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REVIEWS

Comparing the safety of subcutaneous versus transvenous ICDs: a meta-analysis

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Abstract

Purpose The use of transvenous implantable cardioverter defibrillators (TV-ICDs) is associated with multiple risks related to the presence of the defibrillator leads within the venous system and right side of the heart, including endocarditis, venous occlusion, tricuspid regurgitation, and potential lead failure. The emergence of subcutaneous ICDs (S-ICDs) may potentially overcome the aforementioned disadvantages. However, evidence validating the safety of S-ICDs relative to TV-ICDs is limited. The present study aimed to synthesize and analyze available data from published studies to comprehensively compare transvenous and subcutaneous ICDs.

Methods Different databases were searched for full-text publications with a direct comparison of TV- and S-ICDs. Fixed effect models were applied to pooled data, and no study-to-study heterogeneity was detected.

Results Data from 7 studies totaling 1666 patients were pooled together. Compared to S-ICDs, the risk of suffering device-related complications was higher in patients with TV-ICDs (OR = 1.71; 95% CI: 1.23–2.38). The number of patients with an S-ICD who suffered inappropriate shocks (IS) was not significantly different than patients with a TV-ICD (OR = 0.92; 95% CI: 0.65–1.30). Subgroup analysis indicated that the TV-ICD group had a higher risk of IS due to supraventricular oversensing (OR = 3.29; 95% CI: 1.92–5.63) while T-wave oversensing tending to cause IS in the S-ICD group (OR = 0.09; 95% CI: 0.03–0.23). The risk of device-related infection in the S-ICD group was not any lower than that in the TV-ICD group (OR = 1.57; 95% CI: 0.67–3.68). The survival rate without any complications during a 1-year follow-up period was similar between the 2 groups (HR = 1.23; 95% CI: 0.81–1.86), although it was assumed that the trend leaned toward more complications in patients with a TV-ICD.

Conclusion The present study verified the safety of S-ICDs based on pooled data. Although there were no differences between TV- and S-ICDs in the short term, fewer adverse events were found in patients with S-ICDs during long-term follow-up.

Keywords Transvenous implantable cardioverter defibrillator · Subcutaneous implantable cardioverter defibrillator · Inappropriate sensing · Infection

1 Introduction

An implantable automatic defibrillator can help to recognize and treat potentially fatal ventricular arrhythmias timely and efficiently [1]. Dating back to the 1980s, however, implantable cardioverter defibrillators (ICDs) were far different than what is currently used, particularly in that a thoracotomy is no longer necessary to place the defibrillation lead in the epicardium. Due to potential postoperative complications, operative morbidity, and mortality associated with the implantation, ICD use was limited [2].

With technological advances, a novel ICD system was developed, with transvenous defibrillation leads and a generator implanted in a subpectoral pocket, which gradually replaced the previous model, and became the currently widely used transvenous ICD (TV-ICD). However, intravenous and intracardiac implants can also cause other problems, such as cardiac perforation, tricuspid regurgitation, venous stenosis, thrombophlebitis, and endocarditis. Most of these complications are related to the transvenous defibrillation leads [3–5]. Additionally, some patients may not be ideal candidates for TV-ICDs due to limited vascular access (internal

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arteriovenous hemodialysis fistula, persistent left with absent right superior vena cava, and peripheral venous embolism), congenital cardiovascular malformation, or repeated occurrence of serious cardiac device-related infections [6–9]. Transvenous leads with abnormalities may need to be replaced, but the extraction of these leads may cause additional adverse events [9].

