASopathy syndromes may be at risk of sudden cardiac death and should not be excluded from consideration of implantable cardioverter-defibrillator implantation. Further multicentre studies are required to delineate optimal risk stratification strategies in patients with RASopathy-related hypertrophic cardiomyopathy, including an assessment of the role of severity of left ventricular hypertrophy and electrocardiogram abnormalities.

Genetics. Sarcomere protein gene mutations are the commonest cause of hypertrophic cardiomyopathy beyond infancy[7,9], and there is good agreement on which genes should be screened in non-syndromic hypertrophic cardiomyopathy, although no specific comment on paediatric hypertrophic cardiomyopathy is usually made. Due to the limited number of genes for diagnostic purposes, targeted panel next-generation sequencing has evolved as the method of choice. Gene panels generally include eight sarcomere genes, including *MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3, and ACTC1*.[21] Among patients with hypertrophic cardiomyopathy and a pathogenic sarcomeric gene variant, the two most common genes implicated are beta myosin heavy chain

7 (*MYH7*) and myosin-binding protein C3 (*MYBPC3*). Several reports suggest that clinical screening should commence during early childhood and not be delayed until 10 or 12 years of age.[22,23,81]

There have been very few paediatric studies assessing genotype–phenotype correlations, but a family screening study for hypertrophic cardiomyopathy suggested that *MYH7/MYBPC3* variant positive patients were at highest risk of developing early hypertrophic cardiomyopathy and then experiencing an event or requiring a major intervention. All events occurred in phenotype-positive children.[81] Genotype-positive individuals who remain phenotype negative by 18 years of age have a variable frequency of phenotype conversion, ranging from 10 to 50%.[22,82] In one paediatric study Troponin I (*TNNI3*) and Troponin T (*TNNT2*), variants were predictive for the risk of lethal arrhythmic events.[22] The PRIMaCY study suggested that genotype-positive individuals had a 1.3-fold higher risk of experiencing a sudden cardiac death event when compared to individuals who were genotype-negative on genetic testing after accounting for all clinical risk factors, although no assessment of individual genes or the presence of additional co-existent genetic variation was made, and the addition of genotype status did not improve the performance of the model.[15] Data from the SHaRe registry have recently shown that patients with childhood-onset sarcomeric hypertrophic cardiomyopathy had a 63% increased risk for the overall cardiac composite outcome compared with non-sarcomeric childhood-onset hypertrophic cardiomyopathy, with no significant increased hazard identified for the ventricular arrhythmia composite.[10] Larger studies are needed to analyse and incorporate genotype-specific differences in risk predictions.

This writing group considers that the prognostic value of identifying sarcomere gene variant carriers in children without phenotypic manifestations is unclear.

Age. Different multicentre studies have investigated age at diagnosis or at presentation as a potential risk factor for death. Presentation in infancy (<1 year of age) was associated with an increased risk of cardiovascular death[5,6,8,83,84]; however, the cause of death in this subgroup is most commonly associated with congestive heart failure and non-cardiovascular causes, rather than sudden cardiac death.[85] One study reported an increased risk of sudden cardiac death or malignant arrhythmia occurring in children above 13 years of age,[24] and a population-based study showed that 8–16-year-olds had a significantly higher mortality rate in sudden cardiac death than 17–30-year-olds, with the highest rate between the ages of 9 and 14 years.[44] Maurizi et al.[22] evaluated 100 hypertrophic cardiomyopathy patients from 1 to 16 years old at diagnosis to describe the long-term outcome of paediatric onset hypertrophic cardiomyopathy and to identify age-specific arrhythmic risk factors. In their cohort, patients aged ≤12 years at diagnosis showed significantly more cardiovascular events, including lethal arrhythmic events (defined as sudden cardiac death or aborted cardiac arrest in patients who were successfully resuscitated or who received appropriate implantable cardioverter-defibrillator shocks), compared to those diagnosed >12 years at diagnosis; however, age at diagnosis was not a predictor of lethal arrhythmic events on multivariate analysis. More recently, data from the International Paediatric Hypertrophic Cardiomyopathy Consortium on 639 children diagnosed with hypertrophic cardiomyopathy under 12 years of age were compared with 568 children diagnosed between 12 and 18 years; age at presentation did not influence the prevalence of adverse outcomes, including sudden cardiac death and

malignant ventricular arrhythmia, but children diagnosed in pre-adolescence had adverse events at younger ages.[11]

In the HCM Risk-Kids model developed by the International Paediatric Hypertrophic Cardiomyopathy Consortium to predict 5-year sudden cardiac death risk during childhood (age ≤16 years), age at diagnosis was not a predictor of sudden cardiac death, and its inclusion in the paediatric model did not improve its performance.[14] In contrast, the PRIMaCY sudden cardiac death risk prediction model[15] included age at diagnosis as a variable, considering its non-linear association with sudden cardiac death identified in the evaluated cohort. The authors found that sudden cardiac death risk increased with increased age at diagnosis, starting from 5 years of age. In particular, they noted that patients diagnosed before 5 years of age had a higher frequency of non-sudden cardiac death death and transplant than those diagnosed later, and that these events occurred mostly in infants (i.e., age <1 year). On the other hand, early-onset hypertrophic cardiomyopathy patients had a lower frequency of sudden cardiac death events than those diagnosed after 5 years of age. This difference, however, may be partly related to the higher non-sudden cardiac death mortality and transplant in the first years of age.

This writing group considers that the risk of sudden cardiac death occurring in infancy and below 5 years of age is very low. There are data to suggest an increased risk of sudden cardiac death in the age range between 5 and 14 years.

Proposed risk factors for which there is no evidence of an association with sudden cardiac death risk in childhood hypertrophic cardiomyopathy

Sex
The penetrance of autosomal dominant mutations causing hypertrophic cardiomyopathy is both age-related and sex-related, with higher penetrance in males at least below 40 years of age.[86,87] However, a substantial proportion of non-syndromic hypertrophic cardiomyopathy cases in childhood are sporadic rather than familial, around 31–38% in geographical cohorts,[25,44] and between 47 and 52% in large tertiary centre collaborations.[14,15] Nevertheless, there is still a male predominance in studies of childhood hypertrophic cardiomyopathy, ranging from 55% males in a study diagnosing cases by school screening[88], to 58–62% in geographical cohorts,[25,44] and to 60–69% in tertiary centre studies.[14,15,26,38] Consistently, however, the sex proportion of subjects with sudden cardiac death is either identical to, or only marginally different from, the sex proportion among survivors. Neither univariate Cox hazard regression[26,44] nor multivariate analysis[14,15,25] has found sex to be a risk factor for sudden death in childhood hypertrophic cardiomyopathy, with two very large multicentre studies having ample statistical power to detect even small increases in risk.[14,15]

This writing group considers that sex is not an independent risk factor for sudden cardiac death in childhood hypertrophic cardiomyopathy.

Family history of sudden cardiac death
In adults with hypertrophic cardiomyopathy, the presence of a family history of premature sudden cardiac death is accepted as a major risk factor both in American Heart Association/American College of Cardiology guidelines[21] and in the European Society of guidelines.[1] Paediatric studies, however, have consistently failed to demonstrate that a malignant family history is an independent risk factor for sudden death in childhood

hypertrophic cardiomyopathy.[24-26,28,38,84] This is unlikely to result from lack of statistical power, as relative risks or hazard ratios are 1.0 or close to 1 in most individual studies.[24,38] Possible explanations for this apparent difference in the role of family history of sudden cardiac death in children compared to adults include a lower proportion of familial hypertrophic cardiomyopathy cases in childhood, higher prevalence of *de novo* disease or incomplete reporting of family linkage, as well as the possibility that follow-up times in paediatric studies are relatively short and children may not have developed the phenotype until later in adulthood.[82] However, even if the analysis is restricted to familial paediatric hypertrophic cardiomyopathy only, the hazard ratio is still not significant (1.2 [0.5–2.8]), and the specificity is low (55%).[25] While even in paediatric hypertrophic cardiomyopathy there are some families with multiple deaths occurring at young age, family history was not an independent risk factor on multivariate analysis[25] and all paediatric hypertrophic cardiomyopathy cases with a malignant family history who died suddenly also had additional clinical markers of increased risk, whereas those with malignant family history who did not have any adverse events showed a more benign clinical phenotype.[25] Two very large multicentre studies have provided further evidence that a family history of sudden cardiac death is not an independent risk factor, both PRIMaCY-sudden cardiac death[15] with 572 patients and 53 individuals reaching the end points, and HCM Risk-Kids[14] with 1024 patients and 89 end points reached; in the latter, family history of sudden cardiac death had a hazard ratio of 1.01.

This writing group considers that, while the presence of a malignant family history may be an indication for detailed early investigations for risk stratification and for a more frequent follow-up, it is not an independent risk factor for sudden cardiac death in childhood hypertrophic cardiomyopathy and should not be used to justify implantable cardioverter-defibrillator implantation in children in the absence of additional clinical risk factors.

Review of proposed risk assessment strategies

European Society of Cardiology 2014 guidelines

The European Society of Cardiology (ESC) 2014 guidelines proposed using a risk calculation algorithm for adult patients, HCM Risk-SCD, but this was not validated in patients below 16 years of age.[1] A brief section on risk stratification in children states that risk assessment is hampered by lack of data, but that "there is general agreement" that unexplained syncope, severe left ventricular hypertrophy, non-sustained ventricular tachycardia, and family history of sudden cardiac death would constitute major risk factors, and that ≥2 risk factors would constitute an indication to consider implantation of a primary prevention implantable cardioverter-defibrillator. This approach was formally evaluated by Norrish et al. in a United Kingdom cohort of 411 patients (295 with complete data) with median follow-up 5.5 years; comparing freedom from major arrhythmias in the low-risk group (0–1 risk factors) with the high-risk group of ≥2 risk factors, there was no significant difference in the respective Kaplan–Meier survival curves (log-rank = 0.34).[89] The discrimination ≥2 risk factors in identifying patients having a major arrhythmia event by 5 years of follow-up had a C-statistic of 0.62 [0.52–0.72], with a positive predictive value of only 12.5% and a negative predictive value of 93.9%. Only 3/43 (7%) of patients experiencing a major arrhythmia were identified by the ≥2 risk factors criterion.[89]

This writing group considers that the ESC 2014 guidelines have insufficient sensitivity for clinical use in children.

