Clinical outcomes and programming strategies of implantable cardioverter defibrillator (ICD) devices in paediatric hypertrophic cardiomyopathy: a UK national cohort study

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Abstract

Aims

Sudden cardiac death (SCD) is the most common mode of death in paediatric hypertrophic cardiomyopathy (HCM). This study describes the implant and programming strategies with clinical outcomes following internal cardioverter defibrillator (ICD) implant in a well-characterised national paediatric HCM cohort.

Methods

Data from 90 patients undergoing ICD implantation at a median age 13 (+/-3.5) for primary (n=67, 74%) or secondary prevention (n=23, 26%) were collected from a retrospective, longitudinal multi-centre cohort of children (<16 years) with HCM from the United Kingdom.

Results

Seventy-six (84%) had an endovascular system (14 (18%) dual coil), 3 (3%) epicardial and 11 (12%) subcutaneous system. Defibrillation Threshold (DFT) testing was performed at implant in 68 (76%). Inadequate DFT in 4 led to implant adjustment in 3 patients. Over a median follow up of 54 months (IQR 28,111), 25 (28%) patients had 53 appropriate therapies (ICD shock n=45, anti-tachycardia pacing (ATP) n=8), incidence rate 4.7 per 100 patient years (95% CI 2.9-7.6). Eight inappropriate therapies occurred in 7 (8%) patients (ICD shock n=4, ATP n=4), incidence rate 1.1/100 patient years (95% CI 0.4-2.5). 3 patients (3%) died following arrhythmic events despite a functioning device. Other device complications were seen in 28 patients (31%), including lead-related complications (n=15) and infection (n=10). No clinical, device or programming characteristics predicted time to inappropriate therapy or lead complication.

Conclusions

In a large national cohort of paediatric HCM patients with an ICD, device and programming strategies varied widely. No particular strategy was associated with inappropriate therapies, missed/delayed therapies or lead complications.

Key Words

Hypertrophic Cardiomyopathy, Implantable Cardioverter defibrillator, Childhood

Condensed abstract

In a large national cohort of 90 paediatric HCM patients with an ICD for primary (n=67, 74%) or secondary prevention (n=23, 26%), device and programming strategies varied widely, but none were associated with inappropriate therapies, missed/delayed therapies or lead complications. 3 patients (3%) died following arrhythmic events despite a functioning device

What's new?

- This study is the first to systematically assess different ICD systems and programming strategies in paediatric HCM
- Although limited by patient numbers, no clinical, device or programming strategies were associated with reduced risk of inappropriate therapies or device complications. This suggests that simpler devices (eg single chamber and coil systems) may be preferable for the majority of paediatric HCM patients as is recommended for adult patients.

Introduction

Sudden cardiac death, secondary to malignant ventricular arrhythmias, is the most common mode of death in paediatric hypertrophic cardiomyopathy (HCM), occurring at a rate of 1.2/100 per patient year(1-3). Previous studies have shown Implantable Cardioverter Defibrillators (ICD's) to be effective at terminating malignant arrhythmias(4-6). Current guidelines recommend ICD implantation in both children and adults with HCM based upon the presence of risk factors for lethal arrhythmic events(7, 8). Despite evidence that an appropriately-placed ICD may be a life-saving device, the risk-benefit balance is particularly challenging in young patients due to an increased risk of inappropriate therapies and device-related complications (4, 6, 9). Optimal device choice, programming strategies, and appropriate patient selection are therefore especially important in determining long-term outcome. To date, the long-term risks associated with different device systems in children with HCM have been poorly defined. Additionally, the relative merits of dual chamber systems, dual coil systems, defibrillation threshold testing, subcutaneous ICD and arrhythmia detection parameters have not been assessed in this patient group (9-11). The aim of this study was to describe the programming strategies and clinical outcomes in a well characterised, unselected, national cohort of children with HCM.

Methods

Patients

Patients identified from a previously published cohort of children (diagnosed under the age of 16 years) with non-syndromic HCM from the United Kingdom(1) who had undergone implantation of an ICD in a paediatric care setting under the age of 18 years were included in this study. Additional patients diagnosed after the original cohort (n=11) were identified by the principle investigator at each site. The diagnosis of HCM was made if left ventricular wall thickness was greater than two standard deviations above the body-surface area corrected population mean, not solely explained by abnormal loading conditions(7). Six patients with syndromic HCM (Danon disease n=3, Noonan

syndrome n =2, Emery Dreifuss muscular dystrophy n=1) who had undergone ICD implantation during the same period were excluded.

