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Reduction of inappropriate shock rate through signal filtering (smart-pass) in patients with implantable subcutaneous cardioverter-defibrillator: a systematic review and meta-analysis

Maurizio Santomauro,[1] Mario Petretta,[1] Carla Riganti,[2] Mario Alberto Santomauro,[3] Mariarosaria De Luca,[4] Andrea Santomauro,[5] Antonio Cittadini[4]

[1]IRCCS SYNLAB SDN, Naples; [2]Department of Health Services, Federico II University, Naples; [3]Department of Pharmacy, Sant'Ottone Frangipane Hospital, Ariano Irpino; [4]Department of Translational Medical Sciences, Federico II University, Naples; [5]Emergency Medicine and Critical Care Medicine Department, Vita-Salute San Raffaele University, Milan, Italy

Correspondence: Maurizio Santomauro, IRCCS SYNLAB SDN, Naples Italy.
Tel.: +39 330502275.
E-mail: santomau@unina.it

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Abstract

Subcutaneous implantable cardioverter-defibrillators (S-ICD) are effective in protecting patients against sudden death but expose them to a higher risk of inappropriate shock (IAS). We performed a systematic search of studies published between January 2010 and December 2019 assessing IAS due to cardiac oversensing by the selection process (PRISMA) and identified 17 eligible articles. Fifteen studies were observational, and two studies were retrospective. For the meta-analysis, the final population included 6111 patients: 3356 without SMART pass (SP) filter (group 1) and 2755 with SP filter (group 2). 1614 shocks (appropriate shocks plus IAS) were registered (1245 in group 1 and 369 in group 2). The random effects meta-analysis estimated an overall IAS rate of 7.78% (95% confidence interval: 4.93-10.64) with substantial variability between studies (I square=96.05%, $p<0.001$). The IAS rate was 10.75% (95% confidence interval: 8.49-13.02) for group 1 and 3.61% (95% confidence interval: 1.36-5.86) for group 2 ($p<0.001$). Third-generation S-ICD technology with SP filters reduced the risk of cardiac signal-related IAS.

Key words: subcutaneous implantable cardioverter defibrillator, inappropriate shock, oversensing, malfunctions, sudden death.

Introduction

Cardiovascular mortality, as a consequence of ventricular fibrillation (VF) or ventricular tachycardia (VT), represents a significant health problem despite advances in the management of cardiovascular disease. Worldwide, survival after the out-of-hospital cardiac arrest remains poor. These survivors have different therapeutic options such as anti-arrhythmic drugs, radiofrequency or surgical ablation, or ICD. Nowadays, recently introduced subcutaneous implantable cardioverter-defibrillators (S-ICD) systems are a good alternative to the implant of transvenous ICD (T-ICD) for the prevention of sudden cardiac death in patients with recurrent monomorphic VT responsive to antitachycardia pacing (ATP), or pre-existing unipolar pacemaker leads and without indication for anti-bradycardia pacing or cardiac resynchronization therapy. Moreover, high risk of infections, congenital heart disease, and poor vascular access are strong determinants for the appropriate device selection [1,2]. It seems to be helpful for younger patients with cardiomyopathies or channelopathies in primary prevention [3,4]. Although initial reports indicated an acceptable rate of IAS on patients with S-ICD [5,6], novel mechanisms of noise oversensing have recently been reported [7,8]. In this study we performed a systematic review and meta-analysis on the occurrence of IAS in patients with S-ICD implanted from 2010 to 2019 with and without SMART Pass (SP) filter.

Materials and Methods

Search strategy

A systematic search was limited between January 1, 2010 to December 31, 2019 by 3 investigators, in the following database: PubMed, Embase.com (Elsevier), the Cochrane Library (Wiley), CRD (Centre for Reviews and Dissemination): DARE (Database of Abstracts of Reviews of Effects), HTA (Health Technology Assessment Database) to identify articles with S-ICD IAS rates. The article type was limited to "clinical trial". The following Boolean search terms were utilized: "subcutaneous implantable defibrillator or S-ICD" and "shocks or therapy", "inappropriate" and "cardiac oversensing". By hand-search, records identified through database searching yielded a total of 730 citations.

