Efficacy And Safety Of The Subcutaneous Implantable Cardioverter Defibrillator: A Systematic Review

Running title: Efficacy and safety of subcutaneous ICD

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Abstract

Background: Subcutaneous implantable cardioverter defibrillators (S-ICD) are an alternative to conventional transvenous implantable cardioverter defibrillators (TV-ICD) in patients not requiring pacing. We sought to define the efficacy and safety of S-ICD through literature review.

Methods: We searched MEDLINE and EMBASE for studies evaluating efficacy and safety outcomes among patients undergoing S-ICD implantation. We performed narrative synthesis and pooled efficacy and safety outcomes across studies.

Results: 16 studies were included with 5,380 participants (mean age range 33–56 years). Short-term follow-up data were available for 1670 subjects. The commonest complication was pocket infection, affecting 2.7% (range 0–19%). Other complications included delayed wound healing (0.6%), wound discomfort (0.8%), haematoma (0.4%) and lead migration (0.3%). A total of 3.8% (range 0–12%) of S-ICDs were explanted. The commonest reason for explant was pocket infection. Mortality rates in hospital (0.4%) and during follow-up (3.4% from 12 studies reporting, 2.1% per person-years) were low. The number of patients experiencing ventricular arrhythmia varied across studies from 0 to 12%. Overall shock efficacy for treatment of ventricular arrhythmias exceeded 96%. Inappropriate shocks affected 4.3% (range 0–15%) of patients and was most commonly caused by T-wave oversensing.

Conclusions: Although long-term randomised data are lacking, observational data suggest shock efficacy, peri-procedural and short-term complication rates of the S-ICD are similar to TV-ICD, making the S-ICD a suitable alternative in patients without an indication for pacing.

Introduction

The implantable cardioverter defibrillator (ICD) is recommended to prevent sudden cardiac death from ventricular tachyarrhythmia in patients with primary and secondary prevention indications. The transvenous ICD (TV-ICD) is an established therapy with excellent outcome data. However, implant-related complications associated with transvenous lead placement, including pneumothorax, cardiac perforation and tamponade, occur in 3%, [1] while long-term complications such as infection, endocarditis and lead failure occur in up to 20% of TV-ICD leads at 10 years.[2] Extraction of transvenous leads carries significant morbidity and mortality.[3] The subcutaneous defibrillator (S-ICD) system is entirely extravascular, offering the potential to address these shortcomings.[4]

The S-ICD was originally developed by Cameron Health and received FDA approval in 2012. The second-generation device (EMBLEM) is manufactured by Boston Scientific. The system is fully extravascular with a lead that is not subjected to the same stresses as a transvenous lead and does not have a lumen, thus reducing the long-term risk of lead failure. In the event of lead failure, removal of the S-ICD lead is not associated with the hazards of vascular or intracardiac complications as seen with TV-ICD lead extraction. The main limitation of the S-ICD is that it does not provide anti-tachycardia pacing (ATP), and other than a short period of post-shock pacing, cannot provide sustained pacing for bradyarrhythmia. A few reviews of the S-ICD system have evaluated many of the studies[5-7] but these reviews do not pool clinical outcomes.

Initial short-term outcome data from a number of observational studies are favourable with low complication rates when compared to the TV-ICD.[8,9] However, many of these reports stem from single centres and include small patient numbers. We reviewed current

evidence supporting the use of S-ICD devices from primary evaluations of efficacy and safety outcomes.

Methods

Search strategy and study eligibility

A search of MEDLINE and EMBASE was performed on 21 April 2016 using the search terms: "(subcutaneous ICD) OR (subcutaneous implantable cardioverter defibrillator)." Two independent reviewers (CSK and CDC) reviewed the titles and abstract for potential inclusion. Articles, including conference abstracts, were considered if they were primary studies of S-ICD reporting quantitative safety and efficacy outcomes. Case reports, studies of fewer than ten participants, letters and editorials were excluded but relevant reviews were retrieved to identify additional studies. The full manuscripts of screened results were retrieved and final inclusion was determined by two independent reviewers (CSK and CDC) with adjudication by a third (FA).

Data extraction and analysis

Independent data extraction was performed by two reviewers (CWW and CDC), including information on study design, patient demographics, follow-up and results. The extracted data was independently checked by two other reviewers (FA and CC). Data synthesis was performed by CSK and CDC by pooled analysis. Using Microsoft Excel, we conducted a pooled analysis of all reported efficacy and safety events. For a common outcome across different studies, the number of patients with events was summated across studies and divided by the total number of participants to yield the pooled rate, which is expressed as a percentage. Events during follow up were expressed as both a pooled rate and

an event rate per person-years of follow up. Person-years were calculated by multiplying the number of subjects by the mean period of follow up in years.

