Disease Severity and Exercise Testing Reduce S-ICD Left Sternal ECG Screening Success in Hypertrophic Cardiomyopathy

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Abstract

Background

The features of the Hypertrophic Cardiomyopathy (HCM) ECG make it a challenge for Subcutaneous ICD (S-ICD) screening. We aimed to investigate the causes of screening failure at rest and on exercise to inform optimal S-ICD ECG vector development.

Methods and Results

131 HCM patients (age:50 ±16 years ,92M;39F) with ≧1HCM risk factor for sudden death underwent S-ICD ECG screening at rest and on exercise. Fifty patients (38%) were ineligible for S-ICD due to screening failure in every lead vector - 33 (66%) failed in the supine position; 12 patients (24%) failed in the standing position and 5 (10%) on exercise. In patients who could exercise and passed screening at rest, 31(44%) had one vector safety, 16(23%) had two vector safety and 24(33%) had three vector safety. Increased R:T-wave ratio in the S-ICD screening ECG (OR 4.0, CI 3.0-5.3, p<0.001) was associated with screening failure, while R/T ratio <3 in Avf (OR 0.3, CI 0.12-0.69, p=0.006) and increasing age (OR0.97, CI 0.95-0.99, p=0.03) were associated with reduced screening failure. ESC risk score was higher in those failing screening (Risk score 5.5% (IQR 3.2-8.7) in failed vs 4.5% (IQR 2.9-7.4) in passed; p=0.04).

Conclusions

HCM patients have a significant incidence of screening failure which is determined primarily by the increased R:T ratio on the screening ECG and lead aVF. High-risk patients have an increased screening failure rate. Optimization of sensing algorithms is required in order to ensure that the highest risk HCM patients can benefit from S-ICD implantation.

Keywords Hypertrophic Cardiomyopathy; Arrhythmia; S-ICD; S-ICD screening.

Background

The implantable cardioverter-defibrilator (ICD) has been a groundbreaking advance in the prevention of sudden cardiac death (SCD)[1]. However, the complications of current transvenous implantable devices, such as infection and lead failure are a significant and expanding problem, particularly with the improved survival of younger recipients[2-9]. In patients with hypertrophic cardiomyopathy (HCM), where devices are frequently implanted for primary prevention in young individuals, complication rates are often unacceptably high[10,11]. The advent of the Subcutaneous Internal Cardiac Defibrillator (S-ICD), represents an important alternative avoiding intravascular leads[12-14] as reflected in the IDE[13] study and EFFORTLESS [15] registries where young patients with inherited channelopathies or non-ischemic cardiomyopathy including HCM were implanted[16] .

The S-ICD continuously senses the surface ECG from three bi-polar vectors derived from its subcutaneous poles and ICD generator positions (Figure 1A). The QRS and T-wave morphology are templated within the device and this is used in combination with internal algorithms to differentiate between ventricular and supraventricular arrhythmias[17]. Thus the quality of the ECG recorded from the surface, as well as the amplitude and ratio of the T-wave and QRS complexes are a critical element in the screening process of eligibility for the device. Previous studies have suggested that up to 7.4% of patients fail screening and that hypertrophic cardiomyopathy (HCM) may increase the odds of screening failure due to large amplitude T-wave and QRS complexes in these patients[18]. However, either limited numbers of patients with HCM have been recruited in previous studies[18] or high risk HCM patients likely to represent those clinically considered for ICD have been underrepresented[18,]. Additionally systematic screening on exercise, when QRS and T-wave morphology

frequently change has not been performed systematically[19,20].This study aimed to assess the proportion of HCM patients without pacing indications and ≧1 of the AHA guideline[21,22] risk factors for sudden cardiac death (SCD) were eligible for the S-ICD on the basis of screening at rest and on exercise.