American Heart Association/American College of Cardiology 2020 Guidelines

The updated American Heart Association/American College of Cardiology Guidelines published in 2020[21] contain a few short sections dealing with recommendations for paediatric patients, which are relatively similar to those in 2011.[37] They recommend implantation of a primary prevention implantable cardioverter-defibrillator in children with one or more of the following risk factor: unexplained syncope, massive left ventricular hypertrophy, non-sustained ventricular tachycardia, or a family history of sudden cardiac death. The guidelines acknowledge that the positive predictive value of this approach is poor, and that "new risk factor algorithms with higher positive predictive value are needed, especially in children."[21] There are only two additions compared to the 2011 guidelines: massive left ventricular hypertrophy is defined as "risk maximised around a Z-score of 20" (although there is no definition of which normative data should be used), in contrast to the earlier definition of Z-score >6; and a suggestion that the physician should "consider the presence of massive late gadolinium enhancement" in the risk assesssment[21]. The performance in paediatric hypertrophic cardiomyopathy of the presence of zero, one, or two or more of these classical risk factors was assessed by Norrish et al. in 2019, showing no significant difference on Kaplan–Meier survival curve analysis of the freedom from major arrhythmic events between individuals with 0 and 1 risk factor at 5 years follow-up[89]; a further multicentre study confirmed a non-significant C-statistic for 1≥ risk factor of 0.55.[47]

This writing group considers that the use of only one risk factor as potential indication for implantable cardioverter-defibrillator-implantation does not confer significant discrimination for risk of sudden cardiac death in childhood hypertrophic cardiomyopathy and agrees that new risk factor algorithms with higher positive predictive value are needed.

Multiparametric paediatric risk prediction models

Hypertrophic cardiomyopathy Risk-Kids

Following the demonstration of poor discriminatory power of the paediatric ESC2014 guidelines,[89] a major effort at collecting a large group of paediatric hypertrophic cardiomyopathy patients with the aim of constructing a paediatric-specific risk assessment algorithm was launched. This eventually collected 1024 patients from 39 participating centres.[14] Five pre-selected parameters, based on a meta-analysis of published data in childhood hypertrophic cardiomyopathy,[90] were included: maximal left ventricular wall thickness (as a continuous variable and expressed as a Z-score rather than an absolute value), left atrial diameter Z-score (also as a continuous variable), presence of unexplained syncope, presence of non-sustained ventricular tachycardia, and left ventricular outflow tract obstruction gradient (continuous variable). Family history of sudden cardiac death and age were not included in the model development as they were not significant. Missing values were imputed by computer analysis of chained equations.[14] Internal validation in 527 patients with complete data and 34 end points within the first 5 years of follow-up, demonstrated a C-statistic of 0.69 [0.66–0.72], similar to the adult HCM Risk-SCD score.[18] A calculated HCM Risk-Kids annual percent risk of ≥6% identified 26/32 patients with a major arrhythmia event within 5 years (sensitivity 76%).[14] However, 45.2% of those with a cut-off ≥6% did not reach the end point within 5 years. Limitations of the model include the large amount of missing data with use of imputed data.[91] The apparently paradoxical reduction of sudden cardiac death risk with

increasing left ventricular outflow tract obstruction gradient assigned to the algorithm has also been raised as a concern, as discussed in detail above. A large-scale external validation study of HCM Risk-Kids was reported in 2022, confirming the ability of the model with a threshold of >6% risk at 5 years to identify over 70% of children with a major arrhythmic event and a C-statistic of 0.75.[93] Additional external validation was provided from a national cohort, in which similar performance was observed (C-statistic 0.69, sensitivity 73%, positive predictive value 22%, and negative predictive value 95%).[47] In this study, using data from ≥7 years of age in patients with a diagnosis in infancy improved the C-statistic to 0.76, and combining HCM Risk-Kids score with electrocardiogram risk score improved specificity and C-statistic compared with either measure alone.[47] The HCM Risk-Kids model is available online (www.hcmriskkids.org).

PRIMaCY-sudden cardiac death

Following the publication of hypertrophic cardiomyopathy Risk-Kids, a separate paediatric-specific model was developed in a North American multicentre retrospective cohort (PRIMaCY) of 572 patients up to 18 years of age and validated using data from 285 patients from the SHaRe registry.[15] Risk factors were selected on the basis of an association with the end point of an arrhythmic event in a development cohort and included age at diagnosis, documented non-sustained ventricular tachycardia, unexplained syncope, septal diameter z-score, left ventricular posterior wall diameter z-score, left atrial diameter z-score, and peak left ventricular outflow tract obstruction gradient. The presence of a pathogenic sarcomeric variant was also explored in an additional model, but this did not improve model performance, possibly due to small numbers of genotyped patients. Over a total of 2855 patient-years follow-up, 53 patients experienced a sudden cardiac death or equivalent event, with a median time from diagnosis to event of 2.2 years. C-statistics of 0.75 and 0.71 were reported for the development and external validation cohorts, respectively, but confidence intervals for the performance estimates were not reported, nor was the final equation made available, but the model is available online (www.primacycalculator.com). Given that both the development and internal validation and the external validation cohorts for the hypertrophic cardiomyopathy Risk-Kids model are nearly twice as large as PRIMaCY, confidence intervals would be expected to be wider than in HCM Risk-Kids, reflecting uncertainty in the estimates due to small patient numbers and missing data. The authors assessed the performance of the model dividing the cohort into three risk tertiles (<4.7% (low), 4.7–8.3% (medium), and >8.3 (high risk) at 5 years) and showed good agreement, but with large confidence intervals.

This writing group considers that HCM Risk-Kids outperforms the ESC 2014 and AHA/ACC 2020 risk assessment strategies. Further independent external validation studies of the HCM Risk-Kids and PRIMaCY models side by side are needed to compare performance in clinical practice. Incorporation of additional clinical risk factors may improve their performance.

Implantable cardioverter-defibrillator management in paediatric hypertrophic cardiomyopathy

Determining the need for primary prevention implantable cardioverter-defibrillator therapy in paediatric patients involves careful balancing of risks and benefits. Implantable cardioverter-defibrillator implantation is effective in reducing mortality in children with severe hypertrophic cardiomyopathy but is also associated with a high complication and re-intervention rate. Ideally, the benefits of therapy should outweigh its risks; thus, the risk of receiving appropriate implantable cardioverter-defibrillator therapy should outweigh the risk of adverse events related to implantable cardioverter-defibrillator implantation. In addition, risks and benefits carry different weights for each different patient, parent, and doctor. These factors need to be examined, balanced, and discussed with paediatric patients and their caregivers, thereby leading to a thoroughly shared decision to implant or to not implant an implantable cardioverter-defibrillator.

Device and lead systems

The choice of device systems and leads in children with hypertrophic cardiomyopathy requiring implantable cardioverter-defibrillator therapy is not essentially different compared to children with other cardiac diseases. In small children, non-transvenous systems are commonly used with the device placed in the right anterior abdominal wall, the ventricular pacing and sensing lead epicardially, and the shock array subcutaneously in the left thorax. Other techniques have also been reported, including placement of the shock array in the pericardial or pleural space.[94,95] In older children, as in adults, transvenous implantable cardioverter-defibrillator systems are mostly used. Lead failures are more common in non-transvenous systems as compared to transvenous systems with a failure rates of 29% versus 7%, respectively, over a median follow-up of 4.3 year.[96,97] A recent study describing a retrospective implantable cardioverter-defibrillator cohort of 90 paediatric hypertrophic cardiomyopathy patients showed a re-intervention rate of 35.6% over a median follow-up of 4.6 years for generator replacement (10%), lead replacement (13.3%), lead repositioning (3.3%), system infection (5.6%), system upgrade (5.6%), or implantable cardioverter-defibrillator pocket erosion (1.1%).[20]

Limitation of the amount of implantable cardioverter-defibrillator leads decreases the chance of lead-related complications. The additional value of an atrial lead is limited to anti-bradycardia pacing of patients in sinus rhythm, rare cases of early-onset atrioventricular (AV) conduction disease (e.g., variants in PRKAG2 gene), and can be considered in cases with poorly controlled left ventricular outflow tract obstruction where AV sequential pacing has been described to reduce left ventricular outflow tract obstruction.[98]

There is no additional value of atrial sensing in discrimination of supraventricular tachycardia or sinus tachycardia from ventricular tachycardia.[96,99,100]

In recent years, S-implantable cardioverter-defibrillator has been used increasingly, especially in young patients, including paediatric hypertrophic cardiomyopathy patients.[101,102] There were no lead failures in the S-implantable cardioverter-defibrillator group.[102] Screening for S-implantable cardioverter-defibrillator fails in 14 to 38% of hypertrophic cardiomyopathy patients due to higher risk of T-wave sensing which may improve by alternative placement of the screening electrodes.[103] S-implantable cardioverter-defibrillator therapy in hypertrophic cardiomyopathy patients appears effective in the recognition and termination of ventricular tachycardia/ventricular fibrillation even in the presence of extreme left ventricular hypertrophy.[104,105] Cardiac pacing and thereby antitachycardia pacing is impossible in S-implantable cardioverter-defibrillator which can be a disadvantage for hypertrophic cardiomyopathy patients with monomorphic ventricular tachycardia as presenting rhythm. Recently, a retrospective implantable cardioverter-defibrillator series on clinical outcome

and programming strategies in 90 paediatric cardiomyopathy patients showed 20% of patients receiving appropriate therapy to be successfully cardioverted by antitachycardia pacing for monomorphic ventricular tachycardia, without the need for high-voltage therapy.[20]

In paediatric hypertrophic cardiomyopathy patients, implantable cardioverter-defibrillator systems have gradually changed away from dual-chamber and dual-coil systems towards single-chamber systems and S-implantable cardioverter-defibrillators. These simpler systems may be preferable for most paediatric hypertrophic cardiomyopathy patients, since they reduce the risk of device-related complications without significantly increasing the risk of inappropriate therapies.

This writing group considers that transvenous, non-transvenous, and subcutaneous implantable cardioverter-defibrillators are equally effective in primary and secondary prevention of sudden cardiac death in paediatric hypertrophic cardiomyopathy. Dual-chamber implantable cardioverter-defibrillators are not superior to single-chamber implantable cardioverter-defibrillators in supraventricular or sinus tachycardia discrimination. Lead failure problems are more common in non-transvenous systems in comparison with transvenous systems, and the most simple implantable cardioverter-defibrillator systems are associated with the least possible (lead failure) complications. Therefore, this writing group considers the most appropriate implantable cardioverter-defibrillator system in paediatric hypertrophic cardiomyopathy to be the least complicated complying system after careful consideration of the patient's weight, the potential indication for atrial pacing and the potential expected effect of antitachycardia pacing in relation to available device properties.