Results

Study selection

A total of 16 studies were included and the process of study selection is shown in Figure 1. [10-26]

Study participant characteristics

The 16 studies took place between 2009 and 2015. Study size ranged from 18 to 3717 subjects, with a total of 5380 patients undergoing S-ICD implantation (Table 1). The largest analysis of 3717 patients was from the National Cardiovascular Data Registry, reporting in-hospital outcomes for S-ICD implantation in the US.[14] The second largest study of 889 participants was an international pooled analysis of subjects recruited into the IDE (S-ICD system Investigational Device Exemption Clinical Study) and EFFORTLESS trials, reporting follow-up data to 2 years.[11]

Mean age of patients ranged from 33 to 64 years with 62–92% of patients being male. Most patients (68%) had a primary prevention indication (Table 2). Ischaemic heart disease was present in 42%. A further 44% had non-ischaemic cardiomyopathy. The remaining 14% had congenital heart disease, a channelopathy, idiopathic ventricular fibrillation or other

unstated diagnosis. Mean follow-up, excluding studies reporting only in-hospital outcomes, ranged from 61 to 2117 days (4 to 1585 patient years).

Adverse outcomes

Reported complications and their frequency are shown in Table 3. The commonest complication was pocket infection (2.7%, range 0–19%, 14 studies, 44 events/1654 total participants, 1.7% per person-years of follow up). Other complications included delayed wound healing (0.6%, 7 studies, 7 events/1145, 0.4% per person-years of follow up), wound discomfort (0.8%, 9 studies, 10 events/1327, 0.5% per person-years of follow up), haematoma (0.4%, 10 studies, 22 events/5044, 0.5% per person-years of follow up) and lead migration (0.3%, 10 studies, 14 events/5059, 0.4% per person-years of follow up). Device malfunction included premature battery depletion (1.2%, 10 studies, 16 events/1384, 0.7% per person-years of follow up) and failure to communicate with the device (0.3%). The highest rate of premature battery depletion was 9% in an early cohort study.[22] A battery manufacturing issue was identified that led to a field safety notification in June 2011. Subsequent rates of premature battery depletion were lower (0.6% in the pooled analysis of the IDE study and EFFORTLESS registry).[11] Mortality rates in hospital and during follow up were 0.4% (10 studies, 15 events/4235) and 3.4%(12 studies, 52 events/1547) respectively. Follow up arrhythmic death was confirmed in two study participants (0.1%). Other causes of death were not stated.

A total of 3.8% (range 0–12%) of S-ICDs were explanted from 11 studies (57 events/1514; 2.2% per person-years of follow up; Supplementary Table 1), most commonly for pocket infection (1.8%, 29 events/1585, 1.1% per person-years of follow up). Other explant indications included need for pacing, inappropriate shocks (IAS) and unsuccessful defibrillation threshold (DFT) testing. Where described, 16 patients undergoing S-ICD

explant subsequently received a TV-ICD (16 events/36, 44%). Generator repositioning or explant for erosion was required in 1.5%; this was highest in a published cohort from UK centres (8%).[17] In the series with the longest follow-up period (mean 2117 days), most device removal (25/31) was for elective battery replacement.[22] Median device longevity was 5 (4.4–5.6) years.

Defibrillator threshold testing

A total of 77% of patients undergoing S-ICD implantation underwent DFT testing (range 75–100% from studies reporting on DFT testing; Supplementary Table 2). This was successful on the first attempt in 89% of cases (range 70–100%). Reprogramming to reverse shock polarity or increasing to maximum output improved DFT success to 96%. A further 2% of patients had successful DFT following repositioning of the generator. The device was explanted in 0.4% due to high DFT testing. In the largest cohort, DFT success rates were 92.7% at ≤65J and 99.7% at ≤80J.[26] Submuscular placement of the S-ICD generator did not affect the DFT.[21] In a small cohort of patients with hypertrophic cardiomyopathy (HCM), DFT was effective in all those tested at 65J.[24] A 50J shock was effective in 80% and a 35J shock effective in 83% of those tested. The DFT was higher with increasing BMI.[24]