Methods

Study Population

One-hundred-and-thirty-one consecutive patients with HCM and ≧1 risk factor for SCD were screened for eligibility for S-ICD, during their outpatient clinic visit, between July 2014 and September 2015. Three patients were under investigation for suspected HCM with a family history of sudden cardiac death. The cohort did not include any patients being clinically evaluated for S-ICD, to avoid selection bias. Patients were excluded if they were <20 or >70 years of age or had sustained monomorphic VT. Patients with a pre-existing ICD were included and 19 of these were intermittently paced. The study was approved by our local research ethics committee, and all patients provided informed consent.

Screening Protocol

ECG screening was undertaken by placing ECG electrodes on the xiphoid, sterno-manubrium junction, normal lead position V6 and the right lower abdomen (ground electrode), to simulate the 3 sensing vectors of the S-ICD(Figure 1A). A 30-second ECG was recorded in the supine and standing positions as well as standing step exercise to a heart rate of 120bpm. The 3-lead ECG's were recorded on the Boston Scientific Zoom programmer (Boston Scientific. inc), at a paper speed of 25mm/s with the ECG gain set to 5, 10 and/or 20 mm/mV. The ECG template screening tool (Figure 1B&C), as provided by Boston Scientific was used to assess whether each of the 3 vectors was suitable for the S-ICD. A patient was considered suitable if at least 1 vector passed in all three screening positions (supine, standing and exercise). Screening analysis was performed by KP & NS, There were disparities in 3 cases, where PL was the adjudicator. Alternative screening positions were not assessed as part of the protocol, as the study was designed as a prospective assessment of standard screening methodology and there were time constraints for patients in clinic.

Data Collection

Patient demographic data were collected from the medical records. Left ventricular ejection fraction (LVEF) was estimated using either visual methods or Simpsons bi-plane method by the hospital echocardiography department. 12-Lead ECG parameters were collected from the most recent supine surface ECG. All 12-Lead ECG data are expressed with the machine calibrated to 10mm/mV, while 3-Lead ECG parameters are expressed in relation to a calibration of 5mm/mV.

Statistical Analysis

Parametric data are expressed as mean and standard deviation and analyzed using a Student's t-test. Non-parametric data are expressed as median and interquartile range (IQR), and analyzed using Mann Whitney U-test. Categorical data are expressed as percentages and analyzed using chi-square test. Clinical predictors of failure of screening protocol were analyzed using multivariable analysis. Factors associated with increased screening failure or success at a P-value of <0.05 were input into the model. Where there was significant pairwise correlation between factors; correlation of >0.8; these were eliminated and all remaining variables put into a manual backwards elimination model. P-values <0.05 were considered significant. Postural variation between vectors associated with passing or failing screening were assessed using logistic regression. Three-lead-ECG factors associated with screening failure were analyzed by logistic regression. Statistical analysis was performed using R statistical computing software (Version 3.2.2) [23].

Results

Baseline Characteristics

One-hundred-and-thirty-one consecutive patients with HCM and ≧1 risk factor for sudden death[22] were screened in our outpatient department. Clinical characteristics of the patients (70% male, mean age : 50 ±16 years) are shown in Table 1. Eleven patients where in atrial

fibrillation at the time of screening. In total 51(39%) patients had a pre-existing ICD, 45(34%) for primary prevention and 6(5%) for secondary prevention. 10 patients were unable to exercise, either due to their clinical condition or their request not to exercise. Fourteen patients (11%) had a previous myomectomy and 4 patients (3%) had a previous alcohol septal ablation. Forty-six patients(35%) were on no medication.Table 1).

Eighty one patients (62%) had ≥2 conventional risk factors for SCD[21,22]. Based on the European Society of Cardiology (ESC) risk assessment score[24,25], 53 patients (41%) were high risk (5-year risk ≥6%), 24 patients (18%) were intermediate risk (5-year risk of 4%≥ & <6%), and 54 patients (41%) were low risk (5-year risk <4%).

Eligibility for S-ICD based on 3-Lead ECG Vector screening

In total 50 patients (38%) were ineligible for S-ICD due to screening failure on the basis of failure in every S-ICD lead vector (Table 2.). Figure 2A shows the percentage of all patients passing or failing S-ICD screening in the supine position, with additional failures during standing and exercise (Figure 2B &C) as a percentage of total patients screened. Of the 50 patients that failed screening- 33 (66%) failed screening in the supine position; a further 12 patients (24%) failed screening in the standing position and 5 patients (10%) on exercise.