Effectiveness and complications

Benefits
Appropriate implantable cardioverter-defibrillator therapy in paediatric hypertrophic cardiomyopathy. Appropriate implantable cardioverter-defibrillator therapy in paediatric hypertrophic cardiomyopathy patients is reported in 9–28%[14,19,28,106] and occurs more often in children who had an implantable cardioverter-defibrillator implanted for secondary prevention compared to primary prevention (47–70% versus 14–16%, respectively; mean follow-up 4–5 years).[15,19,20,28,107,108]

Potential risks
Inappropriate implantable cardioverter-defibrillator therapy. Inappropriate implantable cardioverter-defibrillator therapy is still designated as major problem associated with implantable cardioverter-defibrillator implantation in children and adolescents diagnosed with hypertrophic cardiomyopathy, primary arrhythmia substrates or CHD. The majority of literature describes inappropriate implantable cardioverter-defibrillator therapy occurring in ranges between 10 and 33% with a predilection for paediatric patients in comparison with adults.[96,101,102,109–116]

Series addressing implantable cardioverter-defibrillator implantation in paediatric hypertrophic cardiomyopathy used to report inappropriate therapy rates between 18 and 28%[19,28,106], but recently a tendency towards a decrease in inappropriate implantable cardioverter-defibrillator therapy towards 8 to 13% was described.[20,107]

No patient or device-related indices investigating age and weight at implant,[19,20,112] implantation for primary or secondary prevention,[19,20,28,106] (anti-arrhythmic) medication,[19,20,106] left ventricular outflow tract obstruction, myocardial wall thickness, different strategies for implantable cardioverter-defibrillator programming,[20] and single- versus dual-chamber devices,[20,28,96,99] have been identified as risk factors, nor for prevention of inappropriate implantable cardioverter-defibrillator therapy. In addition, no difference in inappropriate therapy rate was found comparing transvenous, subcutaneous, or non-transvenous implantable cardioverter-defibrillators.[101,102]

Causes of inappropriate therapy. Inappropriate therapies are due to lead dysfunction, electromagnetic noise, T-wave oversensing, and misclassification of supraventricular tachycardia or sinus tachycardia.[20,96,109,110,112,115,117]

Missed implantable cardioverter-defibrillator therapy. Implantable cardioverter-defibrillator therapy can be missed, delayed, or fail to cardiovert arrhythmia which can lead to mortality despite implantable cardioverter-defibrillator implantation. Missed therapy is described to occur in 1–8% of patients during a median follow-up between 2 and 8 years.[20,28,110,112]. Undersensing (e.g., due to very small R-waves during ventricular fibrillation), sustained ventricular tachycardia below rate where therapy programmed, or battery depletion are some of the underlying causes. Awareness of the potential haemodynamic compromise caused by slow ventricular tachycardia in hypertrophic cardiomyopathy patients is important, particularly in patients with severe diastolic dysfunction, since slower rates are usually not programmed into implantable cardioverter-defibrillator ventricular tachycardia detection zones. Clinically, this subset of patients may experience haemodynamic benefit from implantable cardioverter-defibrillator therapy during (haemodynamically significant) slow ventricular tachycardia. The downside however of programming lower ventricular tachycardia detection zones is an increased risk for inappropriate shocks due to sinus or atrial tachycardia, although using Holter or exercise stress test information about the normal maximal heart rate in the patient may mitigate this risk.[96]

Infection. Infections ranging from superficial wound infection to skin erosion and endocarditis are reported between 1 and 33% of implantable cardioverter-defibrillator patients, with a higher incidence in children compared to adults.[19,20,95,96,110,114,115,118] With respect to subcutaneous implantable cardioverter-defibrillators, pocket infection and skin erosion are reported in 3–13% of patients, and no systemic infections are described.[20,101,102,119,120]

Periprocedural systemic antibiotic prophylaxis is warranted at the time of implantable cardioverter-defibrillator implantation in order to prevent implantation-related infections. The Heart Rhythm Society and American Heart Association recommend prophylaxis with anti-staphylococcal antimicrobial drugs (e.g., Cefazolin or Vancomycin in case of cephalosporin allergy).[121] The presence of a (transvenous) implantable cardioverter-defibrillator per se is not an indication for endocarditis prophylaxes according to current guidelines.[122]

Psychosocial impact and quality of life. Diagnosis of hypertrophic cardiomyopathy in children may lead to a lower health-related quality of life.[123] To the best of our knowledge, no literature is available addressing the impact of implantable cardioverter-defibrillator implantation on psychosocial functioning of paediatric patients with hypertrophic cardiomyopathy in particular. For the general population of paediatric implantable cardioverter-defibrillator

patients, higher levels of anxiety, depression, and sleeping disorders are described, and quality of life is reported to be lower when compared to normative controls and patients with CHD or pacemakers.[124–129] A history of implantable cardioverter-defibrillator shocks does not seem to show an association with generic or disease-specific health-related quality of life.[126,130] Conflicting results exist with respect to the experience of implantable cardioverter-defibrillator shocks and depression or anxiety.[125,127] These data suggest that the availability of appropriate mental health resources and clinic-based screening tools to assess for anxiety and depression might be of potential benefit for this population. A recent explorative study investigating unmet needs in implantable cardioverter-defibrillator paediatric patients and parents indicated knowledge and understanding of cardiac events in addition to how an implantable cardioverter-defibrillator will affect their lives, as most imported unmet needs for the patients.[131] For the parents, their focus on over-protectiveness and their children's emotional needs appeared to be unmet needs. Further research is needed to investigate the potential benefits of additional tools aiming to help patients better understand their new recommended lifestyle and medical conditions.

Defibrillation threshold testing

In the adult population, defibrillation threshold testing during implantation does not show significant benefit in shock efficacy or reduction in arrhythmic death.[132–134] However, the majority of paediatric electrophysiologists still prefer to assess defibrillation efficacy during implantable cardioverter-defibrillator implantation.[20,135] The reason for this difference probably lies on the one hand in the different indications for implantable cardioverter-defibrillator implantation in children compared with adults. On the other hand, the small (and changing) body size and the sometimes complex surgical and anatomic substrates necessitating non-transvenous implantable cardioverter-defibrillator implanting techniques potentially affect the defibrillation efficacy.

No association between the performance of defibrillation threshold testing and subsequent failure or delay of therapy during 4.5 years follow-up was described in 90 paediatric implantable cardioverter-defibrillator patients with hypertrophic cardiomyopathy.[20]

Regarding *transvenous* implantable cardioverter-defibrillators, there is no technical reason to expect the defibrillation efficacy in children to be different from its performance in adults. The additional value of defibrillation threshold testing of transvenous implantable cardioverter-defibrillators in children without a specific risk for abnormal defibrillation efficacy is therefore debatable, particularly as the maximum available energy is programmed for defibrillation therapy. However, still few paediatric electrophysiologists choose to programme a lower than the maximum available energy for defibrillation guided by defibrillation threshold value at implantation. Adherence to a protocol that programmes minimal required defibrillation energy requires additional defibrillation threshold testing with growth as the defibrillation threshold might change with growth, consequently necessitating to increase the programmed defibrillation energy output during follow-up.

Regarding *non-transvenous* (epicardial) implantable cardioverter-defibrillators, serial defibrillation threshold testing showed an increase of defibrillation threshold related to body length during a mean follow-up of 2 years[136] and a significant number of failures over a mean follow-up of over 5 years.[94,137] Major change in defibrillation threshold may be specifically expected with somatic

growth in patients with subcutaneous and pleural arrays associated with long defibrillation vectors and change in the vector with time. These data emphasise the role for regular serial defibrillation threshold testing in children with non-transvenous implantable cardioverter-defibrillators during follow-up, as with growth or thoracic deformities (e.g., scoliosis) their defibrillation vectors, and thereby implantable cardioverter-defibrillator efficacy might change.

The most recent guideline on optimal implantable cardioverter-defibrillator programming and testing recommends defibrillation threshold testing in patients undergoing a *S-implantable cardioverter-defibrillator* implantation.[138] This recommendation is based on the lack of data regarding the safety and efficacy of not performing defibrillation threshold testing in patients receiving a S-implantable cardioverter-defibrillator system during publication of this guideline in 2015. Currently, the clinical practice and prospective validation of the PRAETORIAN score is being performed in a dedicated randomised controlled trial.[139] The PRAETORIAN score is a potentially promising scoring system being capable of predicting shock efficacy and of identifying patients at high risk of conversion failure, thus questioning regular defibrillation threshold testing necessity.[140] A recent clinical observational study showed that non-defibrillation threshold testing during S-implantable cardioverter-defibrillator implantation had no impact on the safety of defibrillation therapy and overall patients' survival.[141]

This writing group considers that defibrillation threshold testing during transvenous implantable cardioverter-defibrillator implantations and follow-up does not appear to confer significant benefit in shock efficacy or reduction in arrhythmic death. However, for non-transvenous (epicardial) implantable cardioverter-defibrillator,s defibrillation threshold testing is warranted at implant and regularly with somatic growth in case of long and/or changing defibrillation vectors. For subcutaneous devices, defibrillation threshold testing at implant is advised according to current guidelines.

Implantable cardioverter-defibrillator programming, remote monitoring, and pharmacological therapy for hypertrophic cardiomyopathy implantable cardioverter-defibrillator carriers

Implantable cardioverter-defibrillator programming. The primary purpose of implantable cardioverter-defibrillator implantation is the prevention of sudden cardiac death. Besides, inappropriate shocks should be avoided and unnecessary implantable cardioverter-defibrillator shock therapy minimised. Large adult series have shown that implantable cardioverter-defibrillator shocks can be reduced by programming faster rates for tachycardia detection, prolonged detection duration, antitachycardia pacing, algorithms that discriminate supraventricular tachycardia from ventricular tachycardia, and specific programming to minimise the sensing of noise. A meta-analyses including 7687 adults (56% ischemic heart disease) investigated the effect of these programmed implantable cardioverter-defibrillator settings aiming to reduce nonessential implantable cardioverter-defibrillator therapies. They observed a 30% relative decrease of all-cause mortality and a 50% relative reduction of inappropriate implantable cardioverter-defibrillator shocks with therapy reduction programming versus conventional implantable cardioverter-defibrillator programming.[142] Implantable cardioverter-defibrillator programming consensus statements have been composed and updated based on these observations.[138,143] Recently, Ananwattanasuk et al. assessed the outcomes of device programming according

to these consensus statements and concluded that "guideline concordant programming" was associated with a 53% reduction in implantable cardioverter-defibrillator therapy without a difference in mortality.[144]

Although the majority of patients included in the large implantable cardioverter-defibrillator trials constitute of adult heart failure and ischemic heart disease patients, these trials provide the best and only available data to be extrapolated for implantable cardioverter-defibrillator programming in paediatric implantable cardioverter-defibrillator patients. At the same time, it has to be kept in mind that paediatric implantable cardioverter-defibrillator patients constitute a group of more heterogeneous diagnoses, complying different (more active) lifestyles and in addition encounters challenges inherent to somatic growth and development. Guidelines for implantable cardioverter-defibrillator programming in children are not available. The principles of adult implantable cardioverter-defibrillator programming guidelines are generally used and shown to be effective in the only available described hypertrophic cardiomyopathy implantable cardioverter-defibrillator paediatric series.[20] Table 1 shows a general proposal for implantable cardioverter-defibrillator programming in (paediatric) hypertrophic cardiomyopathy patients.[138,143]

Tachycardia detection is generally programmed in highest heart rate zones with long detection times in order to avoid inappropriate and minimise unnecessary implantable cardioverter-defibrillator shocks. Similar to other cardiomyopathies, slower ventricular tachycardias might be poorly tolerated haemodynamically in patients with severe diastolic dysfunction, and therefore for these patients, lower programmed tachycardia rates should be considered. For secondary prevention implantable cardioverter-defibrillators, in patients in whom the clinical ventricular tachycardia rate is known, it is reasonable to programme the slowest tachycardia therapy zone at least 10 bpm below the documented hemodynamically significant tachycardia rate. Tachycardia therapy in the ventricular tachycardia zone consists of shock therapy. In the ventricular tachycardia zone, haemodynamically tolerated slow ventricular tachycardias should preferably not be treated by implantable cardioverter-defibrillator shock therapy. Programme antitachycardia pacing therapy within the faster ventricular tachycardia zones is considered (in patients with antitachycardia pacing-capable implantable cardioverter-defibrillator therapy devices) followed by shock therapy if not successful. Shock therapy is programmed to the maximum available energy or in case defibrillation threshold testing is preferred, at least 10 Joules above the defibrillation threshold. A monitor zone without therapy can be considered in the very slow ventricular tachycardia zones (in order to be informed about the existence of slow ventricular tachycardias).