Data collection

Anonymised, non-invasive clinical data were collected, including demographics; symptoms; medical therapy; family history; ambulatory electrocardiography (ECG); two dimensional (2D), Doppler and colour transthoracic echocardiography; and exercise testing as reported previously(1). Detailed ICD-related data were collected by the principal investigator at each site. Baseline data points were age and weight at implant; medications at implant; physician-determined ICD indication; system configuration (generator type and position, lead(s) type and position); presence of prior ventricular arrhythmias; defibrillation testing and outcome if performed; and implant complications. Initial programming strategies were collected and included VF therapies (programmed rate, detection duration, +/- ATP during charging, manufacturer-specific discriminators); VT zone (programmed rate for monitoring and therapies, therapy type); and bradycardia pacing set-up. Thereafter, programming strategies were collected at each appropriate, inappropriate or missed therapy, and following any device-related procedure. The detection duration was recorded in either number of beats or number of seconds, depending on the manufacturer. For comparison purposes, those with detection duration in beats were converted to duration in seconds by using the programmed upper detection rate and detection duration. Long-term complications, lead and generator longevity, need for system revision and final clinical outcome were identified for all patients.

Outcomes

The primary patient outcomes were: all-cause mortality, cardiac transplantation, appropriate or inappropriate therapies, and ICD-related complications. ICD therapies were considered appropriate when triggered by VF or sustained VT. Interventions were defined as inappropriate when in the setting of expert-adjudicated sinus tachycardia, supraventricular tachycardia or device/lead malfunction. Cardiac rhythm at the time of ICD therapy was adjudicated by each implanting centre,

and included analysis of the tachogram and the EGM of the stored episode. Discrimination of the underlying rhythm was typically based upon regularity of arrhythmia cycle length and stability of far-field electrogram morphology. Those adjudicated to represent polymorphic VT (PMVT) were included in the ventricular fibrillation (VF) group for analysis. Patients were classified as lost to follow up if last clinical review was more than 3 years ago.

Statistical analysis

Normally distributed continuous variables are described as mean +/- standard deviation with two or three group comparisons made using Student's T test or ANOVA respectively. Skewed data are described as median (interquartile range) with two group comparisons performed using Wilcoxon rank sum. Categorical distributions were compared using the chi-squared test. Survival free from ICD intervention or ICD-related complication was calculated using the Kaplan Meier product limit method. Patients were censored at the time of cardiac transplantation. Cox regression analysis was used to identify variables predictive of outcomes. In order to investigate possible era effects, patients were grouped by the year of ICD implantation (2000-2005, 2006-2010, 2011-2015, 2016 onwards). Statistical analysis was performed using StataCorp 2015. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP.

Ethics

Local ethical committee approval was obtained at each participating site. The data underlying this article cannot be shared publicly as consent for participants did not include public dissemination of patient data.

Results

Demographics

90 patients (Male n=57, 63.3%) underwent ICD implantation between 2000 and 2018 (2000-2005, n=18, 20.0%; 2006-2010, n=25, 27.8%; 2011-2015, n=29, 32.2%; 2016 onwards n=18, 20%). 63 patients (70.0%) were receiving one or more antiarrhythmic medications at the time of implantation: B Blockers (n=61, 67.8%); Disopyramide (n=13, 14.4%); Amiodarone (n=6, 6.7%); Calcium channel blocker (n=7, 7.8%). The clinical characteristics of the patient group is described and compared to the complete UK cohort in table 1.

ICD characteristics

Clinical and ICD system characteristics at the time of ICD implantation are described in Table 2 and Figure 1. Defibrillation testing (DFT) was performed in 68 (75.6%) initial implants, in whom the first shock was successful in 64 (94.1%). In those 4 patients with unsuccessful initial shock, 3 had implant-related adjustments at the same procedure (one device repositioned from pre-pectoral to sub-pectoral, one had repositioning of the shock coil, and one had the addition of a second subcutaneous array to achieve an improved shock vector). In one patient, the initial shock at 21J was unsuccessful, but a second DFT at 31J was successful and no implant-related adjustment was made. At revision procedures, DFT's were performed in 10 out of 37 total revision procedures (2 when generator only, 8 when lead and generator). Change in implant strategy by era is shown in Figure 2.

