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SYSTEMATIC REVIEW AND META-ANALYSIS

Subcutaneous Versus Transvenous Implantable Defibrillator Therapy: A Systematic Review and Meta-Analysis of Randomized Trials and Propensity Score–Matched Studies

Khi Yung Fong *; Colin Jun Rong Ng, MBBS*; Yue Wang, MD, MRCP, MMed; Colin Yeo, MBBS, DRCPSC; Vern Hsen Tan, MBBS, MRCP, CCDS, CEPS

BACKGROUND: Subcutaneous implantable cardioverter-defibrillators (S-ICDs) have been of great interest as an alternative to transvenous implantable cardioverter-defibrillators (TV-ICDs). No meta-analyses synthesizing data from high-quality studies have yet been published.

METHODS AND RESULTS: An electronic literature search was conducted to retrieve randomized controlled trials or propensity score–matched studies comparing S-ICD against TV-ICD in patients with an implantable cardioverter-defibrillator indication. The primary outcomes were device-related complications and lead-related complications. Secondary outcomes were inappropriate shocks, appropriate shock, all-cause mortality, and infection. All outcomes were pooled under random-effects meta-analyses and reported as risk ratios (RRs) and 95% CIs. Kaplan–Meier curves of device-related complications were digitized to retrieve individual patient data and pooled under a 1-stage meta-analysis using Cox models to determine hazard ratios (HRs) of patients undergoing S-ICD versus TV-ICD. A total of 5 studies (2387 patients) were retrieved. S-ICD had a similar rate of device-related complications compared with TV-ICD (RR, 0.59 [95% CI, 0.33–1.04]; P=0.070), but a significantly lower lead-related complication rate (RR, 0.14 [95% CI, 0.07–0.29]; P<0.0001). The individual patient data–based 1-stage stratified Cox model for device-related complications across 4 studies yielded no significant difference (shared-frailty HR, 0.82 [95% CI, 0.61–1.09]; P=0.167), but visual inspection of pooled Kaplan–Meier curves suggested a divergence favoring S-ICD. Secondary outcomes did not differ significantly between both modalities.

CONCLUSIONS: S-ICD is clinically superior to TV-ICD in terms of lead-related complications while demonstrating comparable efficacy and safety. For device-related complications, S-ICD may be beneficial over TV-ICD in the long term. These indicate that S-ICD is likely a suitable substitute for TV-ICD in patients requiring implantable cardioverter-defibrillator implantation without a pacing indication.

Key Words: cardiac arrythmias ■ implantable cardioverter-defibrillator ■ meta-analysis

Implantable cardioverter-defibrillators (ICDs) improve survival in patients with a history of ventricular arrhythmias and among selected patients with reduced left ventricular function regardless of cause.[1,2] Transvenous ICDs (TV-ICDs) have long been the mainstay of therapy for these patients,[3] but the incidence

Correspondence to: Vern Hsen Tan, MBBS, MRCP, CCDS, CEPS, Department of Cardiology, Changi General Hospital, Singapore, 2 Simei Street 3, Singapore 529889. Email: tan.vern.hsen@singhealth.com.sg

*K. Y. Fong and C. J. R. Ng are co-first authors.

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CLINICAL PERSPECTIVE

What Is New?

- This meta-analysis uses both study-level data and individual patient data from high-quality studies, comparing subcutaneous implantable cardioverter-defibrillator versus conventional transvenous implantable cardioverter-defibrillator therapy.
- Subcutaneous implantable cardioverter-defibrillator was superior to transvenous implantable cardioverter-defibrillator in terms of lead-related complications while demonstrating comparable efficacy and safety.
- In addition, there was a suggestion of long-term benefit of subcutaneous implantable cardioverter-defibrillator over transvenous implantable cardioverter-defibrillator with regard to device-related complications, which is yet unrevealed because of the low number of high-quality studies in the literature.

What Are the Clinical Implications?

- Subcutaneous implantable cardioverter-defibrillator is likely a suitable alternative for transvenous implantable cardioverter-defibrillator for patients requiring implantable cardioverter-defibrillator implantation without a pacing indication, although further research is needed to elucidate the long-term safety and efficacy of both modalities.

Nonstandard Abbreviations and Acronyms

ATP	antitachycardia pacing
IAS	inappropriate shocks
IPD	individual patient data
PRAETORIAN	Prospective Randomized Comparison of Subcutaneous and Transvenous Implantable Cardioverter Defibrillator Therapy
PSM	propensity score–matched study
S-ICD	subcutaneous implantable cardioverter-defibrillator
TV-ICD	transvenous implantable cardioverter-defibrillator

of short- and long-term device-related complications remains high.[4,5] The reported 10-year mechanical complication rates are as high as 1 in 4,[6] and many such complications occur in connection with the device leads,[5] which remains the Achilles' heel of the TV-ICD system despite continued advancements in technology. Moreover, if transvenous lead extraction is eventually required, there is a risk of major complications necessitating urgent cardiac surgery, which carries significant morbidity and mortality.[7]

Against this backdrop, subcutaneous ICDs (S-ICDs) offer several advantages over TV-ICD in principle. These include eliminating the risks of vascular access–related complications and reducing or eliminating the need for fluoroscopy during implantation,[8] a lower risk of severe infection,[9] and a lower rate of acute lead-related complications such as lead dislodgement.[10]

Current recommendations for the use of S-ICD are based purely on nonrandomized studies,[3,11] as they were published before the release of data from the randomized PRAETORIAN[12] (Prospective Randomized Comparison of Subcutaneous and Transvenous Implantable Cardioverter Defibrillator Therapy) trial. Accordingly, there is a need for a comprehensive comparison of S-ICD to TV-ICD based on high-quality data. Given that PRAETORIAN[12] is the only published randomized controlled trial (RCT) addressing this issue, we sought to also pool data from propensity score–matched studies (PSMs) related to this issue. PSMs have shown to be empirically equivalent to RCTs in generating unbiased estimates of the efficacy of treatment while eliminating confounding factors and biases to a large extent.[13,14]

Therefore, the objective of this meta-analysis is to evaluate the performance of S-ICD versus TV-ICD in patients with an indication for ICD, focusing on device-related complications and lead-related complications as primary outcomes and using data from RCTs and PSMs.

METHODS

Data Access and Responsibility

Tan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. This article makes use of publicly available data from published studies; therefore, no original or additional data are available for sharing.

Literature Search

This systematic review and meta-analysis of S-ICD versus TV-ICD was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[15] The study design and review protocol were registered with the International Prospective Register of Systematic Reviews.