Antitachycardia pacing therapy. Programme antitachycardia pacing during charging or as sole therapy for one or multiple therapy cycles in patients with antitachycardia pacing-capable implantable cardioverter-defibrillator therapy devices for all ventricular tachyarrhythmia detection zones is considered.[21] Antitachycardia pacing should be programmed to deliver at least one antitachycardia pacing attempt with a minimum of eight stimuli and a cycle length of 84–88% of the tachycardia cycle length for ventricular tachyarrhythmia's. Specifically, for hypertrophic cardiomyopathy patients, it has been shown that in more than one-third of patients, the presenting ventricular arrhythmia is frequently monomorphic ventricular tachycardia, which has been shown to be effectively converted to sinus rhythm by

antitachycardia pacing without the need for high-voltage therapy (in 74–85% of attempted patients).[20,145] In cases where antitachycardia pacing is documented to be ineffective or pro-arrhythmic, it should not be activated.

Implantable cardioverter-defibrillator remote monitoring
Remote monitoring has been proven to reduce the rate of inappropriate shocks in adult implantable cardioverter-defibrillator patients.[146–148] Due to the early recognised and transmitted clues for lead failure by remote monitoring, the majority of lead failures is diagnosed before clinical complications such as inappropriate shocks occur.[149,150] Not surprisingly given the higher incidence of lead failure in children in comparison with adults, remote monitoring also improves the management of children with implantable cardioverter-defibrillators.[149,151]

Recently, a large meta-analysis demonstrated remote monitoring of implantable cardioverter-defibrillator patients to result in increased effectiveness for lower costs over a 5-year period, compared to the current standard care with regular in hospital clinic visits for surveillance.[152]

In addition, remote monitoring might contribute to the efficacy and adherence to pharmacologic therapy and lifestyle advices. By programming remote monitoring alert on heart frequency's documented in the monitoring zone, this information can be used for optimising patient-tailored therapy and advise, potentially decreasing the risk for ventricular arrhythmias requiring implantable cardioverter-defibrillator therapy.

The writing group considers that, although guideline-directed implantable cardioverter-defibrillator programming has been investigated in a limited extent in hypertrophic cardiomyopathy children, there is no reason to assume that its principles would not be effective within this patient group. However, careful consideration of systolic and diastolic function and attention to available information on previously treated arrhythmic events is warranted for patient-tailored programming. Anti-tachycardia pacing can be effective to convert ventricular tachycardia to sinus rhythm in children with hypertrophic cardiomyopathy. Implantable cardioverter-defibrillator remote monitoring is valuable in children with hypertrophic cardiomyopathy based on current evidence in adults showing reduction in the rate of inappropriate shocks, cost effectiveness, and potential contribution to patient-tailored follow-up, treatment, and patient/parent's convenience.

Pharmacological therapy
In patients with hypertrophic cardiomyopathy and implantable cardioverter-defibrillators, preventing recurrent ventricular tachycardia is important in the prevention of recurrent implantable cardioverter-defibrillator shocks. There are no randomised controlled trials investigating the efficacy of anti-arrhythmic medication in hypertrophic cardiomyopathy. None of the currently available anti-arrhythmic agents are 100% effective, probably due to the various underlying pathophysiologic mechanisms responsible for ventricular arrhythmia in hypertrophic cardiomyopathy.[153] Beta-blockers, sotalol, and amiodarone are generally used as anti-arrhythmic agents in hypertrophic cardiomyopathy.[21,57,154–157] In addition to beta-blockers, disopyramide and calcium channel blockers are guideline-recommended agents for the management of heart failure symptoms (by the improvement of diastolic left ventricular filling) and left ventricular outflow tract obstruction.[21] The latter medications also have anti-arrhythmic properties.

Awareness for potential decrease in arrhythmia rate by anti-arrhythmic drugs is emphasised, particularly for sotalol,

disopyramide, and amiodarone. Anti-arrhythmic drugs may slow clinical ventricular tachycardia under the implantable cardioverter-defibrillator tachycardia detection zone, while simultaneously increasing QRS duration and decreasing systolic ventricular function, resulting in worse haemodynamic toleration of slower ventricular tachycardia.

Amiodarone is preferably not used as first choice anti-arrhythmic therapy due to significant side effects including hyper- or hypothyroidism associated with its use, particularly in children. It is therefore usually reserved for the treatment of ventricular arrhythmias in cases where other medications fail.

Some hypertrophic cardiomyopathy patients experience ventricular arrhythmia in response to (even slow) sinus tachycardia. In addition to lifestyle advises limiting vigorous exercise, it might be considered for these patients to limit the maximum heart rate by beta-blockers.

Inappropriate implantable cardioverter-defibrillator therapy can be triggered by misinterpretation of sinus tachycardia as ventricular arrhythmia. Pharmacologic limitation of maximum sinus frequency below the programmed lowest ventricular tachycardia therapy zones can be facilitated by treating also primary prevention, non-obstructive implantable cardioverter-defibrillator hypertrophic cardiomyopathy patients with beta-blockers.

The intended effect of pharmacologic therapy on arrhythmia, but also on sinus frequency limitation for primary prevention implantable cardioverter-defibrillator patients in particular, can be evaluated by Holter electrocardiogram recording during daily life settings and by exercise stress testing.

This writing group considers that none of the currently available anti-arrhythmic agents are 100% effective in the prevention of ventricular arrhythmia in hypertrophic cardiomyopathy. However, in the presence of an implantable cardioverter-defibrillator, anti-arrhythmic therapy potentially decreases the risk of an arrhythmic event requiring implantable cardioverter-defibrillator therapy. In addition, beta-blockade can be useful for heart rate modulation, potentially to decrease the risk of an arrhythmic event and to limit sinus node frequencies below the lowest ventricular tachycardia therapy zone.

Physical activity and sports participation in paediatric hypertrophic cardiomyopathy – implantable cardioverter-defibrillator carriers

The possibility of participation in physical activity including competitive sports is primarily based on the diagnosis and physiology of the patient, rather than the presence of the implantable cardioverter-defibrillator.[158] Guidelines considering the management of hypertrophic cardiomyopathy patients are used to advise against competitive sports for patients with hypertrophic cardiomyopathy. However, recent studies showed that vigorous exercise was associated with favourable diastolic function in hypertrophic cardiomyopathy and was not associated with ventricular arrhythmias, nor with increased risk for major cardiac events.[159–161] Based on these findings, both the recent European recommendations[162] and 2020 AHA/ACC guidelines [21] encourage controlled moderate-intensity exercise but discourage participation in intensive exercise programmes and competitive sports in patients with hypertrophic cardiomyopathy and phenotype leading to implantable cardioverter-defibrillator indication. Children can typically participate in physical education at school which is, however, not graded or scored. There is lack of data to make formal recommendations regarding isometric exercise. Valsalva manoeuvre or standing from the squatting position may be used

to uncover significant exercise-induced left ventricular outflow tract obstruction. In such patients and in those with resting left ventricular outflow tract obstruction, isometric exercise should be discouraged.[21]

Safety of sports in young patients with an implantable cardioverter-defibrillator has been recently evaluated in a Multinational ICD Sports Registry.[163] The primary end points were death or resuscitated cardiac arrest during sports or injury during sports because of arrhythmia or shock. Secondary end points included system malfunction and incidence of ventricular arrhythmias requiring multiple shocks for termination. Thirty of the 129 studied athletes (23.3%) had hypertrophic cardiomyopathy. There were no tachyarrhythmic deaths, nor externally resuscitated tachyarrhythmia during or after sport participation and no severe injury resulting from arrhythmia-induced syncope or shock during sports. Appropriate shocks during sport competition or practice occurred in 4/18 individuals, of which all were in the highly competitive subgroup, with an overall rate of 1.5 appropriate shocks during sports per hundred person-years. Five athletes received inappropriate shocks during sports. The rate of inappropriate shocks may be decreased by programming the first therapy zone to cut-offs higher than 200 beats per minute.[164] The authors conclude [163] that restriction from sports activity would not have a large impact on the overall burden of treated arrhythmias. Lead malfunction rates (20% during 10 years) were similar or better to previously reported in unselected paediatric implantable cardioverter-defibrillator populations,[117] but only few patients participated in aggressive contact sports. Implantable cardioverter-defibrillator protection devices may be used to protect the generator from dynamic impact and are currently commercially available.

Recently published recommendations do not regard participation in competitive sports in the individual patient with cardiomyopathy and implantable cardioverter-defibrillator as absolute contraindication and place it rather in the 2B class (may be considered).[21,162,165] The indications for an implantable cardioverter-defibrillator in competitive athletes should, however, not differ from the general population with a diagnosis of cardiomyopathy. The desire of the athlete with cardiomyopathy to compete should not constitute a primary (or unique) indication for implantable cardioverter-defibrillator implantation.[158,162]

This writing group considers that controlled moderate-intensity exercise is encouraged, but participation in intensive exercise programmes and competitive sports in patients with hypertrophic cardiomyopathy and an implantable cardioverter-defibrillator is discouraged. Programming the first therapy zone to cut-offs higher than 200 beats per minute may decrease the risk of inappropriate shocks in athlete implantable cardioverter-defibrillator patients. Implantable cardioverter-defibrillator protection devices may be used to protect the generator from dynamic impact.

