ESC European Society of Cardiology
Europace (2023) **25**, 1–9
https://doi.org/10.1093/europace/euad270

CLINICAL RESEARCH

Clinical course of hypertrophic cardiomyopathy patients implanted with a transvenous or subcutaneous defibrillator

Pietro Francia [1]*, Matteo Ziacchi [2], Carmen Adduci [1], Ernesto Ammendola[3], Paolo Pieragnoli [4], Paolo De Filippo [5], Antonio Rapacciuolo [6], Valeria Rella [7], Federico Migliore [8], Stefano Viani [9], Maria Beatrice Musumeci[1], Elena Biagini [2], Mariolina Lovecchio[10], Rossella Baldini [1], Giulio Falasconi [11,12], Camillo Autore[1], Mauro Biffi [2†], and Franco Cecchi [4,7†] on behalf of the S-ICD Rhythm Detect Investigators

[1]Cardiology, Department of Clinical and Molecular Medicine, Sant'Andrea Hospital, University Sapienza, Rome, Italy; [2]Institute of Cardiology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Policlinico S.Orsola-Malpighi, Bologna, Italy; [3]Department of Translational Medical Sciences, University of Campania 'Luigi Vanvitelli', Monaldi Hospital, Naples, Italy; [4]Careggi University Hospital, University of Florence, Florence, Italy; [5]Papa Giovanni XXIII Hospital, Bergamo, Italy; [6]Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy; [7]Department of Cardiovascular, Neural and Metabolic Sciences, IRCCS, Istituto Auxologico Italiano, San Luca Hospital, Milan, Italy; [8]Department of Cardiac, Thoracic Vascular Sciences and Public Health University of Padova, Padova, Italy; [9]Second Cardiology Division, Cardio-Thoracic and Vascular Department, University Hospital of Pisa, Pisa, Italy; [10]Boston Scientific, Milan, Italy; [11]Campus Clínic, University of Barcelona, Barcelona, Spain; and [12]IRCCS Humanitas Research Hospital, Milan, Italy

Received 30 May 2023; accepted after revision 9 August 2023; online publish-ahead-of-print 19 September 2023

Aims

The implantable cardioverter-defibrillator (ICD) is a life-saving therapy in patients with hypertrophic cardiomyopathy (HCM) at risk of sudden cardiac death. Implantable cardioverter-defibrillator complications are of concern. The subcutaneous ICD (S-ICD) does not use transvenous leads and is expected to reduce complications. However, it does not provide bradycardia and anti-tachycardia pacing (ATP). The aim of this study was to compare appropriate and inappropriate ICD interventions, complications, disease-related adverse events and mortality between HCM patients implanted with a S- or transvenous (TV)-ICD.

Methods and results

Consecutive HCM patients implanted with a S- ($n = 216$) or TV-ICD ($n = 211$) were enrolled. Propensity-adjusted cumulative Kaplan–Meier curves and multivariate Cox proportional hazard ratios were used to compare 5-year event-free survival and the risk of events. The S-ICD patients had lower 5-year risk of appropriate (HR: 0.32; 95%CI: 0.15–0.65; $P = 0.002$) and inappropriate (HR: 0.44; 95%CI: 0.20–0.95; $P = 0.038$) ICD interventions, driven by a high incidence of ATP therapy in the TV-ICD group. The S- and TV-ICD patients experienced similar 5-year rate of device-related complications, albeit the risk of major lead-related complications was lower in S-ICD patients (HR: 0.17; 95%CI: 0.038–0.79; $P = 0.023$). The TV- and S-ICD patients displayed similar risk of disease-related complications (HR: 0.64; 95%CI: 0.27–1.52; $P = 0.309$) and mortality (HR: 0.74; 95%CI: 0.29–1.87; $P = 0.521$).

Conclusion

Hypertrophic cardiomyopathy patients implanted with a S-ICD had lower 5-year risk of appropriate and inappropriate ICD therapies as well as of major lead-related complications as compared to those implanted with a TV-ICD. Long-term comparative follow-up studies will clarify whether the lower incidence of major lead-related complications will translate into a morbidity or survival benefit.

* Corresponding author. Tel: +39 06 3377 5979. *E-mail address*: pietro.francia@uniroma1.it
† These authors contributed equally to this work.

