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Subcutaneous Versus Transvenous Implantable Defibrillator Therapy

A Meta-Analysis of Case-Control Studies

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ABSTRACT

OBJECTIVES This study aims to conduct a meta-analysis comparing efficacy and safety outcomes between subcutaneous implantable cardioverter-defibrillator (S-ICD) and transvenous implantable cardioverter-defibrillator (TV-ICD).

BACKGROUND The S-ICD was developed to minimize complications related to the conventional TV-ICD. Direct comparison of clinical outcomes between the 2 devices has been limited by varying patient characteristics and definitions of complications with no randomized trials completed comparing these systems.

METHODS Studies in the PubMed and Embase databases and secondary referencing sources were systematically reviewed. Studies meeting criteria were included in the meta-analysis. Baseline characteristics and outcome data of the S-ICD and TV-ICD groups were appraised and analyzed. A random-effects model was used to derive odds ratio (OR) with 95% confidence interval (CI).

RESULTS Five studies met inclusion criteria. Baseline characteristics were similar between the S-ICD and TV-ICD groups. Fewer lead complications occurred in the S-ICD group compared to the TV-ICD group (OR: 0.13; 95% CI: 0.05 to 0.38). The infection rate was similar between the S-ICD and TV-ICD groups (OR: 0.75; 95% CI: 0.30 to 1.89). There were no differences in system or device failures between groups (OR: 1.13; 95% CI: 0.43 to 3.02). Overall, inappropriate therapy (T-wave oversensing, supraventricular tachycardia, episodes of inappropriate sensing) was similar between the 2 groups (OR: 0.87; 95% CI: 0.51 to 1.49). However, the nature of inappropriate therapy was different between the S-ICD and TV-ICD groups. Both devices appear to perform equally well with respect to appropriate shocks.

CONCLUSIONS S-ICD reduced lead-related complications but was similar to TV-ICD with regard to non–lead-related complications, including inappropriate therapy. These results support the concept that S-ICD is a safe and effective alternative to TV-ICD in appropriate patients. (J Am Coll Cardiol EP 2017;■:■–■) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

ECG = electrocardiography

OR = odds ratio

S-ICD = subcutaneous implantable cardioverter-defibrillator

SVT = supraventricular tachycardia

TV = transvenous

TV-ICD = transvenous implantable cardioverter-defibrillator

The implantable cardioverter-defibrillator (ICD) is effective treatment of both primary and secondary prevention of sudden cardiac death (1–3). Despite this lifesaving therapy, ICD use is associated with both short- and long-term complications leading to considerable morbidity and mortality (4). Transvenous (TV) leads are vulnerable to complications such as lead fractures, which in turn lead to inappropriate therapy and infections. Device-related infection rates vary between 0.67% and 1.49% over a 3- to 12-month follow-up period (5–7). Mechanical lead failures arising from hardware malfunction can result in oversensing, inappropriate shocks, and inability to deliver appropriate therapy. Long-term lead failure rates up to 20% have been reported (8).

The subcutaneous implantable cardioverter-defibrillator (S-ICD) is a novel technology that has been designed to limit complications associated with the transvenous implantable cardioverter-defibrillator (TV-ICD). Traditionally, S-ICD has been used in patients with difficult venous access. Thus, congenital heart disease patients with venous anomalies (either inherited or acquired) are good candidates for S-ICD, especially those who are expected to outlive the life expectancy of their TV leads, thus requiring device extractions later in life. Moreover, S-ICD may be considered in patients with channelopathies or those undergoing renal replacement therapies requiring chronic venous access.