References

1. Elliott PM, Anastasakis A, Borger MA, et al. ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the

Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014; 35: 2733–2779. DOI 10.1093/eurheartj/ehu284.

2. Arola A, Jokinen E, Ruuskanen O, et al. Epidemiology of idiopathic cardiomyopathies in children and adolescents. A nationwide study in Finland. Am J Epidemiol 1997; 146: 385–393. DOI 10.1093/oxfordjournals.aje.a009291.

3. Nugent AW, Daubeney PE, Chondros P, et al. The epidemiology of childhood cardiomyopathy in Australia. N Engl J Med 2003; 348: 1639–1646. DOI 10.1056/NEJMoa021737.

4. Lipshultz SE, Sleeper LA, Towbin JA, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med 2003; 348: 1647–1655. DOI 10.1056/NEJMoa021715.

5. Nugent AW, Daubeney PE, Chondros P, et al. Clinical features and outcomes of childhood hypertrophic cardiomyopathy: results from a national population-based study. Circulation 2005; 112: 1332–1338. DOI 10.1161/CIRCULATIONAHA.104.530303.

6. Norrish G, Field E, McLeod K, et al. Clinical presentation and survival of childhood hypertrophic cardiomyopathy: a retrospective study in United Kingdom. Eur Heart J 2019; 40: 986–993. DOI 10.1093/eurheartj/ehy798.

7. Kaski JP, Syrris P, Esteban MT, et al. Prevalence of sarcomere protein gene mutations in preadolescent children with hypertrophic cardiomyopathy. Circ Cardiovasc Genet 2009; 2: 436–441. DOI 10.1161/CIRCGENETICS.108.821314.

8. Colan SD, Lipshultz SE, Lowe AM, et al. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. Circulation 2007; 115: 773–781.

9. Morita H, Rehm HL, Menesses A, et al. Shared genetic causes of cardiac hypertrophy in children and adults. N Engl J Med 2008; 358: 1899–1908. DOI 10.1056/NEJMoa075463.

10. Marston NA, Han L, Olivotto I, et al. Clinical characteristics and outcomes in childhood-onset hypertrophic cardiomyopathy. Eur Heart J 2021; 42: 1988–1996. DOI 10.1093/eurheartj/ehab148.

11. Norrish G, Cleary A, Field E, et al. Clinical features and natural history of preadolescent nonsyndromic hypertrophic cardiomyopathy. J Am Coll Cardiol 2022; 79: 1986–1997. DOI 10.1016/j.jacc.2022.03.347.

12. McKenna WJ, Deanfield JE. Hypertrophic cardiomyopathy: an important cause of sudden death. Arch Dis Child 1984; 59: 971–975.

13. McKenna WJ, Franklin RC, Nihoyannopoulos P, Robinson KC, Deanfield JE. Arrhythmia and prognosis in infants, children and adolescents with hypertrophic cardiomyopathy. J Am Coll Cardiol 1988; 11: 147–153.

14. Norrish G, Ding T, Field E, et al. Development of a novel risk prediction model for sudden cardiac death in childhood hypertrophic cardiomyopathy (HCM risk-kids). JAMA Cardiol 2019; 4: 918–927. DOI 10.1001/jamacardio.2019.2861.

15. Miron A, Lafreniere-Roula M, Steve Fan CP, et al. A validated model for sudden cardiac death risk prediction in pediatric hypertrophic cardiomyopathy. Circulation 2020; 142: 217–229. DOI 10.1161/CIRCULATIONAHA.120.047235.

16. Lipshultz SE, Orav EJ, Wilkinson JD, et al. Risk stratification at diagnosis for children with hypertrophic cardiomyopathy: an analysis of data from the Pediatric Cardiomyopathy Registry. Lancet 2013; 382: 1889–1897. DOI 10.1016/S0140-6736(13)61685-2.

17. O'Mahony C, Jichi F, Ommen SR, et al. International external validation study of the 2014 European Society of Cardiology Guidelines on Sudden Cardiac Death Prevention in Hypertrophic Cardiomyopathy (EVIDENCE-HCM). Circulation 2018; 137: 1015–1023. DOI 10.1161/CIRCULATIONAHA.117.030437.

18. O'Mahony C, Jichi F, Pavlou M, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J 2014; 35: 2010–2020. DOI 10.1093/eurheartj/eht439.

19. Maron BJ, Spirito P, Ackerman MJ, et al. Prevention of sudden cardiac death with implantable cardioverter-defibrillators in children and adolescents with hypertrophic cardiomyopathy. J Am Coll Cardiol 2013; 61: 1527–1535. DOI 10.1016/j.jacc.2013.01.037.

20. Norrish G, Chubb H, Field E, et al. Clinical outcomes and programming strategies of implantable cardioverter-defibrillator devices in paediatric hypertrophic cardiomyopathy: a UK National Cohort Study. Europace 2021; 23: 400–408. DOI 10.1093/europace/euaa307.

21. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2020; 76: e159–e240. DOI 10.1016/j.jacc.2020.08.045.

22. Maurizi N, Passantino S, Spaziani G, et al. Long-term outcomes of pediatric-onset hypertrophic cardiomyopathy and age-specific risk factors for lethal arrhythmic events. JAMA Cardiol 2018; 3: 520–525. DOI 10.1001/jamacardio.2018.0789.

23. Norrish G, Jager J, Field E, et al. Yield of clinical screening for hypertrophic cardiomyopathy in child first-degree relatives: evidence for a change in paradigm. Circulation 2019; 140: 184–192. DOI 10.1161/CIRCULATIONAHA.118.038846.

24. Moak JP, Leifer ES, Tripodi D, Mohiddin SA, Fananapazir L. Long-term follow-up of children and adolescents diagnosed with hypertrophic cardiomyopathy: risk factors for adverse arrhythmic events. Pediatr Cardiol 2011; 32: 1096–1105. DOI 10.1007/s00246-011-9967-y.

25. Ostman-Smith I, Sjoberg G, Rydberg A, Larsson P, Fernlund E. Predictors of risk for sudden death in childhood hypertrophic cardiomyopathy: the importance of the ECG risk score. Open Heart 2017; 4: e000658. DOI 10.1136/openhrt-2017-000658.

26. Ziolkowska L, Turska-Kmiec A, Petryka J, Kawalec W. Predictors of long-term outcome in children with hypertrophic cardiomyopathy. Pediatr Cardiol 2016; 37: 448–458. DOI 10.1007/s00246-015-1298-y.

27. Yetman AT, Hamilton RM, Benson LN, McCrindle BW. Long-term outcome and prognostic determinants in children with hypertrophic cardiomyopathy. J Am Coll Cardiol 1998; 32: 1943–1950.

28. Kamp AN, Von Bergen NH, Henrikson CA, et al. Implanted defibrillators in young hypertrophic cardiomyopathy patients: a multicenter study. Pediatr Cardiol 2013; 34: 1620–1627. DOI 10.1007/s00246-013-0676-6.

29. Romeo F, Cianfrocca C, Pelliccia F, et al. Long-term prognosis in children with hypertrophic cardiomyopathy: an analysis of 37 patients aged less than or equal to 14 years at diagnosis. Clin Cardiol 1990; 13: 101–107. DOI 10.1002/clc.4960130208.

30. Spirito P, Autore C, Rapezzi C, et al. Syncope and risk of sudden death in hypertrophic cardiomyopathy. Circulation 2009; 119: 1703–1710. DOI 10.1161/CIRCULATIONAHA.108.798314.

31. Balaji S, DiLorenzo MP, Fish FA, et al. Risk factors for lethal arrhythmic events in children and adolescents with hypertrophic cardiomyopathy and an implantable defibrillator: an international multicenter study. Heart Rhythm 2019; 16: 1462–1467. DOI 10.1016/j.hrthm.2019.04.040.

32. Bharucha T, Lee KJ, Daubeney PE, et al. Sudden death in childhood cardiomyopathy: results from a long-term national population-based study. J Am Coll Cardiol 2015; 65: 2302–2310. DOI 10.1016/j.jacc.2015.03.552.

33. Maskatia SA, Decker JA, Spinner JA, et al. Restrictive physiology is associated with poor outcomes in children with hypertrophic cardiomyopathy. Pediatr Cardiol 2012; 33: 141–149. DOI 10.1007/s00246-011-0106-6.

34. McMahon CJ, Nagueh SF, Pignatelli RH, et al. Characterization of left ventricular diastolic function by tissue Doppler imaging and clinical status in children with hypertrophic cardiomyopathy. Circulation 2004; 109: 1756–1762.

35. Ostman-Smith I, Wettrell G, Keeton B, et al. Echocardiographic and electrocardiographic identification of those children with hypertrophic cardiomyopathy who should be considered at high-risk of dying suddenly. Cardiol Young 2005; 15: 632–642.

36. Norrish G, Ding T, Field E, et al. Relationship between maximal left ventricular wall thickness and sudden cardiac death in childhood onset hypertrophic cardiomyopathy. Circ Arrhythm Electrophysiol 2022; 15: e010075. DOI 10.1161/CIRCEP.121.010075.

37. Gersh BJ, Maron BJ, Bonow RO, et al. ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart

38. Decker JA, Rossano JW, Smith EO, et al. Risk factors and mode of death in isolated hypertrophic cardiomyopathy in children. J Am Coll Cardiol 2009; 54: 250–254. DOI 10.1016/j.jacc.2009.03.051.

39. Pettersen MD, Du W, Skeens ME, Humes RA. Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. J Am Soc Echocardiogr 2008; 21: 922–934. DOI 10.1016/j.echo.2008.02.006.

40. Kampmann C, Wiethoff CM, Wenzel A, et al. Normal values of M mode echocardiographic measurements of more than 2000 healthy infants and children in central Europe. Heart 2000; 83: 667–672. DOI 10.1136/heart.83.6.667.

41. Colan SD. Normal echocardiographic values for cardiovascular structures. In: Lai WW, Cohen MS, Geva T, Mertens L (eds). Echocardiography in Pediatric and Congenital Heart Disease. Wiley-Blackwell, West Sussex, UK, 2009: 765–785. Appendix 1.

42. Ho CY, Cirino AL, Lakdawala NK, et al. Evolution of hypertrophic cardiomyopathy in sarcomere mutation carriers. Heart 2016; 102: 1805–1812. DOI 10.1136/heartjnl-2016-310015.

43. Maron MS, Olivotto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003; 348: 295–303.

44. Ostman-Smith I, Wettrell G, Keeton B, et al. Age- and gender-specific mortality rates in childhood hypertrophic cardiomyopathy. Eur Heart J 2008; 29: 1160–1167.

45. Geske JB, Ong KC, Siontis KC, et al. Women with hypertrophic cardiomyopathy have worse survival. Eur Heart J 2017; 38: 3434–3440. DOI 10.1093/eurheartj/ehx527.