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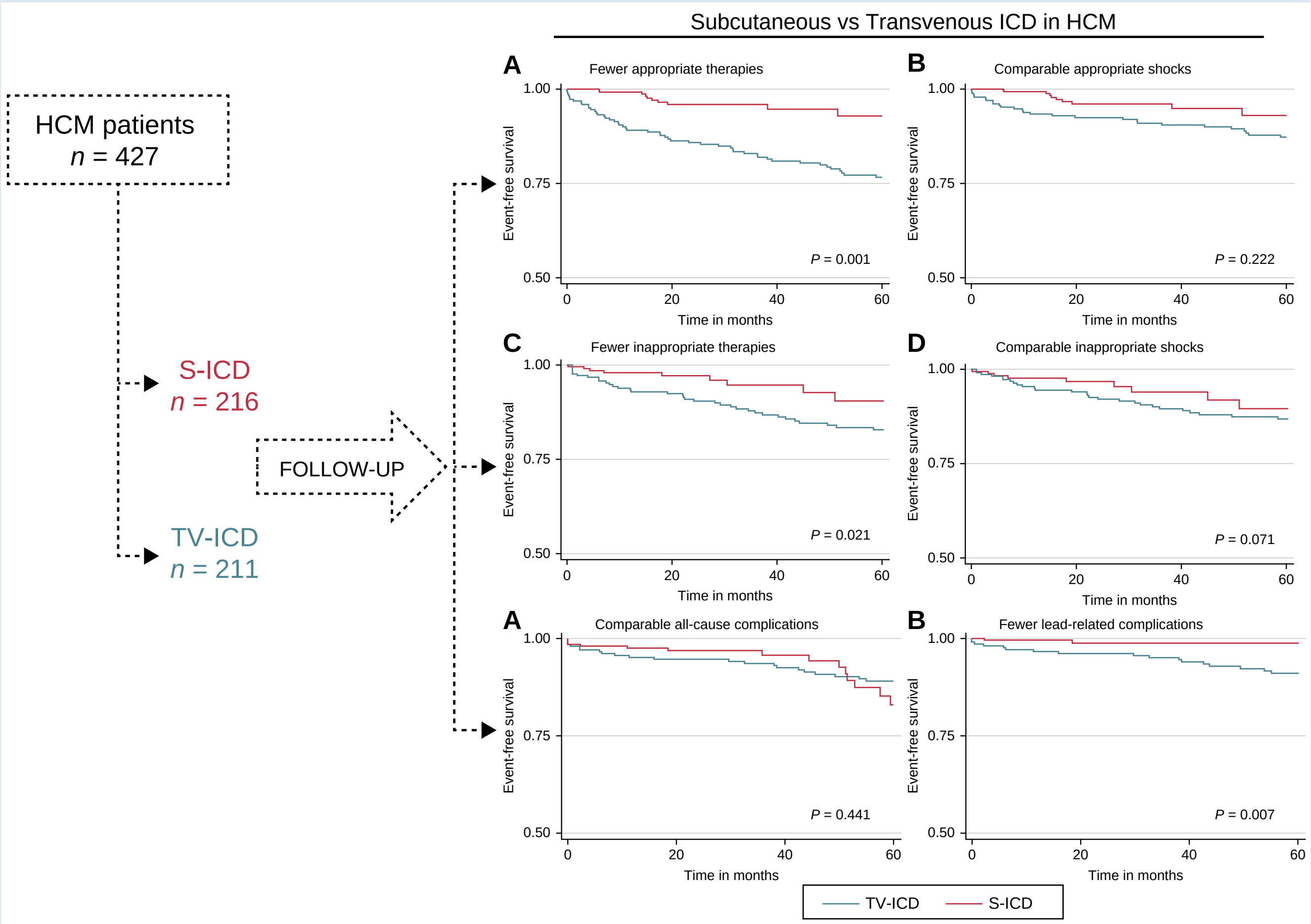
Graphical Abstract



Keywords Hypertrophic cardiomyopathy • Implantable cardioverter-defibrillator • Subcutaneous implantable cardioverter-defibrillator • Device-related complications

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What's new?

- In patients with hypertrophic cardiomyopathy (HCM), the subcutaneous implantable cardioverter-defibrillator is associated with a lower incidence of appropriate and inappropriate therapies when compared to the transvenous implantable cardioverter-defibrillator (TV-ICD). This difference is primarily driven by a higher occurrence of anti-tachycardia pacing (ATP) interventions in patients with TV-ICDs.
- Lead-related complications are higher in HCM patients with TV-ICDs.
- The benefits of ATP should be balanced against the risks of lead-related complications.

Introduction

The implantable cardioverter-defibrillator (ICD) is an established life-saving therapy in patients with hypertrophic cardiomyopathy (HCM) at high risk for sudden cardiac death (SCD).[1,2] However, ICD therapy entails short- and long-term complications that may erode its clinical benefits.[3–5] Indeed, the majority of young ICD candidates with HCM is predictably more exposed to long-term ICD drawbacks due to their long life expectancy and active lifestyle.[6] Most ICD complications are due to intracardiac leads, an essential component of transvenous ICDs (TV-ICDs). The subcutaneous ICD (S-ICD) does not use intracardiac leads and would therefore be expected to reduce complications[7–10] particularly in young patients who have long life expectancy and active lifestyle.[6,11]

According to the US and European guidelines,[12,13] if bradycardia or anti-tachycardia pacing (ATP) or cardiac resynchronization therapy are not needed, ICD candidates equally benefit from a TV- or S-ICD. A pooled analysis of the EFFORTLESS and IDE cohorts[14] reported that the S-ICD was as safe and as effective both in HCM and non-HCM patients. Moreover, a recent[15] analysis of the Boston Scientific ALTITUDE database showed that HCM patients with S-ICDs had a significantly lower therapy rate than patients with TV-ICDs. However, this study exclusively examined ICD therapies and did not encompass any clinical characterization of patients, clinical events, disease progression, or complications.

In a retrospective analysis of a large cohort of HCM patients implanted with a S-ICD or a TV-ICD, we aimed to compare the rate of appropriate and inappropriate therapies, procedure- and device-related complications as well as disease-related major adverse events and mortality.

Methods

Study subjects

Nine Italian centres participating in the Rhythm Detect clinical registry recruited consecutive HCM patients implanted with a S-ICD between November 2013 and March 2021 and a control group of HCM patients that received a TV-ICD between May 1995 and September 2020. The study consisted in a retrospective analysis of prospectively collected data. Hypertrophic cardiomyopathy diagnosis was based on echocardiographic demonstration of a hypertrophied and non-dilated left ventricle (LV) in the absence of any other disease that could lead to a comparable LV hypertrophy.[1,2] Sudden cardiac death risk stratification was conducted by the managing cardiologist. Primary prevention patients were referred for ICD implantation according to the ESC 5-year SCD risk score[1] or when presenting one or more established risk factors for SCD as per AHA guidelines.[2,16,17] This study was approved by all local institutional review boards. All participants provided written informed consent.