Of the patients that passed screening in the supine position (Figure 2D), 47(48%) had one vector safety, 28(29%) had two vector safety and 23(23%) had three vector safety. In patients who passed screening in the standing position (Figure 2E), 39(45%) had one vector safety, 29(34%) had two vector safety and 18(21%) had three vector safety. Finally 10 patients who passed screening in the supine and standing positions were unable to exercise

due to mobility issues. Thus in the 71 patients who were able to exercise and passed all screening (Figure 2F), 31(44%) had one vector safety, 16(22%) had two vector safety and 24(34%) had three vector safety.

Figure 2G-I. shows the number of patients passing or failing in the supine, standing and exercise positions, in relation to their screening vector. Logistic regression suggested that the primary vector was statistically more likely to fail screening in the supine (Fail 62%, Pass 38%, OR 1.6, CI 1.1-2.6, P=0.03) and standing positions (Fail 59%, Pass 41%, OR 2.2, CI 1.2-4.0, P=0.007), while the alternate vector was more likely to pass in the standing (Fail 39%, Pass 61%, OR 1.5, CI 1.05-2.4, P=0.03) and during exercise (Fail 21%, Pass 79%, OR 1.9, CI 1.2-8, P=<0.001).

Twenty-two patients (44%) failed due to a large amplitude QRS complex for the template, 17 (34%) due to a T-wave morphology not fitting the template, 10 (20%) failed because of a broad QRS for the template, and 1 (2%) patient had frequent ectopy as a cause for screening failure. The differences in maximal QRS deflection, QRS width, T-wave amplitude and R/T ratio between passing and failing screening on the 3-Lead ECG calibrated to 5mm/mV are shown in Figure 3. Logistic regression demonstrated an increased R/T-wave ratio in patients that failed screening (OR 4.0, CI 3.0-5.3, p<0.001). While patients that passed vector screening in HCM had a broader QRS (OR 1.02, CI 1.01-1.03, p<0.001) and larger amplitude T-waves (OR 1.6, CI 1.5-1.8, p<0.001). Patients who failed screening showed *no significant difference in* QRS amplitude at the chosen significance level, with a median maximal deflection 9mm (IQR 6-12) vs. 7mm (IQR 4-14), (OR 1.01, CI 0.98-1.03, p=0.326).

Clinical and 12-Lead ECG Factors Influencing Screening Pass or Failure

Clinical:

Factors associated with screening success or failures are shown in Table 2. There was no gender difference in screening failure rate, 34 males (36% of all males) and 16 females (41% of all females) failed screening; p = 0.81. Younger patients were more likely to fail than older patients. The mean age of patients passing was 54-years vs 46-years for patients failing p = 0.006. Patient weight (n=127) was not associated with an increased screening failure rate (p=0.35). Conventional risk factors were not associated with a failure of screening, however patients with a family history of SCD appeared to show an increase rate of screening failure vs success (62% vs 31 % respectively, p<0.001). Posterior wall thickness was not associated with an increased failure rate (p=0.11). Patients with pre-existing ICD's were not more likely to fail screening p = 0.7. Of the patients who were intermittently paced 16 (84%) passed screening. Maximal LVOT velocity was greater in patients who passed vs failed screening (22mmHg vs 10mmHg respectively, p=0.009)

Surface 12 lead ECG:

Surface ECG characteristics that were significantly different between patients who passed and failed screening are shown in Table 2. QRS duration (114 milliseconds vs 100 milliseconds; p=0.004) and QTc interval (455 milliseconds vs 438; p=0.02) were found to be significantly different between patients passing and failing respectively. T-wave factors associated with a screening pass or fail were maximal T-wave amplitude (6mm vs 5mm; p=0.03) in any lead, maximal T-wave amplitude in lead I (2mm vs 1.5mm; p=0.005) and maximal T-wave amplitude in Lead avF (2mm vs 1.5mm; p=0.03). An increased ratio of the R-wave to T wave in lead avF (2.5 vs 5; p=0.003) was associated with a risk of screening

failure, while a low ratio of R/T in avF was associated with an increased likelihood of passing screening (53% vs 22%; p=<0.001).

