Title: Propensity-score Matched Comparison of Subcutaneous and Transvenous Implantable Defibrillator Therapy in the SIMPLE and EFFORTLESS studies.

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Short title: S-ICD versus TV-ICD therapy

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Background

Comparison of outcomes between subcutaneous and transvenous implantable cardioverter-defibrillator (S-ICD and TV-ICD) therapy is hampered by varying patient characteristics and complication definitions.

Objective

The aim of this analysis is to compare clinical outcomes of S-ICD and TV-ICD therapy in a matched cohort.

Methods

Patients implanted with de novo ICDs without need for pacing were selected from two studies: SIMPLE (n=1091 single and n=553 dual chamber TV-ICDs) and EFFORTLESS (n=798 S-ICDs). S-ICD patients were 1:1 matched on propensity score to TV-ICD patients. Propensity scores were calculated using 15 baseline characteristics including diagnosis. Kaplan-Meier estimates for complications requiring invasive intervention, appropriate shocks and inappropriate shocks were calculated at 3-year follow-up.

Results

The primary analysis yielded 391 patients pairs with balanced baseline characteristics, with mean age 55±14 years, 49% ischemic cardiomyopathy, mean LVEF 40%, 71% primary prevention and 89% of TV-ICDs were single chamber. Follow-up was mean 2.9 years in the S-ICD arm versus 3.3 in the TV-ICD arm. All-cause complications occurred in 9.0% of S-ICD versus 6.5% of TV-ICD patients, p=0.29. Appropriate shocks occurred in 9.9% of S-ICD versus 13.8% in TV-ICD patients, p=0.03 and inappropriate shocks in 11.9% in S-ICD versus 8.9% in TV-ICD patients (p=0.07). Total shock burden (20 versus 31, p=0.05) and appropriate shock burden per 100 patients years (9 versus 18, p=0.02) were lower for S-ICD patients, while inappropriate shock burden was equal (11 versus 13, p=0.56).

Conclusion

The earliest experience of the S-ICD demonstrates similar outcomes as contemporary TV-ICD therapy in a matched comparison with predominately single-chamber devices at three-year follow-up.

Condensed abstract (max 50)

In this matched cohort, subcutaneous ICD patients had significantly fewer lead complications and non-significantly more pocket and infectious complications than transvenous ICD patients. The incidence of patients with inappropriate shocks and the burden of shock per 100 patient years were not significantly different between the two groups.

What's new?

1. This largest matched analysis of clinical outcomes of transvenous and subcutaneous ICD therapy with over 7500 patient years follow-up.

2. The S-ICD had significantly fewer lead complications than TV-ICDs, but did not reduce the overall complication rate.

3. The incidence of patients with appropriate shocks and the burden of appropriate shocks per 100 patients years was significantly lower in the S-ICD arm.

4. There were significantly fewer appropriate shocks in the S-ICD arm and both all-cause shocks and inappropriate shocks were not significantly different.

Keywords

1. Implantable cardioverter-defibrillator
2. Complications
3. Shocks

Abbreviations

ATP – Anti-tachycardia pacing

DFT- Defibrillation Threshold Testing

ICD – Implantable cardioverter-defibrillator

S-ICD – Subcutaneous Implantable Cardioverter-defibrillator

TV-ICD – Transvenous Implantable Cardioverter-defibrillator

NYHA - New York Heart Association Classification

IQR – Interquartile range

SCD – Sudden Cardiac Death

VT – Ventricular tachycardia

VF – Ventricular fibrillation

Introduction

Implantable cardioverter-defibrillators (ICD) effectively reduce mortality in patients with a high risk of sudden cardiac death.(1) However, patients implanted with a conventional transvenous ICD (TV-ICD) suffer from complications that arise from endocardial leads. Lead-related complications include dislodgement, venous occlusion, lead failure and systemic infections, which can result in device malfunction and morbidity.(2)

The subcutaneous ICD (S-ICD) was developed to reduce lead-related complications.(3) The S-ICD system consists of a pulse generator and lead which are both positioned outside the thoracic cavity.(4) The lead of the S-ICD flexes with the smoother and slower respiratory movement of the chest wall instead of the rapid cardiac contractions that result in more mechanical stress on TV-ICD leads. Additionally, the subcutaneous position reduces the risk of systemic infection or endocarditis as the lead is not positioned in the vasculature or endocardium.

In current clinical practice, most S-ICDs are implanted in younger patients, with low co-morbidity, low structural heart disease and an average age of 50 years at implant in the largest published cohort. These patients may be more likely to experience complications as well as inappropriate shocks compared to the general ICD population, because of their active lifestyle.(5,6) Although several retrospective matched studies comparing clinical outcomes in patients with TV-ICDs and S-ICDs have been conducted with varying results, a comparison with sufficient power to detect differences in outcomes over a longer follow-up duration and with multicenter design is lacking.(7-10)

The objective of the current analysis is to compare mid-term clinical outcomes of S-ICD and TV-ICD therapy in a propensity matched cohort derived from two large, contemporary, multicenter studies.

Methods

Data sources

Data from two recent trials were used for this analysis: the randomized multicenter SIMPLE study (Shockless IMPLant Evaluation, n=2500, NCT00800384) and the single arm multicenter EFFORTLESS study (Evaluation oF Factors ImpacTing CLinical Outcome and Cost EffectiveneSS of the S-ICD, n=994, NCT01085435) of which the designs and main results have been published previously. Briefly, the SIMPLE study (funding and devices by Boston Scientific, Marlborough, Massachusetts, USA) randomized patients undergoing single, dual or resynchronization defibrillator implantation to peri-procedural defibrillation testing versus no defibrillation testing.(11) The EFFORTLESS registry (funding and devices by Boston Scientific, Marlborough, Massachusetts, USA) is a multicenter observational study that enrolled patients implanted with an S-ICD both prospective and retrospective.(12)

Study population

Patients aged >18 years and implanted with a de novo VVI or DDD transvenous ICD or a subcutaneous ICD were included: (SIMPLE n=1091 single and n=553 dual chamber TV-ICDs; EFFORTLESS n=798 S-ICDs). Patients excluded from this analysis were those implanted with a transvenous CRT-D, history of pacemaker, ICD or CRT-P/D at baseline or paced rhythms at baseline or post-implant (Figure 1).