The S-ICD, however, has its own limitations. In contrast to the TV-ICD, S-ICD lacks pacing capacity and therefore cannot provide antitachycardia pacing. Antitachycardia pacing has been an important component of tachyarrhythmia therapy for SCD by terminating dangerous arrhythmias before their escalation. Despite the perception that S-ICD is similarly useful as the TV-ICD in many clinical scenarios, there remains a considerable disparity in S-ICD usage, due to lack of experience with the new device and absence of comparative literature. Moreover, the S-ICD was approved for use based on prospective trials in the absence of control groups (9). Accordingly, no randomized trials have compared the S-ICD with TV-ICD. However, a few case-control and retrospective studies have directly compared the efficacy and complications in recipients of these 2 devices. To overcome this paucity in the current literature, we conducted the first meta-analysis to summarize and compare clinical outcomes between S-ICD and TV-ICD, including lead-related and unrelated complications, inappropriate therapies, and appropriate shocks.

METHODS

SEARCH STRATEGY. A systemic review was conducted of the PubMed and Embase databases from the year 2000 to present by searching for the key words "subcutaneous ICD," "transvenous ICD," "conventional ICD," "dual-chamber ICD," or "single chamber ICD." To identify additional studies, we also searched references of relevant research.

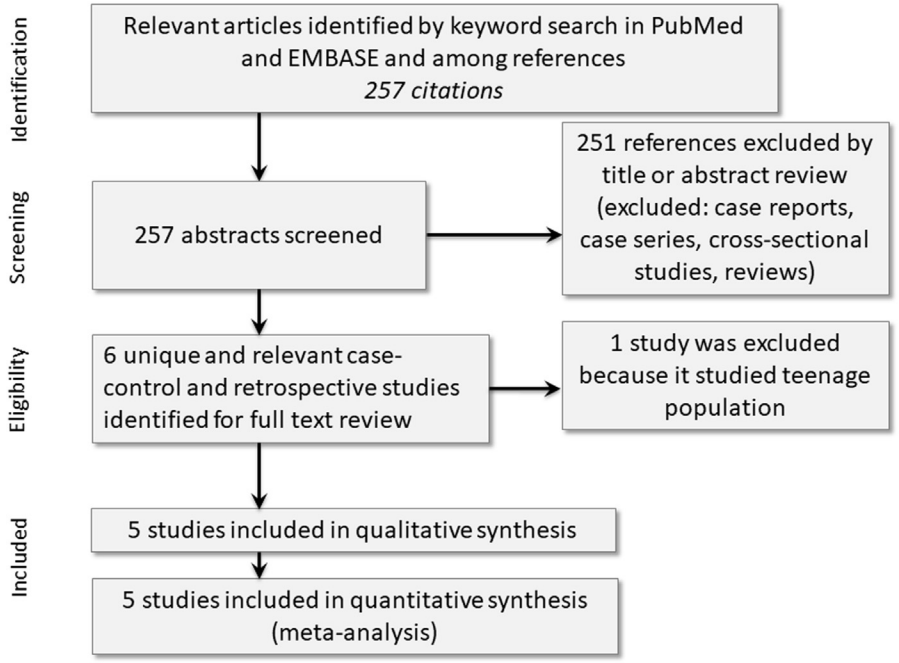
STUDY SELECTION. Studies were eligible for review based on the following criteria: 1) studies that directly compared clinical outcomes between S-ICD and TV-ICD in adult patients; and 2) articles that contained data on ICD lead complications, nonlead complications such as infection rate, hematoma, pneumothorax, system or device failure, inappropriate therapy, and episodes of appropriate therapy. All case reports or case series were excluded after title and abstract reviews. By this process, 6 studies were identified for full text reviews (10–15). The study by Pettit et al. (15) was excluded after further review because it included a teenage population. In the end, 5 studies were included in the meta-analysis (**Figure 1**).

DATA EXTRACTION. Two reviewers (J.L., X.J.) independently performed literature review, data extraction, and data entry. Any discrepancy was resolved by a third reviewer (I.B.R.). The data that were extracted included title of the study; authors; publication year; sample size (number of patients in the S-ICD and TV-ICD groups); patients' baseline demographic data such as age, gender, and ejection fraction; proportion of patients with coronary artery disease, nonischemic heart disease, hypertrophic cardiomyopathy, or heart failure (ischemic, nonischemic, and mixed); indication for ICD (primary vs. secondary prevention); and outcome data such as lead-related complications, non-lead-related complications (infection, hematoma, pneumothorax, system/device failure), episodes of inappropriate therapies, and appropriate shocks.