ICD-related risks are dependent not only on the experience of the surgeon but also on previously existing comorbidities such as diabetes, diseases requiring steroid therapy, or the presence of infection prior to device implantation [1]. Recently, subcutaneous ICDs (S-ICDs) have become a suitable alternative for patients without pacing needs. Due to the subcutaneous placement of the defibrillation leads, the risks of vascular injury, intravenous and intracardiac infection, lead extraction, and excessive radiation during fluoroscopy (especially when a lead extraction is required) may be significantly reduced compared to those for TV-ICDs [10]. Nonetheless, it remains uncertain whether S-ICDs might lead to inappropriate shocks (IS), and safety is not guaranteed without regular pacing and anti-tachycardia pacing (ATP) modes [11]. Additionally, there have been concerns about whether S-ICDs are different from TV-ICD in regard to the rate of complications.

To date, there have been only a few clinical studies on S-ICDs, and they were all small-scale designs, except for the EFFORTLESS S-ICD study by Boston Scientific, which included > 1000 patients [12]. Therefore, we felt that a comprehensive investigation to integrate the data of these existing studies would provide a profound understanding of S-ICDs. Auricchio et al. [13] summarized data from studies on TV- and S-ICDs, and the differential rate of IS between the two was analyzed by meta-regression. However, no meta-analysis has directly compared the efficacy and safety of conventional TV-ICDs and the more recently developed S-ICDs. As such, the present study aimed to synthesize and analyze the results from clinical studies with a direct comparison of TV- and S-ICDs, to comprehensively evaluate the advantages and disadvantages of S-ICDs.

2 Methods

2.1 Search strategy

The present study design was stringently conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14]. A total of five databases, including PubMed, Ovid, EBSCO, Web of Science, and the Cochrane Library, were searched for keywords such as “transvenous,” “subcutaneous,” and “implantable cardioverter defibrillator” to retrieve pertinent literature published prior to July 2020.

2.2 Study selection criteria and data extraction

All studies were retrieved and data were collected independently by two investigators who were not informed of the protocol for the present study and who verified the quality and eligibility of the literature found. The included literature met the following criteria: English language; direct comparison between TV- and S-ICDs; full-text as opposed to abstract only; and clear definition of ICD-related complications, for example, IS or device infection requiring intervention. The causes of IS were generally divided into T-wave oversensing and supraventricular oversensing (atrial fibrillation, and atrial, sinus, or supraventricular tachycardia). Exclusion criteria included studies on TV- or S-ICDs alone; case reports, case series, and review articles; and inhospital studies, or studies with follow-up ≤ 6 months. In cases of different publications of the same study, the one with the complete data was chosen.

Important statistics such as the number of total patients and the number of patients with clearly defined events were carefully collected. Basic demographic data and follow-up duration were recorded as well. The Newcastle-Ottawa Scale was used to assess the quality of the included studies (Supplementary Table).

2.3 Data synthesis and analysis

Fixed effects models were used for data integration and to compare TV- and S-ICDs in regard to the difference in total complications, device infection requiring intervention, and IS. The results were presented as odds ratio (OR) and illustrated as forest plots. Additionally, publication bias was assessed using Begg’s adjusted rank correlation test and was shown as a funnel plot. Survival curve data from the included publications were extracted as previously described [15]. Then, these data were further processed using the previously described method to calculate the integral hazard ratio (HR) and depict the free-event survival curve [16].

3 Statistics

Statistical heterogeneity was assessed using inverse variance (I-V) statistics. Statistical analyses were performed using Stata 12.0 software (Stata Corp, College Station, TX, USA). Survival data were extracted using Engauge Digitizer 4.1 software. HR and Kaplan-Meier curves were obtained using GraphPad Prism 5 software. As a limited number of pieces of literature were included, sensitivity analysis was not necessary. Heterogeneity was calculated, and the included studies were considered to have low heterogeneity if $I^2 < 50\%$ and p value > 0.05; therefore, the fixed effect model was used. The results of the heterogeneity analysis are shown in the forest

plot. All p values were two-tailed, and the statistical significance was set at 0.05.