Clinical endpoints

The primary outcome of the study was device-related complications, which were defined as all system-related complications requiring invasive intervention. The primary therapy outcomes were both appropriate and inappropriate shocks. Inappropriate shocks were those shocks delivered for heart rhythms other than ventricular tachycardia (VT) or ventricular fibrillation (VF). Appropriate shocks were all shocks delivered for VT or VF. Shock efficacy was evaluated in the same manner as the SIMPLE trial where the first appropriate therapy was used, in order to exclude multiple episodes per patient where subsequent shocks would be correlated to the first event. The first shock in the

first appropriately treated VT/VF episode was considered failed if the shock did not terminate the arrhythmia. All complications and therapy endpoints were adjudicated by a single internal adjudication committee of the sponsor prior to the current analysis to ensure that uniform definitions were applied in both cohorts.

Statistical Analysis

S-ICD patients were 1:1 matched to single-chamber TV-ICDs based on propensity scores using a <0.2 caliper. The remaining S-ICD patients were matched using the same caliper to dual-chamber TV-ICDs. Propensity score were calculated using logistic regression with device type (S-ICD or TV-ICD) as dependent outcome and 15 baseline characteristics (Table 1) as independent variables.

In the secondary analysis all eligible patients were included and stratified for their propensity scores in ten strata, using the same baseline variables as in the main analysis expect for LVEF, QRS duration, height and weight as these had missing data. The stratum-specific estimates of treatment effect were then pooled across strata to estimate an overall treatment effect. A sensitivity analysis was performed to assess the effect of the learning curve in the S-ICD arm by excluding the chronologic first 12 implants per implanter and their matched controls, as previously a significant decrease in device-related complications was shown at >12 implants per individual implanter.(13)

Baseline variables of the matched cohort were compared by calculating standardized mean differences and Chi-square test, Student's t-test or Mann-Whitney U test when appropriate. We used the Kaplan-Meier method to estimate the cumulative incidence of outcomes at three-year follow-up and compared using a log-rank test stratified by quintile of propensity score. Hazard ratios were obtained from Cox proportional hazard models and proportional mean models for recurrent events, and odds ratios from logistic models. All models adjusted for the baseline characteristics (Table 1). Cox and logistic regression models were stratified by quintile of propensity score for the propensity score matched analysis and by sub classification decile for the stratification analysis. Therapy rates per 100 patients-years are unadjusted and calculated by dividing the total number of shock by the

total follow-up duration. Statistical analyses were performed by N.W. using SAS, version 9.4, SAS Institute Incorporation, Cary, NC, USA.

Results

Demographics

The two study populations consist of a total of 994 S-ICD patients and 2500 TV-ICD patients of which 2442 (S-ICD n=798, TV-ICD n=1644) met the inclusion and exclusion criteria. In the unmatched cohort all baseline characteristics were significantly different (Table 1, left columns). Propensity score matching identified 391 patient-pairs with balanced baseline characteristics and no significant differences, which were used for the primary analysis (Table 1, right columns). The mean age in the matched cohort was 55±14 years, in 49% the diagnosis was ischemic cardiomyopathy, the mean left ventricular ejection fraction (LVEF) was 40%. In 71% of patients the indication for ICD therapy was primary prevention and 89% of TV-ICDs were single chamber devices. Follow-up was median 2.9±1.4 years in the S-ICD arm versus 3.3±0.8 in the TV-ICD arm.

Complications

Complications requiring invasive interventions occurred in 9.0% (95%CI 6.5%-12.3%) of S-ICD versus 6.5% (95%CI 4.4%-9.4%) in TV-ICD patients at three year follow-up, p=0.29 **(Figure 2**). Complications related to the lead occurred in 0.3% (95%CI 0.0%-1.8%) of S-ICD patients versus 2.3% (95%CI 1.2%-4.4%) of TV-ICD patients, p=0.03 (**Table 2)**. There were a total of nine lead complication in the transvenous arm, of which one was related to the atrial lead and eight were ventricular lead complications. Device-infection requiring invasive intervention was observed in 2.6% (95%CI 1.4%-4.7%) of S-ICD patients versus 0.5% (95%CI 0.1%-2.0%) of TV-ICD patients, p=0.09. None of these infection resulted in infective endocarditis and eight out of ten S-ICD patients and both TV-ICD patients were extracted. Complications related to the pulse generator pocket, which included erosion, hematoma. Pulse generator movement, wound discomfort and pocket seroma, were seen in 3.8% (95%CI 2.2% - 6.3%) of S-ICD patients versus 1.8% (95%CI 0.9% - 3.8%) of TV-ICD patients,

p=0.14. The mortality rate was non-significantly lower rate in the S-ICD arm, HR = 0.74, 95%CI 0.41-1.35, p=0.32). The three-year survival rate in the S-ICD arm was 93.7% versus 91.5% in the TV-ICD arm. A detailed table of complications is available in the supplemental table 2 and 3.

Therapy

There were fewer patients in the S-ICD group, 9.9% (95% CI 7.0%-13.9%), who received appropriate shocks compared to the TV-ICD group, 13.8% (95% CI 10.8%-17.8%), p=0.03 (**Figure 3**). First shock conversion efficacy for the first spontaneous episode of VT/VF was not different between S-ICD and TV-ICD (88.6% vs 88.6%, p=1.00). Inappropriate shocks occurred numerically more often in S-ICD patients, 11.9% (95%CI 8.8%- 15.9%) compared to TV-ICD patients 7.9% (95%CI 5.6%-11.1%), p=0.07 (Figure 4). The majority (77%) of inappropriate shocks in TV-ICD patients were due to SVT compared to 17% in S-ICD patients. The majority of inappropriate shocks (67%) in S-ICD patients were due to oversensing, of which 48% was cardiac and 19% non-cardiac oversensing.