The Newcastle-Ottawa Scale was used to appraise the quality of the case-control studies. All studies have a score of 5 or above. Total score of each study is given in **Table 1**.

DATA ANALYSIS AND SYNTHESIS. The meta-analysis was conducted using RevMan 5.3 software (Cochrane Collaboration, London, United Kingdom). Age and ejection fraction of the baseline patient characteristics were analyzed and reported as mean with 95% confidence interval (CI). A random-effects model was used to derive odds ratio (OR) with 95% CI on dichotomous outcome data.

FIGURE 1 Study Selection Process



Summary of the selection process of case-control studies included in the meta-analysis.

PUBLICATION BIAS. Funnel plots for the effects size of lead complications, infection, device failures, and inappropriate therapies are shown in Online Figure 1. However, when fewer than 10 studies were included in the meta-analysis, the power of the test may have been too low to detect true asymmetry from chance, so no definitive information can be drawn.

RESULTS

Of the 6 studies that included both S-ICD and TV-ICDs, 5 case-control and retrospective studies meeting the inclusion criteria were selected for the meta-analysis. The baseline characteristics of the cohorts are summarized in Table 2. The populations were similar with regard to age, gender, indications for ICD (primary vs. secondary prevention), and proportion of patients with ischemic heart disease, cardiomyopathy (ischemic, nonischemic, and dilated), or hypertrophic cardiomyopathy (Table 2).

Comparison of clinical outcomes between the S-ICD and TV-ICD groups is summarized in Table 3. Lead complications were significantly less in the S-ICD group compared to the TV-ICD group (OR: 0.13; 95% CI: 0.05 to 0.38) (Figure 2A). Nonlead complications were also analyzed. The total infection rate was 0.35% (8 of 2,269) among S-ICD recipients, and the infection rate was similar between the S-ICD and TV-ICD groups (OR: 0.75; 95% CI: 0.30 to 1.89) (Figure 2B). System or device failure was not significantly different between the S-ICD and TV-ICD groups (OR: 1.13; 95% CI: 0.43 to 3.02) (Figure 2C). Prevalence of inappropriate therapy [T-wave oversensing, supraventricular tachycardia (SVT), episodes of inappropriate sensing] was similar between the 2 groups (OR: 0.87; 95% CI: 0.51 to 1.49) (Figure 2D). However, the nature of inappropriate therapy was different between the S-ICD and TV-ICD groups. Inappropriate therapies in the TV-ICD group were primarily due to SVT (Figure 2E), whereas inappropriate shocks in the S-ICD group were mostly episodes

TABLE 1 Quality of Each Nonrandomized Case-Control Study Included in the Meta-Analysis Individually Appraised Based on the Newcastle-Ottawa Scale

First Author (Year) (Ref. #)	Selection	Comparability	Exposure
Köbe et al. (2013) (14)	★★★	★★	★
Brouwer et al. (2016) (11)	★★★	★★	★★
Honarbakhsh et al. (2016) (10)	★★★	★★	★
Friedman et al. (2016) (12)	★★★★	★★	★
Mithani et al. (2016) (13)	★★★	★★	★

TABLE 2 Baseline Characteristics of Studies Included in the Meta-Analysis*

		Baseline Characteristics							
		N		Male		Age (yrs)		Ejection Fraction (%)	
First Author (Ref. #)	Year	S-ICD	TV-ICD	S-ICD	TV-ICD	S-ICD	TV-ICD	S-ICD	TV-ICD
Köbe et al. (14)	2013	69	69	50	50	45.7 ± 15.7	47.7 ± 14.7	46.2 ± 15.6	40.6 ± 15.9
Brouwer et al. (11)	2016	140	140	84	87	41	42	50	49
Honarbakhsh et al. (10)	2016	69	69	52	52	35 ± 13	40 ± 10	57 ± 15	58 ± 13
Friedman et al. (12)	2016	1920	3840	1293	2609	54	53.9	31.2	31.3
Mithani et al. (13)	2016	71	71	¾	¾	¾	¾	¾	¾