Aims and endpoints

This study compared the rate of ICD therapies for VT/VF and system-, implant-, and disease-related complications in a cohort of HCM patients implanted with a S-ICD or TV-ICD.

Appropriate ICD therapy was defined as ATP or shock for VT or VF. A therapy was considered successful when able to convert the ventricular arrhythmia within 5 s. A *post hoc* analysis evaluated the relative contribution of shocks and ATP interventions to the rate of appropriate therapies. Shock and ATP efficacy were defined as the percentage of successful shocks or ATP of total shocks or ATP, respectively. Implantable cardioverter-defibrillator interventions were considered inappropriate when triggered by heart rate exceeding the programmed threshold as a consequence of either supraventricular arrhythmia, sinus tachycardia, T-wave or non-cardiac signal oversensing. Inappropriate peri-implant S-ICD shocks caused by air entrapment within the parasternal lead tunnel[18] were classified as implant-related complications, as they directly result from a phenomenon that occurs during the surgical implantation procedure itself, rather than during follow-up.

Appropriate and inappropriate ICD therapies, ICD-related complications, and procedure-related complications were collected and reported by the investigating centres. The ICD-related complications were defined as device- or lead-related adverse events that resulted in invasive interventions, unplanned drug therapies, or significant deviation from scheduled follow-up visits. Lead-related complications included infection, perforation, pneumo/haemothorax, lead dislodgement, and lead fracture or failure. Disease-related complications and mortality data were collected throughout the follow-up.

Implantable cardioverter-defibrillator implantation, defibrillation testing, and device programming

Transvenous ICD patients received a single-, dual-chamber, or biventricular ICD according to clinical indications. Subcutaneous ICD patients underwent eligibility testing through surface electrocardiogram (ECG) screening by means of a dedicated ECG morphology tool or an automatic screening tool.[19–21] Subcutaneous ICD lead tunnelling was performed according to the two- or three-incision technique, and the pulse generator was positioned in a subcutaneous or intermuscular pocket.[22–24] Post-implant defibrillation testing was conducted according to the centre's standard practice.[25,26]

Arrhythmia detection criteria, ATP, and shock therapies were programmed at the discretion of the implanting electrophysiologist.

Statistical methods

Descriptive statistics are reported as mean ± standard deviation (SD) for normally distributed continuous variables, or medians and interquartile range (IQR) in the case of skewed distribution. Categorical variables are reported as absolute frequencies and percentages. Differences were compared by means of *t*-test, Mann–Whitney *U* test, and χ^2 or Fisher's exact test, as appropriate.

Multivariate Cox proportional hazard models were used to determine the association between the type of ICD implanted (S- or TV-ICD) and the study endpoints. Variables considered clinically relevant were entered into multivariate models. The risk model for appropriate therapies was adjusted for sex, primary/secondary prevention, ESC 5-year SCD risk, end-stage disease, apical aneurism, and conditional VT zone availability. The model for inappropriate therapies was adjusted for age, sex, history of atrial fibrillation, and conditional VT zone availability. The risk for device- and disease-related complications and mortality was age- and sex-adjusted. The propensity score was used for stratification and covariate adjustment. After calculating the propensity score, we defined five strata. On each of the stratum, we checked the balance of the individual covariates in S- and TV-ICD subjects. This ensured that the propensity score's distribution was similar across groups within each block and that the propensity score was properly specified. After the propensity score was balanced within blocks across the treatment and comparison groups, we checked for balance of individual covariates across S- and TV-ICD groups within blocks of the propensity score. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by fitting the model with the propensity score strata and the dichotomous variable representing the exposure (S- or TV-ICD).

To further account for baseline differences in the two cohorts, a 1:1 propensity-matched analysis was separately performed between TV-ICD and S-ICD patients according to different variables (matched cohorts). The variables matched were (i) age, sex, and ESC 5-year risk of SD for the appropriate ICD therapy analysis, (ii) age, sex, history of atrial fibrillation, and active conditional VT therapy zone with discriminators for supraventricular rhythms for the inappropriate therapy analysis, and (iii) age for the major lead-related complications analysis. For the analysis, we used a calliper width of 0.2.

In the univariate analysis, survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Adjusted survival curves were derived from the fitted Cox regression models. All statistical tests were performed two-sided at the 5% significance level.

The STATA version 17.0 (STATA Corp., College Station, TX) was used to perform statistical analyses.

Results

Patients' characteristics and implantable cardioverter-defibrillator programming

We retrospectively analysed 427 consecutive HCM patients that received a S-ICD ($n = 216$) or a TV-ICD ($n = 211$). Baseline characteristics and risk factors are presented in *Table 1*. Twenty-four (5.6%) patients underwent ICD implantation after sustained VT/VF (secondary prevention). Median ESC 5-year SCD risk of primary prevention patients > 16 years old ($n = 401$) was 4.41% (IQR: 2.88–6.64) (*Table 1*). Patients with lower ESC risk score were implanted due to the presence of additional risk factors (principally apical aneurysm, end-stage disease, or late gadolinium enhancement (LGE) at cardiac magnetic resonance). Among TV-ICD patients, 131 (62.0%) received a single-, 74 (35%) a dual-chamber, and 6 (3%) a biventricular ICD. Fewer patients had conditional therapy zone programmed in the TV-ICD group as compared to the S-ICD group (89.6% vs. 98.6%; $P < 0.001$). Transvenous ICD patients had lower programmed therapy rate both in the conditional zone (171 bpm, IQR: 167–182 vs. 220 bpm, IQR: 200–220; $P < 0.01$) and the VF zone (214 bpm, IQR: 200–222 vs. 250 bpm, IQR: 250–250 bpm; $P < 0.01$). In the majority of S-ICDs ($n = 183$; 84.7%), the SMART Pass algorithm was enabled.