Initial programming strategies

All patients had VF therapies activated with a median rate 220 bpm (IQR 210,230; range 188-250) and median detection time 9.6 sec (IQR 3-11.5) [Figure 3]. Rate was not significantly associated with age (R^2 0.0333, P 0.0849). 21 (23.3%) had a single VF therapy zone programmed. VT therapies were activated in 23 (25.6%) patients (mean rate 195 +/-18.9, range 145-220bpm), 6 (26%) of whom had a prior documented VT episode. A further 44 patients had a VT zone programmed for monitoring only. 41 (53.9%) of those with an endovascular device had ATP activated during charging

Follow up

Patients were followed up for a median of 53.6 months' post ICD implant (IQR 27.6, 110.6). 52 (57.8 %) remained under the age of 18 years at last follow up. 76 (84.4%) were alive without transplant, 5 (5.6%) had undergone cardiac transplantation, 8 (8.9%) had died (arrhythmic n=3, congestive cardiac failure n=1, non-cardiovascular n=1, unknown cause n=3) and 1 (1%) was lost to follow up. Clinical outcomes are described in Figure 4.

The 3 arrhythmic deaths are described in detail in Supplementary Table 1. Briefly, 1 developed refractory VF on induction of general anaesthesia [for battery replacement and atrial lead extraction], 1 suffered an arrhythmic storm with severe neurological sequelae, and 1 had treatment resistant VT which failed to revert to sinus rhythm despite multiple shock therapies. 2 of the 3 patients did not have DFT at implantation.

ICD System Outcomes and Complications

Appropriate Therapies

25 patients (27.8%) had 53 appropriate therapies (ICD shock n=45 (85.0%); anti-tachycardia pacing (ATP) n=8 (15%)) with an overall incidence rate of 4.7 per 100 patient years (95% CI 2.88 – 7.66). Freedom from appropriate therapy was 91.6% (96% CI 83.1-95.9) and 71.8% (95% CI 59.3-81.0) at 1 and 5 years, respectively. Presenting rhythm was monomorphic ventricular tachycardia (VT) in 18 episodes (7 within VT zone with active therapies, 11 within VF zone), and PMVT/VF in 35 episodes (monomorphic VT documented to degenerate to VF in 4). 5 patients received 7 ATP therapies for monomorphic VT. In these, ATP successfully terminated the arrhythmia without the need for high voltage therapy in 6 episodes (85%). Secondary prevention indication for ICD implantation was the only predictive risk factor for appropriate therapy on univariable analysis (table 3, supplementary figure 1). Freedom from appropriate therapy for those with a primary prevention device was 86.4% (95%CI 73.1-93.4) at 5 years.

Inappropriate Therapies

7 (7.8%) patients had 8 inappropriate therapies (ICD shock n=4, ATP n=4) with an overall incidence rate of 1.06 per 100 patient years (95% CI 0.44-2.54). Inappropriate shock was caused by lead migration (n=1), T-wave over-sensing (n=2) and supraventricular tachycardia (n=1). All episodes of inappropriate ATP occurred in VT Zone with active therapies (sinus/supraventricular tachycardia n=3, lead noise n=1). No patient or device-related indices were significantly associated with inappropriate therapy on univariable analysis, including the presence of an atrial lead (p=0.649) or the programming on of VT therapies (p=0.274) (Table 3).

Delayed, missed or failed ICD therapy

ICD therapy was delayed, missed or unsuccessful for 8 ventricular arrhythmias occurring in 7 patients [delayed (n=3), unsuccessful (n=3) or failure to deliver (n=2)] leading to significant harm in 4 patients [neurological impairment and death (n=2), death (n=1), neurological impairment (n=1)] (supplementary table 1 and 3). There were no device or programming related factors associated with delayed, missed or failed therapy on univariable analysis. 5 of the 7 patients had DFT at implant, 4 of which were successful. One patient had re-positioning of the device to a sub-pectoral location. There was no association between the performance of DFT and subsequent delayed/missed/failed therapy (5 of 7 (71%) versus 63 of 83 (76%), P value 0.291).

Device-related complications and system longevity

ICD-related complications were seen in 28 patients (31.1%) (infection n=10, lead complications n=15, other n=3) as described in table 4 and supplementary table 2. Of 10 infections; 5 were suspected/proven system infections requiring system extraction in 4 (1 was treated conservatively following multiple negative cultures), and 5 were superficial wound infections (supplementary table 2).