TABLE 2 Continued

	Indications				Underlying Heart Disease					
	Primary Prevention		Secondary Prevention		Cardiomyopathy (Ischemic, Nonischemic, Dilated)		CAD or Ischemic Heart Disease		HCM	
First Author (Ref. #)	S-ICD	TV-ICD	S-ICD	TV-ICD	S-ICD	TV-ICD	S-ICD	TV-ICD	S-ICD	TV-ICD
Köbe et al. (14)	41	34	28	35	25	32	11	13	10	4
Brouwer et al. (11)	93	86	¾	¾	54	71	33	38	¾	¾
Honarbakhsh et al. (10)	56	56	13	13	10	10	¾	¾	41	42
Friedman et al. (12)	¾	¾	¾	¾	846	1677	879	1747	123	242
Mithani et al. (13)	¾	¾	¾	¾	¾	¾	¾	¾	¾	¾

Values are n or mean ± SD unless otherwise indicated. *Baseline characteristics of the participants were statistically not significant between the S-ICD and TV-ICD groups.
CAD = coronary artery disease; HCM = hypertrophic cardiomyopathy; S-ICD = subcutaneous implantable cardioverter-defibrillator; TV-ICD = transvenous implantable cardioverter-defibrillator.

of oversensing (sensing of noise and T-wave oversensing, among others) (Figure 2F).

Only 2 studies in this meta-analysis reported data on appropriate shocks delivered by S-ICD versus TV-ICD. Köbe et al. (14) reported 3 of 69 patients in the S-ICD group experienced appropriate shocks, whereas 2 of 69 patients in the TV-ICD group experienced appropriate shocks. Brower et al. (11) reported an appropriate shock rate of 17% (95% CI: 6.3% to 26.4%) among S-ICD recipients and 21.3% (95% CI: 12.6% to 27.3%) among TV-ICD recipients. This difference, after adjusting for ICD programming, was found to be insignificant by Brouwer et al. (11).

DISCUSSION

The initial evaluation of an entirely subcutaneous ICD system was described by Bardy et al. (16) in 2010. The investigators conducted 2 small, single-group trials of permanent device implantation and found that the S-ICD successfully and consistently detected and converted ventricular fibrillation, as well as successfully detected and treated 12 episodes of SVT. However, the preliminary data from the study were not adequate to show the relative benefit of the S-ICD compared to the TV-ICD. The study also was not able to draw conclusions about whether S-ICD was superior to TV-ICD with respect to lead stability or failure (16).

Since the study by Bardy et al. (16), 2 large prospective studies [IDE (S-ICD system IDE Clinical Investigation) and EFFORTLESS (Boston Scientific Post Market-S-ICD Registry)] have been conducted to evaluate the safety and efficacy of the S-ICD in large diverse populations. In a pooled analysis of the 2-year results of these 2 studies, Burke et al. (17) provided further support for the safety and efficacy of the S-ICD in patients with primary and secondary indications, showing that the device has very high shock efficacy for spontaneous SVT and a decreasing incidence for inappropriate shocks.