Studies selection and data extraction

Overall, 610 citations were identified after the removal of duplicates. The references were screened by two independent researchers (SMA and CF) and, in case of disagreement, a third researcher (IL) was involved to resolve the differences. The selection process (PRISMA Flow Diagram) is displayed in Figure 1 [9]. Search criteria and methodology were approved by all authors. Titles and abstracts retrieved in the search were reviewed, and observational and comparative studies reporting IAS rates in S-ICD were selected. Case reports, review articles, abstracts, meta-analysis and editorials were excluded. If there were multiple publications from the same study, the latest study with the most complete data available was selected, and the other publications were not used to avoid overlapping cohorts. Because randomized controlled trials (RCT) and non-RCT were included in this meta-analysis, we used the Jadad scale to assess the quality of the RCT, whereas the methodological index for non-randomized studies (MINORS) scale [10] was used to assess non-RCT. If two independent evaluations conflicted, all authors participated in a discussion to resolve the controversy. For included studies, only data on S-ICD patients were extracted. Extracted data included: SP filter, patients' mean age, number of total shocks delivered, follow-up (FU) duration, IAS. Data were extracted by one author and were reviewed by additional authors.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical data as percentages. Differences between groups were analyzed by t-test or chi-square test, as appropriate. The main effect size of the study was proportion of patients experiencing IAS during follow-up (also referred in the text as IAS rate). The user-written Stata meta prop-one package [11] was used to pool proportions and to present weighted sub-group and overall estimates with inverse-variance weights. For this purpose, the random-effects model with the logit transformation was applied, and the result displayed as forest plot. Study specific 95% confidence intervals were calculated using the Clopper-Pearson exact method. Between-study heterogeneity was evaluated with Cochran's Q and I square statistics. When statistical heterogeneity was substantial, meta-regression analysis was performed to identify potential confounders (namely, SP filter, patients' mean age, number of total shocks delivered, FU duration). The IAS rate was modeled on the log scale as a linear combination of the regression factors. P-values <0.05 were considered statistically significant. Statistical analysis was performed using the Stata software 16.0 (StataCorp 4905 Lakeway Drive College Station, Texas 77845 USA). The presence of publication bias was graphically assessed using a funnel plot, a simple graphical display of a measure of study size against logit of IAS rate. The interpretation of funnel plots is facilitated by the inclusion of diagonal lines representing the 95% confidence limits around the summary treatment effect, showing the expected distribution of studies in the absence of bias [12]. Because these diagonal lines are not strict 95% limits but rather a region in which 95% of the observed effects are expected to fall if the true effects are homogenous, they are referred to as "pseudo 95% confidence limits". To evaluate potential publication bias, the test proposed by Egger et al was also performed [13].

Results

After excluding 580 articles for not meeting inclusion/exclusion criteria, 30 articles remained to be assessed for eligibility. Following assessment of the full-text articles, 13 were excluded because shocks were not specified or rates of inappropriate therapy, rather than just shocks, were given. A total of 17 studies were included in the analysis [2,3,5,6,8,14-25] (Table 1). The final population for the meta-analysis included 6111 patients, 3356 without SP filter (Group 1) and 2755 with SP filter (Group 2). Years of enrolment for the studies ranged from 2010 to 2019 (median 2016); 15 studies were observational, and two studies were retrospective. One study enrolled patients in a remote monitoring system (LATITUDE). Shock incidence was calculated for patients with SP program enabled (SMART-PASS ON) or disabled (SMART-Pass OFF) at implantation, censoring patients when SP programming changed or at the last transmission. The total number of appropriate shocks (AS) plus IAS was 1614, 1245 in Group 1 and 369 in Group 2. The random effects meta-analysis estimated an overall IAS rate of 7.78% (95% C.I. 4.93-10.64) with substantial variability between studies (I square = 96.05%, $P<0.001$) (Figure 2). The IAS rate was 10.75% (95% C.I. 8.49-13.02) for Group 1 and 3.61% (95% C.I. 1.36 – 5.86) for Group 2 ($P<0.001$). Results of multivariable meta-regression analysis are reported in Table 2. As shown, SP filter Group and FU length explained a significant degree of between study variability ($P < 0.001$), lowering the residual heterogeneity (I square residual = 37.88%). The IAS rate was higher in Group 1 than in Group 2 and progressively increased with the length of FU. The funnel plot appears symmetrical (Figure 3), without evidence of bias using the Egger weighted regression method (P = 0.06).

Discussion

To the best of our knowledge, this is the first meta-analysis evaluating the impact of SP filters on the incidence of IAS in a large number of patients who underwent to S-ICD implantation. The results demonstrate that the IAS rate was significantly higher in the trials of S-ICD without SP filter as compared to the IAS rate of trials with SP filter. Indeed, the mean IAS rate for S-ICD without SP filter was 10.75%, ranging from 5.00% in the study of Aydin et al. [15] to 20.71% in the study of Brouwer et al. [18]. Conversely, the mean IAS rate for S-ICD with SP filter was 3.61%, ranging from 0.18% in the study of Gold et al. [19] to 9.30% in the study of Liang et al. [25]. In previous studies on conventional T-ICD trials, the IAS rate, ranged from 4% to 18% [3]. With modern devices and programming, these percentages dropped (2.8%-3.7%) over the last 2 years [26,27].