4 Results

4.1 Literature search and general description of included studies

After excluding 156 duplicates from 3513 articles to be searched, 3343 articles were also excluded for not meeting the inclusion/exclusion criteria. A total of seven articles met the eligibility requirements [17–23]. The flow diagram of the publication filtration is shown in Fig. 1. Data from 1666 patients with follow-up durations ranging from 6 to 48 months were pooled together, and the characteristics of the included studies can be found in Table 1. At baseline, demographic characteristics showed no significant difference between the TV- and S-ICD groups (Table 2).

4.2 Comparison of device-related complication

During the follow-up period, total implant-related complications were reported in five articles, without heterogeneity (I^2 = 0). These complications included IS, pocket erosion, defibrillation threshold failure, lead failure, and device infection requiring intervention [17, 18, 20, 21, 23]. Compared to patients with S-ICDs (n = 795), the risk of suffering from total device-related complications was higher in patients with TV-ICDs (n = 782) in a fixed effect model (OR = 1.71; 95% CI: 1.23–2.38), indicating a predominance of S-ICD. Although three studies had negative results, a significant difference was obtained after pooling the data together (Fig. 2) [18, 20, 21].

Of the included studies, six articles described a number of patients with a device-related infection requiring intervention [17, 18, 20, 22, 23]. Contrary to the conventional perspective, the risk of device-related infection in the S-ICD group (n = 826) was comparable to that of the TV-ICD group (n = 826), without a significant difference (OR = 1.73; 95% CI: 0.86–3.51) from a fixed effect model (Fig. 3a). Since only one article mentioned the occurrence of infection prior to ICD placement, a risk-stratified analysis could not be carried out [18].

Patients with IS were reported by seven articles, and the proportion of patients with IS in the S-ICD group (n = 831) was similar to that in the TV-ICD group (n = 835) [17–23]. There was no significant difference between the two groups (OR = 0.92; 95% CI: 0.65–1.30), indicating an equal risk of IS (Fig. 3b). Of the included articles, five reported that the IS had two primary causes: T-wave oversensing and supraventricular oversensing (i.e., atrial fibrillation and atrial, sinus, or supraventricular tachycardia) [17, 18, 20, 21, 23]. Therefore, a subgroup analysis of IS was further performed to assess the distribution of causes of IS between the two groups (Fig. 4). Surprisingly, the subgroup comparison indicated that TV-ICDs had a higher risk of IS due to supraventricular oversensing (OR = 3.29; 95% CI: 1.92–5.63), while T-wave oversensing more frequently caused IS in the S-ICD group (OR = 0.09; 95% CI: 0.03–0.23).

4.3 Analysis of short-term and long-term survival with freedom from total complications

Of the four articles that presented an event-free survival curve, only one had a follow-up duration of less than 1 year [17–19, 21]. Therefore, survival data with a follow-up duration longer than 1 year were collected for long-term survival analysis, and the studies with a follow-up of less than a year were used to synthesize the short-term survival curve (Supplementary Fig. 1a). The complication-free survival rate for patients with an S-ICD was similar to that of those with a TV-ICD over a year-long follow-up period (HR = 1.23; 95% CI: 0.81–1.86). However, the difference between TV- and S-ICDs emerged with a long-term follow-up. The S-ICD curve entered the plateau stage at approximately 40 months postimplantation, while the TV-ICD curve showed a continuous downward trend in general (Supplementary Fig. 1b). This revealed that the probability of total complications in patient with an S-ICD was evidently less than that in patients with TV-ICDs over time (HR = 2.13; 95% CI: 1.36–3.32).