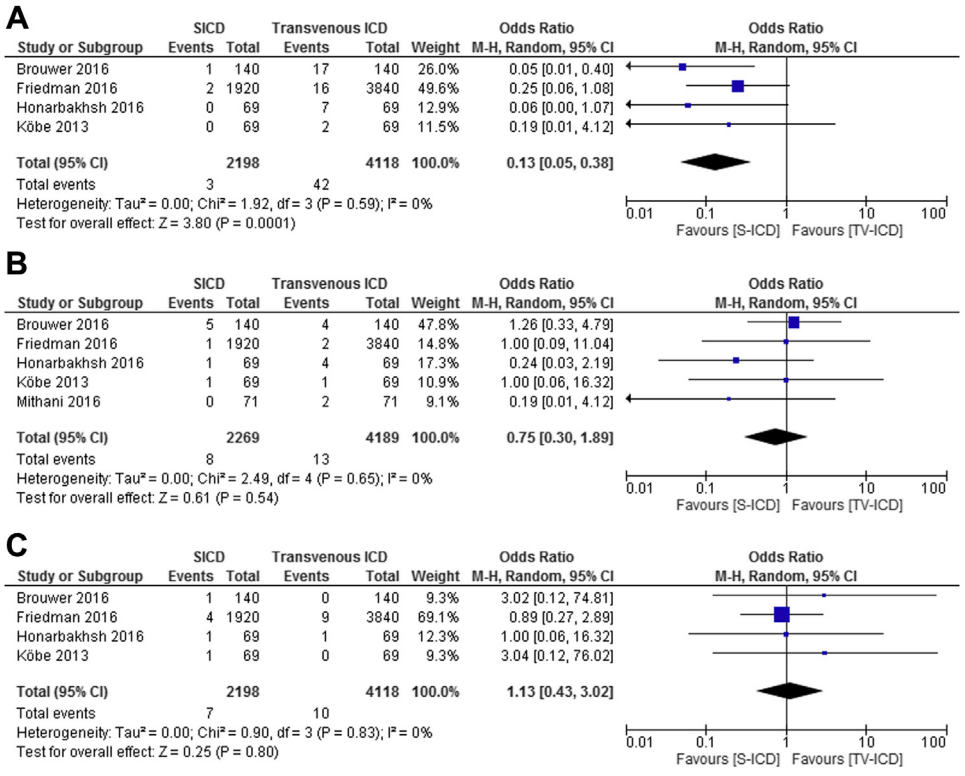
We present the first meta-analysis of case-control and retrospective studies comparing the clinical outcomes and complication rates between S-ICD and

TABLE 3 Clinical Outcomes Between S-ICD and TV-ICD Groups

	S-ICD	TV-ICD	OR (95% CI)
Lead complications	0.14	1.02	0.13 (0.05–0.38)
System failure	0.32	0.24	1.13 (0.43–3.02)
Infection	0.34	0.31	0.75 (0.30–1.89)
Total inappropriate therapy	8.30	9.46	0.87 (0.51–1.49)
T-wave oversensing, episode oversensing	8.99	0.72	9.81 (2.60–37.05)
SVT	1.08	10.43	0.12 (0.0–0.35)

Values are % unless otherwise indicated.
CI = confidence interval; OR = odds ratio; SVT = supraventricular tachycardia; other abbreviations as in Table 2.

FIGURE 2 **Comparison of Clinical Outcomes and Complications Between S-ICD and TV-ICD**



(A) Fewer lead complications occurred in the S-ICD group compared to the TV-ICD group (OR: 0.13; 95% CI: 0.05 to 0.34). **(B)** Infection rate was similar between the S-ICD and TV-ICD groups (OR: 0.66; 95% CI: 0.27 to 1.60). **(C)** Fewer system or device failures occurred in the S-ICD group, but this did not reach statistical significance (OR: 0.94; 95% CI: 0.37 to 2.41). **(D)** Inappropriate therapies (T-wave oversensing, SVT, episodes of inappropriate sensing) were similar between the 2 groups (OR: 0.81; 95% CI: 0.48 to 1.36). **(E)** Inappropriate therapies in TV-ICD group were primarily due to SVT. **(F)** Inappropriate shocks in S-ICD were mostly episodes of oversensing (sensing of noise, T-wave oversensing). CI = confidence interval; OR = odds ratio; S-ICD = subcutaneous implantable cardioverter-defibrillator; SVT = supraventricular tachycardia; TV-ICD = transvenous implantable cardioverter-defibrillator.