Shock efficacy

The number of patients experiencing VF or sustained VT varied from 0 to 12%. Many studies did not detail the number of episodes of sustained ventricular arrhythmia. Eight studies offered information on shock efficacy. First shock efficacy varied from 58% in one study (95% CI 36–77%) [10] to 90% in the largest cohort study.[11] Overall shock

efficacy of the S-ICD system for treatment of ventricular arrhythmias is reported at ≥96%.[10,11,17] Aydin *et al* calculated an overall shock efficacy of 96.4% (95% confidence interval 12.8-100%).[10] In the pooled analysis of the IDE study and EFFORTLESS registry, 90.1% of VT/VF was terminated with the first shock and 98.2% terminated within the 5 shocks available.[11] In the UK multicentre study all 24 appropriate shocks delivered for VT/VF successfully terminated the arrhythmia.[17]

Inappropriate shocks

Inappropriate shocks (IAS) affected 4.3% (range 0–15%, 2.9% per person-years of follow up) of patients receiving an S-ICD (Supplementary Table 3). The commonest cause was T-wave oversensing (TWOS). Inappropriate therapy due to supraventricular tachycardia (SVT) and artefact from noise or myopotentials was rare. A software upgrade introduced in October 2009 reduced rates of IAS due to TWOS. However, 15% of patients in one series experienced IAS with devices that had the upgrade,[17] and 22% of HCM patients had at least one IAS in another recent study.[15] Inappropriate therapy also decreased following introduction of dual zone programming and with reprogramming of the sensing vector.[15]

Studies with matched transvenous implantable cardioverter defibrillator controls

Three non-randomised studies matched a total of 2060 patients undergoing S-ICD implantation with TV-ICD controls.[18,20,26] Most (1920) of these patients were from a US propensity-matched cohort comparing in-hospital outcomes.[14] There were more pericardial effusions (6 vs. 0), cardiac perforations (3 vs. 0) and pneumothoraces (8 vs. 0) in the TV-ICD group but fewer haematomas (3 vs. 9). Rates of DFT success (90%, 60/97 vs. 91% 59/65) were similar. Implantation time was comparable at 71 minutes for the S-ICD and 65 minutes for a single chamber TV-ICD.[18] Length of hospital stay was also comparable (1.1 days for the S-ICD vs. 1.0 days for a single chamber ICD and 1.2 days for a dual

chamber ICD).[14] There were 18 lead revisions in the TV-ICD group compared to two in the S-ICD group. Infection rates were similar (five in the TV-ICD group compared to two in the S-ICD group). In the two studies with short-term follow-up, rates of appropriate (9/140 for the TV-ICD vs. 3/140 for the S-ICD) and inappropriate therapy (4/140 for the TV-ICD vs. 5/140 for the S-ICD) were similar.

Subgroups

Two small, single centre studies examined S-ICD use in 34 HCM patients.[15,24] During follow up, 6 patients (18%) had TWOS, with 5 (15%) receiving IAS. One device (3%) was explanted due to IAS. Treatment of ventricular arrhythmias was successful in the one patient with sustained VT.[11] Two studies compared patients requiring dialysis (45 patients) with non-dialysis controls (120 patients).[13,19] Rates of peri-procedural complications and DFT success were comparable. Dialysis patients had a longer length of hospital stay.[19] Although device-related infections were more frequent in the non-dialysis group (10/120 vs. 0/45), this difference did not reach statistical significance in either study. Rates of IAS were similar at follow-up (annual event rate 6.0% in the dialysis group vs. 6.8% in the non-dialysis group, P=0.51 and 11% vs. 8%, P=0.6), although there were more appropriate shocks in the dialysis group (annual event rate of 17.9% vs. 1.4% P=0.02 and 22% vs. 6%, P=0.06. Shock efficacy for ventricular arrhythmias was high and comparable in dialysis and non-dialysis patients.[19]

Discussion

This review of 16 studies with 5380 S-ICD implants, demonstrates the safety and efficacy of this therapy. The rate of implant-related complications was low. While shock

efficacy is reported to be high, this finding is based on relatively low event rates and limited follow-up time. The S-ICD is a promising alternative to the TV-ICD in patients without need for pacing when vascular access is limited or when complications associated with transvenous lead placement would pose excessive risk. The S-ICD may also be a suitable replacement system for patients with an explanted TV-ICD.The S-ICD was shown to be effective at treating ventricular arrhythmias. Although first shock efficacy was 58% in one early series of 40 patients,[10] a larger prospective registry of 889 patients demonstrated 90% efficacy.[11] Overall shock efficacy is over 96%. This is comparable to the TV-ICD, which has first shock efficacy of approximately 90% and overall efficacy of over 98%.[27-30] Equivalent shock efficacy was not a documented outcome in the non-randomised studies comparing the S-ICD with the TV-ICD as the event rate was low,[14,20] although the sensitivity of arrhythmia algorithms in VF detection appears equivalent between the two systems at time of implant.[8] Across all 16 studies, two S-ICDs were explanted for failure to convert a ventricular arrhythmia.