Table 1 Characteristics of included studies

Author	Year	Region	Number of patients	Study design	Mean follow-up duration
Köbe, et al.	2013	Germany	138	Case-control study	7.2 months
Honarbakhsh, et al.	2016	UK	138	Propensity score matching case-control study	32 months
Brouwer, et al.	2016	Netherlands	280	Propensity score matching case-control study	48 months
Mithani, et al.	2016	USA	182	Case-control study	6 months
Pettit, et al.	2013	UK	17	Observational study	29 months
Boveda, et al.	2018	France	62	Retrospective cohort	6 months
Knops, et al.	2020	Europe and USA	849	Randomized control	49.1 months

Table 2 Characteristics of patients' demography at baseline (TV-ICD vs. SC-ICD)

Author	Age (year)		Male (%)		LVEF (%)		IHD (%)		AF (%)		DM (%)		Primary prevention (%)		CKD (%)		*p* value
	TV-ICD	SC-ICD	TV-ICD	SC-ICD	TV-ICD	SC-ICD	TV-ICD	SC-ICD	TV-ICD	SC-ICD	TV-ICD	SC-ICD	TV-ICD	SC-ICD	TV-ICD	SC-ICD	
Köbe, et al.	47.7 ± 14.7	46.2 ± 15.6	50 (72.5)	50 (72.5)	40.6 ± 15.9	46.2 ± 15.6	13 (18.8)	11 (15.9)	NG	NG	NG	NG	34 (50)	41 (59.4)	NG	NG	NS
Honarbakhsh, et al.	40 ± 10	35 ± 13	52 (75)	52 (75)	58 ± 13	57 ± 15	4 (6)	6 (9)	NG	NG	0 (0)	0 (0)	56 (81)	56 (81)	1 (1.4)	1 (1.4)	NS
Brouwer, et al.	41.5 ± 13.3	40 ± 19.3	87 (62)	84 (60)	49 ± NG	50 ± NG	41 (29)	26 (19)	21 (15)	13 (9)	5 (4)	8 (6)	86 (61)	93 (66)	11 (7.9)	12 (8.6)	NS
Mithani, et al.	56.3 ± 12.7	54.9 ± 13.6	50 (54.9)	51 (56)	27.8 ± 11.7	26.8 ± 12.1	40 (44)	34 (37.4)	15 (16.5)	14 (16.4)	38 (41.8)	37 (40.7)	70 (76.9)	74 (81.3)	5 (5.5)	19 (20.9)	NS
Pettit, et al.	11 ± 8.9	14.5 ± 5.9	6 (75)	5 (56)	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NS
Boveda, et al.	61.5 ± 11.2	58.7 ± 13.2	6 (20)	6 (20)	29.6 ± 5.2	32.6 ± 7.4	22 (71)	15 (48)	NG	NG	5 (16)	3 (10)	20 (65)	18 (58)	NG	NG	NS
Knops, et al.	64 (56–70)	63 (54–69)	345 (81.6)	363 (79.1)	30 (25–35)	30 (25–35)	298 (70.4)	289 (67.8)	93 (22.1)	115 (27.0)	126 (29.9)	112 (26.3)	339 (80.1)	346 (81.2)	NG	NG	NS

TV-ICD, transvenous implantable cardioverter defibrillator; SC-ICD, subcutaneous implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; AF, atrial fibrillation; DM, diabetes mellitus; CKD, chronic kidney disease; NG, not given; NS, not significant

4.4 Publication bias analysis

Begg's test was used to analyze publication bias and showed a symmetrical distribution of the included publications (p = 0.462) in a funnel plot (Supplementary Fig. 2), indicating that publication bias did not exist among the articles included in the present study.

5 Discussion

The objective of the present study was to systematically assess the complications of S-ICDs compared to TV-ICDs. Our analysis included seven independent studies, completed between 2013 and 2020. To our knowledge, this is the first meta-analysis to compare complication and event-free survival rates between patients with TV- and S-ICDs. Data from our analysis indicated that the rates of IS and device infection requiring intervention were similar between patients with TV- and S-ICDs. Subgroup analysis revealed that the primary causes of IS were supraventricular and T-wave oversensing for TV- and S-ICDs, respectively. S-ICDs were thought to present a lower risk of lead-related infection; however, without enough studies reporting corresponding data, subgroup analysis or risk stratification could not be performed. Survival analysis indicated that patients with S-ICDs had a lower risk of adverse events over a long-term follow-up when compared to patients with TV-ICDs. Contrarily, the event-free survival rate was similar between the two groups when compared over a relatively short follow-up period.