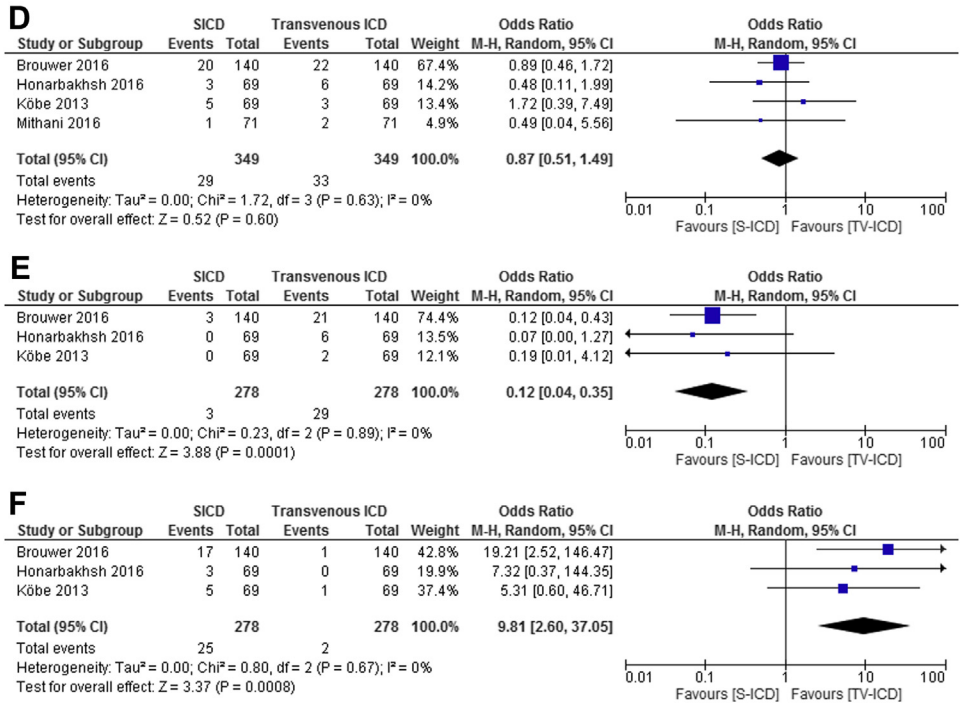
Continued on the next page

TV-ICD recipients. Our main findings are that S-ICD reduced lead-related complications but was similar to TV-ICD with regard to non-lead-related complications. Prevalence of inappropriate therapy was not statistically different between the 2 groups. In addition, the 2 devices appear to perform equally well with respect to appropriate shocks based on the 2 studies that reported such data.

As noted previously, no published randomized trials have compared S-ICD and TV-ICD. However, the PRAETORIAN (Prospective, RAndomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy) trial is a randomized, controlled, multicenter study comparing the advantages and disadvantages of S-ICD. The study includes a total of 700 patients randomized to either S-ICD or TV-ICD (1:1), and the study is powered to assess the noninferiority of S-ICD compared to TV-ICD with respect to the composite primary endpoint of ICD-related complications and inappropriate therapy. This trial, the first of its kind, will help to shed additional light on how the 2 devices compare with regard to clinical outcome endpoints when results become available in 2019 (18).

INFECTION. Infective complications were defined as device-related infections that necessitated removal of the ICD system and/or antibiotic treatment, including endocarditis and pocket infection. Two of the 5 studies (Friedman et al. [12] and Brouwer et al. [11]) did not distinguish between infections treated with antibiotics alone and those requiring surgical extraction. In the remaining 3 studies, all infections required surgical lead extraction. In the study by

FIGURE 2 Continued



Mithani et al. (13), no patient in the S-ICD group had an infection requiring lead extraction, whereas 2.8% of patients (2 of 71) in the TV-ICD group required lead extraction. In the study by Köbe et al. (14), 1 patient each from the S-ICD and TV-ICD groups suffered infection requiring lead extraction (total of 69 patients in each group). Honarbakhsh et al. (10) found 1 of 69 patients in the S-ICD group required lead extraction versus 4 of 69 patients in the TV-ICD group. Complications related to lead extractions were not analyzed in the studies.