Two independent reviewers (K.Y.F. and C.J.R.N.) searched PubMed, EMBASE, Web of Science, and the Cochrane Controlled Register of Trials (CENTRAL) for relevant articles without language restrictions. The search strategy included the concepts of S-ICD, TV-ICD, RCTs, and PSMs (Table S1). In addition, bibliographies

of included studies were screened, and a search on Google Scholar using the first and last author of each included study was conducted to ensure that the review included all relevant studies. The search was conducted from database inception to September 25, 2021. Retrieved abstracts and full texts were reviewed by 2 independent investigators (K.Y.F. and C.J.R.N.); conflicts were resolved after discussion among the authors in this article (K.Y.F., C.J.R.N., Y.W., C.Y., and V.H.T.). RCTs or PSMs comparing S-ICD versus TV-ICD in patients with an ICD indication or at risk of sudden cardiac death were included in this review. If multiple publications of the same trial were retrieved, the most recent and informative publication was included.

Case-control studies that did not use PSM, case reports, case series, reviews, and conference abstracts were excluded. Studies reporting in-hospital outcomes without long-term follow-up were also excluded. Corresponding authors of the studies were contacted to provide unpublished data if any.

Data from the included studies were extracted by K.Y.F. and C.J.R.N. using a standardized data collection template with predefined data fields including study characteristics, patient demographics, and outcomes. RCTs were assessed for risk of bias by K.Y.F. and C.J.R.N. using the Cochrane Risk of Bias 2 tool for RCTs, and PSMs were assessed using the Newcastle-Ottawa Scale.

Comparative Meta-Analysis

The primary outcomes measured were (1) device-related complications, which was defined as the occurrence of complications necessitating invasive intervention; and (2) lead-related complications, which include lead failure, lead dislodgement, cardiac perforation, and pneumothorax. Secondary outcomes were inappropriate shocks (IAS), which include cardiac oversensing, supraventricular tachycardia, or atrial fibrillation (AF); appropriate shock; all-cause mortality; and infection. For all outcomes, the respective number of events and number of participants per arm were analyzed and reported as risk ratios (RRs) and 95% CIs. Random-effects Mantel–Haenszel models were used in light of heterogeneity in TV-ICD devices used and to support generalization inferences beyond the included studies.[16] Heterogeneity was considered low, moderate, or considerable for I^2 values <40%, 40% to 75%, and >75%, respectively.[17]

Individual Patient Data Meta-Analysis

Considering the rapid advancements in ICD therapy, more precise methods are needed to quantify the comparison of S-ICD against TV-ICD. The primary outcome of device-related complications was supported by Kaplan–Meier curves with risk tables in several included studies. Hence, an online software application[18] that implemented analytical methods outlined by Guyot et al[19] was used to attain information on survival from device-free complications of individual patients and pool them under an individual patient data (IPD) meta-analysis, which is recognized as the gold standard approach for evidence synthesis.[20–24] Images of Kaplan–Meier curves from included studies were digitized to obtain step function values and step timings. Survival information of individual patients was then recovered based on the numerical solutions to the inverted Kaplan–Meier product-limit equations and provided risk tables. The IPD data set was reconstructed by K.Y.F. and was approved by C.J.R.N. and V.H.T. by visual comparisons and by comparing log-rank values of the reconstructed data set against originally reported values where available.

As part of the 1-stage meta-analysis, the Kaplan–Meier method was used to determine freedom from device-related complications. To account for between-study heterogeneity, Cox models with random-effects γ-frailties and stratification were conducted to determine the hazard ratios (HRs) of patients treated with S-ICD versus TV-ICD. The analysis was based on Cox regression stratified on study subgroups, which models interstudy heterogeneity by allowing patients belonging to a particular study to assume a baseline hazard unique to that study. We also modeled hierarchical random effects using a shared-frailty approach in which individual patients within each study are assumed to be similarly prone to complications as other individuals belonging to that study. The proportional hazards assumption was also verified with the Grambsch–Therneau test[25] and by plotting scaled Schoenfeld residuals.[26]

To conclude our sensitivity analysis, we computed summary HRs for individual studies based on the reconstructed IPD data set and pooled them under the conventional 2-stage frequentist meta-analysis with inverse variance weighting. The random-effects model was applied in view of the numerically high heterogeneity term (I^2). Funnel plot symmetry was visually assessed for publication bias.

All analyses were conducted in R-4.1.2 (with packages “meta,” “dmetar,” “metafor,” and “survival”), with $P<0.05$ regarded to indicate statistical significance. Institutional review board approval was not required as this study only analyzed publicly available data from published studies.

RESULTS

Study Selection

The search strategy retrieved 1336 studies. A total of 504 duplicates were removed, and the remaining 832

studies were screened by title and abstract. A total of 9 studies were identified for full-text review, and 1 RCT[12] and 4 PSMs[27–30] comprising 2387 patients were included in this study (Figure 1).

Study Characteristics

Publication years of the included studies ranged from 2016 to 2021, and the number of participants in each study ranged from 138 to 849 (Table). The mean age of the patients ranged from 35 to 64 years. Across all studies, a majority of patients (75.4%) received an ICD for primary prevention. The proportion of patients with diabetes and hypertension varied greatly among studies, ranging from 0% to 28% for diabetes and 7.2% to 55% for hypertension. Patients in 3 studies had a mean or median left ventricular ejection fraction <40%, whereas the remaining 2 studies had a figure >45%. Patients were followed up for a duration ranging from 30 to 60 months. All PSM studies were ranked as good quality (Newcastle-Ottawa Scale score 7–9); the RCT was deemed to have an overall low risk of bias (Table S2).

Clinical Outcomes

Among 5 studies[12,27–30] (2387 patients), S-ICD had a similar rate of device-related complications (Figure 2) at follow-up compared with TV-ICD (RR, 0.59 [95% CI, 0.33–1.04]; P=0.070; I^2=75%). Of these, lead-related complications (Figure 3) occurred significantly less with S-ICD (RR, 0.14 [95% CI, 0.07–0.29]; P<0.0001; I^2=0%).

In the IPD analysis of long-term device-related complications, 4 studies (2049 patients) reported Kaplan–Meier curves with risk tables for this outcome. The primary analysis using a 1-stage stratified Cox model did not violate the proportional hazards assumption (Figure S1), and this model did not yield any differences in freedom from device-related complications (shared-frailty HR, 0.82 [95% CI, 0.61–1.09; P=0.167]; stratified HR, 0.83 [95% CI, 0.62–1.10; P=0.200]) (Figure 4). When HRs were pooled in a 2-stage meta-analysis, HRs ranged from 0.36 to 1.38, and the pooled HR was 0.80 (95% CI, 0.34–1.90; P=0.468; I^2=63%) (Figure S2).