The incidence of all-cause shocks (both appropriate and inappropriate shocks) did not differ between the groups (S-ICD 18.5%, 95%CI 14.7%-23.2%, TV-ICD 19.2%, 95%CI 15.6%-23.6%), p=0.62 (supplemental Figure). Anti-tachycardia pacing (ATP) was delivered prior to shock in 72.2% of appropriately treated episodes, and 89.0% of treated monomorphic VT episodes. The shock rates are unadjusted for device programming as this was not available for the TV-ICD patients. The all-cause shock burden per 100 patient-years was lower in the matched cohort, 20 in the S-ICD group versus 31 in the TV-ICD group, p=0.05 (Table 3). The difference was driven by a lower burden of appropriate shocks (9 vs 18 per 100 patients years, p=0.02), while the inappropriate shock burden did not differ (11 versus 13, p=0.56).

Patients that required an upgrade (S-ICD patients to single, dual-chamber or resynchronization defibrillator or TV-ICD single-chamber ICD patients to dual-chamber, or TV-ICD to resynchronization

defibrillator) were 1.3% (95%CI 0.5%-3.6%) in the S-ICD group and 2.1% (95%CI 1.0%-4.4%) in the TV-ICD group, p=0.48).

Secondary analyses

The secondary analysis stratified 2387 patients (97.7% of the initial cohort) for their propensity score (supplemental Table 1). The stratified hazard ratio for device-related complications was 1.21 (95%CI 0.87-1.69), p=0.26 (Table 2). For appropriate shock incidence the stratified hazard ratio was 0.59 (95%CI 0.43-0.80), p<0.001. The stratified hazard ratio for inappropriate shock incidence was 1.24 (95%CI 0.88-1.90), p=0.22. The hazard of all endpoints for the matched and stratification analysis is shown in Figure 5. Both all-cause shock burden (19 versus 36, p<0.001) and appropriate shock burden (9 versus 23, p<0.001) per 100 patient-years were significantly lower in the S-ICD group in the stratification cohort, while the inappropriate shock burden was not significantly different (10 versus 13, p=0.14) (Table 3).

Sensitivity analysis S-ICD learning curve

When the effect of the learning curve was considered for S-ICD implants, the rate of complications improved but did not significantly affect the comparison to matched TV-ICD patients. The hazard ratio for complications was 1.07 (95% CI: 0.73 to 1.56) p=0.74. The hazard ratio for inappropriate shock incidence adjusted for learning curve effect was 1.31 (95% CI: 0.90 to 1.89) p=0.16.

Discussion

Main findings

This study comparing clinical outcomes of S-ICD and TV-ICD therapy in two contemporary multicenter studies has several important findings. First, device-related complications did not differ significantly at three years of follow-up. Second, there were significantly fewer lead complications in the S-ICD arm. Third, the incidence of appropriate shocks was significantly lower in the S-ICD group and the incidence of inappropriate shocks was non-significantly lower in the TV-ICD group. The shock

burden for both all shocks and appropriate shocks was significantly lower for S-ICD, while the inappropriate shock burden was not significantly different.

Complications

Although the overall rate of device-related complications was low and similar in the two groups, differences in type of complications that occurred were observed. This study compared S-ICD to predominately single-chamber ICDs which would be expected to have the lowest complication rate for TV-ICDs. No recalled leads were included in this analysis, which may explain the low rate of lead complications observed. However; there were significantly fewer lead complications in the S-ICD group in both propensity matched (0.3% vs 2.3%, p=0.03) and stratification analysis (HR 0.19, p<0.001), despite mean follow-up duration of three years. This finding is consistent with a previous matched analysis that compared S-ICD to predominately dual chamber devices (11.5% in TV-ICD vs 0.9% in S-ICD) as well as in a recent meta-analysis comparing subcutaneous and transvenous ICD therapy.(7-10)

The S-ICD group had numerically more infectious complications in the propensity matched cohort, however the rate of infection complication was not significantly different in both the matched analysis and the stratification analysis. Infections occurred in just two patients (0.5%) in the TV-ICD matched group, while 29 (1.9%) occurred in TV-ICD match eligible patients. Rates of other non-lead related complications such as implant procedure and pocket related complications were similar, though pocket related complications were higher in the S-ICD group in the stratification cohort.

A previous study with data from the NCDR registry comparing acute procedure related complication revealed no significant difference between S-ICDs and single- or dual-chamber TV-ICDs.(14) However, when comparing single versus dual chamber TV-ICD, a lower rate of complications is seen in single chamber ICDs in both acute and longer term follow-up.(15) A single center matched comparison of S-ICDs and TV-ICDs in a cohort of predominately HCM and channelopathy patients revealed a

significantly higher complication rate in TV-ICD patients (20.3% versus 4.3%) during a mean follow-up of 30 months, although the observed complication rate may be higher than typically reported.(7)

In order to truly determine the position of the S-ICD, prolonged follow-up is needed as the benefits are expected on the long-term with respect to lead complications. It is well known that transvenous leads fail at higher rates between five and ten years post implant than in the first five years post implantation. The importance of long-term follow-up is underscored by the median survival of ICD patients in the Swedish ICD registry, which is more than ten years compared to most ICD studies reporting follow-up of only a few years.