Implantable cardioverter-defibrillator interventions for spontaneous VT/VF episodes

The average follow-up time was 26.5 ± 19.0 in the S-ICD group and 46.9 ± 20.1 months in the TV-ICD. The 5-year cumulative rate of first appropriate therapy (ATP or shock) was significantly lower among

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Table 1 Clinical characteristics of S- and TV-ICD patients

	S-ICD *n* = 216	TV-ICD *n* = 211	*P*
Males, *n* (%)	165 (76.4)	103 (48.8)	<0.001
Age at ICD implantation (years)	43 ± 14	50 ± 15	<0.001
Body mass index	26.3 ± 4.4	26.4 ± 4.4	0.729
Clinical			
Primary prevention, *n* (%)	203 (94)	200 (95)	0.718
LVOT obstruction, *n* (%)	56 (25.9)	62 (29.4)	0.424
Myectomy, *n* (%)	13 (6)	20 (9.5)	0.181
NYHA III or IV, *n* (%)	6 (2.8)	21 (10)	<0.001
Atrial fibrillation, *n* (%)			
Paroxysmal	15 (6.9)	24 (11.4)	0.008
Persistent	3 (1.4)	9 (4.3)	
Permanent	10 (4.6)	21 (10)	
Risk factors			
Family history of SD, *n* (%)	56 (25.9)	75 (35.5)	0.031
Unexplained syncope, *n* (%)	31 (14.4)	59 (28.0)	0.001
Max LV wall thickness > 30 mm, *n* (%)	36 (16.7)	59 (28.0)	0.005
NSVT, *n* (%)	63 (29.2)	125 (59.2)	<0.001
End-stage disease, *n* (%)	33 (15.3)	32 (15.2)	0.974
Apical aneurysm, *n* (%)	10 (4.7)	11 (5.2)	0.78
LGE, *n* (%)	148 (68.5)	126 (59.7)	0.031
ESC 5-year risk of SD (%)	3.74 (2.56–5.58)	5.47 (3.45–8.83)	<0.001
Risk ≥ 6% (high); *n* (%)	43 (21.4)	82 (41)	<0.001
Risk 4–6% (intermediate); *n* (%)	46 (22.9)	55 (27.5)	
Risk < 4% (low); *n* (%)	112 (55.7)	63 (31.5)	
Echo			
LA diameter (mm)	45.2 (7.2)	47.0 (8.1)	0.013
LVOT gradient (mmHg)	9 (5–23)	13 (6–35)	0.055
Max LV wall thickness (mm)	22.8 ± 5.3	23.4 ± 6.7	0.325
EF (%)	60.1 ± 9.4	62.2 ± 13.0	0.166
Drug therapy			
Beta-blockers, *n* (%)	169 (78.2)	170 (80.6)	0.552
Amiodarone, *n* (%)	11 (5.1)	24 (11.4)	0.018
ACE-inh. or AT1-blockers, *n* (%)	27 (12.5)	49 (23.2)	0.004

EF, ejection fraction; ICD, implantable cardioverter-defibrillator; LA, left atrium; LV, left ventricle; LGE, late gadolinium enhancement; LVOT, left ventricular outflow tract; NSVT, nonsustainedventricular tachycardia; S-ICD, subcutaneous implantable cardioverter-defibrillator; TV-ICD, transvenous implantable cardioverter-defibrillator.

S- vs. TV-ICD patients (10.5%, 95%CI: 5.6–19.5% vs. 29.7%, 95%CI: 22.5–39.3; $P = 0.001$) (*Figure 1A*). Clinical characteristics and ICD programming of patients with and without appropriate therapies are reported in *Table 2*. In propensity-adjusted multivariate Cox regression, S-ICD patients had a significant risk reduction of appropriate ICD interventions (ATP or shock) (HR: 0.32; 95%CI: 0.15–0.65; $P = 0.002$). The 5-year cumulative rate of first appropriate shock was not significantly different between the two groups (10.5%, 95%CI: 5.6–19.5% vs. 15.3%, 95%CI: 10.5–22.4; $P = 0.222$) (*Figure 1B*). In propensity-adjusted multivariate Cox regression, S- and TV-ICD patients had similar risk of appropriate shock (HR: 0.58; 95%CI: 0.27–1.29; $P = 0.185$). Among the 49 patients with TV-ICD and appropriate ICD therapies, 23 (47%) received interventions for arrhythmias in the conditional VT zone, while 9 out of 10 patients with appropriate shocks from S-ICDs had arrhythmias in the VF zone.

First shock efficacy was 100% (10/10 shocks) in the S-ICD and 96.3% (26/27 shocks) in the TV-ICD group ($P = 0.53$). In the TV-ICD group, the first VT/VF was treated with a shock in 15 (30.6%) and ATP in 34 (69.4%) patients. Anti-tachycardia pacing terminated 21 (42.8%) out of 49 first VT/VF episodes. When considering only VTs that were treated with an ATP ($n = 34$), the success rate was 61.7%. Arrhythmias that were not terminated by ATP self-terminated ($n = 1$) or were shocked ($n = 12$).