58 patients (64.4%) required no re-intervention upon their ICD. 9 (10%) patients required a generator replacement alone at median 6 (IQR 4.2-7) years post-implantation, without any further

invasive intervention upon the rest of their ICD system. A further 23 (25.6%) patients required a total of 26 more extensive system revisions (1 n=21, 2 n=5). Primary reason for system revision included lead replacement (n=12), lead repositioning (n=3), system infection (n=5), upgrading of system (endovascular n=1, dual chamber n=2, CRT-D n=1, S-ICD n=1) and ICD pocket erosion (n=1). Within the lead replacement group, lead failure occurred in 6 patients necessitating revision (atrial lead n=1, high voltage lead n=5) at median 2.8 (IQR 2.2-3.8) years post-implant, 2 of whom had a thin high voltage lead. There was no significant difference in lead failure rate between thin and standard high voltage leads (HR 1.55 (95% CI 0.28-8.50), p value 0.612). No clinical characteristics predicted time to a composite outcome of lead complication or inappropriate therapy (Supplementary table 3).

Subcutaneous devices

12 patients had subcutaneous devices implanted for primary (n=9, 75%) or secondary (n=3, 25%) prevention. Median age at time of implant was 13 years (IQR 12,16) with a median weight 70Kg (IQR 39.7, 85, minimum 34, maximum 93). Over a median follow up of 27.4 months (IQR 12.9, 58.8), 3 patients (25%) had 5 appropriate therapies and 1 had an inappropriate shock secondary to T-wave over-sensing in sinus tachycardia. 1 patient had prolonged asystole following a successful shock due to failure of anti-bradycardia pacing and was upgraded to a dual chamber endovascular system. Two patients had S-ICD removal: one for infection (2 months after implant) and one for conversion to a dual chamber endovascular system (9 months after implant). Three patients required generator replacement at a mean follow up time of 70 months

Discussion

This study describes ICD implant and programming strategies for paediatric HCM patients in a national cohort. A wide variety of approaches were seen, with a gradual evolution away from dual coil systems and performing DFTs, towards increasing use of single coil systems or S-ICD's. In keeping with previous studies in childhood, both appropriate therapies and device-related complications occurred more frequently than in adults, although the rate of inappropriate shocks is lower than in previous paediatric studies (5, 6, 10, 12, 13) (Supplementary table 4). No clinical, device or programming strategies were associated with an increased risk of inappropriate therapies or device complications.

System and programming strategies over time

Previous studies in paediatric HCM have described the prevalence of appropriate and inappropriate therapies and device-related complications (5, 6, 12-14) but there has been no previous systematic assessment of system and programming strategies in this population. As device implantation and programming strategy was determined by the treating clinician, this cohort describes a wide range of approaches, which is reflective of current and historical national clinical practice. Over time, there was an increasing number of subcutaneous systems implanted, particularly for primary prevention. For endovascular systems, a gradual reduction in the number of dual chamber and dual coil devices was seen, reflecting the recognition that more complex systems may be associated with an increased incidence of complications (14). The number of dual chamber and dual coil devices implanted in the present study are lower than in the largest mixed cohort paediatric ICD series reporting detailed programming strategies (14). This may reflect the different underlying population - 44% of patients in that study had congenital heart disease and only 24 patients had HCM. Although DFT was performed in all patients between 2000-2006, this had fallen to 41% in the most recent era. This is despite evidence that clinicians are more likely to perform DFT in younger adult patients with more severe hypertrophy(11), and that DFT may have increased utility in patients with a single,

rather than dual, coil system(15). Overall, paediatric practice is mirroring trends that have to date only been documented in adult cohorts.

Device therapies

The rate of appropriate therapies in this study is consistent with previous paediatric ICD cohorts and higher than that reported in adult cohorts(16), suggesting that younger patients may be at greater risk of lethal arrhythmic events(17, 18). As this group of patients had *a priori* been defined as 'high risk' by clinicians, it was not our intention to investigate risk factors for appropriate therapies. However, in agreement with previous studies, those with a secondary prevention device were more likely to receive an appropriate therapy(5, 6, 10).

Of those patients receiving a primary prevention device, 14% had an appropriate therapy over 5 years follow up. There was a trend towards an increasing incidence of appropriate shocks over time, which may indicate improved patient selection, although the guidelines upon which implantation decisions are based have not changed (7, 8). Historically, VF has been considered to be the most common cause of SCD in HCM, with monomorphic VT occurring relatively infrequently and associated with LV apical aneurysms in adults(19, 20). The high proportion of patients with monomorphic VT as the presenting arrhythmia (34%) in this cohort is in agreement with other recent reports from adult cohorts(20), and suggests that the burden of monomorphic VT in paediatric HCM may be higher than previously recognised. Only 23 patients (26%) had ATP therapies activated, but 5 of these received 7 appropriate ATP therapies for monomorphic VT. Successful ATP therapy in 6 of these 7 episodes may have avoided the need for high voltage therapy.