Across 3 studies (1467 patients), mortality did not differ significantly between S-ICD and TV-ICD (RR, 1.02 [95% CI, 0.58–1.81]; P=0.943; I^2=21%) (Figure S3). Across 5 studies (2387 patients), there was a similar rate of infection (RR, 0.94 [95% CI, 0.34–2.55]; P=0.897; I^2=48%) (Figure S4). Among 5 studies (2387 patients), there was no significant difference in IAS therapy delivered between S-ICD and TV-ICD (RR, 1.06 [95% CI, 0.78–1.45]; P=0.695; I^2=0%) (Figure S5). Cardiac oversensing as a cause of IAS (4 studies, 2249 patients) was more common in S-ICD (RR, 11.44 [95% CI, 4.12–31.74]; P<0.0001; I^2=0%) (Figure S6), whereas

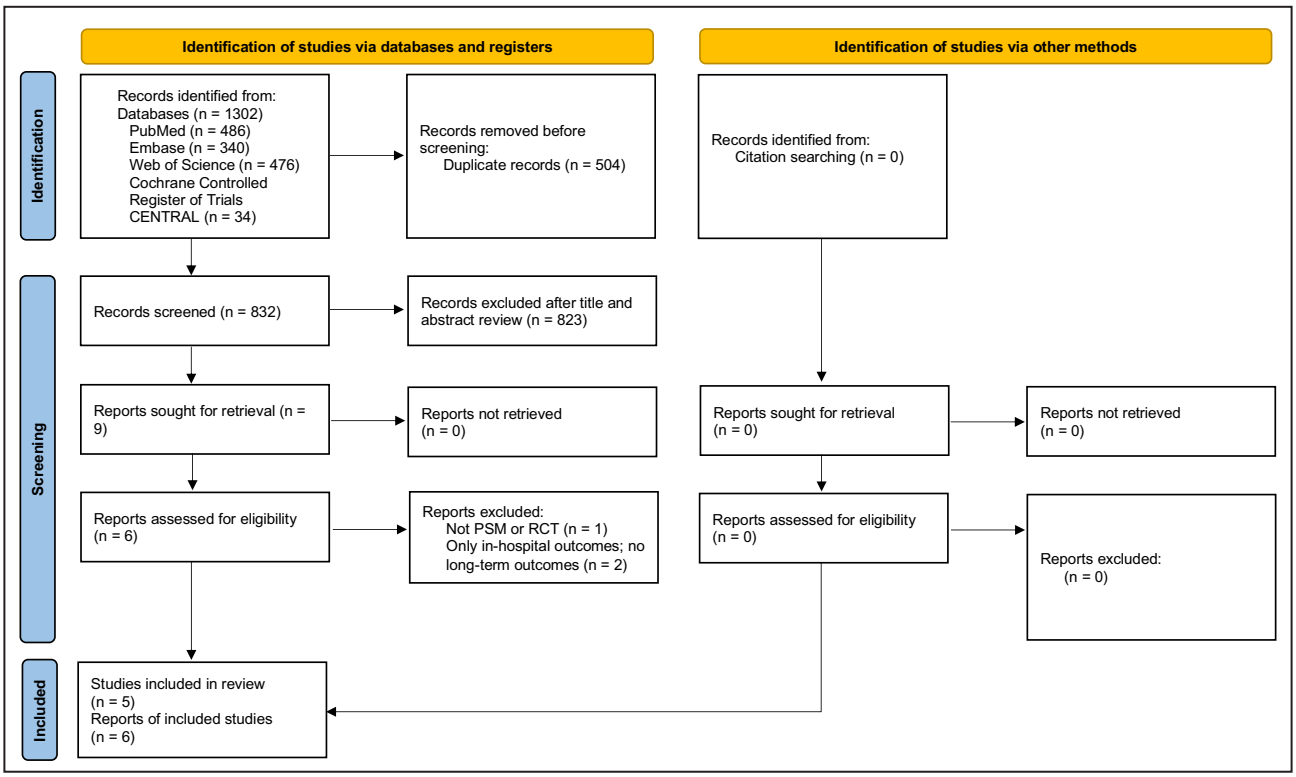

Figure 1. Modified Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of identified studies.
PSM indicates propensity score–matched study; and RCT, randomized controlled trial.

Table. Characteristics of Included Studies

Study	Participating countries	Study type	Arm	Number of patients (women)	Age, y*	Primary prevention, n (%)	Ischemic cardiomyopathy, n (%)	LVEF, %*	Diabetes, n (%)	Hypertension, n (%)	CABG, n (%)	AF, n (%)	Follow-up duration, mo*
Brouwer et al, 2016[27]	Netherlands	PSM	S-ICD	140 (56)	41 (26–52)	93 (66)	26 (19)	50	8 (5.7)	30 (21)	3 (0.21)	13 (9.3)	60
			TV-ICD	140 (53)	42 (32–50)	86 (61)	41 (29)	49	5 (3.6)	34 (24)	3 (0.21)	21 (15)	
Honarbakhsh et al, 2017[28]	United Kingdom	PSM	S-ICD	69 (17)	35±13	56 (81)	6 (9)	57±15	0	6 (8.7)	NR	NR	32±21
			TV-ICD	69 (17)	40±10	56 (81)	5 (7)	58±13	0	4 (5.8)	NR	NR	31±19
POINTED (Palmisano et al, 2021)[29]	Italy	PSM	S-ICD	169 (31)	55.6±13.0	142 (84)	71 (42)	37.9±14.7	31 (18)	89 (53)	18 (11)	39 (23)	30.3 (16.1–46.0)
			TV-ICD	169 (42)	57.4±15.5	130 (77)	60 (36)	37.9±14.4	34 (20)	95 (56)	15 (8.9)	50 (30)	31.3 (19.1–53.4)
PRAETORIAN (Knops et al, 2020)[12]	United States, Europe	RCT	S-ICD	426 (89)	63 (54–69)	346 (81)	289 (68)	30 (25–35)	112 (26)	227 (53)	86 (20)	115 (27)	48
			TV-ICD	423 (78)	64 (56–70)	339 (80)	298 (70)	30 (25–35)	126 (30)	240 (57)	85 (20)	93 (22)	51
SIMPLE-EFFORTLESS (Brouwer et al, 2018)[30]	Multiple countries worldwide	PSM	S-ICD	391 (92)	54±16	272 (70)	187 (48)	39.4±17.3	66 (17)	168 (43)	51 (13)	80 (20)	35±17
			TV-ICD	391 (72)	55±13	279 (71)	194 (50)	39.8±16.9	64 (16)	169 (43)	42 (11)	77 (20)	40±10

AF indicates atrial fibrillation; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; NR, not reported; POINTED, Impact on Patient Outcome and Healthcare Utilization of Cardiac Implantable Electronic Devices Complications Registry; PRAETORIAN, Prospective Randomized Comparison of Subcutaneous and Transvenous Implantable Cardioverter Defibrillator Therapy; PSM, propensity score–matched study; RCT, randomized controlled trial; S-ICD, subcutaneous implantable cardioverter-defibrillator; SIMPLE-EFFORTLESS, Shockless Implant Evaluation and Evaluation of Factors Impacting Clinical Outcome and Cost Effectiveness Trials; and TV-ICD, transcutaneous implantable cardioverter-defibrillator.
*Data are reported as mean±SD, median (interquartile range), or mean.

supraventricular tachycardia/AF as a cause of IAS (5 studies, 2387 patients) was more common in TV-ICD (RR, 0.27 [95% CI, 0.15–0.48]; $P<0.0001$; $I^2=2\%$) (Figure S7). Delivery of appropriate shock therapy across 3 studies (1129 patients) was similar between both groups (RR, 0.87 [95% CI, 0.38–1.98]; $P=0.732$; $I^2=77\%$) (Figure S8). Funnel plots for all outcomes were visually symmetrical and not suggestive of publication bias.