The rate of successful DFT was approximately 98%. Success was lower with increased BMI, acute myocardial inflammation,[10] in HCM and in younger patients.[31] Success rates for DFT testing in the TV-ICD is similar at 95–98%.[32] Interestingly, only 77% of patients undergoing S-ICD implantation underwent DFT testing, despite the manufacturer's recommendation. This low rate of testing was accounted for mainly by the large US cohort study, in which only 2791 of 3717 patients underwent a DFT.[24] The reason for this is unclear.

This review found implantation complication rates for the S-ICD comparable to those for the TV-ICD. The National Cardiovascular Database ICD Registry reports a 3.1% risks of major in-hospital adverse events for the TV-ICD.[1] The S-ICD carries no risk of haemothorax or pneumothorax as placement is entirely extrathoracic. The commonest

complication was pocket infection affecting 2.7% of implants, with 1.8% requiring subsequent device explant. This was higher than the 0.7% infection rate for TV-ICDs.[33] The highest rates of pocket infection were reported in the UK series (12%),[17] but this was an early series reporting initial experience. Procedure time, a factor that influences infection risk, was similar in a direct comparison of S-ICD with TV-ICD implantation,[18]. A two-incision technique may lower wound complication rates and has not been associated with increased lead displacement or migration over 12 months of follow up in over 100 patients.[16] Submuscular device placement may reduce risk of erosion, although this has only been demonstrated in a small randomised single-centre study.[25] In comparison with S-ICDs, there are limited data on the long-term performance of submuscular TV-ICDs. Submuscular placement was a contributory factor in the UK Medicines and Healthcare products Regulatory Agency advisory concerning header problems with the Boston Scientific Teligen ICD and there have been concerns that increased stress may increase the risk of premature lead failure.[34] Submuscular placement is associated with increased morbidity during lead extraction[35] and longer procedure times compared to subcutaneous implantation.[36]

No lead failures were reported in the above studies and lead migration was uncommon (0.3%). Premature battery depletion occurred in 1.2% of cases. This improved following correction of a battery manufacturing issue. Median battery longevity for the first generation S-ICD from the series with the longest follow-up period was 5 years.[22] However, Boston Scientific claim 40% increased longevity for the revised EMBLEM S-ICD, with an estimated lifespan of 7.3 years. It is important to note that mean follow-up exceeded 1 year in only 7 of the 16 studies, and only one study had mean follow-up exceeding 5 years. It is therefore beyond the scope of the current analysis to provide an accurate picture of the real-world rate of device malfunction, including premature battery depletion.

Rates of death and arrhythmic death were low during follow-up (3.4%, 2.1% per person-years, and 0.1% respectively). One arrhythmic death occurred due to persistent VT falling below the programmed detection rate (180 bpm) for the device.[17] Another death occurred in a patient deemed unsuitable for a TV-ICD due to obliteration of both the left and right ventricular apices with Loeffler's syndrome, who experienced bradycardia prior to VF.[11]

The rate of device explant for patients developing a pacing indication was 0.6%. In an early series 5% of S-ICDs were explanted due to the need for pacing or cardiac resynchronisation therapy (CRT). However, 67% of this cohort had ischaemic heart disease, and the mean LVEF was 34%.[22] In studies of TV-ICDs, only 3–4% of patients develop bradycardia requiring pacing during subsequent follow-up device interrogation.[37] This contrasts with heart failure patients, where frequency of upgrade to CRT varies from 4–28%.[38,39] Patient selection prior to S-ICD implantation is critical, with particular consideration needed for patients with left ventricular systolic dysfunction, those with monomorphic VT amenable to ATP, and those likely to develop a pacing indication.