Patient risk:

ESC 5 year risk was significantly higher in patients who failed screening (5.5%/5y vs 4.5%/5y, p=0.04). Patients deemed high risk by the ECS 5 year risk score[24], accounted for a greater proportion of screening failures (27 of 50 patients (54%); p=0.02), as shown in Table 2. There was also a trend towards patients with ≥2 conventional risk factors[21,22] failing screening p=0.08. Patients at low risk[24] showed a trend towards increased screening success (p=0.06).

Screening failure:

Variables that differed significantly (p=<0.05) between screening pass or failure were assessed for pairwise correlation between each other. Variables without correlation to each other were then all input into a manual backwards elimination multivariable logistic regression mode. The final model variables are seen in Table 3. Multivariable logistic regression analysis demonstrated that R/T <3 in lead AVF, was associated with lower odds of screening failure (OR 0.3, 95%CI 0.12-0.69; p = 0.006), and increasing age per year made screening failure less likely (OR 0.3, 95%CI 0.95-0.99; p = 0.03).

Screening vector screening safety in relation to ESC Risk profile

As shown in Table 2, 50-patients (38%) failed ECG screening using the one-vector safety rule. Using the more stringent 2-vector safety rule 93 patients (71%) failed screening for the

device. **Supplemental Figure 1**. shows that the screening failure with one vector and two vector safety. Using one vector safety, screening failure increased with increasing ESC-Risk score, from low (28%), through to intermediate (33%) and high risk (51%). Using the recommended 2-vector safety, 67% of low risk patients failed, 71% of intermediate risk patients failed and 76% of high risk patients failed screening.

Discussion

The S-ICD is a groundbreaking and important clinical tool in the management of patients at risk of ventricular arrhythmia. Its use has now become standard practice particularly in young patients with inherited cardiac syndromes [15,16,26,27]. This is the first systematic study to look specifically at S-ICD eligibility of HCM patients with one or more conventional AHA risk factors for SCD at rest and on exercise in the limited standard screening positions. Although the majority of patients (62%) with HCM passed screening assessment for the device, 38% of patients failed screening. ESC 5-year Risk was associated with increased screening failure rate (5.5%/5yr vs 4.5%/5yr, p=0.04) and patients deemed higher risk were more likely to fail screening, accounting for 54% of failed screenings (p=0.02). On multivariate analysis an R/T ratio of <3 in aVF (OR 0.3, p=0.006) and increasing age per year (OR 0.97, p=0.03) were associated with lower occurrence of screening failure. Of the patients who passed screening for the device 55% had >1 vector safety while 45% of patients passed with one

vector safety using conventional supine and standing screening, with similar findings (41%) on exercising the patients. Though the majority of failures occurred in the supine (66%) and standing positions (24%), 10% of total screening failures occurred on exercise. The primary vector was the most likely to fail screening (Figure 2).

Eligibility For S-ICD

Eligibility for S-ICD based on pre-implant ECG screening is reported to be in the range of 80-95%[18,28,29]. Previous studies[18] in a mixed SCD risk cohort have suggested that HCM is an independent risk factor for S-ICD screening failure. Two previous studies have specifically assessed screening failure in patients with HCM[19,20]. Francia et al. [20] investigated screening failure in 47 patients and found a failure rate of 7% using the standard supine and standing screening method, and 15% in patients who were exercised. Recently Maurizi et al.[19] screened a cohort of 165 patients with HCM, and found a 16% screening failure rate, however, they did not screen these patients on exercise, where T wave oversensing may be a particular problem[30]. Our study shows the highest screening failure rate (38%) in a cohort of higher risk HCM patients (41% High risk & 18% Intermediate ESC Score Risk), who are more representative of patients being considered for ICD implantation in standard clinical practice. It is interesting to note in the study of Maurizi et al.[19] that in their small cohort (n=22, 13% of total cohort) of “high-risk” patients, 36% of patients failed screening with at least one-vector safety. Thus our study shows comparable results of screening failure in patients who are most likely to be clinically considered for an ICD.