Therapy

The total shock incidence in this matched analysis was not significantly different and trended lower in the S-ICD group, which was driven by a reduction in appropriate shock incidence in the S-ICD group. Also, the total shock burden and appropriate shock burden was significantly lower in the S-ICD group. The rate of shocks per 100 patient years (20 for S-ICD; 31 for TV-ICD) is similar to the rates observed in the ADVANCE III single chamber cohort which demonstrated a 50% reduction comparing long detection (30/40 intervals) vs standard (18/24).(25) The S-ICD rate of appropriate (9) and inappropriate (11) therapy was also similar to the rate in ADVANCE III long-detection arm (14 and 10) per 100 patient years.(16) Although information on programmed settings for delay to therapy was not available for the TV-ICD group in this matched analysis, it is probable that the nominally longer time to therapy for the S-ICD allows some VTs to terminate spontaneously leading to the observed reduction in appropriate shocks. It is important to consider that S-ICD patients in this cohort were selected for the device only if their physicians did not expect them to benefit from ATP. Therefore, the results are not applicable to an unselected population such as patients with (prolonged) non-sustained and sustained monomorphic ventricular tachycardia. Currently, a novel ATP enabled leadless cardiac pacemaker (LCP) is in development that can be wirelessly commanded by the S-ICD

to initiate ATP. In the future the LCP may be added to an implanted S-ICD system when a patient has monomorphic VT that cannot be treated with anti-arrhythmic drugs or ablation.(17)

Previous studies reported an inappropriate shock rate of 7% at one-year follow-up for the S-ICD.(6) These results are often, but inaccurately, compared to TV-ICD cohorts such as MADIT-RIT with a 2% yearly rate that not only applied therapy reduction programming but also excluded patients with atrial fibrillation. The perceived rate of inappropriate shocks is based largely on studies of older patients of which many had CRT-D devices. It has been shown that ICD patients have more than double the rate of inappropriate shocks compared to CRT-D recipients.(18) It is also known that younger patients have a higher rate of inappropriate shocks.(5) In the ICD cohort in MADIT-RIT and the single-chamber ICD cohort in ADVANCE III over 12 months the incidence of inappropriate shock was 5%, both with an average age of over 63 and 62 respectively, whereas patients in this cohort were on average 55 years of age. This matched analysis demonstrates the importance of balancing patient characteristics when comparing inappropriate shocks.

Device programming also influences the incidence of inappropriate shocks. In this analysis we could only control patient characteristics due to unavailability of device programming in the TV-ICD group. Although there was a trend towards more inappropriate shocks in the S-ICD group, the absolute inappropriate shock rate differed by 4% at three years of follow-up. The currently ongoing UNTOUCHED S-ICD study, which applies the same inclusion criteria and device programming as MADIT-RIT, will determine how the S-ICD inappropriate shock rate compares to the inappropriate shock rate in TV-ICD patients.(19) Also, the UNTOUCHED study incorporates the second generation S-ICD that employs the improved rhythm discrimination algorithms to reduce T-wave oversensing.(20)

Clinical implications

The results from this study support the use of the S-ICD as a valuable alternative to a TV-ICD in the patient population represented in this study. The premise of the S-ICD is to reduce lead

complications, particularly lead failure, that occurs over the long-term. To date, no spontaneous lead failures have been reported for the S-ICD. Another concern that may have limited adoption of the first generation S-ICD is the reported inappropriate shock rate. This study puts the inappropriate shock rate in the appropriate context and may reassure both implanters and patients that the absolute difference in the first generation S-ICD over three years follow-up was 4%.

Limitations

The retrospective nature of this analysis and the difference in the design of the EFFORTLESS and SIMPLE studies introduce several important limitations that apply to this manuscript. The first limitation concerns the unavailability of details on programming of the therapy zones (Fast VT and VF zone) in the SIMPLE database. Therefore, we were unable to control for this factor that is strongly associated with the incidence of both appropriate and inappropriate shocks. Secondly, the population included in the primary matched cohort does not represent the general ICD population in most Western countries. Patients were relatively young with only moderately impaired LVEF. Thirdly, the follow-up duration of in this study was probably too short to assess the benefit of the S-ICD with respect to long-term lead complications. This study has also several strengths. First, the sample size of both the primary and secondary analysis provide sufficient power to detect meaningful clinical differences in clinical outcomes. The multicenter design of both studies increases the generalizability of the results from this analysis.

Conclusion

The earliest experience of the S-ICD demonstrates a similar complication rate as contemporary TV-ICD therapy in a matched comparison with predominately single chamber devices at three year follow-up. There were significantly fewer lead complications in the S-ICD arm. The incidence of appropriate shocks was significantly lower in the S-ICD group and the incidence of inappropriate shocks was non-significantly lower in the TV-ICD group, however the analysis could not be adjusted for device programming. Long-term randomized data is needed to establish the position of the S-ICD.

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403 **Table 1 title**: baseline characteristics of the full and matched cohort.