Inappropriate shocks affected 4.3% of patients, comparing favourably to the 2–10% for TV-ICDs.[40-43] In MADIT-II 11.5% of patients with a TV-ICD experienced at least one IAS.[44] Conservative programming reduced the annual IAS rate to 2.4–4%.[45,46] The highest IAS rate amongst S-ICD studies was in the UK registry (15%).[17] Only a third of patients had dual zone programming at implant. Dual zone programming utilises a VF zone, with detection determined solely by ventricular rate, and a second VT detection zone at a lower rate, which uses ECG morphology and stability criteria to discriminate between SVT

and VT. This significantly reduces rates of IAS.[47] In the IDE study, dual zone programming reduced the 2-year IAS rate from 26.4% to 10.3%.[48] Consequently, Burke et al reported a 34% decrease in 6-month incidence of IAS from the first quartile of patients enrolled into their combined registry compared to the last.[6] Inappropriate therapy was also caused by TWOS in patients with HCM and congenital heart disease with abnormal baseline ECGs. Rates of IAS were high in the HCM population due to large T waves and relatively small R waves, particularly during exercise.[21] HCM is an independent predictor for lack of suitability for an S-ICD.[49] Recommendations such as exercise-based examination of sensing vectors[47] and fulfilment of at least two ECG vectors instead of one highlight the importance of careful patient selection to reduce the risk of IAS.[13,18] Altering the sensing vector post-implant can also reduce IAS.

Data from observational registries of S-ICDs compared to historical TV-ICD control populations are promising, although no randomised studies compare the S-ICD with the TV-ICD.[10,14,16] The currently-recruiting PRAETORIAN trial aims to compare the S-ICD and TV-ICD in 850 patients with a class I or class IIa ICD indication without need for pacing. The results of this trial are eagerly awaited.[50]

There are limitations to our systematic analysis. Aside from two reports, most other studies had fewer than 100 participants. Most studies reported early experience of S-ICD implantation and therefore events rates may not reflect those of experienced centres. This technology is still in its infancy and long-term data are still awaited. There was also significant heterogeneity in reporting between studies. A minority reported efficacy of DFT testing and reporting of complications was not standardised. Duration of follow-up varied widely (61 to 2117 days), which may impact the complication rates reported.

In conclusion, although randomised controlled trials with long-term safety data are lacking, observational studies demonstrate equivalent shock efficacy and similar complication rates for the S-ICD compared to the TV-ICD in patients without a pacing indication.

Contributorship

FA conceived and planned the study. CSK performed the search for relevant studies. Data was screened by CSK and CDC and extracted by CDC, CWW, CC and FA. Data analysis was performed by CSK and CDC. CDC wrote the first draft of the paper. All authors contributed to the interpretation of the findings and critically revised it for intellectual content.

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Table 1: Study design

Study ID	Study design, country, year	No. of S-ICD implants	Participant inclusion criteria	Use of control	Mean follow-up (days)
Aydin 2012	Cohort. Germany. 2010–2011	40	Fulfil criteria for AHA/AHA prevention of primary/ secondary sudden cardiac death. No bradycardia and no indications for ATP	No	229
Burke 2015	Cohort. Worldwide. 2009–2013	882	Primary and secondary prevention	No	651 ± 345
Eckardt 2011	Cohort. Germany. 2010	35	Primary and secondary prevention	No	61
El-Chami 2015	Retrospective cohort study (non-dialysis vs. dialysis). USA. 2010–2015	52 (non-dialysis) 27 (dialysis)	Participants with end-stage renal disease requiring S-ICD for cardiomyopathy, stratified according to dialysis status. Primary and secondary prevention	No	514 (non-dialysis) 227 (dialysis)
Friedman 2016	Cohort. USA. 2012–2015. NCDR ICD registry	3717	All S-ICD implants	Single and dual chamber transvenous ICD controls	Not stated
Fromeyer 2016	Cohort. Germany. 2010–2015	18	S-ICD recipients with HCM	No	951
Hai 2015	Cohort. Hong Kong and Singapore. 2014–2015	21	S-ICD implants	No	107 ± 81
Jarman 2013	Cohort. UK. Up to 2011	111	S-ICD implants	No	381
Kobe 2013	Cohort. Germany. 2010	69	All S-ICD implants and 69 age and sex matched controls with transvenous ICD	Age-sex matched transvenous ICD controls	217 ± 138
Koman 2016	Cohort. Germany. 2012–2015	68 (non-dialysis) 18 (dialysis)	Consecutive S-ICD implants in haemodialysis and non-haemodialysis patients	No	242 ± 238 (non-dialysis) 205 ± 208 (dialysis)
Mithani 2016	Cohort. USA. 2012–2015	71 S-ICD and 71 matched TV-ICD	Matched TV and S-ICD cases	Age-sex matched transvenous ICD controls	180
Smith 2013	Cohort. New Zealand. 2008–2012	73	S-ICD implants with Class I indications for primary and secondary prevention	No	840
Theuns 2015	Cohort. Europe and New Zealand. 2008–2009	55	Class I, IIa/ IIb indication for ICD therapy	No	2117