Underlying Reasons for HCM ECG Screening Failure

Patients with HCM exhibit progressive remodeling of the ventricles over time with dynamic changes on surface ECG[31-33]. These changes are critical to the applicability of S-ICD technology as the device is currently entirely dependent on the surface ECG to determine eligebility. It has previously been described that the severity of 12-lead ECG abnormalities, particularly T-wave abnormalities, QRS-duration and LV hypertrophy, correlate with the severity and evolution of the structural phenotype in HCM[34]. Additionally, the severity of the ECG phenotype correlates with outcome[35], in that those patients with a phenotypically normal ECG appear to have a low mortality compared to those with significant ECG abnormalities[35]. This may explain the higher screening template failure rate in our higher risk cohort, as they may have been more likely to present with an abnormal ECG that is outside the bounds of the current screening template. Our study therefore has major implications regarding the need for careful screening of patients who are at higher risk of SCD and require an ICD according to current clinical guidelines, to ensure they have adequate sensing safety. Additionally, it highlights the importance of careful monitoring of the patients to ensure that the evolution in ECG morphology with disease progression does not alter device sensing. This is particularly relevant in lower risk HCM cohorts where screening failure may be as low as the 13% reported by Mauriziet al. [19] and clinicians may be more inclined to implant an S-ICD, given the lower risk of long term complications. Such patients will benefit from the avoidance of tranvenous lead implantation by monitoring the ECG on follow-up and if significant changes develop, the S-ICD can be optimized to avoid any inappropriate therapies.

3-Lead S-ICD Vector Template Screening

Our study shows that using standard recommended supine and standing screening in only the left sternal position, 45% of the total patients screened passed with one vector safety. Current ESC guidelines[24] recommend ≥2 vector safety on screening before implanting the S-ICD in HCM. Applying this more stringent cut-off would increase the failure rate of screening to 71% (n=93), which is similar to that described by Maurizi et al.[19], where 44% of the entire cohort of patients and 72% of the high-risk cohort of patients were ineligible based on these criteria. Additionally, 10% of total screening failures occurred during exercise, which reflects the importance of screening patients on exercise where T-wave over-sensing is a known problem[20,30].

We noted that the primary vector was statistically more likely to fail screening while the alternate vector was more likely to pass (Figure 2.). Francia et al. [20] also recently reported that the alternate sensing vector was the most compatible in their cohort of HCM patients with a pre-existing ICD. This is contrary to the findings in general population screening[18] where the alternate vector is the most likely to fail screening. In the S-ICD, the alternate vector is orientated at 90° to the frontal plane of the chest, while the primary vector is at 0°, with the secondary vector in between the two. In HCM, the cardiac frontal axis is progressively shifted leftward due to left ventricular hypertrophy[32 33]. This potentially shifts the major depolarizing and repolarizing vectors parallel to the primary screening vector in HCM patients making large QRS and T-wave complexes more likely to cause screening failure. This is particularly notable during standing and exercise where the alternate vector was statistically more likely to pass, perhaps because of the effect of changing position of the heart with posture in realigning the major depolarizing and repolarizing vectors more perpendicular to the alternate screening vector, making T-wave oversensing and problems with large amplitude QRS complexes less likely. It also explains the finding that in patients

with HCM patients, right sternal lead placement appears to have no significant effect in improving screening failure rate[20], as this alters the alternate vector but does little to influence the primary vector which appears to be the predominant sensing vector in screening failure.