IAS in S-ICD typically result from oversensing of cardiac signals (due to SVT identified as ventricular arrhythmias), or due to noncardiac oversensing [7]. The introduction of AST in the pre-implant screening, provided a progressive reduction of IAS and, in turn, proper patient selection. Appropriate patient selection and pre-implantation ECG screening are probably the

most effective way to avoid oversensing-related IAS. Exercise testing during pre-implant ECG screening has been suggested to be useful in assessing vector eligibility in patients with HCM [28]. Rudic et al. proposed the adoption of postoperative exercise screening to exclude oversensing of cardiac and noncardiac signals [29]. Furthermore, post-implant exercise may be executed to improve discrimination when rate-dependent variations in QRS morphology occur. In case of noise induction in the current vector, device reprogramming to a noise-free vector was done. In contrast Larbig et al. analyzed the impact of ergometry guided programming on primary and secondary prevention of TWO [30]. FU analyses did not reveal significant differences related to control group (9.8% vs 8.1%; P = .731). The authors concluded that postoperative ergometry does not seem to be helpful for prevention of cardiac oversensing.
Careful optimized vector selection with device programming led to a further reduction in IAS. Indeed, programming and discrimination algorithms evolved significantly. Dual zone (programming a 170-220 bpm zone with SVT discrimination algorithms plus a zone for heart rate > 220 bpm) significantly decreased the rate of IAS [7]. Earlier studies [5,6], showed a high rate of IAS of 7% per year for the first-generation S-ICD. IAS were mainly attributed to TWO (39%) and SVT above the discrimination zone (24%), which could be lowered by dual-zone programming [6]. After addition of the SP filter and additional advancements, studies reported IAS rates of 3.5% to 6.4% annually so that the risk of IAS with T-ICD and S-ICD become comparable [27]. Noteworthy, in our meta-analysis IAS due to cardiac oversensing was 10.75% for Group 1 and 3.61% for Group 2 (P<0.001) (Fig. 3). Both SP filter Groups and FU length explained a statistically significant degree of between study variability (P < 0.001), lowering the residual heterogeneity to 37.88%. A limitation of this meta-analysis is the high between studies heterogeneity observed. However, at meta-regression analysis SP filter Group and FU length explained a significant degree of between study variability, lowering the residual heterogeneity to 38%. Another limitation is the possible presence of publication bias. In fact, the funnel plots and the Egger weighted regression method may be inaccurate for meta-analyses of proportion studies with low proportion outcomes [13].

Conclusions

Data from clinical studies recommend that the S-ICD is useful to protect patients against sudden death and expose them to less risk of IAS similar T-ICD patients. When interpreting the results of our review summary, it should be considered that the technology of third generation S-ICD with SP filter and the development of AST progressively, have reduced the risk of IAS related to cardiac signals, without eliminating the risk of IAS related to extracardiac signals. However, the current SP filter, incorporated in S-ICD system, mitigates the impact of IAS while maintaining sensitivity and specificity in detecting VT. Therefore, it is essential in the Emergency Department to correctly identify different potentials causes of IAS.

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Table 1. The selected S-ICD studies that investigate the inappropriate shocks in chronological order.

Authors	Year	N pts	Age (years)	Follow-up (months)	Shock	% IAS
Bardy GH et al (5)	2010	55	61±11	10±1	16	9%
Dabiri Abkenari L et al (14)	2011	31	53±16	13.9± 2.5	37	9.6%
Aydin A et al (15)	2012	40	42±15	19±17	30	5%
Olde Nordkamp LR et al (6)	2012	118	50±14	18±7	60	13%
Jarman JW,Todd DM (17)	2013	111	33 (10-87)	13±7	75	15%
Kobe J et al (3)	2013	69	46±16	18±11	6	5.4%
Burke MC et al (2)	2015	882	50±16.9 (7-88)	54±28	328	13.1%
Olde Nordkam LR et al (16)	2015	581	49±18	21±13	101	8.3%
Brouwer TF et al (18)	2016	140	41±39	60±1	32	20.5%
Gold MR et al (19)	2017	1637	52±15	1±1	3	0.2%
Ozkartal T et al (20)	2017	37	47±15	3.7	3	5.4%
Honarbakhsh S et al (21)	2017	69	35±13	31±19	6	4.3%
Mithani AA et al (22)	2018	91	54±13	3±3	2	1.1%
Theuns D et al (8)	2018	1984	48±16	16±6	880	9.7% vs 4.3%
Migliore F et al (23)	2019	44	37±17	12±13	13	2.9%
Khazen C et al (24)	2019	79	44.5±17.2	12.8±13.7	13	8.9%
Liang JJ et al (25)	2019	86	45±16	23±14	9	9.3%

IAS**,** inappropriate shocks; Pts, patients.