DISCUSSION

This review presents a comprehensive, current synthesis of literature comparing S-ICD versus TV-ICD and is the first of its kind to restrict data to that from RCTs and PSMs only. This analysis demonstrated that device-related complications, ICD shock rates (both appropriate and inappropriate), mortality rates, and infection rates were similar between S-ICD and TV-ICD. However, the lead-related complication rate was significantly lower in the S-ICD group compared with the TV-ICD group. Causes of IAS differed between modalities, with cardiac oversensing being significantly more common in the S-ICD group and supraventricular tachycardia/AF being significantly more common in the TV-ICD group.

Lead-Related Complications

A 2017 meta-analysis[31] of case-control studies similarly found that S-ICD was associated with significantly fewer lead-related complications, with no significant difference in infection and IAS incidence. Recently, a 2021 meta-analysis by Rordorf et al[32] also found a significantly lower rate of lead-related complications in S-ICD and highlighted the nonsignificant incidence of device-related complications in both modalities. However, nonrandomized studies were included in their syntheses, adding an element of heterogeneity and bias.

Intuitively, the incidence of lead-related complications should be lower in S-ICD, wherein the leads are placed subcutaneously. This is contrary to TV-ICD leads, which are inserted via the axillary–subclavian venous system and placed endocardially. Indeed, our analysis showed that lead-related complications requiring invasive intervention, such as lead failure, lead dislodgement, cardiac perforation, and pneumothorax, which are severe limitations of TV-ICD,[33] are much less common in S-ICD (RR, 0.14 [95% CI, 0.07–0.29]; $P<0.0001$). This would translate to lower short- and long-term patient morbidity compared with TV-ICD implantation, in which any intervention to address the complication comes with its own risks. Current Class I American Heart Association guidelines recommend that S-ICD be used only in patients with complex anatomy, venous access problems, or high infection risk,[3]

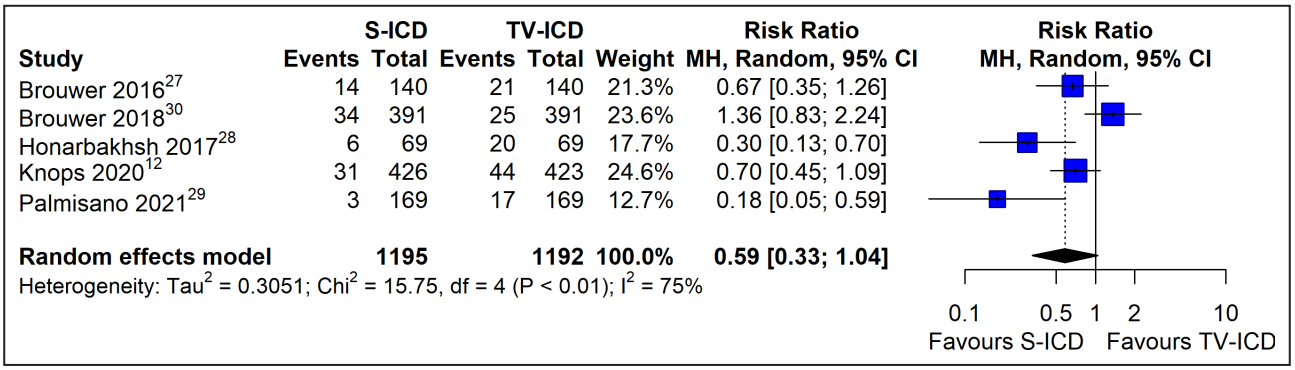

Figure 2. Forest plot of device-related complications across 5 studies.
df indicates degree of freedom; MH, Mantel–Haenszel; S-ICD, subcutaneous implantable cardioverter-defibrillator; and TV-ICD, transcutaneous implantable cardioverter-defibrillator.

whereas Class IIa European Society of Cardiology guidelines are slightly broader, recommending S-ICD as an alternative to TV-ICD when pacing therapy for bradycardia support or cardiac resynchronization or antitachycardia pacing (ATP) is not required.[11] However, our analysis suggests that S-ICD has the potential to become a strong alternative, if not the mainstay, of therapy for patients requiring an ICD without pacing indication.

Device-Related Complications

Despite the lower rate of lead-related complications, the overall incidence of device-related complications—which includes lead-related and non-lead–related complications (including but not limited to device malfunction, sensing issues, or IAS)—was not significantly different between S-ICD and TV-ICD. Nonetheless, the RR and 95% CI were close to the threshold for statistical significance (RR, 0.59 [95% CI, 0.33–1.04]). Using a more robust analytical method in the form of IPD, the 1-stage meta-analysis of survival from device-free complications was again close to but did not achieve significance (shared-frailty HR, 0.82 [95% CI, 0.61–1.09]). However, visual inspection of the pooled Kaplan–Meier curves seemed to suggest a divergence of survival from device-free complications beginning at ≈4 years of follow-up. Loss to long-term follow-up among all studies meant that the divergence was not statistically significant, with only 333 (16.3%) of the original 2049 patients having 5-year follow-up data. Although Palmisano et al[29] did not provide a risk table for the Kaplan–Meier curve of freedom from device-related complications for their matched cohort and hence it was not used in IPD analysis, their Kaplan–Meier analysis of the overall cohort significantly favored S-ICD (P=0.001). This significant favoring from a time-to-event perspective combined with the fact that this study exhibited the largest effect size in the comparative meta-analysis (Figure 2) suggest that its exclusion from IPD analysis may account for the numerical discrepancy between the derived RR and HR. Hence, ongoing trials, such as the ATLAS (Avoid Transvenous Leads in Appropriate Subjects) RCT[34] and PRAETORIAN XL,[12] should aim to achieve follow-up beyond 5 years to advance long-term safety and efficacy data and determine if the observed divergence is truly significant.