IS can cause uncomfortable feelings, although it is not life-threatening. The rate of IS was shown to gradually decrease year after year [13], and it is thought that it can even be eliminated by optimizing programming [24]. However, some recent studies found no difference in IS between patients with TV- and S-ICDs, and existing evidence suggests that patients with S-ICDs had an IS rate equal to that of patients with TV-ICDs. Additionally, there is a well-acknowledged misconception that the main advantage of S-ICDs is a lower risk of infection [1]. However, the present study showed no significant difference between TV- and S-ICDs in regard to infection. This might be a result of bias in data from different studies. Of the included publications, only one article reported the occurrence of infection prior to ICD implantation. Previously existing infection was a risk factor for device-related infection for either *de novo* or reimplantation of ICDs [25]. Additionally, patients with comorbidities such as diabetes and chronic kidney disease were also susceptible to infection [26], confounding factors which should be carefully considered in the study design and data analysis. TV-ICDs are related to lead adhesion and venous stenosis due to fibrosis and thrombosis induced by the intravenous implants [27, 28]. A previously published study in animals showed that the

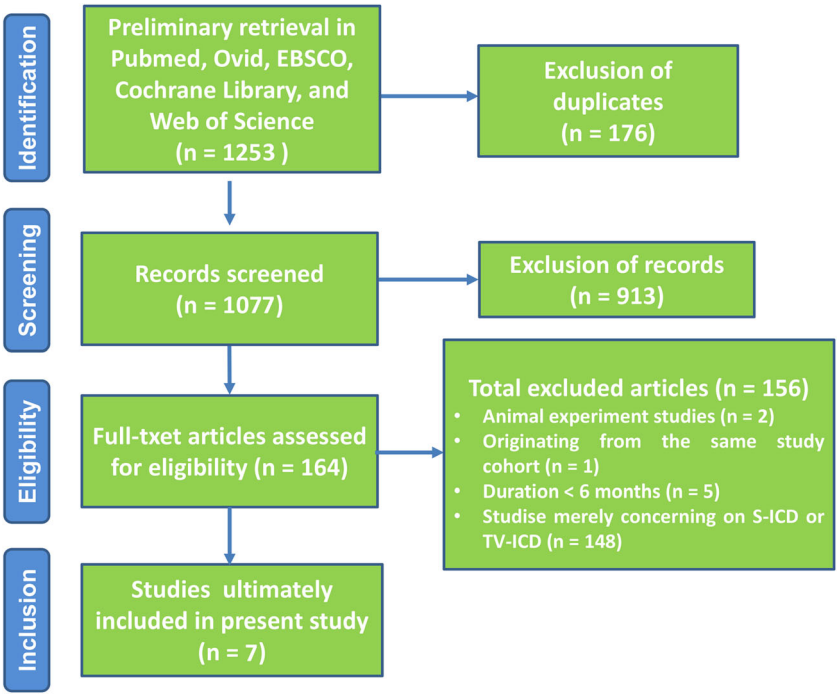

Fig. 1 Flow diagram showing the process of literature filtration

defibrillation lead of TV-ICDs was significantly related to severe venous fibrosis, thrombosis, and stenosis [29]. S-ICDs can overcome this disadvantage without degrading the efficacy of defibrillation [30]. However, S-ICDs do not offer a pacing function; therefore, they are not able to be used for anti-tachycardia pacing treatment or in potentially pacemaker-dependent patients.