	Full cohort				Matched cohort			
Characteristic	**S-ICD (N=798)**	**TV-ICD (N=1644)**	**P-value**	**Standardized Difference**	**S-ICD (N=391**	**TV-ICD (N=391)**	**P-value**	**Standardized Difference**
Age (years) Mean ± SD	49 ± 16	62 ± 12	< 0.001	0.90	54 ± 16	55 ± 13	0.21	0.09
BMI (kg/m^2) Mean ± SD	27 ± 6	28 ± 5	0.035	0.09	28 ± 6	28 ± 5	0.57	0.04
LVEF (%) Mean ± SD	42.9 ± 18.0	34.2 ± 13.5	< 0.001	0.55	39.4 ± 17.3	39.8 ± 16.9	0.71	0.03
QRS (ms) Mean ± SD	104 ± 21	110 ± 26	< 0.001	0.24	106 ± 22	106 ± 20	0.66	0.03
Female	221 (27.7%)	286 (17.4%)	< 0.001	0.25	92 (23.5%)	72 (18.4%)	0.08	0.13
Device								
S-ICD	798 (100.0%)	0 (0.0%)	< 0.001	1.01	391 (100.0%)	0 (0.0%)	< 0.001	0.51
DDD TV-ICD	0 (0.0%)	553 (33.6%)	< 0.001	1.01	0 (0.0%)	45 (11.5%)		
VVI TV-ICD	0 (0.0%)	1091 (66.4%)	< 0.001	1.01	0 (0.0%)	346 (88.5%)		
Primary Prevention	552 (69.2%)	1098 (66.8%)	0.238	0.05	272 (69.6%)	279 (71.4%)	0.58	0.04
Hypertension	238 (29.8%)	1033 (62.8%)	< 0.001	0.70	168 (43.0%)	169 (43.2%)	0.94	0.01
Atrial Fibrillation	121 (15.2%)	347 (21.1%)	< 0.001	0.15	80 (20.5%)	77 (19.7%)	0.79	0.02
Stroke/TIA	43 (5.4%)	155 (9.4%)	< 0.001	0.15	30 (7.7%)	29 (7.4%)	0.89	0.01
Diabetes	90 (11.3%)	457 (27.8%)	< 0.001	0.43	66 (16.9%)	64 (16.4%)	0.85	0.01
Heart Failure	215 (26.9%)	1043 (63.4%)	< 0.001	0.79	155 (39.6%)	153 (39.1%)	0.88	0.01
NYHA								
II	109 (14.1%)	604 (37.0%)	< 0.001	0.84	88 (22.5%)	92 (23.5%)	0.66	0.11
III	54 (7.0%)	268 (16.4%)	< 0.001	0.84	43 (11.0%)	38 (9.7%)		
IV	3 (0.4%)	11 (0.7%)	< 0.001	0.84	2 (0.5%)	0 (0.0%)		
CABG	62 (7.8%)	348 (21.2%)	< 0.001	0.39	51 (13.0%)	42 (10.7%)	0.32	0.07
Impaired Renal Function	58 (7.3%)	267 (16.2%)	< 0.001	0.28	43 (11.0%)	33 (8.4%)	0.23	0.09
Ischemic	258 (33.2%)	1112 (67.6%)	< 0.001	0.73	187 (47.8%)	194 (49.6%)	0.62	0.04
Non-Ischemic Diagnosis								
Channelopathy*	143 (18.4%)	56 (3.4%)	< 0.001	1.03	35 (9.0%)	34 (8.7%)	0.90	0.07
DCM	62 (8.0%)	288 (17.5%)	< 0.001	1.03	41 (10.5%)	33 (8.4%)		
HCM	109 (14.0%)	66 (4.0%)	< 0.001	1.03	37 (9.5%)	39 (10.0%)		
Other‡	205 (26.4%)	122 (7.4%)	< 0.001	1.03	91 (23.3%)	91 (23.3%)		

* ARVD, Brugada, CPVT, Idiopathic VF, LQTS ǂ Non-ischemic cardiomyopathy, valvular disease, structural defect, syncope of unknown origin, myocarditis, cardiac sarcoidosis and unknown.

BMI – Body Mass Index, CABG = Coronary artery bypass graft; DCM - Dilated Cardiomyopathy, HCM - Hypertrophic Cardiomyopathy, LVEF – Left ventricular ejection fraction, NYHA – New York Heart Association classification, TIA – Transient ischemic attack.

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405 **Table 1 caption:** N (%), unless labeled Mean ± SD

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Table 2 title: Clinical outcomes of the matched cohort: three-year complication free rate

	Matched cohort			Stratified Cohort			
	S-ICD n=391	**TV-ICD n=391**		**S-ICD n=798**	**TV-ICD n=1644**		
Category	**Freedom from Complication (%)**	**Freedom from Complication (%)**	**P-value***	**Freedom from Complication (%)**	**Freedom from Complication (%)**	**Hazard Ratio (95%CI)**	**P-value***
All Complications (%)	**34 (91.0)**	**25 (93.5)**	**0.29**	**80 (88.6)**	**155 (90.1)**	**1.21 (0.87, 1.69)**	0.26
Pocket (%)	14 (96.2)	7 (98.2)	0.14	28 (95.9)	34 (97.9)	2.04 (1.10, 3.80)	0.02
Lead (%)	1 (99.7)	9 (97.7)	0.03	5 (99.3)	64 (95.9)	0.18 (0.07, 0.50)	<0.001
Infection (%)	10 (97.4)	2 (99.5)	0.09	21 (97.2)	29 (98.1)	1.41 (0.69, 2.88)	0.35
Implant (%)	7 (98.2)	4 (99.0)	0.32	15 (97.9)	30 (98.1)	1.43 (0.67, 3.02)	0.35
Inappropriate Shock (%)	3 (99.0)	2 (99.5)	0.85	7 (98.9)	10 (99.3)	2.69 (0.73, 9.93)	0.14
Pulse Generator System (%)	1 (99.7)	3 (99.2)	0.38	7 (98.9)	12 (99.2)	1.11 (0.35, 3.55)	0.85
Other (%)	1 (99.7)	0 (100)	N/A	2 (99.6)	1 (99.9)	16.30 (0.48, 556.89)	0.12

Pocket = Erosion, Hematoma. PG movememt, wound discomfort, Pocket Seroma
Lead = Electrode movement, Dislodgment, Unable to capture
Infection = Incision/Superficial Infection, Infection with device removal
Implant = Sub-optimal PG or electrode position, Unable to Convert, perforation with tamponade, Pneumothorax, Thromboembolic events
Inappropriate shock = SVT or Cardiac Oversensing (with invasive intervention)
PG System = Inability to Communicate with the Device, Early ERI, Other - PG system
Other = Near Syncope, Other: Cardiac

Table 2 caption: *P-values derived from Cox-proportional hazard model and follow-up beyond three years was censored.

Table 3 title: Rate of delivered ICD shocks per 100 patient-years

	Propensity score matched cohort				Stratification cohort			
	S-ICD	**TV-ICD**	**HR**	**P-value**	**S-ICD**	**TV-ICD**	**HR**	**P-value**
All shocks	20	31	0.58	0.05	19	36	0.58	<0.001
Appropriate shocks	9	18	0.41	0.02	9	23	0.47	<0.001
Inappropriate shocks	11	13	0.83	0.56	10	13	0.75	0.19

Table 3 Caption: HR – Hazard ratio. P-values are calculated using proportional mean models to allow for recurrent events (Appropriate and inappropriate shock deliveries).