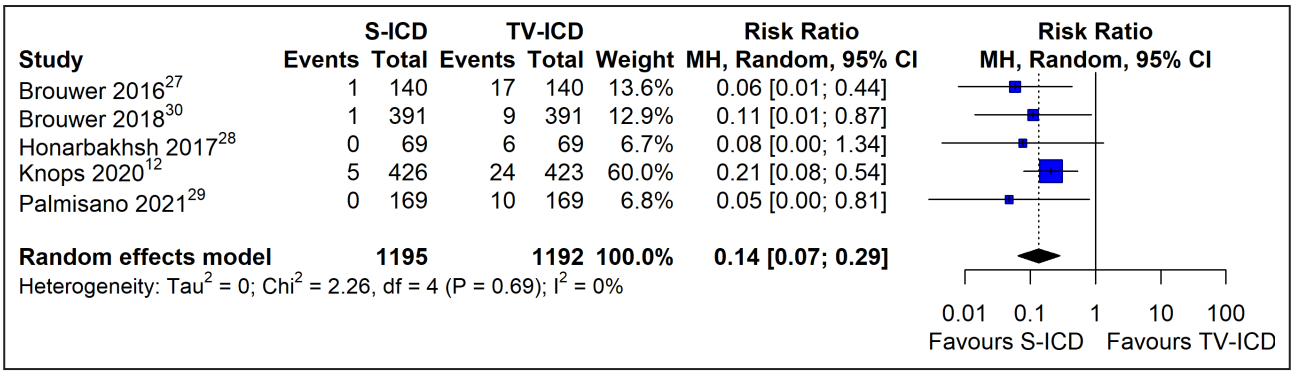

Figure 3. Forest plot of lead-related complications across 5 studies.
df indicates degree of freedom; MH, Mantel–Haenszel; S-ICD, subcutaneous implantable cardioverter-defibrillator; and TV-ICD, transcutaneous implantable cardioverter-defibrillator.

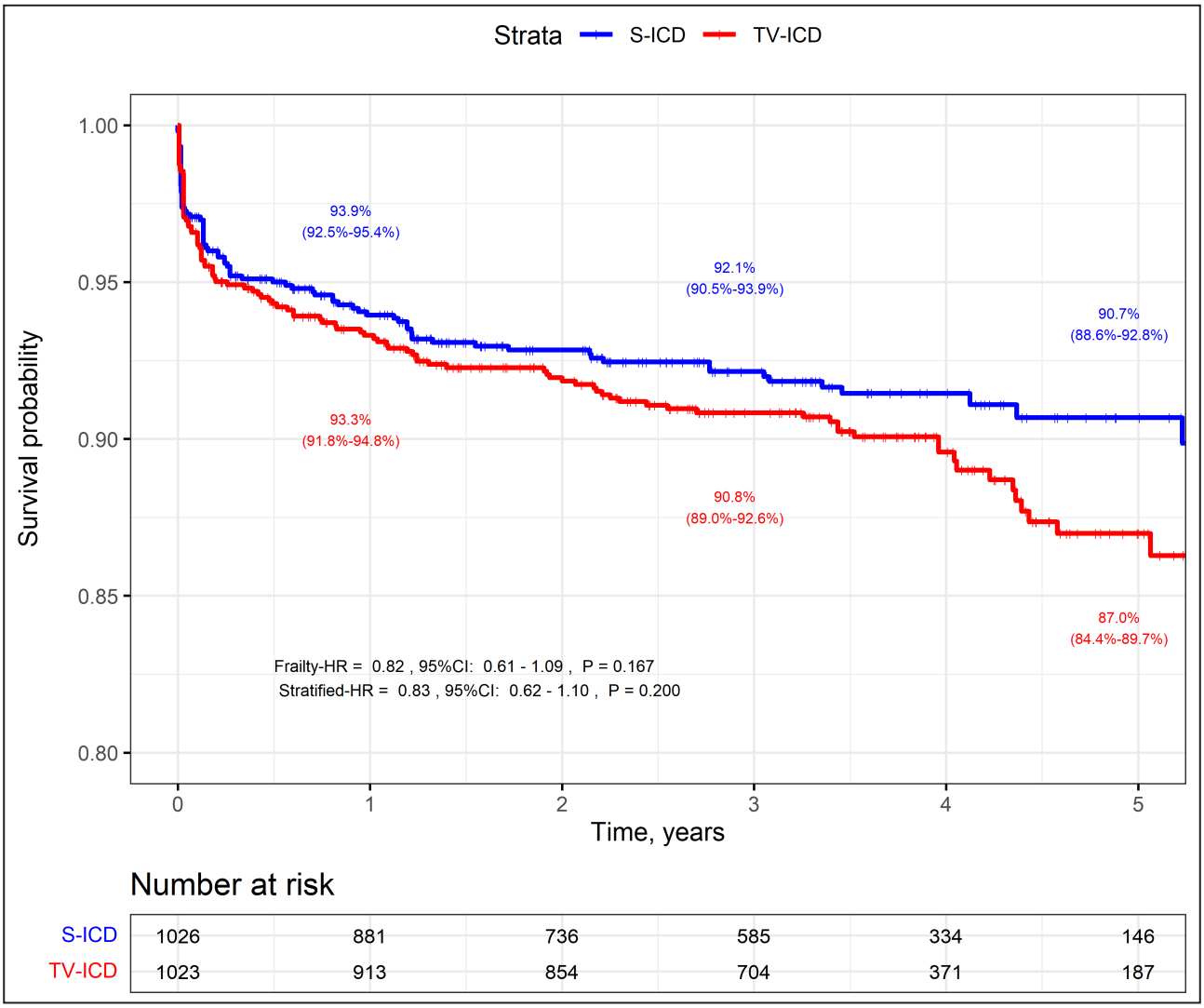

Figure 4. One-stage individual patient data meta-analysis of device-related complications.
Freedom from device-related complications along with 95% CIs are provided for both modalities at 1, 3, and 5 years. HR indicates hazard ratio; S-ICD, subcutaneous implantable cardioverter-defibrillator; and TV-ICD, transcutaneous implantable cardioverter-defibrillator.

Long-term follow-up will also shed more light on the significance of the recent lead advisory.[35]

Non-Lead–Related Complications

Evidently, although lead-related complications were less frequent in S-ICD, they were counterbalanced in part by a higher incidence of non-lead–related complications. Rordorf et al[32] attributed it to the higher risk of pocket-related complications in S-ICD (odds ratio, 2.18 [95% CI, 1.30–3.66]; *P*=0.003), such as infections and hematomas. Our analysis showed that the incidence of infection is similar in both modalities. Although TV-ICD appears more prone to infection because of its intravascular placement, conventional S-ICD implantation employs a parasternal incision that is prone to exposure and also susceptible to infection.[36] Despite this, newer techniques of S-ICD implantation, such as the 2-incision technique, aim to reduce infection and dislodgement without compromising device function.[37] Crucially, infections in TV-ICDs are generally more serious, with a high rate of systemic involvement,[38,39] compared with S-ICD, where infections are much more likely to be local.[40] In the studies included in this analysis, Palmisano et al[29] discussed systemic versus local infection in depth in their nonmatched cohort. All 12 infections occurring in the TV-ICD arm were systemic, whereas the sole infection in the S-ICD arm was not. Moreover, although TV-ICD generator exchange carries a significant infection and mortality risk,[41] S-ICD battery replacement is a simple, low-risk procedure.[42] Despite the lack of stratification into systemic versus local infection among studies, this is a point in favor of S-ICD implantation, particularly in patients who are infection prone.