The first S-ICD implantation occurred in 2008, initiating subsequent clinical studies of S-ICDs. The IDE study, including 330 patients, was aimed at evaluating the efficacy and safety of S-ICDs [30]. The EFFORTLESS S-ICD study, including approximately 1000 patients, was carried out to assess the long-term complications of S-ICDs [12]. Despite the previously mentioned studies having prospective and multi-center designs, they also had drawbacks, because there was no direct comparison of TV- and S-ICDs. Additionally, the MADIT S-ICD study is an ongoing study designed to verify the hypothesis that post-myocardial infarction patients with the comorbidity of diabetes and a relatively preserved ejection fraction have a survival benefit from S-ICD implantation [31]. Exclusion of pacing dependence should be a prerequisite of S-ICD implantation, or as an alternate, and a backup pacing lead should be placed. As such, adverse consequences (death, syncope, hospital admission, and subsequent implantation of pacemaker) caused by a lack of anti-tachycardia and backup pacing function in S-ICDs could not be evaluated.

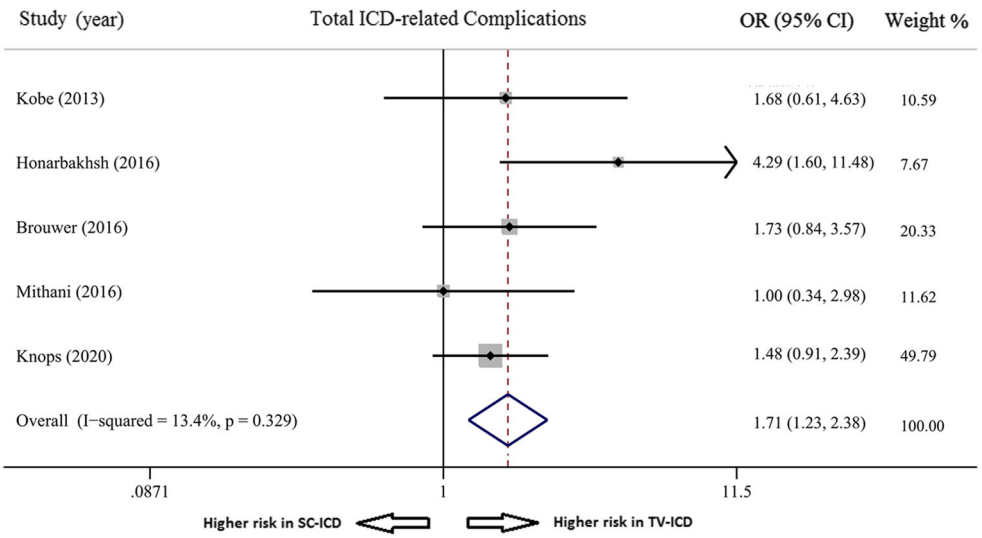

Fig. 2 Systemic comparison of device-related complications

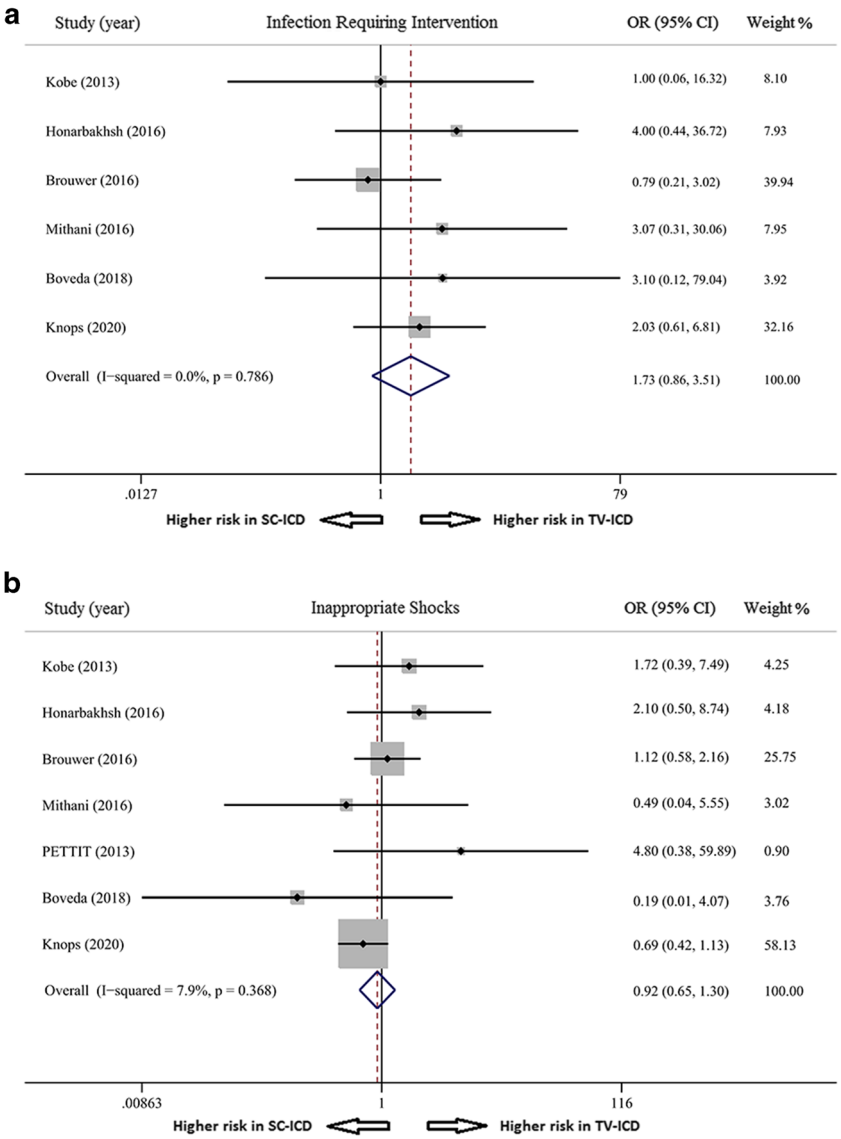

Fig. 3 Comparison between TV- and S-ICDs regarding cardiac device-related infection (**a**) and total inappropriate shock events (**b**)