Figure legends

Figure 1 title: Patient Flowchart

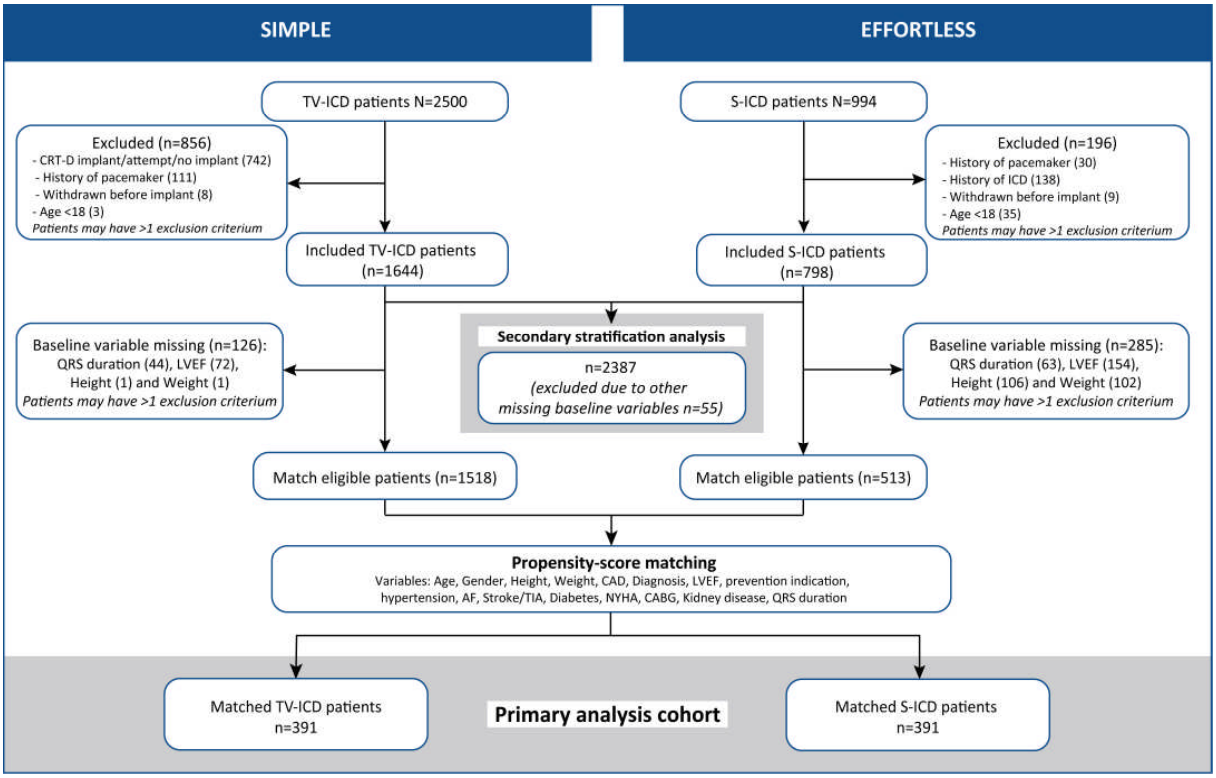


Figure 1 caption: TV-ICD – transvenous implantable cardioverter-defibrillator, S-ICD – subcutaneous implantable cardioverter-defibrillator, CRT-D – cardiac resynchronization therapy defibrillator, ICD – implantable cardioverter-defibrillator, LVEF – left ventricular ejection fraction, CAD – Coronary artery disease, AF – atrial fibrillation, TIA – transient ischemic attack, NYHA – New York Heart Association classification, CABG – Coronary artery bypass graft.

Figure 2 title (REPRESENTIVE FIGURE): KM plot for device-related complications requiring invasive intervention in the primary matched cohort.