IAS rates did not differ significantly between S-ICD and TV-ICD. S-ICD was associated with a higher risk of cardiac oversensing being the cause of IAS, but this was compensated by a higher risk of IAS from supraventricular tachycardia/AF in TV-ICD. Similar findings have been reported in literature: an analysis of the Evaluation of Factors Impacting Clinical Outcome and Cost Effectiveness Trials (EFFORTLESS) registry found that 73% of IAS were from cardiac oversensing (mainly from low-amplitude signal or T-wave oversensing),[43] and another study deemed oversensing without a correcting programming option a serious weakness of S-ICDs.[44] Conversely, the START (Subcutaneous Versus Transvenous Arrhythmia Recognition Testing) study demonstrated that S-ICD was more specific than TV-ICD in detecting supraventricular arrhythmias.[45] This highlights the importance of morphology discrimination algorithms applied in the conditional shock zone in reducing IAS in S-ICDs as opposed to the initial use of interval criteria before applying morphology criteria in TV-ICDs.[46]

Recent developments have addressed oversensing issues in S-ICD, such as dual-zone tachycardia detection[47] and the INSIGHT algorithm with SMART Pass technology to reduce cardiac oversensing.[48] In the PRAETORIAN study, SMART Pass technology was unavailable or not switched on in 78% of patients during the first shock, leading to high IAS. The UNTOUCHED (Understanding Outcomes With the S-ICD in Primary Prevention Patients With Low Ejection Fraction) study, using novel selection and programming techniques, reported the lowest incidence of IAS in S-ICD to date (3.1% at 1 year), a value lower than in many TV-ICD studies.[49] Hence, future studies to compare rates of IAS between the most advanced S-ICDs and TV-ICDs are recommended.

Appropriate Shock Therapy

The rate of appropriate shock therapy was similar in both groups. Our analysis found high heterogeneity among comparative rates of appropriate shocks between both modalities (I^2=90%), likely because of differences in the detection algorithm between studies. The PRAETORIAN trial attributed its higher incidence of appropriate shocks in S-ICD to its inability to deliver ATP and to the double counting of slow ventricular tachycardia if it occurred at a rate below the programmed therapy zone. Brouwer et al[27] attributed their lower incidence of appropriate shocks in S-ICD to its longer charging time, which allows nonsustained ventricular tachycardia to terminate. ATP therapy is painless compared with shocks,[50] and a large study of ATP in patients with a TV-ICD demonstrated a high effectiveness of 88.5% along with a higher mortality rate in patients who received a shock compared with ATP only (HR, 0.70 [95% CI, 0.64–0.77]; P<0.001).[51]

Moreover, the decision to implant an S-ICD must also consider the possibility of ATP use in patients presenting with sustained ventricular tachycardia (secondary prevention indication) or pacing requirement in the future, which may necessitate an upgrade to a cardiac resynchronization therapy defibrillator. The occurrence of a downstream pacing requirement among patients without a preexisting pacing indication has been reported at 34% during a median follow-up of 3.4 years in 1 retrospective cohort study.[52] This underscores the importance of pacing capabilities in the TV-ICD cohort compared with S-ICD. Nonetheless, recent technological progress has resulted in the development of a leadless pacemaker commanded by an S-ICD. Although this has only been tested in animal models so far,[53] a clinical trial is set to investigate its efficacy in the human population[54]; it remains to be seen whether it holds promise for future patients who require both pacing and ICD therapy.

Mortality

Despite the aforementioned differences in infection and inappropriate and appropriate shocks between the 2 modalities, all-cause mortality was not significantly different. It is worth noting that the number of patients in this meta-analysis may not be sufficient to detect differences in mortality. Nevertheless, the absence of a gross difference in mortality events across the included studies is reassuring in considering S-ICD as an alternative to TV-ICD.

Limitations

As with all studies, this study was not without limitations. Our review included only 5 studies because of the strict inclusion criteria aimed at including only high-quality studies. This precluded the use of a meta-regression of covariates affecting individual outcomes, which may offer insight into factors affecting the efficacy of S-ICD versus TV-ICD implantation. Potential prognostic covariates include patient weight, QRS duration,[55] hypertrophic cardiomyopathy, and AF.[43]

Despite the use of IPD reconstruction as a vigorous statistical method that accounts for follow-up and censoring status, we were still unable to account for effects exerted by patient-level prognostic covariates on device-related complications. Furthermore, in the 2-stage meta-analysis, although the 95% CI was found to be close to the threshold of statistical significance, prediction intervals were well beyond the null effect on both sides. This suggests that future studies with similar follow-up periods may experience null effects when treated with either S-ICD or TV-ICD and may be attributable to the moderate degree of heterogeneity found (I^2=63%). The prediction intervals reported here should also be interpreted with caution as a small number of

studies were used in its derivation.[56,57] In addition, the exclusion of 1 study in the IPD meta-analysis led to a numerical disparity between the derived HR and the RR from a comparative meta-analysis of device-related complications. This further highlights the need for more large, high-quality trials to be conducted to determine the true extent of benefit.

Lastly, decisions on the type of ICD to be implanted should still be considered on an individualized basis, with attention to the cost–benefit ratio. Attention must also be paid to S-ICD limitations, including but not limited to excluding patients with ventricular tachycardia of <170 beats per minute or those failing appropriate QRS or T-wave sensing with the S-ICD ECG patient screening tool.[58]

CONCLUSIONS

This meta-analysis of high-quality studies demonstrates that S-ICD is clinically superior to TV-ICD in patients without a pacing indication in terms of lead-related complications while demonstrating comparable efficacy and safety. For the overarching morbidity-related outcome of device-related complications, our analysis suggests that there may be a benefit of S-ICD over TV-ICD in the long term, which is yet unrevealed because of the low number of high-quality studies in literature. These findings indicate that S-ICD is likely a suitable alternative for TV-ICD for patients requiring ICD implantation without a pacing indication. Further research into this field is still needed to compare long-term safety and efficacy in both modalities and to investigate the combination of S-ICD with a leadless pacemaker.

ARTICLE INFORMATION

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Affiliations

Yong Loo Lin School of Medicine, National University of Singapore, Singapore (K.Y.F.); and Department of Cardiology, Changi General HospitalSingapore, (C.J.R.N., Y.W., C.Y., V.H.T.).

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Supplemental Material

Tables S1–S2
Figures S1–S8

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SUPPLEMENTAL MATERIAL

Table S1. Full search phrases used for the respective databases.