46. Javidgonbadi D, Andersson B, Abdon NJ, Schaufelberger M, Ostman-Smith I. Factors influencing long-term heart failure mortality in patients with obstructive hypertrophic cardiomyopathy in Western Sweden: probable dose-related protection from beta-blocker therapy. Open Heart 2019; 6: e000963. DOI 10.1136/openhrt-2018-000963.

47. Ostman-Smith I, Sjoberg G, Alenius Dahlqvist J, Larsson P, Fernlund E. Sudden cardiac death in childhood hypertrophic cardiomyopathy is best predicted by a combination of electrocardiogram risk-score and HCMRisk-Kids score. Acta Paediatr 2021; 110: 3105–3115. DOI 10.1111/apa.16045.

48. El Saiedi S, Behairy NH, Kharabish A, et al. Delayed myocardial enhancement in pediatric hypertrophic cardiomyopathy: correlation with LV function, echocardiography, and demographic parameters. Pediatr Cardiol 2017; 38: 1024–1031. DOI 10.1007/s00246-017-1612-y.

49. Bonura ED, Bos JM, Abdelsalam MA, et al. Cardiac magnetic resonance imaging features in hypertrophic cardiomyopathy diagnosed at <21 years of age. Am J Cardiol 2020; 125: 1249–1255. DOI 10.1016/j.amjcard.2020.01.027.

50. Chaowu Y, Shihua Z, Jian L, Li L, Wei F. Cardiovascular magnetic resonance characteristics in children with hypertrophic cardiomyopathy. Circ Heart Fail 2013; 6: 1013–1020. DOI 10.1161/CIRCHEARTFAILURE.113.000414.

51. Smith BM, Dorfman AL, Yu S, et al. Clinical significance of late gadolinium enhancement in patients <20 years of age with hypertrophic cardiomyopathy. Am J Cardiol 2014; 113: 1234–1239. DOI 10.1016/j.amjcard.2013.12.034.

52. Windram JD, Benson LN, Dragelescu A, et al. Distribution of hypertrophy and late gadolinium enhancement in children and adolescents with hypertrophic cardiomyopathy. Congenit Heart Dis 2015; 10: E258–267. DOI 10.1111/chd.12286.

53. Spinner JA, Noel CV, Denfield SW, et al. Association of late gadolinium enhancement and degree of left ventricular hypertrophy assessed on cardiac magnetic resonance imaging with ventricular tachycardia in children with hypertrophic cardiomyopathy. Am J Cardiol 2016; 117: 1342–1348. DOI 10.1016/j.amjcard.2016.01.032.

54. Axelsson Raja A, Farhad H, Valente AM, et al. Prevalence and progression of late gadolinium enhancement in children and adolescents with hypertrophic cardiomyopathy. Circulation 2018; 138: 782–792. DOI 10.1161/CIRCULATIONAHA.117.032966.

55. Petryka-Mazurkiewicz J, Ziolkowska L, Kowalczyk-Domagala M, et al. LGE for risk stratification in primary prevention in children with HCM. JACC Cardiovasc Imaging 2020; 13: 2684–2686. DOI 10.1016/j.jcmg.2020.06.009.

56. McLeod CJ, Ackerman MJ, Nishimura RA, et al. Outcome of patients with hypertrophic cardiomyopathy and a normal electrocardiogram. J Am Coll Cardiol 2009; 54: 229–233. DOI 10.1016/j.jacc.2009.02.071.

57. Ostman-Smith I, Wettrell G, Riesenfeld T. A cohort study of childhood hypertrophic cardiomyopathy: improved survival following high-dose beta-adrenoceptor antagonist treatment. J Am Coll Cardiol 1999; 34: 1813–1822.

58. Ostman-Smith I, Wisten A, Nylander E, et al. Electrocardiographic amplitudes: a new risk factor for sudden death in hypertrophic cardiomyopathy. Eur Heart J 2010; 31: 439–449. DOI 10.1093/eurheartj/ehp443.

59. Biagini E, Pazzi C, Olivotto I, et al. Usefulness of electrocardiographic patterns at presentation to predict long-term risk of cardiac death in patients with hypertrophic cardiomyopathy. Am J Cardiol 2016; 118: 432–439. DOI 10.1016/j.amjcard.2016.05.023.

60. Haghjoo M, Mohammadzadeh S, Taherpour M, et al. ST-segment depression as a risk factor in hypertrophic cardiomyopathy. Europace 2009; 11: 643–649. DOI 10.1093/europace/eun393.

61. Yetman AT, McCrindle BW, MacDonald C, Freedom RM, Gow R. Myocardial bridging in children with hypertrophic cardiomyopathy–a risk factor for sudden death. N Engl J Med 1998; 339: 1201–1209.

62. Michaelides AP, Stamatopoulos I, Antoniades C, et al. ST segment "hump" during exercise testing and the risk of sudden cardiac death in patients with hypertrophic cardiomyopathy. Ann Noninvasive Electrocardiol 2009; 14: 158–164. DOI 10.1111/j.1542-474X.2009.00291.x.

63. Cortez D, Graw S, Mestroni L. In hypertrophic cardiomyopathy, the spatial peaks QRS-T angle identifies those with sustained ventricular arrhythmias. Clin Cardiol 2016; 39: 459–463. DOI 10.1002/clc.22549.

64. Debonnaire P, Katsanos S, Joyce E, et al. QRS fragmentation and QTc duration relate to Malignant ventricular tachyarrhythmias and sudden cardiac death in patients with hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol 2015; 26: 547–555. DOI 10.1111/jce.12629.

65. Gray B, Ingles J, Medi C, Semsarian C. Prolongation of the QTc interval predicts appropriate implantable cardioverter-defibrillator therapies in hypertrophic cardiomyopathy. JACC Heart Fail 2013; 1: 149–155. DOI 10.1016/j.jchf.2013.01.004.

66. Osterberg AW, Beausejour-Ladouceur V, Stephenson EA, Mital S. Abstract 10353: independent validation of the ECG risk score for sudden death risk stratification in pediatric hypertrophic cardiomyopathy. Circulation 2021; 144: A10353–A10353. DOI 10.1161/circ.144.suppl_1.10353.

67. Norrish G, Topriceanu C, Qu C, et al. The role of the electrocardiographic phenotype in risk stratification for sudden cardiac death in childhood hypertrophic cardiomyopathy. Eur J Prev Cardiol 2022; 29: 645–653. DOI 10.1093/eurjpc/zwab046.

68. Funabashi N, Takaoka H, Horie S, et al. Risk stratification using myocardial peak longitudinal-strain on speckle-tracking transthoracic-echocardiogram to predict major adverse cardiac events in non ischemic hypertrophic-cardiomyopathy subjects confirmed by MDCT. Int J Cardiol 2013; 168: 4586–4589. DOI 10.1016/j.ijcard.2013.06.056.

69. Popovic ZB, Kwon DH, Mishra M, et al. Association between regional ventricular function and myocardial fibrosis in hypertrophic cardiomyopathy assessed by speckle tracking echocardiography and delayed hyperenhancement magnetic resonance imaging. J Am Soc Echocardiogr 2008; 21: 1299–1305. DOI 10.1016/j.echo.2008.09.011.

70. Saito M, Okayama H, Yoshii T, et al. Clinical significance of global two-dimensional strain as a surrogate parameter of myocardial fibrosis and cardiac events in patients with hypertrophic cardiomyopathy. Eur Heart J Cardiovasc Imaging 2012; 13: 617–623. DOI 10.1093/ejechocard/jer318.

71. Ganame J, Mertens L, Eidem BW, et al. Regional myocardial deformation in children with hypertrophic cardiomyopathy: morphological and clinical correlations. Eur Heart J 2007; 28: 2886–2894. DOI 10.1093/eurheartj/ehm444.

72. Smith BM, Dorfman AL, Yu S, et al. Relation of strain by feature tracking and clinical outcome in children, adolescents, and young adults with hypertrophic cardiomyopathy. Am J Cardiol 2014; 114: 1275–1280. DOI 10.1016/j.amjcard.2014.07.051.

73. Ziolkowska L, Mazurkiewicz L, Petryka J, et al. The indices of cardiovascular magnetic resonance derived atrial dynamics may improve the contemporary risk stratification algorithms in children with hypertrophic cardiomyopathy. J Clin Med 2021; 10: 10. DOI 10.3390/jcm10040650.

74. Limongelli G, Monda E, Tramonte S, et al. Prevalence and clinical significance of red flags in patients with hypertrophic cardiomyopathy. Int J Cardiol 2020; 299: 186–191. DOI 10.1016/j.ijcard.2019.06.073.

75. Wilkinson JD, Lowe AM, Salbert BA, et al. Outcomes in children with Noonan syndrome and hypertrophic cardiomyopathy: a study from the Pediatric Cardiomyopathy Registry. Am Heart J 2012; 164: 442–448. DOI 10.1016/j.ahj.2012.04.018.

76. Norrish G, Rance T, Montanes E, et al. Friedreich's ataxia-associated childhood hypertrophic cardiomyopathy: a national cohort study. Arch Dis Child 2022; 107: 450–455. DOI 10.1136/archdischild-2021-322455.

77. Limongelli G, Pacileo G, Marino B, et al. Prevalence and clinical significance of cardiovascular abnormalities in patients with the LEOPARD syndrome. Am J Cardiol 2007; 100: 736–741. DOI 10.1016/j.amjcard.2007.03.093.

78. Burch M, Mann JM, Sharland M, et al. Myocardial disarray in Noonan syndrome. Br Heart J 1992; 68: 586–588. DOI 10.1136/hrt.68.12.586.

79. Shaw AC, Kalidas K, Crosby AH, Jeffery S, Patton MA. The natural history of Noonan syndrome: a long-term follow-up study. Arch Dis Child 2007; 92: 128–132. DOI 10.1136/adc.2006.104547.

80. Calcagni G, Limongelli G, D'Ambrosio A, et al. Cardiac defects, morbidity and mortality in patients affected by RASopathies. CARNET study results. Int J Cardiol 2017; 245: 92–98. DOI 10.1016/j.ijcard.2017.07.068.

81. Lafreniere-Roula M, Bolkier Y, Zahavich L, et al. Family screening for hypertrophic cardiomyopathy: is it time to change practice guidelines? Eur Heart J 2019; 40: 3672–3681. DOI 10.1093/eurheartj/ehz396.

82. Lorenzini M, Norrish G, Field E, et al. Penetrance of hypertrophic cardiomyopathy in sarcomere protein mutation carriers. J Am Coll Cardiol 2020; 76: 550–559. DOI 10.1016/j.jacc.2020.06.011.

83. Alexander PMA, Nugent AW, Daubeney PEF, et al. Long-term outcomes of hypertrophic cardiomyopathy diagnosed during childhood: results from a national population-based study. Circulation 2018; 138: 29–36. DOI 10.1161/CIRCULATIONAHA.117.028895.