Torres 2014	Cohort.	USA.	2010–2013	73	S-ICD implants in patients with congenital heart disease	No	At least 720
Weinstock 2016	Cohort.	USA.	2012–2015	16	S-ICD implants in patients with HCM	No	525 (median)
Willner 2015	Cohort.	USA.	Year not stated	22 (submuscular) 12 (subcutaneous)	Submuscular and subcutaneous S-ICD implants	No	110

Table 2: Participant characteristics

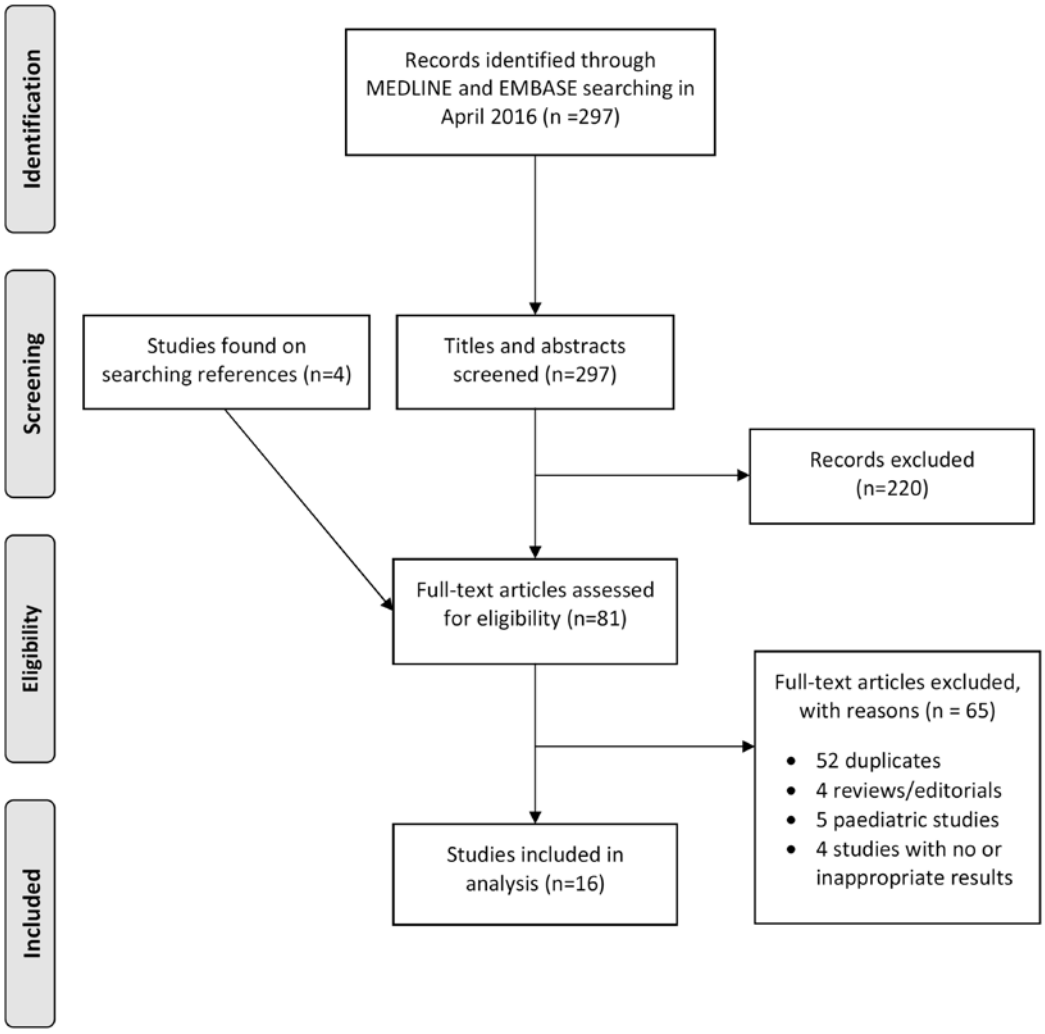
Study ID	Mean age (years)	% Male	Primary prevention (%)	Ischaemic cardiomyopathy (%)	Other cardiomyopathy (%)	Mean ejection fraction (%)	Mean body mass index (kg/m^2)	Previous transvenous system (%)
Aydin 2012	42	70	17 (42.5)	9 (23)	15 (38)	47	27	10 (25)
Burke 2015	50	73	610 (69)	330 (37)	277 (31)	39	28	142 (16)
Eckardt 2011	47	82	18 (51)	Not stated	Not stated	Not stated	Not stated	9 (26)
El-Chami 2015	50 (non-dialysis)	69 (non-dialysis)	45 (87; non-dialysis)	25 (48; non-dialysis)	27 (52; non-dialysis)	28 (non-dialysis)	Not stated	6 (12; non-dialysis)
	61 (dialysis)	59 (dialysis)	19 (70; dialysis)	12 (44; dialysis)	15 (56; dialysis)	25 (dialysis)		4 (15; dialysis)
Friedman 2016	54	69	Not stated	1687 (45)	1740 (47)	32	29	591 (16)
Frommeyer 2016	35	83	14 (78)	0 (0)	18 (100)	63	Not stated	Not stated
Hai 2015	50	83	13 (62)	6 (29)	6 (29)	42	23	3 (14)
Jarman 2013	33 (median)	Not stated	55 (50)	15 (14)	35 (32)	Not stated	Not stated	Not stated
Kobe 2013	46	73	41 (59)	11 (16)	35 (51)	46	Not stated	16 (23)
Koman 2016	62 (non-dialysis)	62 (non-dialysis)	41 (60; non-dialysis)	28 (41; non-dialysis)	31 (46; non-dialysis)	29 (non-dialysis)	31 (non-dialysis)	13 (19; non-dialysis)
	64 (dialysis)	67 (dialysis)	5 (28; dialysis)	9 (50; dialysis)	7 (39; dialysis)	30 (dialysis)	28 (dialysis)	4 (22; dialysis)
Mithani 2016	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	7 (10)
Smith 2013	49	73	54 (74)	30 (41)	32 (44)	44	Not stated	5 (7)
Theuns 2015	56	80	43 (78)	37 (67)	10 (18)	34	28	Not stated
Torres 2014	40	Not stated	71 (97)	0 (0)	Not stated	45	26	Not stated
Weinstock 2016	40	Not stated	13 (56)	0 (0)	16 (100)	57	Not stated	4 (25)
Willner 2015	54 (submuscular)	86 (submuscular)	Not stated	Not stated	Not stated	41 (submuscular)	Not stated	Not stated
	56 (subcutaneous)	92 (subcutaneous)				33 (subcutaneous)		