Table 2. Results of multivariable meta-regression analysis.

IAS rate	Coef.	S. E.	T value	p>t	P>t	95% C. I.
Group	-.0539472	.012617	-4.28	0.001	-.0812046	-.0266898
Age (years)	-.0014142	.0009994	-1.42	0.181	-.0035733	.0007448
Shocks delivered	.0000196	.0000262	0.75	0.468	-.000037	.0000762
Follow-up (months)	.0013331	.0003912	3.41	0.005	.0004879	.0021783
cons	.1308092	.0545776	2.40	0.032	.0129014	.248717

IAS rate, absolute rate of Inappropriate shocks; Coef, coefficient; S.E., standard error; C.I., confidence interval; cons, constant.

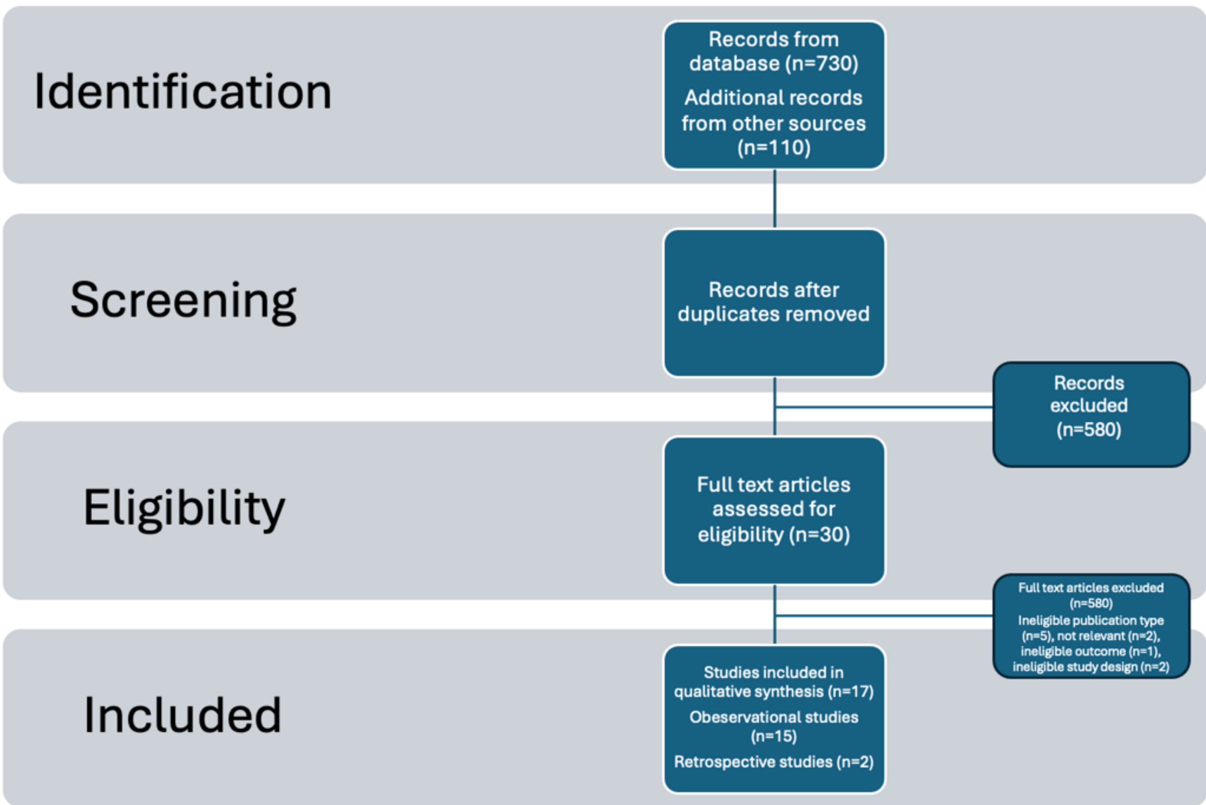

Figure 1. Flow-chart of study selected (PRISMA Flow Diagram).