Pubmed	486 articles
(subcutaneous ICD OR S-ICD OR transvenous ICD OR TV-ICD OR conventional ICD OR dual-chamber ICD OR single chamber ICD OR endovascular defibrillator) AND (random* OR controlled OR propensity)	
Embase	340 articles
('s-icd':ti,ab,kw OR (('subcutaneous':ti,ab,kw OR 'transvenous':ti,ab,kw) AND ('implantable cardioverter-defibrillator':ti,ab,kw OR 'icd':ti,ab,kw)) OR 'tv-icd':ti,ab,kw OR 'conventional icd':ti,ab,kw OR 'dual-chamber icd':ti,ab,kw OR 'single chamber icd':ti,ab,kw OR 'endovascular defibrillator':ti,ab,kw) AND ('randomized':ti,ab,kw OR 'random':ti,ab,kw OR 'randomised':ti,ab,kw OR 'controlled':ti,ab,kw OR 'propensity':ti,ab,kw)	
Web of Science	476 articles
AB = ((subcutaneous ICD OR S-ICD OR transvenous ICD OR TV-ICD OR conventional ICD OR dual-chamber ICD OR single chamber ICD OR endovascular defibrillator) AND (random* OR controlled OR propensity)) OR TI = ((subcutaneous ICD OR S-ICD OR transvenous ICD OR TV-ICD OR conventional ICD OR dual-chamber ICD OR single chamber ICD OR endovascular defibrillator) AND (random* OR controlled OR propensity)) OR KP = ((subcutaneous ICD OR S-ICD OR transvenous ICD OR TV-ICD OR conventional ICD OR dual-chamber ICD OR single chamber ICD OR endovascular defibrillator) AND (random* OR controlled OR propensity)) OR SU = ((subcutaneous ICD OR S-ICD OR transvenous ICD OR TV-ICD OR conventional ICD OR dual-chamber ICD OR single chamber ICD OR endovascular defibrillator) AND (random* OR controlled OR propensity))	
Cochrane Controlled Register of Trials CENTRAL	34 articles
#1 subcutaneous ICD	
#2 transvenous ICD	
#3 dual-chamber ICD	
#4 single-chamber ICD	
#5 endovascular defibrillator	
#6 #1 #2 #3 OR #4 OR #5	
#7 MeSH descriptor: [Randomized Controlled Trial] explode all trees	
#8 MeSH descriptor: [Propensity Score] explode all trees	
#9 #7 OR #8	
#10 #6 AND 11	

Date searched: September 25, 2021

Table S2. Risk-of-bias analysis of included studies.

Cochrane Risk-of-Bias tool for randomized controlled trials						
Study ID	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
PRAETORIAN (Knops 2020)	+	+	+	+	+	+

Newcastle-Ottawa Scale for nonrandomized trials				
Study ID	Selection	Comparability	Exposure	Total
Brouwer 2016	***	**	**	7
Honarbakhsh 2017	***	**	**	7
POINTED (Palmisano 2021)	***	**	**	7
SIMPLE-EFFORTLESS (Brouwer 2018)	***	**	**	7

+ Denotes low risk of bias.

Legend for Newcastle-Ottawa scale:

- Selection: maximum 4 stars
- Comparability: maximum 2 stars
- Exposure: maximum 3 stars
- Total: maximum 9 stars
- Studies with 7-9 stars are considered to be at low risk of bias.

Figure Legends

95%CI, 95% confidence interval; HR, hazard ratio; MH, Mantel-Haenszel; IV, inverse-variance; S-ICD, subcutaneous implantable cardioverter-defibrillator; TV-ICD, transcutaneous implantable cardioverter-defibrillator

Figure S1. Verification of the proportional-hazards assumption with Schoenfeld residuals.

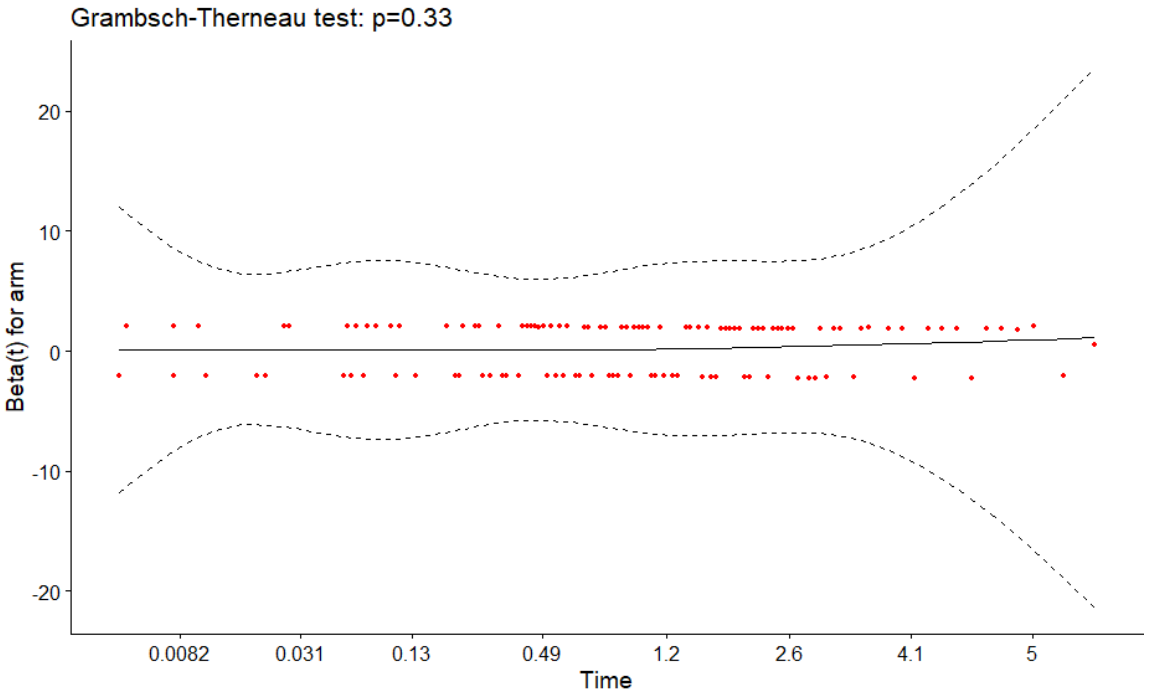

Figure S2. Two-stage Individual Patient Data meta-analysis of device-related complications.