In the matched cohort ($n = 248$), S-ICD patients were matched 1:1 to the nearest TV-ICD pair by gender (per cent male: 61.3% vs. 64.5%; $P = 0.59$), age (46 ± 15 vs. 46 ± 14; $P = 0.85$), and 5-year risk of SCD

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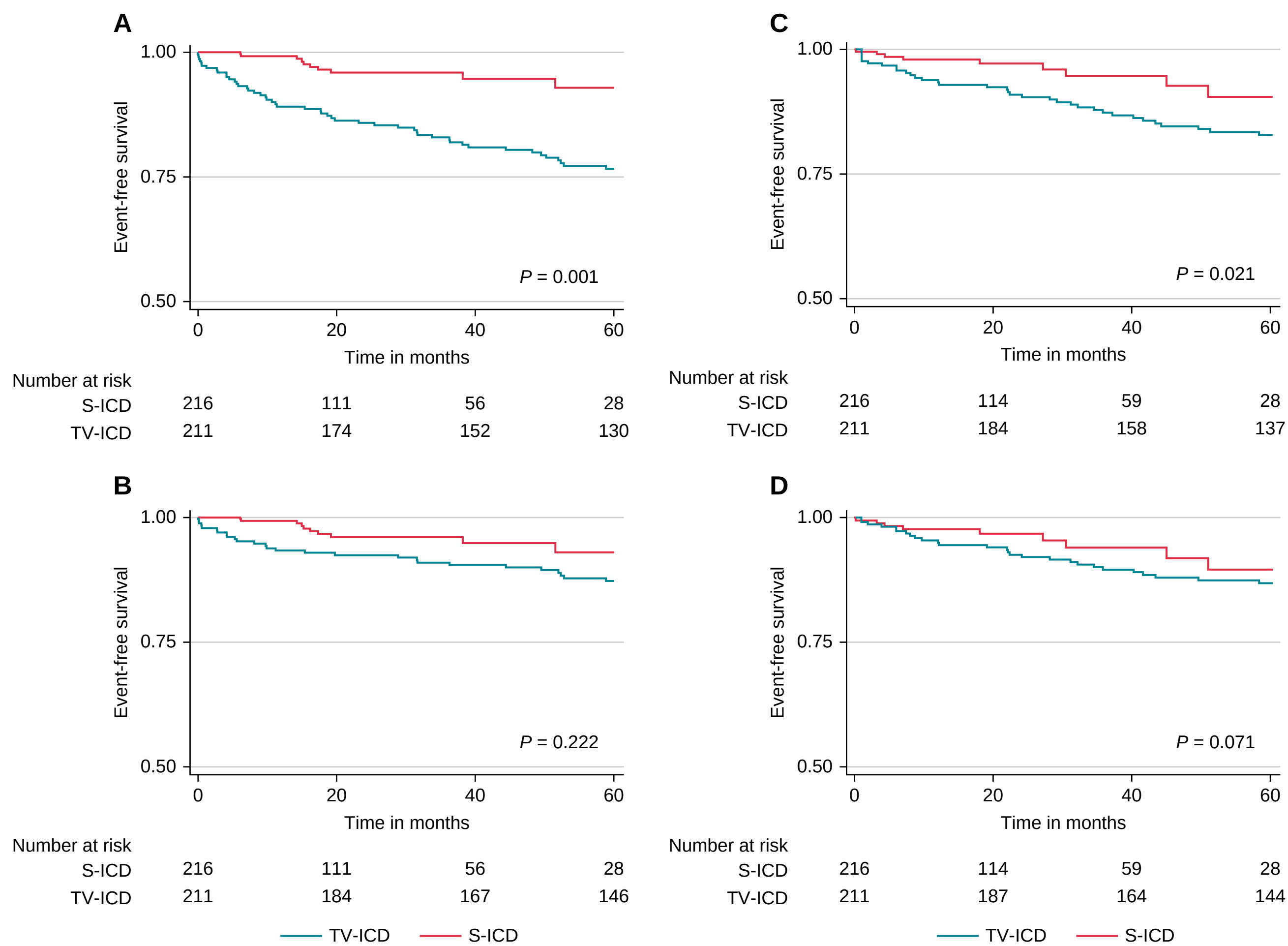

Figure 1 Covariate-adjusted Kaplan–Meier curves showing time to first appropriate therapy (panel *A*: shock or ATP; panel *B*: shock only) and to first inappropriate therapy (panel *C*: shock or ATP; panel *D*: shock only). S-ICD, subcutaneous implantable cardioverter-defibrillator; TV-ICD, transvenous implantable cardioverter-defibrillator.

according to the ESC model (5.4 ± 3.0 vs. 5.3 ± 3.2; $P = 0.69$). As in the general cohort, the 5-year cumulative rate of first appropriate therapy (ATP or shock) was significantly lower among S- vs. TV-ICD patients (8.5%, 95%CI: 1.0–16.8% vs. 22.1%, 95%CI: 14.2–29.4; $P = 0.007$), while the rate of first appropriate shock was not significantly different between the two groups (8.5%, 95%CI: 1.0–16.8% vs. 14.1%, 95%CI: 7.4–20.4; $P = 0.30$).

Inappropriate implantable cardioverter-defibrillator interventions

The 5-year cumulative rate of first inappropriate ICD therapy (either ATP or shock) was significantly lower among S-ICD patients (9.3%, 95%CI: 4.8–17.9% vs. 19.8%, 95%CI: 14.2–27.7; $P = 0.021$, *Figure 1C*). In propensity-adjusted multivariate Cox regression, S-ICD patients had lower risk of inappropriate ICD interventions (HR: 0.44; 95%CI: 0.20–0.95; $P = 0.038$). The 5-year cumulative rate of first inappropriate shock was non-significantly different between the two groups (9.3%, 95%CI: 4.8–17.9% vs. 15.4%, 95%CI: 10.6–22.5; $P = 0.071$) (*Figure 1D*). In propensity-adjusted multivariate Cox regression, S-ICD patients had a non-significant trend towards lower risk of inappropriate ICD shocks (HR: 0.50; 95%CI: 0.22–1.13; $P = 0.095$). The most common cause of inappropriate shock was non-cardiac or T-wave oversensing in the S-ICD group (75% of inappropriate therapies) and atrial fibrllation/supraventricular tachycardia (AF/SVT) (59% of inappropriate therapies) in the TV-ICD group.