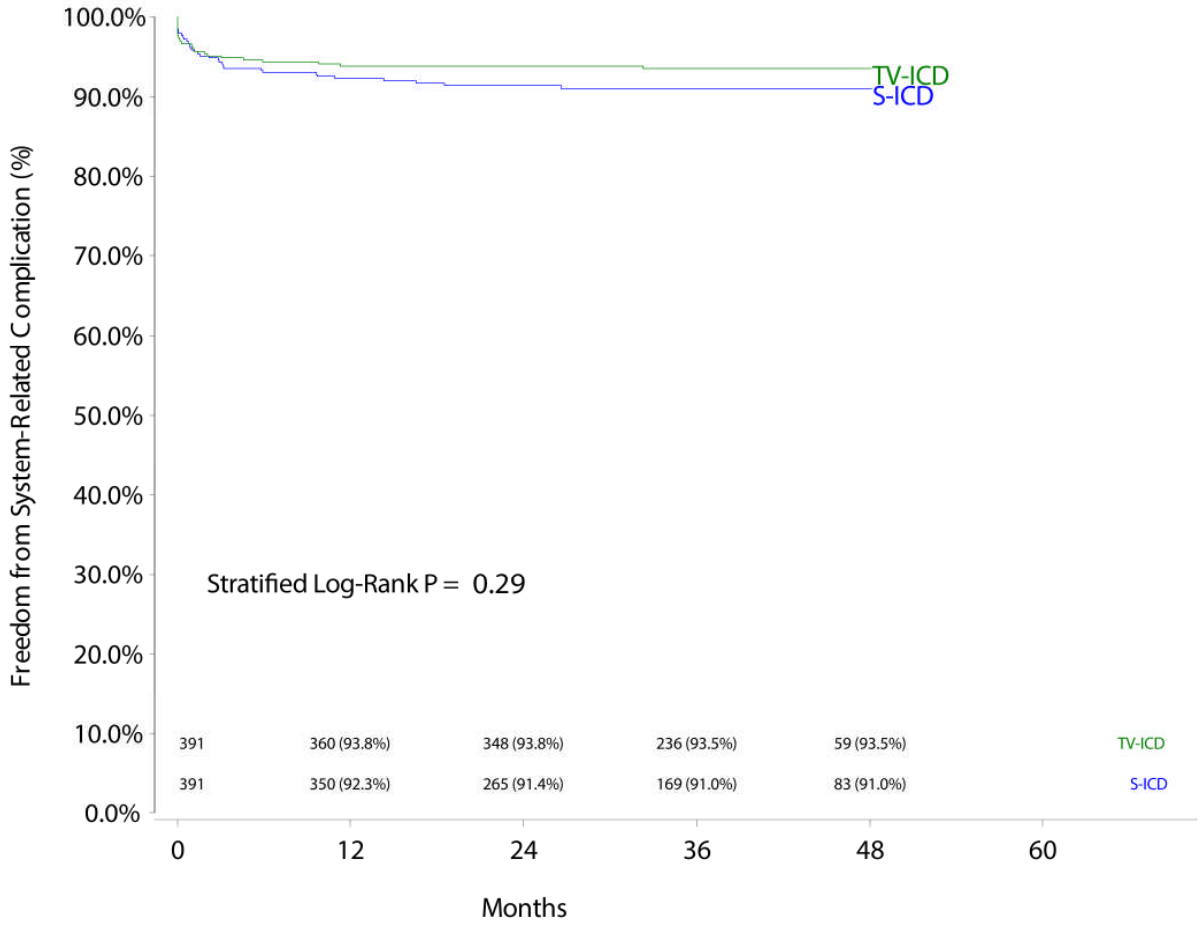
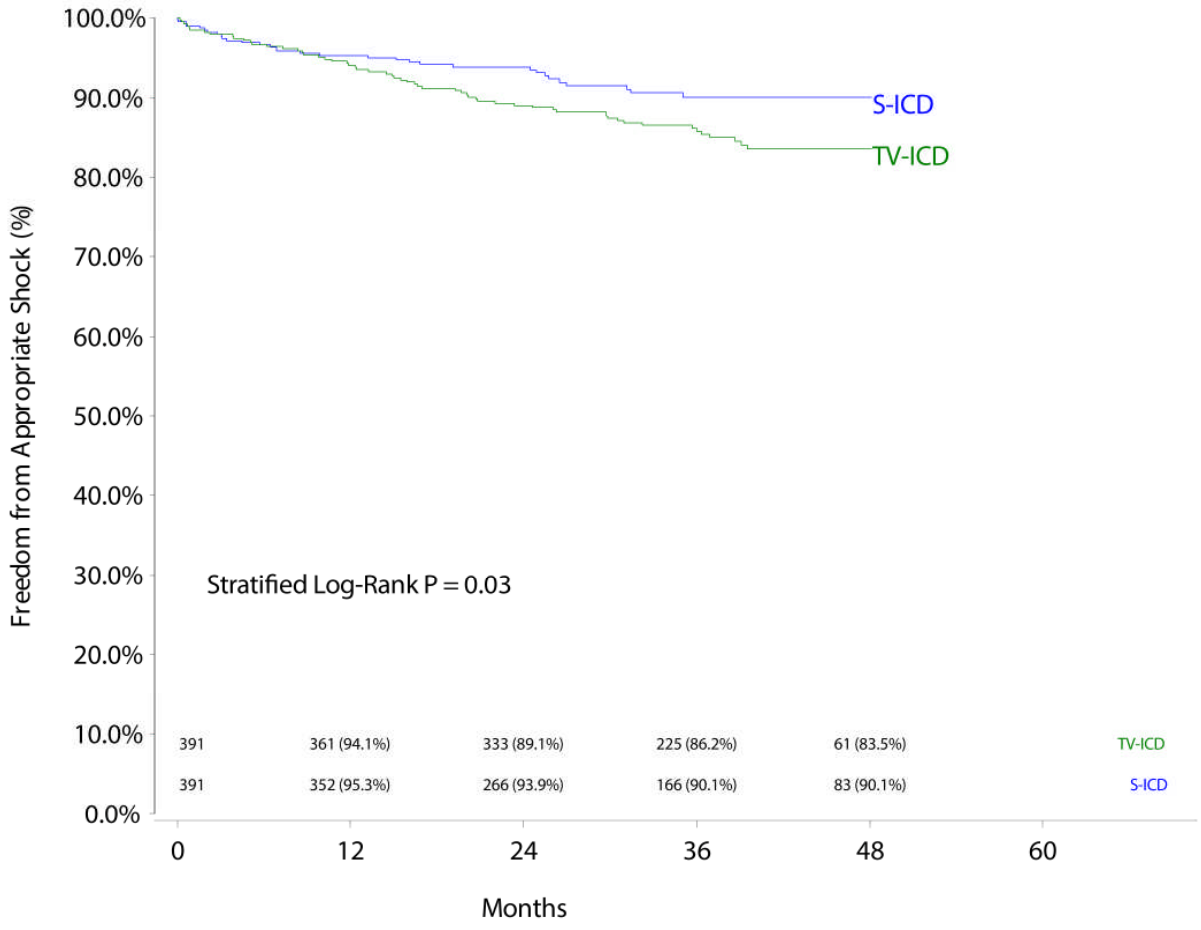


Figure 2 caption (REPRESENTIVE FIGURE): S-ICD – subcutaneous implantable cardioverter-defibrillator, TV-ICD – transvenous implantable cardioverter-defibrillator**.**

437 **Figure 3 title:** KM plot for appropriate shocks in the primary matched cohort.



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439 **Figure 3 caption:** S-ICD – subcutaneous implantable cardioverter-defibrillator, TV-ICD – transvenous

440 implantable cardioverter-defibrillator.