The PRAETORIAN study, with a direct comparison of TV- and S-ICDs, was designed to further investigate the efficacy and safety of S-ICDs [32]. Recently, results of the PRAETORIAN investigation have been published, which update our ideas. In the PRAETORIAN study, appropriate ICD therapy (including anti-tachycardia pacing), death from any cause, major adverse cardiac events, hospitalization for heart failure, and crossover between the assigned devices as secondary end points were all reported. This well-designed, randomized control study suggested a very low incidence of bradycardia, which requires pacemaker intervention in the S-ICD group. With a large sample size (876 patients), the PRAETORIAN study results indicated that only 5 of the 426 patients in the S-ICD group underwent subsequent implantation of a transvenous pacing lead for the treatment of bradycardia [23]. Therefore, the risk of requiring a pacemaker should be acceptable, if a careful evaluation of the indications and contraindications for S-ICD was performed before the procedure.

As far as we are aware, the present review was the first meta-analysis to systematically and directly compare TV- and S-ICDs regarding device-related complications. In the present meta-analysis, S-ICDs were proven to have fewer complications than TV-ICDs. However, results from the present study should be updated if more prospective, large sample size, randomized, and multicenter clinical trials are published. Finally, cumulative experimentation for S-ICD implantation is highly needed in the future.

6 Limitations

The present meta-analysis included seven studies, all of which were designed as case controls. As some of the included