In the matched cohort ($n = 250$), S-ICD patients were matched 1:1 to the nearest TV-ICD pair by gender (per cent male: 61.9% vs. 58.3%; $P = 0.65$), age (47.6 ± 13 vs. 47.4 ± 13; $P = 0.87$), history of atrial fibrillation (25.0% vs. 18.3%; $P = 0.29$), and availability of conditional VT therapy with active discriminators for supraventricular rhythms (96.5% vs. 95.0%; $P = 0.81$). As in the general cohort, the 5-year cumulative rate of first inappropriate therapy (ATP or shock) was significantly lower among S- vs. TV-ICD patients (10.9%, 95%CI: 1.3–19.6% vs. 23.3%, 95%CI: 15.3–30.5; $P = 0.021$), while the rate of first inappropriate shock was not significantly different between the two groups (10.9%, 95%CI: 1.3–19.6% vs. 18.4%, 95%CI: 11.1–25.1; $P = 0.11$).

Implantable cardioverter-defibrillator-related complications

The 5-year cumulative rate of ICD-related complications was similar (11.7%, 95%CI: 7.6–17.9% vs. 15.3%, 95%CI: 9.2–25.5; $P = 0.441$)

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Table 2 Clinical and device characteristics of patients with and without appropriate ICD therapies

	Appropriate ICD therapy $n = 59$				No appropriate ICD therapy $n = 368$				
	All*	S-ICD^ ($n = 10$)	TV-ICD^ ($n = 49$)	P^	All*	S-ICD^ ($n = 206$)	TV-ICD^ ($n = 162$)	P^	P*
Males, *n* (%)	32 (54.2)	10 (100)	22 (44.9)	0.001	236 (64.1)	155 (75.2)	81 (50)	<0.001	0.144
Age (y)	50.6 ± 12.9	45.7 ± 13.1	51.7 ± 12.7	0.182	46 ± 15	42.9 ± 14.4	49.0 ± 15.1	<0.001	0.007
Risk factors									
ESC 5-year risk of SD, % (IQR)	5.9 (2.8–8.4)	3.8 (1.9–6.8)	6.4 (3.0–8.7)	0.094	4.2 (2.7–6.4)	3.6 (2.5–5.5)	5.2 (3.4–7.1)	<0.001	0.021
End-stage disease, *n* (%)	14 (23.7)	3 (30)	11 (22.4)	0.609	51 (13.9)	30 (14.6)	21 (13.0)	0.659	0.050
Apical aneurysm, *n* (%)	6 (10.2)	1 (10)	5 (10.2)	0.984	15 (4.1)	9 (4.4)	6 (3.7)	0.749	0.045
ICD programming									
Conditional VT, *n* (%)	56 (94.9)	10 (100)	46 (93.9)	0.422	346 (94.0)	203 (98.5)	143 (88.3)	<0.001	0.786
Lower VT zone, (bpm)	171 (170–190)	210 (200–220)	171 (167–176)	<0.001	200 (180–220)	220 (200–220)	174 (167–182)	<0.001	<0.001
Lower VF zone, (bpm)	214 (200–230)	250 (240–250)	214 (200–222)	<0.001	240 (217–250)	250 (250–250)	214 (200–222)	<0.001	<0.001

ICD, implantable cardioverter-defibrillator; S-ICD, subcutaneous implantable cardioverter-defibrillator; TV-ICD, transvenous implantable cardioverter-defibrillator.

(*Table 3* and *Figure 2A*). The distribution of complications was different among the two study groups. Lead failure and device infection were the main complications in TV-ICD patients, while the most common complications in S-ICD patients were early battery depletion and peri-implant inappropriate shock due to air entrapment in the parasternal lead tunnel (*Table 3*).

When considering major lead-related complications (including infections, cardiac perforation, dislodgement, fracture, or failure), the 5-year rate of events was significantly lower in the S-ICD group (2.0%, 95%CI: 0.5–8.1% vs. 9.3%, 95%CI: 5.8–15.0; $P = 0.007$) (*Figure 2B*). In propensity-adjusted multivariate Cox regression analysis, S-ICD patients had lower risk of major lead-related complications (HR: 0.17; 95%CI: 0.038–0.79; $P = 0.023$). In the matched cohort ($n = 300$), S-ICD patients were matched 1:1 to the nearest TV-ICD pair by age (46.3 ± 14.5 vs. 45.7 ± 13.9; $P = 0.68$). As in the general cohort, the 5-year rate of major lead-related complications was significantly lower in the S-ICD group (1.1%, 95%CI: 1.0–3.0% vs. 9.6%, 95%CI: 4.4–14.4; $P = 0.023$).

Disease-related complications and mortality

The 5-year cumulative rate of disease-related complications was comparable among the two groups (7.2%, 95%CI: 3.4–15.1% vs. 11.4%, 95% CI: 7.4–17.6; $P = 0.498$). The 5-year risk in propensity-adjusted multivariate Cox regression was also non-significantly different (S-ICD HR: 0.64; 95%CI: 0.27–1.52; $P = 0.309$). The single most frequent cardiovascular event was hospitalization for heart failure (16 out of 21 events, 76.2%). There were no S-ICD patients explanted and re-implanted with a TV-ICD because of the need for pacing. However, one patient waiting for heart transplant died two months after S-ICD implantation with acute heart failure and third-degree AV block.