The S-ICD is designed for optimal lead and generator position to achieve the lowest possible DFT and appropriate sensing vectors[13]. The sternal position of the lead and lateral siting of the can mean that only the primary vector is deployed maximally orthogonal to the cardiac axis with the alternate vector being the least orthogonal in patients with structurally normal hearts. In HCM there is a leftward shift of the cardiac axis[32 33], and the opposite is true. This is evident in the screening ECG as demonstrated in this study and others[18,19]

The major cause for screening failure was large amplitude QRS complexes. This is reflected in the finding of larger maximal QRS amplitude in patients that failed, and a larger R/T ratio (Figure 3.). The finding of T-waves not fitting the screening template as a second major cause for screening failure, despite such patients having smaller maximal T-wave amplitude, suggests that the morphology of the T-wave and not amplitude alone determine screening failure. It is interesting to note that in the study of Mauriziet al. [19], T-wave inversion in the 12-Lead ECG was associated with screening failure. This warrants further investigation, particularly in relation to the design of the screening template.

Clinical Characteristics of Failure

The major clinical factor associated with an increased risk of screening failure was the presence of an increased ESC 5-year Risk score (median 5.5%/5yr in failed patients vs 4.5%/5yr in pass patients; p=0.04). High risk patients accounted for 54% of failed screening

patients (p=0.02). Using the 1-vector and 2-vector safety rule, the majority of patients who passed S-ICD screening were from the low risk cohort, with screening failure increasing with ESC-Risk score (Figure 4.). This has important implications because 45% of patients who would be considered for an ICD based on the ESC risk score[24,25] and 44% of patients based on the AHA guidelines[22], would potentially be ineligible for the device employing a one vector safety rule. It is well known that lower risk patients appear to display a more normal phenotypic ECG[35], while increasing phenotypic expression of HCM on cardiac MRI has been associated with progressive severity of ECG abnormalities[34]. It is interesting to note that patients that passed screening were older, and this is reflected in the multivariable analysis where increasing age was associated with lower screening failure rate. This may reflect the natural history of the ECG in HCM where R wave amplitude in aVL & septal leads have been reported to decline over time[31,32], thus making potential screening failure due to large voltage QRS complexes less likely. An R/T ratio <3 in aVF was associated with a lower screening failure rate, highlighting this lead as a potential surrogate marker of screening template ECG failure, due to tall R-waves. This is in keeping with our finding of R/T ratio being associated with screening failure in the 3-lead screening ECG.

Future Directions.

Screening failure could be improved by filtering of R wave and T wave amplitude in the device to account for features of the HCM ECG, such that the current ECG template employed can be modified to increase the ECG screening success rate. Identical band pass filtering as employed by the implanted S-ICD is due to be introduced in an automated screening tool as opposed to the current manual template which coupled with the

SMARTPASS algorithm to prevent T wave oversensing may help reduce screening failure. This will need to be formally addressed in future studies. Alternatively utilizing a tailored floating bipole away from the heart implanted at a site of optimal R wave sensing or integrating signals from the 3 vectors to achieve an optimal R:T wave ratio as a summation of sensed surface ECG data could be considered. This would enable the minimization of large amplitude R waves and the subtraction of large T waves avoiding the need to implant additional hardware that has to communicate with the generator. A move towards bespoke and remote sensing electrode positions which are patient specific and allow the sensing field to be independent of the shock field could prove an advantage in such patients. Ultimately, potential screening/sensing problems could be solved with leadless sensors/pacing electrodes that would ensure endocardial R-wave sensing in combination with the S-ICD. An additional atrial sensor could further optimize the discrimination between SVT and VT.

Limitations

Screening was performed at rest and exercise with no assessment of right sided lead positioning, central sternal or posterior S-ICD generator placement. This may have resulted in the higher screening failure rate reported in this study. However, a recent study reported that right sided lead placement did not significantly increase screening success rate in HCM patients[20]. We were also limited to exercising the patients to a maximal heart rate of 120bpm (for ethical safety reasons), whereas standard treadmill testing with exercise to maximal heart rate as is routinely performed in our institution, may have further altered failure rate of patients on exercise. Additionally, we only report failure of screening patients for the S-ICD, no published data exist regarding the correlation between the screening ECG template and sensing within the implanted S-ICD itself where there are differences in the S-ICD sensing algorithms which the manual ECG template alone does not account for.