The total infection rate among S-ICD recipients was 0.35% in our meta-analysis, which is lower than the infection rate of 3.9% (95% CI: 2.2% to 5.7%) among S-ICD recipients reported in a study analyzing early results of the EFFORTLESS S-ICD registry in 2013 (19). The EFFORTLESS S-ICD registry was an international, nonrandomized, standard-of-care, multicenter registry designed to collect long-term, system-related, clinical, and patient-reported outcome data from S-ICD implanted patients since June 2009. The higher rates of infection in the registry may be related to procedural inexperience with appropriate skin and other preoperative preparations, as well as unfamiliarity with the surgical approach of left lateral thoracotomy and tunneling of the lead. Further support for this hypothesis was noted in the S-ICD IDE study, in which most of the infections occurred during the early aspects of the trial (9). The longer observation time in the EFFORTLESS registry may have also partly contributed to the higher infection rate. The follow-up times of the studies included in this meta-analysis varied, but most were <3 years. Our meta-analysis did not demonstrate a significant difference in infections between the S-ICD and TV-ICD groups (OR: 0.75; 95% CI: 0.30 to 1.89). This may be an unexpected finding, as S-ICD has been hypothesized to be more beneficial in patients at higher risk for intravascular infections. However, 2 of the 5 studies did demonstrate a higher incidence of infection in the TV-ICD group, although this failed to reach statistical significance. Therefore, it is possible that the meta-analysis was inadequate to detect the true difference in infection complications. A more plausible explanation for this finding may be that S-ICD infections were primarily related to device implantation, which, given the similarity between the 2 procedures, was not expected to be different from TV-ICD. Regardless, the consequences of S-ICD infection appear to be less severe, as no intravascular infection has been noted with S-ICD infection. Once available, long-term data will help to differentiate the infection rates related to the presence or absence of leads specifically. In this regard, the ongoing post-marketing study would be beneficial.

LEAD COMPLICATIONS. Our study also showed that lead complications were reduced in the S-ICD group compared to the TV-ICD group (OR: 0.13; 95% CI: 0.05 to 0.38). This finding reinforces the concept that TV leads are truly the "Achilles heel" of the traditional ICD. The S-ICD group experienced similar system failures as the TV-ICD group.

INAPPROPRIATE THERAPY. The prevalence of inappropriate therapy among S-ICD recipients in our meta-analysis was 8.3%. This rate was comparable to that reported in the EFFORTLESS registry, which reported a 360-day inappropriate shock rate of 7% among S-ICD recipients (18). The majority of inappropriate shocks in the EFFORTLESS study were due to oversensing (85%), most frequently T-wave oversensing. The inappropriate therapy rate among TV-ICD recipients in our meta-analysis was 9.4%, comparable to that of other TV-ICD registries and trials, which reported ranges from 4% to 18% (20–22).

Our study found that S-ICD and TV-ICD had similar rates of inappropriate therapies, but they differed in nature. Inappropriate therapies in the TV-ICD group were driven by aberrant atrial rhythms (SVT), whereas inappropriate shocks in S-ICD were either noise or T-wave oversensing. Our finding was consistent with data reported from existing registries and single-arm trials on the 2 devices (20–22). The better performance of S-ICD with SVT may be due to the software's reliable morphology discriminator in its conditional shock zone. The emergence of better technology may further help to reduce noise oversensing and thus the inappropriate therapy currently experienced with the first-generation S-ICD devices. For instance, Brisben et al. (23) have devised a new algorithm that reduces T-wave oversensing episodes by 40%, which has the potential for a clinically meaningful decrease in inappropriate shocks.