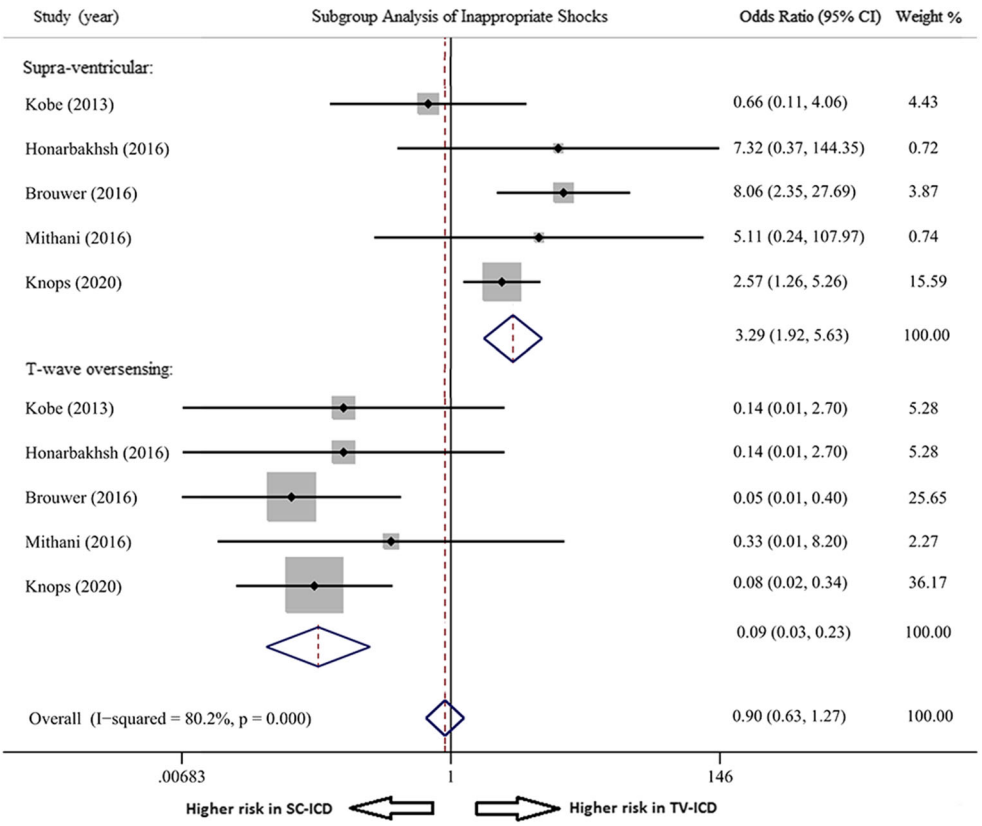

Fig. 4 Subgroup analysis of inappropriate shocks resulting from different mechanisms: supraventricular oversensing (**a**) and T-wave oversensing (**b**)

articles had deficits, such as no randomization, a retrospective design, or a small scale, the present meta-analysis had these deficits as well. Furthermore, only a few articles were eligible based on the selection criteria; thus, sensitivity analysis was not possible. Only one article mentioned the occurrence of infection prior to ICD implantation. Additionally, patients who received steroids or had comorbidities such as diabetes and chronic kidney disease were also susceptible to infection, and these confounding factors were not presented in the included studies. Therefore, risk-stratified analysis could not be performed. Consequently, large-scale, prospective, multicenter, and randomized clinical trials are still needed to clearly explore confounding factors.

7 Conclusion

The present study quantitatively and comprehensively analyzed the differences in complications between TV- and S-ICDs via meta-analysis. Compared to TV-ICDs, the risk of suffering from total device-related complications was lower in patients with S-ICDs. The proportion of patients who experienced IS in the S-ICD group was similar to that of the TV-ICD group. Subgroup analysis indicated that patients with TV-ICDs had a higher risk of IS due to supraventricular oversensing, while T-wave oversensing was the primary cause of IS in S-ICD patients. The risk of device-related infection in the S-ICD group was no lower than that for the TV-ICD group. The complication-free survival rate was similar between the TV- and S-ICD groups over a 1-year follow-up period. The probability of complication occurrence was lower in the S-ICD group. As a result, S-ICDs could be a viable alternate to TV-ICDs, chosen to decrease the long-term risk of device-related complications.

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Data Availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Competing interests The authors declare that they have no conflict of interest.

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