Conclusion

The S-ICD has been a groundbreaking and important leap forward in the management of patients with risk of ventricular arrhythmia and its applicability is ever expanding [26] Although the majority of patients in our cohort of patients with HCM and ≥1 indication for ICD[22] passed based on >1 vector safety on surface ECG screening, 38% of patients were ineligible for the S-ICD with one vector safety, and 71% were ineligible with ≥2 vector safety as recommended in the ESC guidelines[24] based only on standard screening methodology with left parasternal sensing. The median ESC risk score was higher in patients who failed screening, while 10% of total failures occurred on exercise. This highlights the need for careful screening and selection of S-ICD candidates with HCM, including consideration of alternative screening positions. This should not deter from implanting devices in HCM patients as in HCM patients who pass screening for S-ICD as the device has an excellent safety and efficacy profile[16]. New and more advanced screening algorithms are required to make this important device available to a wider population of with unusual ECG morphologies.

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Table 1. Baseline Characteristics

Clinical Characteristics	
Male sex, n (%)	92(70%)
Age in years (mean)	51±16
Weight in kg (median)	82 (IQR 70-93)
ICD	
Primary Prevention, n (%)	45(34%)
Secondary Prevention, n(%)	6(5%)
LVEF (median)	65 (IQR 60-70)
LA size in mm (median)	45 (IQR 41-51)
Max Wall Thickness in mm (median)	17 (IQR 15-20)
Posterior Wall Thickness in mm (median)	10 (IQR 9-11)
Peak LVOT gradient in mmHg (median)	16 (IQR 5-61)
Risk Factors	
LVOT obstruction, n (%)	52 (40%)
Family History SD, n (%)	56(43%)
Syncope, n (%)	44(34%)
NSVT, n (%)	74(56%)
Max Wall Thickness ≧30 mm, n (%)	3(1.5%)
Altered BP response to Exercise, n(%)	61(47%)
12-Lead ECG Characteristics	
PR Interval in milliseconds (median)	172 (IQR 155-192)
QRS duration in milliseconds (median)	108 (IQR 100-129)
QT interval in milliseconds (median)	447 (IQR 427-477)
ESC 5 Year Risk	
High Risk n(%)	53(41%)
Intermediate Risk n(%)	24(18%)
Low Risk n(%)	54(41%)
Conventional Risk Factors ≥2	81(62%)
Anti-Arrhythmic medications, n(%)	
Beat Blocker	46(35%)

Clinical Characteristics	
Calcium Channel Antagonist	15(11%)
Beta Blocker + Calcium Channel Antagonist	5(4%)
Beta Blocker + Disopyramide	3(2%)
Beta Blocker + Amiodarone	2(1.5%)
Calcium Channel Antagonist + Amiodarone	2(1.5%)
Disopyramide	2(1.5%)
Dronedarone	1(0.8%)

ICD = implantable cardiac defibrillator; LVEF = left ventricular ejection fraction; LA = left atrium; LVOT = left ventricular outflow tract; NSVT = non sustained ventricular tachycardia

Table 2. Clinical Characteristics of Patients Passing vs Failing S-ICD screening

	Pass (N = 81)	Fail (N = 50)	P-Value
Male Sex, n(%)	58(72%)	34(68%)	0.81
Age in years (mean)	54±16	46±16	0.006
Weight in kg (median)	82 (IQR 70-98)	82 (IQR 69-88)	0.35
ICD	30(37%)	21(42%)	0.7
Max Wall Thickness in mm (median)	18 (IQR 15-20)	16 (IQR 13-20)	0.11
Posterior Wall Thickness in mm (median)	10 (IQR 9-11)	9 (IQR 8-10)	0.11
Syncope, n (%)	24(30%)	20(40%)	0.3
Family History SD, n (%)	25(31%)	31(62%)	<0.001
NSVT, n (%)	44(54%)	30(59%)	0.65
Altered BP response to Exercise, n(%)	40(49%)	21(42%)	0.52
LA Size in mm (median)	45 (IQR 41-50)	45 (IQR 40-51)	0.83
LVEF (median)	65 (IQR 60-70)	65 (IQR 60-70)	0.47
Max LVOT velocity (median)	22 (IQR 6-80)	10 (IQR 4-32)	0.009
12-lead ECG Factors			
PR interval in milliseconds (median)	173 (IQR 157-193)	171(IQR 154-192)	0.74
QRS duration in milliseconds (median)	114 (IQR 100-160)	100 (IQR 94-120)	0.004
QTc interval in milliseconds (median)	455(IQR 430-489)	438(IQR 420-464)	0.02