Previous studies have suggested that children are at greater risk of inappropriate therapies (5, 6). In this study, the incidence of inappropriate therapies was lower than in previous paediatric ICD series and consistent with adult ICD data (5, 6, 12, 13, 21). Half of inappropriate therapies were ATP (n=4). There were no differences in the inappropriate therapy rates across different eras, suggesting the pattern of change seen over this period in device and programming strategies was not responsible

for this finding. The small number of inappropriate therapies in this cohort limits the power of the study to identity clinical risk factors. However, the presence of a dual chamber device, which could theoretically allow for improved rhythm discrimination, was not associated with the risk of inappropriate therapies on univariable analysis. This is similar to reports from adult cohorts where, although the presence of atrial tachycardias increased the risk of inappropriate therapies, no reduction of risk was seen with the addition of an atrial lead(22). In the largest comparable paediatric study (n=144), Garnreiter et al(14) reported an increased incidence of inappropriate therapies in the presence of a dual chamber system, history of supraventricular tachycardia or shock programmed in VT therapy zones on univariable analysis, an effect which disappeared on multi-variable analysis. That study was a single centre paediatric cohort with a more homogenous approach to device and programing strategy, although more variable underlying condition (44% congenital heart disease, HCM 17%). Of note, the majority of inappropriate shocks in our cohort were most likely not preventable with either an additional atrial lead or programming strategies (e.g. lead migration or T wave over-sensing). The lack of conclusive evidence in this large cohort of paediatric HCM patients that dual chamber devices provide superior protection from inappropriate therapies suggests that they should be reserved for patients with a pacing indication as is recommended for adult patients(7). In support of this, in wider paediatric practice single-lead pacing systems have been advocated to reduce the potential for lead-related complications (23), as discussed below.

Missed therapies

A major finding in this study is the fact that 7 patients (7.8%) had 8 missed or delayed therapies, resulting in significant harm in 4. All patients had endovascular systems and 4 had dual chamber devices. On univariable analysis, no device or programming strategy was associated with preventing a missed therapy. Programmed VF detection times were very variable and rates were not determined by age. There was no significant difference between VF rates or detection times in those

with or without appropriate, inappropriate or missed therapies. Although small numbers may have limited our ability to detect a difference, the findings are in keeping with previous paediatric studies (14). Importantly, failed therapies were not more common in those without DFT testing at implantation. This is in keeping with reports from adult cohorts which showed that DFT testing did not predict shock efficacy(11).The findings also highlight particular difficulties in setting VT therapy zones. Two patients had slow ventricular tachycardias (< 150bpm) and a further patient had a variable VT rate, which intermittently dropped below the therapy zone. Neither of the patients with slow VT had atypical clinical features; both presented with an out of hospital arrest, one had additional recognised risk factors for SCD at the time of presentation (significant LV hypertrophy (MWT 24mm), dilated left atrium and unexplained syncope) and both had preserved LV systolic function (LVEF >80%). Although all patients in the cohort had non-syndromic disease, the absence of genetic testing results in these two patients means that we cannot exclude the possibility of non-sarcomeric disease.

Complications

In agreement with previous studies in childhood, this cohort of young patients had a higher rate of implant complications compared to adult cohorts (16, 21), with no association between the incidence of ICD complications and era. Four patients (4%) had confirmed infective endocarditis, all of which occurred with the first ICD system. A higher incidence of system infections during childhood is unexplained but has consistently been reported in the literature(6, 12). Patient factors, such as more frequent bacteraemic episodes during childhood, or system factors, including lower clinician procedure familiarity, could be hypothesised as the cause for this observation. In a less homogenous cohort, Dechert et al (13)reported a higher proportion of ICD revisions over a median follow up of 4.9 years (43 patients (33%) requiring 60 revisions). However, the underlying reason for revision was similar to the present study, with over half of system revisions being for lead failure or fracture. Both cohorts included thin high voltage leads (eg Durata, Sprint Fidelis, Riata) which have been shown to

have an increased risk of failure and have subsequently been recalled. In our cohort, thin leads were not associated with an increased risk of lead complications (HR 1.55 (95% CI 0.28-8.50), p 0.612), but this comparison is limited by small numbers. Robust patient selection methods remain important as this group of patients will continue to be exposed to the increased risk of ICD-related complications over follow up.