Table 3: Adverse outcomes

Study ID	Total patients	Lead migration	Pocket infection	Haematoma	Delayed wound healing	Discomfort	Premature battery depletion	Failure of device communication	Death in hospital	Total deaths during follow-up	Death rate per person-years (%)
Aydin 2012	40	0	0	0	0	0	0	0	0	0	0
Burke 2015	882	7 episodes (5 patients)	17 episodes (14 patients)	4	3	8	5	3	Not reported	26	1.6
Eckardt 2011	35	0	0	1	0	0	0	0	0	1	17.1
El-Chami 2015	52 (non-dialysis)	Not reported	0	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	2	2.7 (non-dialysis)
	27 (dialysis)	Not reported	5	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	1	6.0 (dialysis)
Friedman 2016	3717	5	3	11	Not reported	Not reported	Not reported	Not reported	13	Not reported	Not reported
Frommeyer 2016	18	1	0	0	0	0	1	0	0	0	0
Hai 2015	21	0	2	Bleeding in 2 cases (haematoma not specifically mentioned)	4	0	0	0	0	0	0
Jarman 2013	111	1	11	0	Not reported	2 cases of erosion causing chronic pain	2	0	0	1	0.9
Kobe 2013	69	0	1	1	0	0	0	1	0	1	2.4
Koman 2016	68 (non-dialysis)	0	5 (non-dialysis)	Not reported	Not reported	Not reported	Not reported	Not reported	0 (non-dialysis)	5 (non-dialysis)	11.1 (non-dialysis)
	18 (dialysis)		0 (dialysis)	Not reported	Not reported	Not reported	Not reported	Not reported	2 (dialysis)	2 (dialysis)	19.8 (dialysis)
Mithani 2016	71	Not reported	0	1	Not reported	0	Not reported	Not reported	Not reported	2	5.7
Smith 2013	73	Not reported	1	Not reported	Not reported	Not reported	3	Not reported	Not reported	3	1.8