	Pass (N = 81)	Fail (N = 50)	P-Value
QRS Amplitude Factors (mm)			
Maximal S Wave Any Lead (median)	23(IQR 17-30)	20 (IQR 17-25)	0.07
Maximal R-Wave Any Lead (median)	14 (IQR 11-25)	15 (IQR 11-17)	0.35
Max R-Wave Lead I (median)	8 (IQR 5-12)	7 (4-9)	0.30
Max R-Wave Lead avF	6 (IQR 4-12)	8 (IQR 1-7)	0.18
T-wave Factors (mm)			
Maximal T-wave amplitude any lead	6 (IQR 4-9)	5 (IQR 4-7)	0.03
Max T-wave Lead I (median)	2 (1-4)	1.5 (1-2.5)	0.005
Max T-wave Lead avF (median)	2 (1-3)	1.5 (1-2.5)	0.03
T-peak to T-end Lead V5 (median)	80 (IQR 60-80)	60 (IQR 40-80)	0.14
R/T Ratios			
Max R/T Any Lead (median)	2.5 (IQR 1.5-3.8)	2.7 (IQR 1.9-3.7)	0.6
R/T Lead I (median)	3.2 (IQR 2-5.25)	3.8 (2.2-8.9)	0.08
R/T Lead avF (median)	2.5 (IQR 1.3-5.1)	5 (IQR 3-8)	0.003
Max R/T <3 in any lead, n(%)	45(56%)	23(46%)	0.37
R/T <3 in avF, n(%)	43(53%)	11(22%)	<0.001
ESC 5 Year Risk	4.5 (IQR 2.9-7.4)	5.5 (IQR 3.2-8.7)	0.04
High Risk	26 (32%)	27 (54%)	0.02
Intermediate Risk	16 (20%)	8 (16%)	0.76
Low Risk	39 (48%)	15 (30%)	0.06
Conventional Risk Factors ≥2	45 (56%)	36 (72%)	0.08

Table 3. Predictors of Screening Failure

	Multivariable Analysis		
	OR	**95% CI**	**P-Value**
Age per year	0.97	0.95-0.99	**0.03**
Maximal T-wave amplitude any lead per millimetre	0.90	0.76-1.04	0.18
T wave amplitude in Lead I	0.77	0.55-0.10	0.1
R/T <3 in aVF	0.30	0.12-0.69	**0.006**
Max LVOT velocity per mmHg	0.99	0.98-1.00	0.07

Figure Legends:

Figure 1. Surface 3-lead ECG position for screening (A), with vectors between the three poles. Example of screening the screening template (B), with different profiles to fit the shape and size of the ECG. The template is used to assess the surface ECG for screening pass or fail (C), with the QRS complex required to cross the “peak-zone” but fit entirely within the shape of the template.

Figure 2. Percentage and number of patients passing or failing screening in the supine, standing and exercise positions (A-C) as a proportion of total screened. Percentage of patients with 1, 2 or 3 qualifying vectors in those who passed, in each of the screening positions shown below (D-F). Lower panel shows the number of patients passing or failing in the alternate, secondary and primary vectors in each of the screening positions (G-I), with statistical significance between passing and failing shown above the bars.

Figure 3. 3-Lead ECG factors influencing screening pass vs failure. Boxplots of differences in QRS amplitude (A), QRS width (B), T-wave amplitude (C) and R/T ratio (D) in the 3-Lead screening ECG, between patients who passed and failed screening. Statistical significance based on logistic regression is shown above each boxplot.