Limitations

As this study is retrospective, it is limited by problems inherent to data design, including missing data and clinician recollection bias. Patients in this cohort were recruited from multiple sites, meaning that variations in patient management, including system selection and device programming, were inevitable. This is also a strength of this study, as it describes the current and historical UK management of this patient group and allowed us to investigate whether differing programming strategies could be employed to reduce complications. It is difficult to compare detection times between manufacturers but a standard and accepted approach was used. The use of discriminators in preventing inappropriate shocks was not explored in this study due to the difficulty in comparing between manufacturers, but would be a subject of interest in further studies. Although this study contains a large cohort of paediatric HCM patients, the small number of patients with inappropriate and missed therapies limits the ability of the study to identify risk factors.

Conclusions

In a large national cohort of paediatric HCM patients with an ICD, device and programming strategies varied widely with era and between centres. Although limited by the relatively low frequency of inappropriate or missed therapies and lead complications, no device or programming factors were associated with these complications. As complication rates remain higher than in adult cohorts, these data could support the use of simpler devices (e.g. single chamber and coil systems) for the majority of paediatric HCM patients, as is recommended for adult patients.

Conflict of interest disclosure

Conflict of interest: none declared

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References

1. Norrish G, Field E, McLeod K, Ilina M, Stuart G, Bhole V, et al. Clinical presentation and survival of childhood hypertrophic cardiomyopathy: a retrospective study in United Kingdom. Eur Heart J. 2019;40(12):986-93.

2. Maurizi N, Passantino S, Spaziani G, Girolami F, Arretini A, Targetti M, et al. Long-term Outcomes of Pediatric-Onset Hypertrophic Cardiomyopathy and Age-Specific Risk Factors for Lethal Arrhythmic Events. JAMA cardiology. 2018;3(6):520-5.

3. Alexander PMA, Nugent AW, Daubeney PEF, Lee KJ, Sleeper LA, Schuster T, et al. Long-Term Outcomes of Hypertrophic Cardiomyopathy Diagnosed During Childhood: Results From a National Population-Based Study. Circulation. 2018;138(1):29-36.

4. Moak JP, Kaski JP. Hypertrophic cardiomyopathy in children. Heart (British Cardiac Society). 2012;98(14):1044-54.

5. Maron BJ, Spirito P, Ackerman MJ, Casey SA, Semsarian C, Estes NA, 3rd, et al. Prevention of sudden cardiac death with implantable cardioverter-defibrillators in children and adolescents with hypertrophic cardiomyopathy. Journal of the American College of Cardiology. 2013;61(14):1527-35.

6. Kaski JP, Tome Esteban MT, Lowe M, Sporton S, Rees P, Deanfield JE, et al. Outcomes after implantable cardioverter-defibrillator treatment in children with hypertrophic cardiomyopathy. Heart. 2007;93(3):372-4.

7. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. 2014 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(39):2733-79.

8. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. The Journal of thoracic and cardiovascular surgery. 2011;142(6):e153-203.

9. Atallah J, Erickson CC, Cecchin F, Dubin AM, Law IH, Cohen MI, 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(24):2393-402.

10. Balaji S, DiLorenzo MP, Fish FA, Etheridge SP, Aziz PF, Russell MW, 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(10):1462-7.

11. Francia P, Adduci C, Semprini L, Palano F, Santini D, Musumeci B, et al. Prognostic Implications of Defibrillation Threshold Testing in Patients With Hypertrophic Cardiomyopathy. J Cardiovasc Electrophysiol. 2017;28(1):103-8.

12. Kamp AN, Von Bergen NH, Henrikson CA, Makhoul M, Saarel EV, Lapage MJ, et al. Implanted defibrillators in young hypertrophic cardiomyopathy patients: a multicenter study. Pediatr Cardiol. 2013;34(7):1620-7.

13. Dechert BE, Bradley DJ, Serwer GA, Dick Ii M, Lapage MJ. Implantable Cardioverter Defibrillator Outcomes in Pediatric and Congenital Heart Disease: Time to System Revision. Pacing Clin Electrophysiol. 2016;39(7):703-8.

14. 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(5):937-42.

15. Kumar KR, Mandleywala SN, Madias C, Weinstock J, Rowin EJ, Maron BJ, et al. Single Coil Implantable Cardioverter Defibrillator Leads in Patients With Hypertrophic Cardiomyopathy. The American journal of cardiology. 2020;125(12):1896-900.

16. Schinkel AF, Vriesendorp PA, Sijbrands EJ, Jordaens LJ, ten Cate FJ, Michels M. Outcome and complications after implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: systematic review and meta-analysis. Circ Heart Fail. 2012;5(5):552-9.

17. Norrish G, Ding T, Field E, Ziólkowska L, Olivotto I, Limongelli G, et al. Development of a Novel Risk Prediction Model for Sudden Cardiac Death in Childhood Hypertrophic Cardiomyopathy (HCM Risk-Kids). JAMA cardiology. 2019;4(9):918-27.