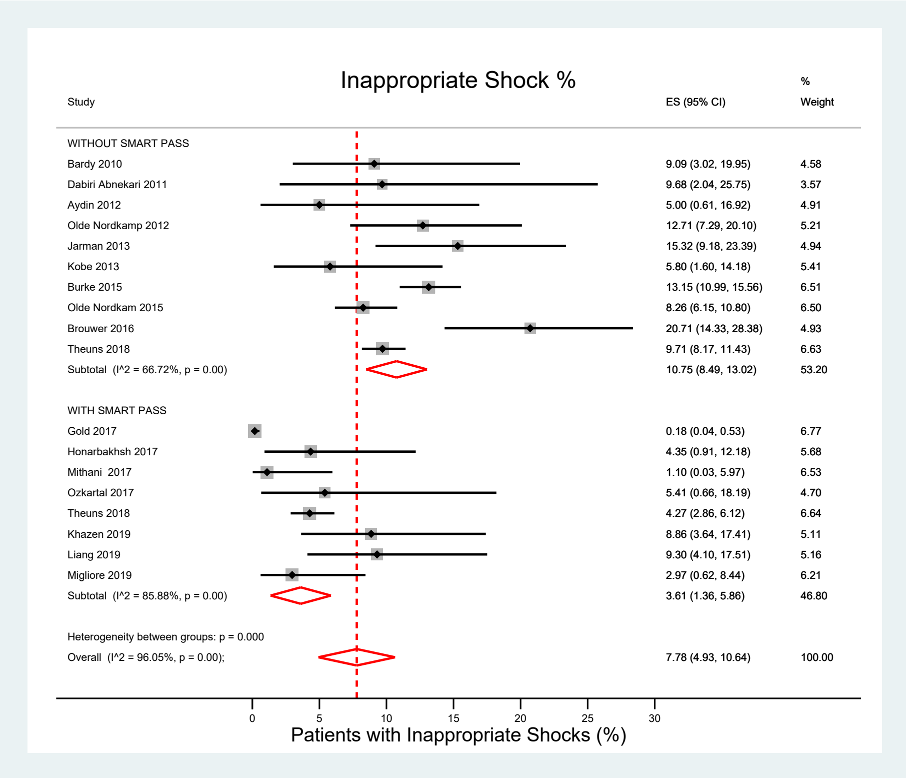

Figure 2. Meta-analysis of the patients with inappropriate shocks without SMART Pass group and with SMART Pass group in the selected S-ICD studies.

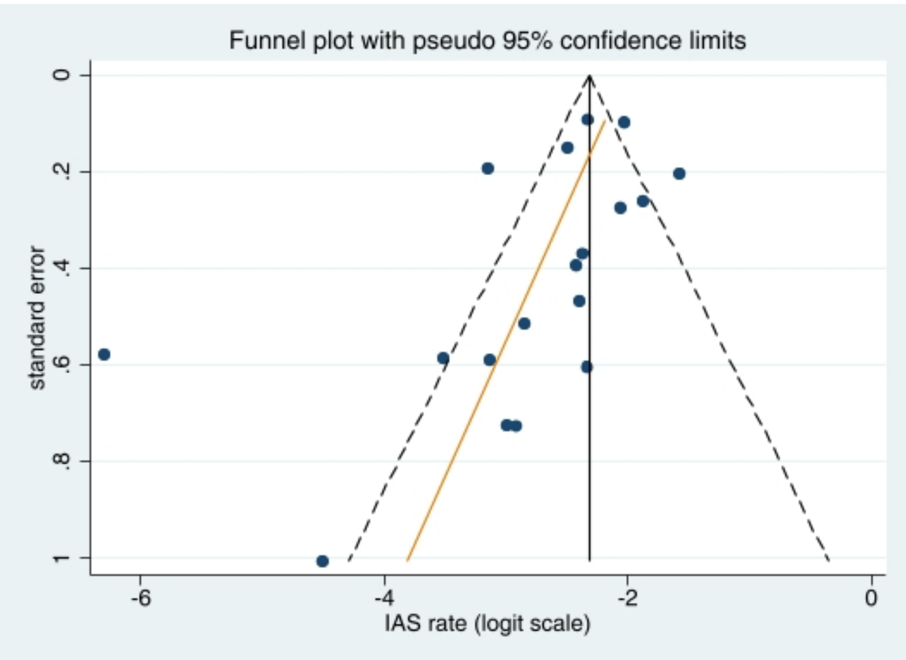

Figure 3. The funnel plot displays the study IASs rate on a logit scale against its standard error for each study included in the meta-analysis. The vertical line indicates the pooled estimate of the overall prevalence rate, with the diagonal lines representing the expected pseudo 95% confidence limits around the summary.