APPROPRIATE SHOCKS. Only 2 of the 5 studies ([Köbe et al. [14] and Brouwer et al. [11]) reported data on appropriate shocks delivered by S-ICD versus TV-ICD. Both studies reported similar rates of appropriate therapies between the 2 devices. Based on review of these limited data, S-ICD appears to perform equally well as TV-ICD with respect to delivering appropriate shocks.

MORTALITY. Overall, mortality rate was low and did not differ between the S-ICD and TV-ICD groups in all 5 studies. Four studies reported mortality at the time of follow-up, which ranged from 180 days to 5 years; 1 study reported in-hospital mortality only. The long-term mortality rate across studies ranged from 0% to 2.8% among ICD recipients. Honarbakhsh et al. (10) reported no mortality in either group at the time of follow-up. Köbe et al. (14) reported a mortality rate of 1.4% in each group. In the study by Brouwer et al. (11), 5-year patient survival was 96.0% (95% CI: 90.1% to 100.0%) in the S-ICD arm versus 94.8% (95% CI: 90.7% to 99.0%) in the TV-ICD arm ($p = 0.42$). Mithani et al. (13) reported 1.4% (1 of 71) mortality rate in the S-ICD group and 2.8% (2 of 71) mortality rate in the TV-ICD group.

STUDY LIMITATIONS. Our meta-analysis has several limitations. First, meta-analysis is limited by the small number of studies currently published directly comparing efficacy and safety outcomes of S-ICD and TV-ICD. With fewer than 10 studies, we were unable to test formally for funnel plot asymmetry, as the power of the test was too low to distinguish chance from real asymmetry. A second limitation of the study is the variability of the follow-up regimen of the different studies. The study by Friedman et al. (12) evaluated the in-hospital outcomes associated with adoption of S-ICD and TV-ICD, whereas the mean follow-up duration for other studies ranged between 180 days and 5 years. This somewhat limits the comparability of the studies. In addition, candidacy of S-ICD is screened by electrocardiography (ECG) designed to identify patients susceptible to T-wave oversensing. Patients with T-wave inversions in leads I, II, and aVF on a standard ECG were found to be 23 times more likely to fail than patients without these ECG abnormalities (24). Recipients of TV-ICD did not undergo this screening test. Even though the study population in all 5 studies included in the meta-analysis were propensity-matched for baseline characteristics and major comorbidities, it is unclear whether the ECG screening may have eliminated some of the sicker patients from the S-ICD group, thus affecting the outcome. Furthermore, TV lead–associated tricuspid regurgitation and resultant right-sided congestive heart failure have been postulated as adverse consequences of TV-ICD. The studies in this meta-analysis did not compare the potential for developing tricuspid regurgitation or congestive heart failure between TV-ICD and S-ICD recipients. Finally, the studies included in this meta-analysis did not examine any gender differences in the outcomes. Given the limitations, more well-designed, prospective, randomized controlled trials are needed to confirm the findings.

CONCLUSIONS

This meta-analysis conforms to the widely perceived view that S-ICD has certain advantages

over TV-ICD, with fewer lead-related complications. Contrary to what may be expected, our study did not demonstrate a significant difference in infection rate between recipients of the 2 devices. The choice of device type, the risk of lead-related complications versus the rate of inappropriate therapy, and the device-specific limitations of S-ICD, including the lack of pacing capability, should be taken into account on a case-by-case basis. The nonlead complications of S-ICD, such as inappropriate therapy, are expected to improve as the technology improves.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Selection of S-ICD versus TV-ICD must take into consideration the differences in lead-related and non-lead-related complications, as well as device-specific limitations between the 2 devices on a case-by-case basis.

TRANSLATIONAL OUTLOOK: More research studies, in particular, prospective, large, randomized controlled trials, are needed to achieve more comprehensive comparison of efficacy and safety outcomes between S-ICD to TV-ICD, as well as to elucidate any gender differences in the outcomes.

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APPENDIX For a supplemental figure, please see the online version of this paper.