18. 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(8):1096-105.

19. Rowin EJ, Maron BJ, Haas TS, Garberich RF, Wang W, Link MS, et al. Hypertrophic Cardiomyopathy With Left Ventricular Apical Aneurysm: Implications for Risk Stratification and Management. Journal of the American College of Cardiology. 2017;69(7):761-73.

20. Link MS, Bockstall K, Weinstock J, Alsheikh-Ali AA, Semsarian C, Estes NAM, 3rd, et al. Ventricular Tachyarrhythmias in Patients With Hypertrophic Cardiomyopathy and Defibrillators: Triggers, Treatment, and Implications. J Cardiovasc Electrophysiol. 2017;28(5):531-7.

21. O'Mahony C, Lambiase PD, Quarta G, Cardona M, Calcagnino M, Tsovolas K, et al. The long-term survival and the risks and benefits of implantable cardioverter defibrillators in patients with hypertrophic cardiomyopathy. Heart (British Cardiac Society). 2012;98(2):116-25.

22. Vriesendorp PA, Schinkel AF, Van Cleemput J, Willems R, Jordaens LJ, Theuns DA, et al. Implantable cardioverter-defibrillators in hypertrophic cardiomyopathy: patient outcomes, rate of appropriate and inappropriate interventions, and complications. Am Heart J. 2013;166(3):496-502.

23. Silvetti MS, Drago F, Grutter G, De Santis A, Di Ciommo V, Ravà L. Twenty years of paediatric cardiac pacing: 515 pacemakers and 480 leads implanted in 292 patients. Europace : European

pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2006;8(7):530-6.

Table I: Comparing baseline demographics in those with and without an ICD from the UK HCM cohort(1)

	UK non-syndromic cohort (n=433)	**No ICD (n=354)**	**ICD cohort (n= 79+ 11 additional patients)**	**P value**
Male gender (n=433)	286 (66.1%)	236 (66.7%)	57 (63.3%)	
Family history HCM (n=427)	214 (50.1%)	174 (49.7%)	42 (51.2%)	0.806
Family history SCD 1st degree relative (n=430)	45 (10.5%)	32 (9.1%)	15 (18.1%)	**0.018**
Unexplained syncope (n=431)	32 (7.4%)	18 (5.1%)	15 (18.5%)	**<0.001**
VF/VT at presentation (n=433)	22 (5.1%)	7 (2.0%)	18 (20.5%)	**<0.001**
Age at presentation (years) (n=433)	8.6 (+/-5.4)	8.4 +/- (5.6)	9.2 (+/-4.8)	0.209

MWT at baseline (mm) (n=418)	17.1 (+/-7.3)	16.5 (+/-7.1)	20.3 (+/-7.3)	<**0.001**
LA diameter at baseline (mm) (n=268)	31.6 (+/- 8.5)	31.5 (+/-8.6)	32 +/-8.2	0.670
LVOTO at baseline (mmHg) (n=392)	9 (IQR 6, 36)	9 (IQR 6-36)	12 (IQR 6-27)	0.145
Length of follow up (months) (n=433)	82.9 (+/-67)	80.0 (+/-65.6)	95.5 (+/-74.1)	0.065

HCM=hypertrophic cardiomyopathy, SCD = sudden cardiac death, VF = ventricular fibrillation, VT = ventricular tachycardia, NSVT = non-sustained ventricular tachycardia, MWT = maximal wall thickness, LA = left atrial, LVOTO = Left ventricular outflow tract obstruction. Number of observations (n=) refers to UK non-syndromic cohort.

Table II: Characteristics at the time of ICD implantation

Age at time of implant (years)	**Mean (SD)**		**13 (+/- 3.5)**
	< 5		**2 (2.2%)**
	6-10		**20 (22.2%)**
	11-15		**45 (50.0%)**
	16+		**23 (25.6%)**
Weight at time of implant (Kg)	**Mean (SD), Range**		**51.6 (+/-20), 14-102.6**
Indication for device	**Primary**		**67 (74.4%)**
First ICD system	**Endovascular**		**76 (84.4%)**
	Epicardial		**3 (3.3%)**
	Subcutaneous		**11 (12.2%)**
Endovascular system (n=76)	**Thin high voltage lead (data recorded in n=73)**		**21 (28.7%)**
		Sprint Fidelis	**8**
		Durata	**10**
		Riata	**1**
		Recorded as thin only	**2**