Six (2.8%) S-ICD and 19 (9.0%) TV-ICD patients died or underwent heart transplantation within the first 5 years, without differences in the cumulative event rates among groups (9.9%, 95%CI: 6.3–15.6% vs. 6.0%, 95%CI: 2.7–13.5; $P = 0.897$). The propensity-adjusted risk was also comparable (HR: 0.74; 95% 0.29–1.87; $P = 0.521$). There were two sudden cardiac deaths in the S-ICD and two in the TV-ICD group. Of these four patients (two males and two females), three were affected by end-stage HCM, and two had previously received appropriate TV-ICD interventions.

Discussion

This is the largest available retrospective clinical study that compared the outcomes of HCM patients implanted with a TV- or S-ICD. The main findings are that(1) the incidence of appropriate therapies (including ATP) was significantly lower in S-ICD as compared to TV-ICD patients, although the rate of appropriate shocks was comparable;(2) the rate of inappropriate arrhythmia detection followed by therapy delivery was lower in S-ICD patients, mainly as a consequence of ATP interventions in TV-ICD patients; (3) S- and TV-ICD patients experienced similar rate of device-related complications, albeit the risk of major lead-related complications was lower in S-ICD patients; (4) S- and TV-ICD patients displayed similar 5-year disease-related complications rate and survival.

Appropriate implantable cardioverter-defibrillator therapies

The rate of S- and TV-ICD interventions in this study is similar to that reported in previous series of HCM patients.[6,27–29] Transvenous ICD patients had significantly more appropriate ICD interventions as

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Table 3 Complications

	S-ICD ($n = 216$)	TV-ICD ($n = 211$)	*P*
All complications, *n* (%)	15 (6.9%)	21 (9.9%)	0.26
Implant-related, *n* (%)			
Severe pocket haematoma	1 (0.5)	0	0.26
Pneumo/haemothorax	0	1 (0.5)	
Cardiac tamponade	0	1 (0.5)	
Air entrapment with inapp. shock	4 (1.9)	0	
Lead-related, *n* (%)			
Lead failure or fracture	1 (0.5)	8 (3.8)	0.01
Lead dislodgment	0	3 (1.4)	
Device-related, *n* (%)			
Early battery depletion	7 (3.2)	1 (0.5)	0.02
Device hardware malfunction/failure	1 (0.5)	0	
Infections/erosions, *n* (%)			
Infection requiring extraction	1 (0.5)	3 (1.4)	0.02
Infection/erosion requiring revision	0	4 (1.9)	

S-ICD, subcutaneous implantable cardioverter-defibrillator; TV-ICD, transvenous implantable cardioverter-defibrillator.

compared to S-ICD patients. However, mortality was similar between the two groups. This might suggest that TV-ICD patients, owing to their more severe baseline clinical profile, had an excess of ventricular arrhythmia that were effectively treated with ATP. However, the risk of ICD interventions was corrected for relevant confounding clinical variables. Therefore, it is likely that many ICD interventions in the TV-ICD group could represent unnecessary treatments for VTs that would otherwise have ended spontaneously. Indeed, the higher intervention rate in TV-ICD patients was driven by excess ATP therapy, while there was no difference in the shock rate between ICD types. Moreover, half of the TV-ICD patients experienced their first appropriate ICD therapy for arrhythmias occurring in the conditional VT zone, while almost all S-ICD patients who received appropriate shocks had their arrhythmias in the VF zone. These findings are consistent with the results of the MADIT-RIT study[30] and with those recently reported in a large home monitoring-based analysis of ICD interventions in TV- and S-ICD patients with HCM,[15] suggesting that conservative ICD programming is indeed advisable, especially for patients undergoing primary prevention implantation. It is reasonable to speculate that the longer time-to-therapy in S-ICD compared to TV-ICD might be beneficial to reduce unnecessary treatment of self-terminating arrhythmias. Whereas a 19–22 s time-to-therapy is available by shipment and non-modifiable in S-ICDs, a similar setting needs tailored TV-ICD programming, as suggested by several trials and practical recommendations.[30–32] This is particularly important as far as ATP delivery is concerned, which has no delay after arrhythmia detection. The burden of therapies is hence inherently flawed by non-comparable diagnostic settings of TV- and S-ICD devices in retrospective observations. The ATP success rate in this study was close to 60%. Previous studies in HCM[33,34] and non-HCM patients[35] reported variable rates, ranging from 56% to 74%. As this study found a concerning 9.3% 5-year cumulative incidence of major lead-related complications in TV-ICD patients, it should be emphasized that in primary prevention HCM patients, the benefits of ATP should be carefully balanced against the risks of lead-related complications.

Inappropriate therapies, complications, and survival

Transvenous ICD patients had more inappropriate ICD interventions as compared to S-ICD patients. This higher rate was driven by excess of ATP therapies, while there were no differences in the rate of inappropriate shocks. Of note, inappropriate ATP interventions have been reported to increase morbidity and mortality in non-HCM patients[30] and may present a risk for induction of VT/VF.[33] However, as mortality and disease-related complications were comparable between S- and TV-ICD patients, it is reasonable to conclude that redundant ATP therapies did not convey excess morbidity or mortality in our study.