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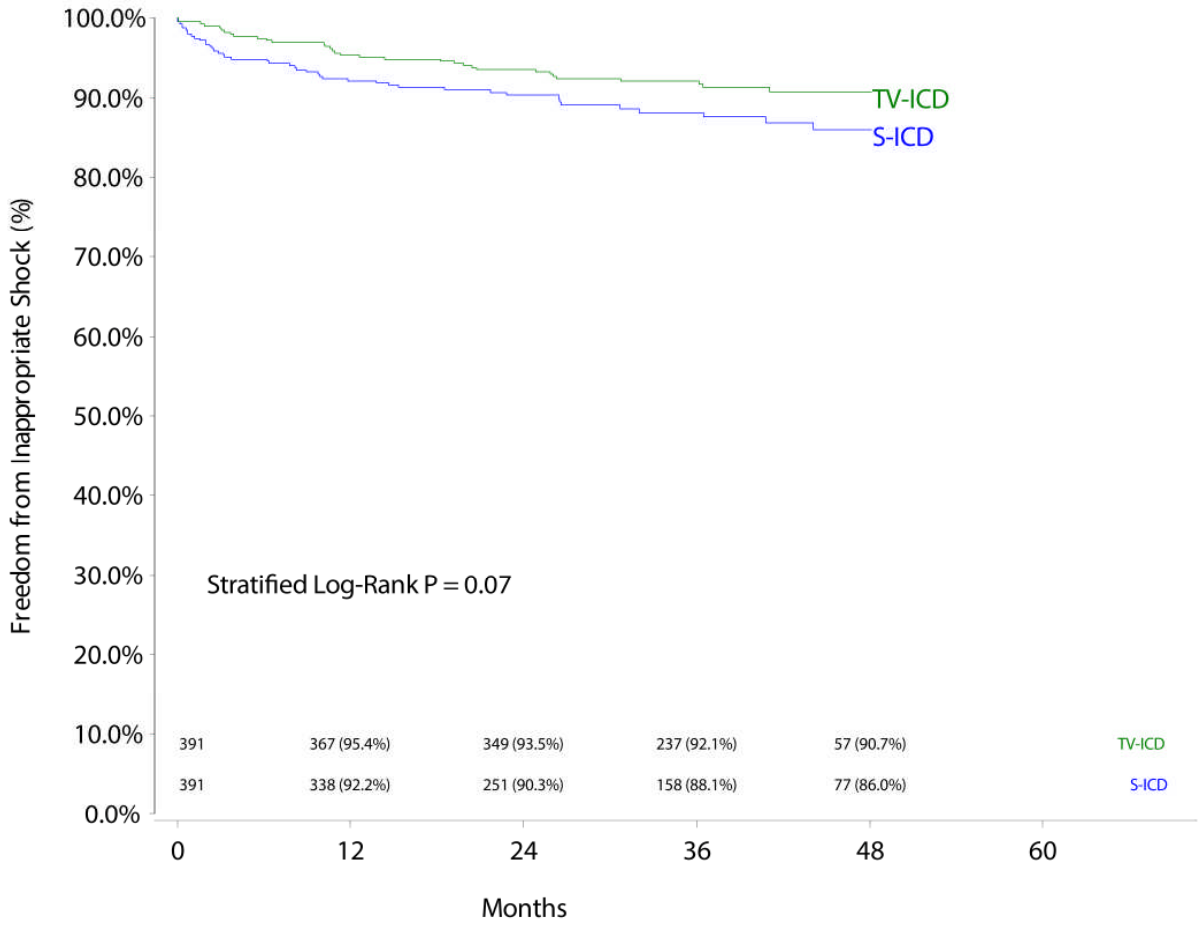
442 **Figure 4 title:** KM plot for inappropriate shocks in the primary matched cohort



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444 **Figure 4 caption:** S-ICD – subcutaneous implantable cardioverter-defibrillator, TV-ICD – transvenous

445 implantable cardioverter-defibrillator.

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Figure 5 title: Hazard of outcome by cohort including propensity matched and full stratification cohorts

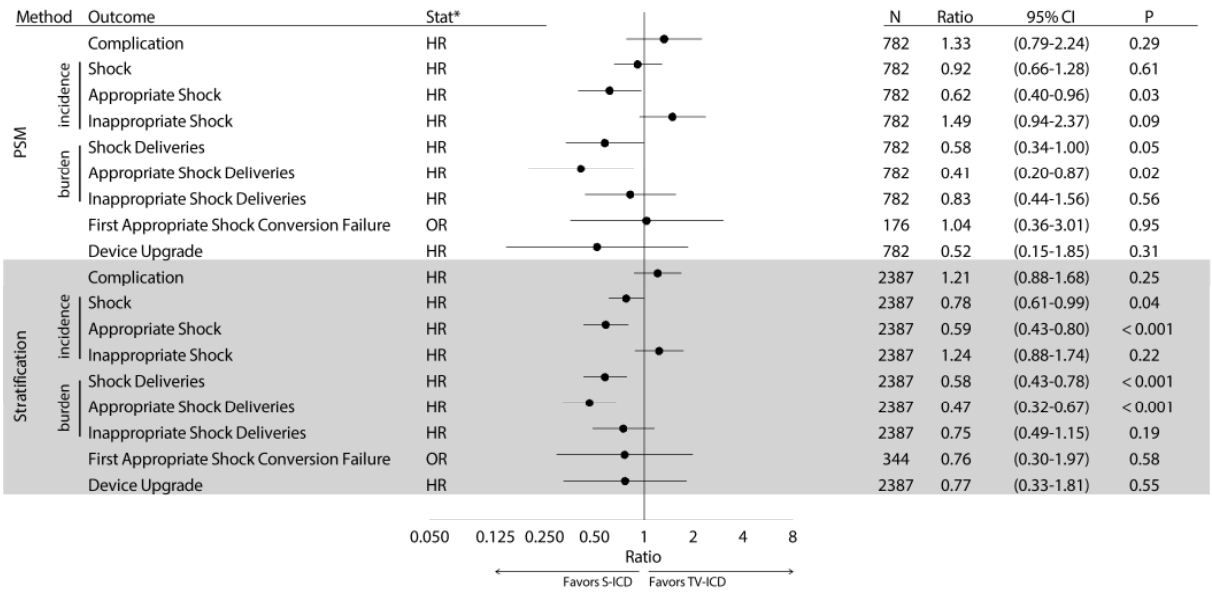

Figure 5 caption: PSM- Propensity-score matched cohort, Stratification – full cohort stratified for propensity score. Hazard ratio's, odds ratio's and p-values were calculated using Cox proportional hazard models or proportional mean models to allow for recurrent events (Appropriate and inappropriate shock deliveries) using all available follow-up (up to and beyond three-years in both arms).