84. El-Saiedi SA, Seliem ZS, Esmail RI. Hypertrophic cardiomyopathy: prognostic factors and survival analysis in 128 Egyptian patients. Cardiol Young 2014; 24: 702–708. DOI 10.1017/S1047951113001030.

85. Norrish G, Kolt G, Cervi E, et al. Clinical presentation and long-term outcomes of infantile hypertrophic cardiomyopathy: a European multicentre study. ESC Heart Fail 2021; 8: 5057–5067. DOI 10.1002/ehf2.13573.

86. Charron P, Carrier L, Dubourg O, et al. Penetrance of familial hypertrophic cardiomyopathy. Genet Couns 1997; 8: 107–114.

87. Terauchi Y, Kubo T, Baba Y, et al. Gender differences in the clinical features of hypertrophic cardiomyopathy caused by cardiac myosin-binding protein C gene mutations. J Cardiol 2015; 65: 423–428. DOI 10.1016/j.jjcc.2014.07.010.

88. Morimoto Y, Miyazaki A, Tsuda E, et al. Electrocardiographic changes and long-term prognosis of children diagnosed with hypertrophic cardiomyopathy by the school screening program for heart disease in Japan. J Cardiol 2020; 75: 571–577. DOI 10.1016/j.jjcc.2019.10.008.

89. Norrish G, Ding T, Field E, et al. A validation study of the European Society of Cardiology guidelines for risk stratification of sudden cardiac death in childhood hypertrophic cardiomyopathy. Europace 2019; 21: 1559–1565. DOI 10.1093/europace/euz118.

90. Norrish G, Cantarutti N, Pissaridou E, et al. Risk factors for sudden cardiac death in childhood hypertrophic cardiomyopathy: a systematic review and meta-analysis. Eur J Prev Cardiol 2017; 24: 1220–1230. DOI 10.1177/2047487317702519.

91. Bonow RO, McNally EM. Risk prediction model in children with hypertrophic cardiomyopathy: a work in progress. JAMA Cardiol 2019; 4: 927. DOI 10.1001/jamacardio.2019.2945.

92. Ostman-Smith I, Javidgonbadi D, Fernlund E. Concerns about the HCM Risk-Kids study. JAMA Cardiol 2020; 5: 362. DOI 10.1001/jamacardio.2019.5783.

93. Norrish G, Qu C, Field E, et al. External validation of the HCM Risk-Kids model for predicting sudden cardiac death in childhood hypertrophic cardiomyopathy. Eur J Prev Cardiol 2022; 29: 678–686. DOI 10.1093/eurjpc/zwab181.

94. Muller MJ, Dieks JK, Backhoff D, et al. Efficacy and safety of non-transvenous cardioverter defibrillators in infants and young children. J Interv Card Electrophysiol 2019; 54: 151–159.

95. Winkler F, Dave H, Weber R, Gass M, Balmer C. Long-term outcome of epicardial implantable cardioverter-defibrillator systems in children: results justify its preference in paediatric patients. Europace 2018; 20: 1484–1490. DOI 10.1093/europace/eux284.

96. Krause U, Muller MJ, Wilberg Y, et al. Transvenous and non-transvenous implantable cardioverter-defibrillators in children, adolescents, and adults with congenital heart disease: who is at risk for appropriate and inappropriate shocks? Europace 2019; 21: 106–113. DOI 10.1093/europace/euy219.

97. Radbill AE, Triedman JK, Berul CI, et al. System survival of nontransvenous implantable cardioverter-defibrillators compared to transvenous implantable cardioverter-defibrillators in pediatric and congenital heart disease patients. Heart Rhythm 2010; 7: 193–198. DOI 10.1016/j.hrthm.2009.10.014.

98. Daubert C, Gadler F, Mabo P, Linde C. Pacing for hypertrophic obstructive cardiomyopathy: an update and future directions. Europace 2018; 20: 908–920. DOI 10.1093/europace/eux131.

99. Lawrence D, Von Bergen N, Law IH, et al. Inappropriate ICD discharges in single-chamber versus dual-chamber devices in the pediatric and young adult population. J Cardiovasc Electrophysiol 2009; 20: 287–290. DOI 10.1111/j.1540-8167.2008.01322.x.

100. Peterson PN, Greenlee RT, Go AS, et al. Comparison of inappropriate shocks and other health outcomes between single- and dual-chamber implantable cardioverter-defibrillators for primary prevention of sudden cardiac death: results from the cardiovascular research network longitudinal study of implantable cardioverter-defibrillators. J Am Heart Assoc 2017; 6: 6.

101. von Alvensleben JC, Dechert B, Bradley DJ, et al. Subcutaneous implantable cardioverter-defibrillators in pediatrics and congenital heart disease: a pediatric and congenital electrophysiology society multicenter review. JACC Clin Electrophysiol 2020; 6: 1752–1761.

102. Quast ABE, Brouwer TF, Kooiman KM, et al. Comparison of complications and shocks in paediatric and young transvenous and subcutaneous implantable cardioverter-defibrillator patients. Neth Heart J 2018; 26: 612–619.

103. Kaczmarek K, Kałowski M, Krzysztof Wranicz J, Ptaszyńsk P, Cygankiewicz I. Conventional and alternative preimplantation ECG screening for subcutaneous ICD in high risk hypertrophic cardiomyopathy patients. J Electrocardiol 2020; 58: 68–73. DOI 10.1016/j.jelectrocard.2019.11.044.

104. Maurizi N, Tanini I, Olivotto I, et al. Effectiveness of subcutaneous implantable cardioverter-defibrillator testing in patients with hypertrophic cardiomyopathy. Int J Cardiol 2017; 231: 115–119. DOI 10.1016/j.ijcard.2016.12.187.

105. Nazer B, Dale Z, Carrassa G, et al. Appropriate and inappropriate shocks in hypertrophic cardiomyopathy patients with subcutaneous implantable cardioverter-defibrillators: an international multicenter study. Heart Rhythm 2020; 17: 1107–1114. DOI 10.1016/j.hrthm.2020.02.008.

106. Kaski JP, Tomé Esteban MT, Lowe M, et al. Outcomes after implantable cardioverter-defibrillator treatment in children with hypertrophic cardiomyopathy. Heart 2007; 93: 372–374. DOI 10.1136/hrt.2006.094730.

107. Rowin EJ, Sridharan A, Madias C, et al. Prediction and prevention of sudden death in young patients (<20 years) with hypertrophic cardiomyopathy. Am J Cardiol 2020; 128: 75–83.

108. Balaji S, DiLorenzo MP, Fish FA, et al. Risk factors for lethal arrhythmic events in children and adolescents with hypertrophic cardiomyopathy and an implantable defibrillator: an international multicenter study. Heart Rhythm 2019, 10.1016/j.hrthm.2019.04.040.

109. Berul CI, Van Hare GF, Kertesz NJ, et al. Results of a multicenter retrospective implantable cardioverter-defibrillator registry of pediatric and congenital heart disease patients. J Am Coll Cardiol 2008; 51: 1685–1691. DOI 10.1016/j.jacc.2008.01.033.

110. Lewandowski M, Syska P, Kowalik I, et al. Fifteen years' experience of implantable cardioverter defibrillator in children and young adults: mortality and complications study. Pediatr Int 2018; 60: 923–930. DOI 10.1111/ped.13660.

111. Goldstein SA, LaPage MJ, Dechert BE, et al. Decreased inappropriate shocks with new generation ICDs in children and patients with congenital heart disease. Congenit Heart Dis 2018; 13: 413–418. DOI 10.1111/chd.12585.

112. Garnreiter JM, Pilcher TA, Etheridge SP, Saarel EV. Inappropriate ICD shocks in pediatrics and congenital heart disease patients: risk factors and programming strategies. Heart Rhythm 2015; 12: 937–942.

113. Dechert BE, Serwer GA, Bradley DJ, Dick M, LaPage MJ. Cardiac implantable electronic device remote monitoring surveillance in pediatric and congenital heart disease: utility relative to frequency. Heart Rhythm 2015; 12: 117–122. DOI 10.1016/j.hrthm.2014.10.009.

114. DeWitt ES, Triedman JK, Cecchin F, et al. Time dependence of risks and benefits in pediatric primary prevention implantable cardioverter-defibrillator therapy. Circ Arrhythm Electrophysiol 2014; 7: 1057–1063. DOI 10.1161/CIRCEP.114.001569.

115. Olde Nordkamp LR, Postema PG, Knops RE, et al. Implantable cardioverter-defibrillator harm in young patients with inherited arrhythmia syndromes: a systematic review and meta-analysis of inappropriate shocks and complications. Heart Rhythm 2016; 13: 443–454. DOI 10.1016/j.hrthm.2015.09.010.

116. Robinson JA, LaPage MJ, Atallah J, et al. Outcomes of pediatric patients with defibrillators following initial presentation with sudden cardiac arrest. Circ Arrhythm Electrophysiol 2021; 14: e008517. DOI 10.1161/CIRCEP.120.008517.

117. Atallah J, Erickson CC, Cecchin F, et al. Multi-institutional study of implantable defibrillator lead performance in children and young adults: results of the Pediatric Lead Extractability and Survival Evaluation (PLEASE) study. Circulation 2013; 127: 2393–2402.

118. Frommeyer G, Feder S, Bettin M, et al. Long-term single-center experience of defibrillator therapy in children and adolescents. Int J Cardiol 2018; 271: 105–108.

119. Silvetti MS, Pazzano V, Verticelli L, et al. Subcutaneous implantable cardioverter-defibrillator: is it ready for use in children and young adults? A single-centre study. Europace 2018; 20: 1966–1973.

120. Bettin M, Larbig R, Rath B, et al. Long-term experience with the subcutaneous implantable cardioverter-defibrillator in teenagers and young adults. JACC: Clin Electrophysiol 2017; 3: 1499–1506. DOI 10.1016/j.jacep.2017.08.017.

121. Blomstrom-Lundqvist C, Traykov V, Erba PA, et al. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections-endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID), and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2020; 41: 2012–2032. DOI 10.1093/eurheartj/ehaa010.

122. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC) Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015; 36: 3075–3128. DOI 10.1093/eurheartj/ehv319.

123. Spanaki A, O'Curry S, Winter-Beatty J, et al. Psychosocial adjustment and quality of life in children undergoing screening in a specialist paediatric hypertrophic cardiomyopathy clinic. Cardiol Young 2016; 26: 961–967. DOI 10.1017/S1047951115001717.

124. Webster G, Panek KA, Labella M, et al. Psychiatric functioning and quality of life in young patients with cardiac rhythm devices. Pediatrics 2014; 133: e964–972. DOI 10.1542/peds.2013-1394.