Consistent with previous reports, inappropriate therapies were mainly due to non-cardiac or T-wave oversensing in S-ICD patients[36] and AF or supraventricular rhythms in TV-ICD patients.[30] Of note, the majority of S-ICDs in this study was provided with the SMART Pass algorithm that minimizes T-wave oversensing. This might have contributed to a lower rate of inappropriate shocks as compared to earlier S-ICD patient series with comparable follow-up.[9] The TV-ICD patients were more commonly affected by AF and were less likely to receive conservative ICD programming. While the risk for inappropriate therapies was propensity-balanced and accounted for the history of AF and ICD programming with conditional VT zone, it is recognized that SVT discrimination algorithms in conditional zone are optimal by shipment programming in S-ICDs but not in TV-ICDs, who need proactive engagement of the treating electrophysiologist. This may play an advantage in preventing inappropriate detection.[37] Also, many early TV-ICDs had less performing discrimination algorithms from contemporary ones, explaining why ICD inappropriate shock rates are generally lower in more recent studies and trend lower in studies with longer follow-up.[38]

Overall, the rate of complications in the S-ICD group is similar to that recently reported in the general population of S-ICD recipients.[9] The incidence of complications in the TV-ICD group is consistent with previous studies in HCM patients.[3,4] In this study, S- and TV-ICD patients had similar 5-year cumulative incidence of complications. However, almost all S-ICD complications were inappropriate shocks owed to air entrapment in the sternal lead tunnel[18,39] and early battery depletion (Boston Scientific Medical Device Advisory for S-ICD models A209 and A219).[40] When considering only major lead-related complications, the incidence was significantly higher in TV-ICD patients. This finding is in line with previous observations in non-HCM patients.[8] Transvenous leads in this study included RIATA® and Sprint Fidelis® models, which are affected by a significant risk of conductor externalization and fracture, respectively. This might have contributed to S-ICD demonstrating a lower rate of lead-related complications. Of note, lead fracture has recently been found to impact on the S-ICD Model 3501 Electrode,[41] although the patients in this series did not experience any adverse effects related to this specific issue.

There were no differences in the 5-year rate of disease-related complications, death, or heart transplantation.

Study limitations

The main study limitation is its retrospective nature. Indeed, selection bias cannot be excluded. Despite accurate adjustment, there might be unknown confounding factors that remained unrecognized, such as detection time and discriminators programming in TV-ICDs, which improved along time. Moreover, TV-ICDs were programmed with lower conditional VT and VF therapy zone heart rates, which make both appropriate and inappropriate therapies more likely to occur. Secondly, as the S-ICD is a newly developed therapy, the average follow-up duration was longer in the TV-ICD group. Thirdly, TV-ICD

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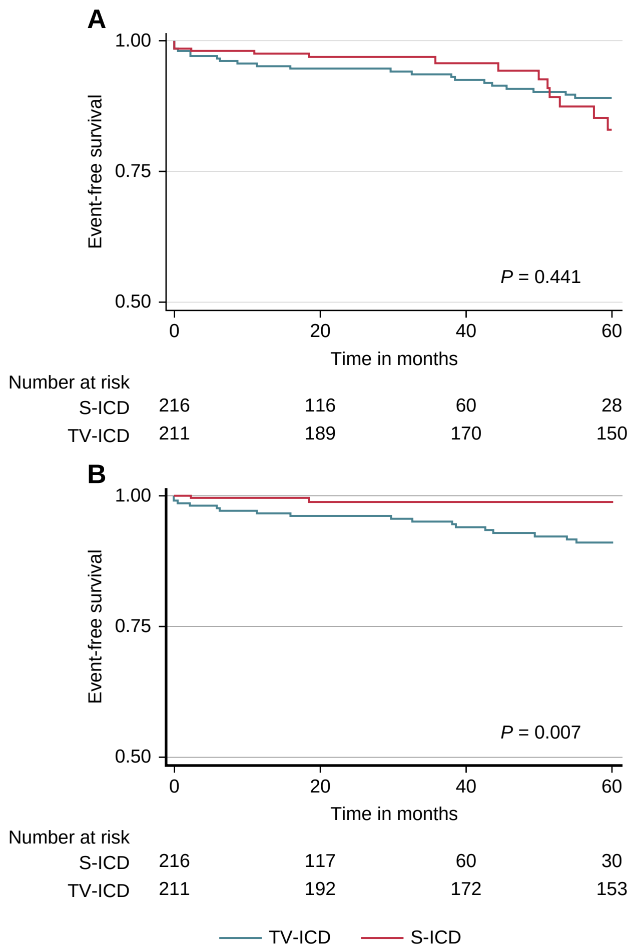

Figure 2 Covariate-adjusted Kaplan–Meier curves showing time to first ICD-related complication (panel *A*) and major lead-related complication (panel *B*). S-ICD, subcutaneous implantable cardioverter-defibrillator; TV-ICD, transvenous implantable cardioverter-defibrillator.

patients had more severe disease and higher baseline risk of ventricular arrhythmias. This difference might reflect the typical clinical profile of earlier ICD candidates with HCM. Although the risk for ICD interventions and complications was propensity-balanced and accounted for clinically relevant differences between groups, only a prospective and preferably randomized study would definitively clarify whether the adoption of one of the two devices confers an advantage in terms of equal efficacy and reduction of complications.

Conclusions

Hypertrophic cardiomyopathy patients implanted with a S-ICD exhibited a lower 5-year risk of appropriate and inappropriate ICD therapies, as well as major lead-related complications, in comparison to those with a TV-ICD. However, it is important to note that the rate of all-cause complications, disease-related complications, and mortality was similar between the two groups. Therefore, additional long-term follow-up is essential to determine whether the observed lower incidence of major complications could potentially lead to a morbidity or survival advantage in HCM patients with a S-ICD implant.

Funding

This research received no specific grant from any funding agency.

Conflict of interest: P.F. received speaker fees from Boston Scientific (BS) and research grants from Abbott and BS. M.Z. received speaker fees from Abbott, Biotronik, and BS. P.D.F. received speaker fees from Abbott, BS, and Medtronic. M.L. is an employee of BS.

Data availability

The experimental data used to support the findings of this study are available from the corresponding author upon reasonable request.

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