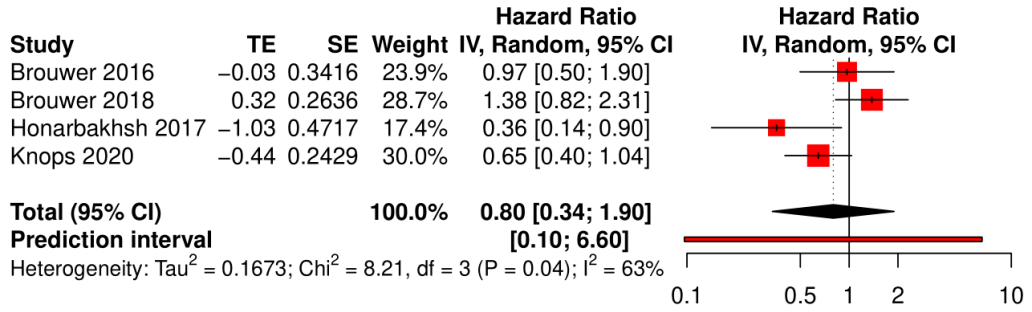

Figure S3. Forest plot of all-cause mortality.

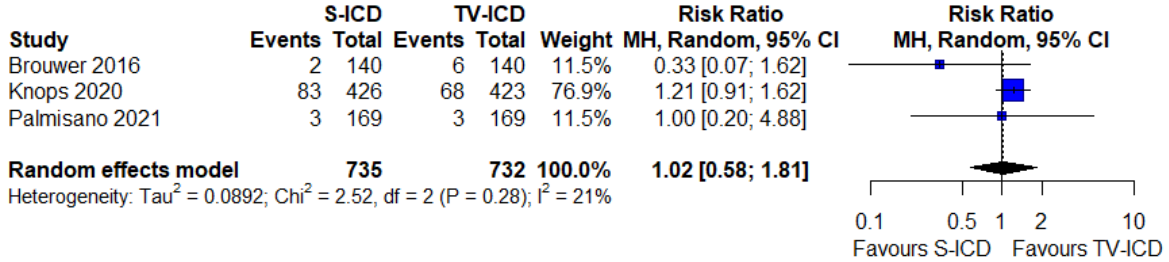

Figure S4. Forest plot of infection.

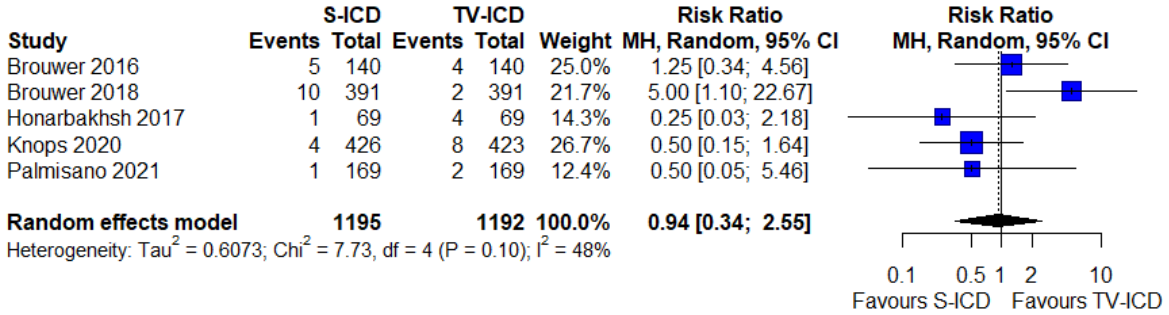

Figure S5. Forest plot of inappropriate shocks.

Study	S-ICD Events	S-ICD Total	TV-ICD Events	TV-ICD Total	Weight	Risk Ratio MH, Random, 95% CI
Brouwer 2016	20	140	22	140	30.2%	0.91 [0.52; 1.59]
Brouwer 2018	3	391	2	391	3.0%	1.50 [0.25; 8.93]
Honarbakhsh 2017	3	69	6	69	5.2%	0.50 [0.13; 1.92]
Knops 2020	41	426	29	423	45.3%	1.40 [0.89; 2.22]
Palmisano 2021	11	169	14	169	16.3%	0.79 [0.37; 1.68]
Random effects model		**1195**		**1192**	**100.0%**	**1.06 [0.78; 1.45]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.69$, df = 4 (P = 0.45); $I^2 = 0\%$

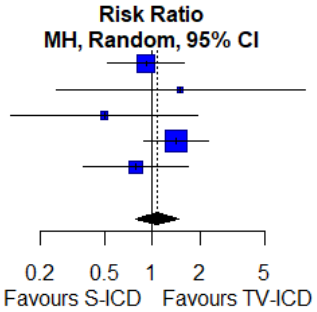

Figure S6. Forest plot of cardiac oversensing as a cause of inappropriate shocks.

Study	S-ICD Events	S-ICD Total	TV-ICD Events	TV-ICD Total	Weight	Risk Ratio MH, Random, 95% CI
Brouwer 2016	17	140	1	140	25.9%	17.00 [2.29; 126.01]
Brouwer 2018	2	391	0	391	11.3%	5.00 [0.24; 103.81]
Knops 2020	24	426	2	423	50.5%	11.92 [2.83; 50.10]
Palmisano 2021	4	169	0	169	12.3%	9.00 [0.49; 165.87]
Random effects model		**1126**		**1123**	**100.0%**	**11.44 [4.12; 31.74]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.47$, df = 3 (P = 0.92); $I^2 = 0\%$

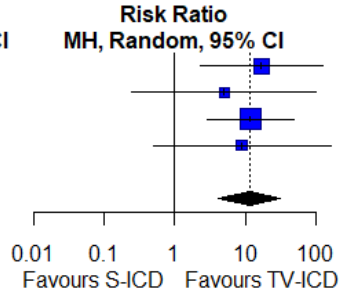

Figure S7. Forest plot of supraventricular tachycardia or atrial fibrillation as a cause of inappropriate shocks.

Study	S-ICD Events	S-ICD Total	TV-ICD Events	TV-ICD Total	Weight	Risk Ratio MH, Random, 95% CI
Brouwer 2016	3	140	21	140	22.3%	0.14 [0.04; 0.47]
Brouwer 2018	0	391	1	391	3.1%	0.33 [0.01; 8.16]
Honarbakhsh 2017	0	69	6	69	3.9%	0.08 [0.00; 1.34]
Knops 2020	11	426	27	423	63.0%	0.40 [0.20; 0.80]
Palmisano 2021	1	169	9	169	7.6%	0.11 [0.01; 0.87]
Random effects model		**1195**		**1192**	**100.0%**	**0.27 [0.15; 0.48]**

Heterogeneity: $Tau^2 = 0.0102$; $Chi^2 = 4.07$, df = 4 (P = 0.40); $I^2 = 2\%$

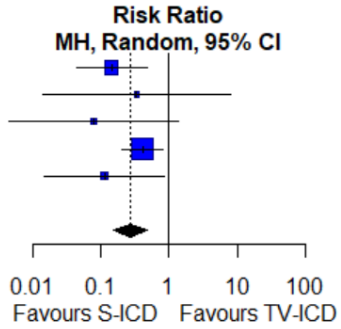

Figure S8. Forest plot of appropriate shock therapy.