	Dual chamber	**46 (60.5%)**
	Dual coil shock lead	**14 (18.4%)**
	Additional shock lead	**1 (azygous)**

N= 90 unless otherwise indicated

SD= standard deviation, ICD = implantable cardioverter defibrillator

Table III: Univariable analysis of risk factors for appropriate and inappropriate therapies

	Appropriate ICD therapies			**Inappropriate ICD therapies**		
	Appropriate therapy (n=25)	**No appropriate therapy (n=65)**	**P value**	**Inappropriate therapy (n=7)**	**No inappropriate therapy (n=83)**	**P value**
Age at implant	12.3 (+/-3.16)	13.2 (+/-3.60)	0.262	14.7 (+/-1.6)	12.8 (+/-3.6)	0.170
Weight at implant	43.9 (+/-17.7)	55.2 (+/-20.8)	0.031	63.2 (+/-7.0)	51.2 (+/-20.9)	0.206
Secondary prevention device	16 (64%)	7 (10.8%)	**<0.001**	2 (28.6%)	21 (25.3%)	0.849
Endovascular device	21 (84%)	55 (84.6%)	0.942	6 (85.7%)	70 (84.3%)	0.923
Dual chamber (n=76)	11 (44.0%)	35 (53.8%)	0.454	3 (42.9%)	43 (51.8%)	0.649

VF detection time (secs)	7.9 (+/- 5.0)	8.8 (+/- 5.5)	0.555	6.3 (+/-4.1)	8.6 (+/-5.4)	0.472
VT therapy zone on	6 (24.0%)	17 (26.2%)	0.834	3 (42.9%)	20 (24.1%)	0.274
ATP therapy on (n=76)	14 (66.7%)	27 (49.1%)	0.169	2 (33.3%)	39 (55.7%)	0.291
B Blockers at baseline (n=89)	20 (87.0%)	50 (80.9%)	0.498	5 (73.3%)	65 (83.3%)	0.095
Any medication at baseline (n=89)	18 (72%)	49 (76.6%)	0.654	4 (57.1%)	63 (76.8%)	0.246
MWT (mm) at baseline(n=80)	20.5 (+/-6.6)	20.6 (+/-7.5)	0.970	22.8 (+/-8.8)	20.4 (+/-7.3)	0.425
LA (mm) at baseline (n=54)	32.4 (+/-8.2)	32.3 (+/-8.4)	0.954	37.8 (+/-9.5)	31.8 (+/- 8.0)	0.112
LVOTO at baseline (mmHg) (n=81)	8 (6, 27)	14 (7, 49)	0.118	9.5 (6,13)	13 (7,36)	0.288

NSVT at baseline (n=73)	3 (13.6%)	2 (3.9%)	0.132	1 (16.7%)	4 (6.0%)	0.320
NYHA >1 at baseline (n=83)	4 (18.1%)	11 (18.0%)	0.988	1 (16.7%)	14 (18.2)	0.926
Follow up time (months)	72.6 (+/-47.8)	67.2 (+/-54.2)	0.665	74.4 (+/-23.6)	68.2 (+/-5.7)	0.766

ICD = implantable Cardioverter Defibrillator, VT = ventricular tachycardia, MWT = maximal wall thickness, LA = left atrial, LVOTO = left ventricular outflow tract obstruction, NSVT = non-sustained ventricular tachycardia, NYHA = New York Heart Association

Table IV: ICD-related Complications occurring during follow up

Type of complication	Detail		
Infections (n=10)	System infection		5
	Superficial infection		5
Lead complication (n=15)	Lead repositioning		3 (atrial n=1, ventricular n=2)
	Lead replacement*	Lead migration	1
		Lead fracture	3 (Atrial n=1, ventricular n=2)
		Taut lead	2 (ventricular n=1, atrial n=1)
		Noise/over-sensing	2 (atrial n=1, ventricular n=1)
		Lead failure	6 (Atrial n=1, ventricular n=5)
		Lead encapsulation	1
Other (n=3)	Pleural effusion		1
	Subclavian vein occlusion		1

	Failure of S-ICD to deliver antibrady pacing	1

ICD= Implantable Cardioverter Defibrillator. RV = right ventricular. S-ICD = subcutaneous ICD. * More than one lead complication n=3

Figure legends

Figure 1

a) Age at time of ICD implantation (years)

b) Weight at time of ICD implantation (Kg)

c) Device type

d) Summary of endovascular systems

Figure 2: Device characteristics by era

Figure 3: Scatterplot showing a) VF zone rate b) VF detection time in all patients

Figure 4) Outcome of childhood HCM patients with an ICD