125. Koopman HM, Vrijmoet-Wiersma CM, Langius JN, et al. Psychological functioning and disease-related quality of life in pediatric patients with an implantable cardioverter defibrillator. Pediatr Cardiol 2012; 33: 569–575. DOI 10.1007/s00246-012-0175-1.

126. Sears SF, Hazelton AG, St Amant J, et al. Quality of life in pediatric patients with implantable cardioverter defibrillators. Am J Cardiol 2011; 107: 1023–1027. DOI 10.1016/j.amjcard.2010.11.027.

127. DeMaso DR, Lauretti A, Spieth L, et al. Psychosocial factors and quality of life in children and adolescents with implantable cardioverter-defibrillators. Am J Cardiol 2004; 93: 582–587. DOI 10.1016/j.amjcard.2003.11.022.

128. Paech C, Ebel V, Wagner F, et al. Quality of life and psychological co-morbidities in children and adolescents with cardiac pacemakers and implanted defibrillators: a cohort study in Eastern Germany. Cardiol Young 2020; 30: 549–559. DOI 10.1017/S104795112000061X.

129. Pyngottu A, Werner H, Lehmann P, Balmer C. Health-related quality of life and psychological adjustment of children and adolescents with pacemakers and implantable cardioverter defibrillators: a systematic review. Pediatr Cardiol 2019; 40: 1–16. DOI 10.1007/s00246-018-2038-x.

130. Czosek RJ, Cassedy AE, Wray J, et al. Quality of life in pediatric patients affected by electrophysiologic disease. Heart Rhythm 2015; 12: 899–908. DOI 10.1016/j.hrthm.2015.01.022.

131. Schneider LM, Wong JJ, Trela A, et al. An exploratory assessment of pediatric patient and parent needs after implantable cardioverter defibrillator implant. Pacing Clin Electrophysiol 2020; 43: 289–296. DOI 10.1111/pace.13876.

132. Healey JS, Hohnloser SH, Glikson M, et al. Cardioverter defibrillator implantation without induction of ventricular fibrillation: a single-blind, non-inferiority, randomised controlled trial (SIMPLE). Lancet 2015; 385: 785–791. DOI 10.1016/S0140-6736(14)61903-6.

133. Kannabhiran M, Mustafa U, Acharya M, et al. Routine DFT testing in patients undergoing ICD implantation does not improve mortality: a systematic review and meta-analysis. J Arrhythm 2018; 34: 598–606.

134. Phan K, Ha H, Kabunga P, et al. Systematic review of defibrillation threshold testing at De Novo implantation. Circ Arrhythm Electrophysiol 2016; 9: e003357.

135. Baysa SJ, Olen M, Kanter RJ, Fishberger SB. Defibrillation testing strategies of pediatric and adult congenital electrophysiologists during ICD implantation. Pacing Clin Electrophysiol 2016; 39: 843–847. DOI 10.1111/pace.12896.

136. Kriebel T, Müller MJ, Ruschewski W, et al. Value of regular defibrillation threshold testing after extracardiac implantable cardioverter defibrillator placement in small children during mid-term follow-up. JACC Clin Electrophysiol 2018; 4: 936–943. DOI 10.1016/j.jacep.2018.03.012.

137. Backhoff D, Müller MJ, Dakna M, et al. Value of defibrillation threshold testing in children with nontransvenous implantable cardioverter defibrillators: are routine DFT tests indicated? Pacing Clin Electrophysiol 2020; 43: 805–813. DOI 10.1111/pace.14003.

138. Wilkoff BL, Fauchier L, Stiles MK, et al. 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. Heart Rhythm 2016; 13: e50–86. DOI 10.1016/j.hrthm.2015.11.018.

139. Quast ABE, Baalman SWE, Betts TR, et al. Rationale and design of the PRAETORIAN-DFT trial: a prospective randomized CompArative trial of SubcutanEous ImplanTable CardiOverter-DefibrillatoR ImplANtation with and without DeFibrillation testing. Am Heart J 2019; 214: 167–174.

140. Quast ABE, Baalman SWE, Brouwer TF, et al. A novel tool to evaluate the implant position and predict defibrillation success of the subcutaneous implantable cardioverter-defibrillator: the PRAETORIAN score. Heart Rhythm 2019; 16: 403–410.

141. Ricciardi D, Ziacchi M, Gasperetti A, et al. Clinical impact of defibrillation testing in a real-world S-ICD population: data from the ELISIR registry. J Cardiovasc Electrophysiol 2021; 32: 468–476.

142. Tan VH, Wilton SB, Kuriachan V, Sumner GL, Exner DV. Impact of programming strategies aimed at reducing nonessential implantable cardioverter defibrillator therapies on mortality: a systematic review and meta-analysis. Circ Arrhythm Electrophysiol 2014; 7: 164–170. DOI 10.1161/CIRCEP.113.001217.

143. Stiles MK, Fauchier L, Morillo CA, Wilkoff BL, Group ESCSD. 2019 HRS/EHRA/APHRS/LAHRS focused update to 2015 expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. Europace 2019; 21: 1442–1443.

144. Ananwattanasuk T, Tanawuttiwat T, Chokesuwattanaskul R, et al. Programming implantable cardioverter-defibrillator in primary prevention: guideline concordance and outcomes. Heart Rhythm 2020; 17: 1101–1106. DOI 10.1016/j.hrthm.2020.02.004.

145. Link MS, Bockstall K, Weinstock J, et al. Ventricular tachyarrhythmias in patients with hypertrophic cardiomyopathy and defibrillators: triggers, treatment, and implications. J Cardiovasc Electrophysiol 2017; 28: 531–537. DOI 10.1111/jce.13194.

146. Callum K, Graune C, Bowman E, Molden E, Leslie SJ. Remote monitoring of implantable defibrillators is associated with fewer inappropriate shocks and reduced time to medical assessment in a remote and rural area. World J Cardiol 2021; 13: 46–54.

147. Guédon-Moreau L, Kouakam C, Klug D, et al. Decreased delivery of inappropriate shocks achieved by remote monitoring of ICD: a substudy of the ECOST trial. J Cardiovasc Electrophysiol 2014; 25: 763–770.

148. Perrin T, Boveda S, Defaye P, et al. Role of medical reaction in management of inappropriate ventricular arrhythmia diagnosis: the inappropriate Therapy and HOme monitoRiNg (THORN) registry. Europace 2019; 21: 607–615. DOI 10.1093/europace/euy284.

149. Malloy LE, Gingerich J, Olson MD, Atkins DL. Remote monitoring of cardiovascular implantable devices in the pediatric population improves detection of adverse events. Pediatr Cardiol 2014; 35: 301–306. DOI 10.1007/s00246-013-0774-5.

150. Ploux S, Swerdlow CD, Strik M, et al. Towards eradication of inappropriate therapies for ICD lead failure by combining comprehensive remote monitoring and lead noise alerts. J Cardiovasc Electrophysiol 2018; 29: 1–10. DOI 10.1111/jce.13653.

151. de Asmundis C, Ricciardi D, Namdar M, et al. Role of home monitoring in children with implantable cardioverter defibrillators for Brugada syndrome. Europace 2013; 15 Suppl 1: i17–i25. DOI 10.1093/europace/eut112.

152. Sequeira S, Jarvis CI, Benchouche A, Seymour J, Tadmouri A. Cost-effectiveness of remote monitoring of implantable cardioverter-defibrillators in France: a meta-analysis and an integrated economic model derived from randomized controlled trials. Europace 2020; 22: 1071–1082.

153. Melacini P, Maron BJ, Bobbo F, et al. Evidence that pharmacological strategies lack efficacy for the prevention of sudden death in hypertrophic cardiomyopathy. Heart 2007; 93: 708–710. DOI 10.1136/hrt.2006.099416.

154. Connolly SJ, Dorian P, Roberts RS, et al. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. JAMA 2006; 295: 165–171. DOI 10.1001/jama.295.2.165.

155. McKenna WJ, Oakley CM, Krikler DM, Goodwin JF. Improved survival with amiodarone in patients with hypertrophic cardiomyopathy and ventricular tachycardia. Br Heart J 1985; 53: 412–416. DOI 10.1136/hrt.53.4.412.

156. Santangeli P, Muser D, Maeda S, et al. Comparative effectiveness of antiarrhythmic drugs and catheter ablation for the prevention of recurrent ventricular tachycardia in patients with implantable cardioverter-defibrillators: a systematic review and meta-analysis of randomized controlled trials. Heart Rhythm 2016; 13: 1552–1559.

157. Tendera M, Wycisk A, Schneeweiss A, Poloński L, Wodniecki J. Effect of sotalol on arrhythmias and exercise tolerance in patients with hypertrophic cardiomyopathy. Cardiology 1993; 82: 335–342. DOI 10.1159/000175883.

158. Writing Committee M, Shah MJ, Silka MJ, et al. PACES expert consensus statement on the indications and management of cardiovascular implantable electronic devices in pediatric patients. Heart Rhythm 2021; 18: 1888–1924.

159. Dejgaard LA, Haland TF, Lie OH, et al. Vigorous exercise in patients with hypertrophic cardiomyopathy. Int J Cardiol 2018; 250: 157–163. DOI 10.1016/j.ijcard.2017.07.015.

160. Pelliccia A, Caselli S, Pelliccia M, et al. Clinical outcomes in adult athletes with hypertrophic cardiomyopathy: a 7-year follow-up study. Br J Sports Med 2020; 54: 1008–1012. DOI 10.1136/bjsports-2019-100890.

161. Saberi S, Wheeler M, Bragg-Gresham J, et al. Effect of moderate-intensity exercise training on peak oxygen consumption in patients with hypertrophic cardiomyopathy: a randomized clinical trial. JAMA 2017; 317: 1349–1357. DOI 10.1001/jama.2017.2503.

162. Pelliccia A, Solberg EE, Papadakis M, et al. Recommendations for participation in competitive and leisure time sport in athletes with cardiomyopathies, myocarditis, and pericarditis: position statement of the Sport Cardiology Section of the European Association of Preventive Cardiology (EAPC). Eur Heart J 2019; 40: 19–33.

163. Saarel EV, Law I, Berul CI, et al. Safety of sports for young patients with implantable cardioverter-defibrillators: long-term results of the multinational ICD sports registry. Circ Arrhythm Electrophysiol 2018; 11: e006305. DOI 10.1161/CIRCEP.118.006305.

164. Olshansky B, Atteya G, Cannom D, et al. Competitive athletes with implantable cardioverter-defibrillators-how to program? Data from the implantable cardioverter-defibrillator sports registry. Heart Rhythm 2019; 16: 581–587. DOI 10.1016/j.hrthm.2018.10.032.

165. Zipes DP, Link MS, Ackerman MJ, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: task force 9: arrhythmias and conduction defects: a scientific statement from the American Heart Association and American College of Cardiology. Circulation 2015; 132: e315–325,.