Theuns 2015	55	Not reported	1	Not reported	Not reported	Not reported	5	Not reported	0	8	2.5
Torres 2014	73	0	0	2	0	0	0	0	0	Not reported	Not reported
Weinstock 2016	16	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Willner 2015	22 (submuscular) 12 (subcutaneous)	Not reported Not reported	0 (submuscular) 1 (subcutaneous incision site infection)	Not reported Not reported	Not reported Not reported	Not reported Not reported	Not reported Not reported	Not reported Not reported	Not reported Not reported	Not reported Not reported	Not reported Not reported
Rate (%)		0.28	2.66	0.44	0.61	0.75	1.16	0.32	0.35	3.36	2.1

Figure 1: Flow diagram of study selection



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Supplementary Table 1: Numbers of device explants

Study ID	Total patients	Explant for IAS	Explant for ATP/pacing	Explant for failed DFT	Explant for failed CV	Explant for pocket infection	Any explant	Intervention for erosion
Aydin 2012	40	0	1	1	2	0	4	0
Burke 2015	882	Not reported	4	Not reported	Not reported	14	18	12 events, 11 patients
Eckardt 2011	35	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
El-Chami 2015	52 (non-dialysis) 27 (dialysis)	1 (non-dialysis) 0 (dialysis)	0 (non-dialysis) 0 (dialysis)	0 (non-dialysis) 0 (dialysis)	0 (non-dialysis) 0 (dialysis)	5 (non-dialysis) 0 (dialysis)	6 (non-dialysis) 0 (dialysis)	0 (non-dialysis) 0 (dialysis)
Friedman 2016	3717	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Frommeyer 2016	18	1	0	0	0	0	1	0
Hai 2015	21	0	0	0	0	0	0	0
Jarman 2013	111	5	0	0	0	4	10	9
Kobe 2013	69	0	0	0	0	1	3 (2 for transplantation)	0
Koman 2016	68 (non-dialysis) 18 (dialysis)	0 (non-dialysis) 0 (dialysis)	Not reported Not reported	0 (non-dialysis) 0 (dialysis)	Not reported Not reported	3 extracted for infection	3 (non-dialysis) 0 (dialysis)	Not reported Not reported
Mithani 2016	71	Not reported	Not reported	Not reported	Not reported	0	Not reported	Not reported
Smith 2013	73	1	0	0	0	1	6	0
Theuns 2015	55	0	3	1	0	1	5	0
Torres 2014	73	0	1	0	0	0	1	0
Weinstock 2016	16	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Willner 2015	22 (submuscular) 12 (subcutaneous)	Not reported Not reported	Not reported Not reported	Not reported Not reported	Not reported Not reported	Not reported Not reported	Not reported Not reported	Not reported Not reported
Event rate from combined studies (%)		1.28	0.63	0.32	0.37	1.83	3.76	1.47

Supplementary Table 2: Defibrillation testing

Study ID	Total patients	DFT performed (%)	DFT successful on first attempt (%)	DFT successful after reprogramming	DFT successful after generator reposition
Aydin 2012	40	40 (100)	39 (98)	0	0
Burke 2015	882	Not reported	Not reported	Not reported	Not reported
Eckardt 2011	35	33 (94)	23 (70)	4 (12)	2 (6)
El-Chami 2015	52 (non-dialysis) 27 (dialysis)	46 (88; non-dialysis) 20 (74; dialysis)	Not reported Not reported	Not reported Not reported	Not reported Not reported
Friedman 2016	3717	2791 (75)	Not reported	Not reported	Not reported
Frommeyer 2016	18	17 (94)	15 (88)	2 (12)	Not necessary
Hai 2015	21	20 (95)	Not reported	Not reported	Not reported
Jarman 2013	111	Not reported	Not reported	Not reported	Not reported
Kobe 2013	69	67 (97)	58 (87)	6 (9)	2 (3)
Koman 2016	68 (non-dialysis) 18 (dialysis)	60 (88; non-dialysis) 16 (89; dialysis)	Not reported Not reported	Not reported Not reported	Not reported Not reported
Mithani 2016	71	Not reported	Not reported	Not reported	Not reported
Smith 2013	73	Not reported	Not reported	Not reported	Not reported
Theuns 2015	55	Not reported	Not reported	Not reported	Not reported
Torres 2014	73	72 (99)	Not reported	Not reported	Not reported
Weinstock 2016	16	15 (94)	15 (100)	Not necessary	Not necessary
Willner 2015	22 (submuscular) 12 (subcutaneous)	29 in total (85)	29 (100)	Not necessary	Not necessary
Event rate from combined studies (%)		77	91		

Supplementary Table 3: Inappropriate shocks

Study ID	Total patients	Patients with IAS	Total no. of IAS	IAS: TWOS	IAS: SVT	IAS: noise/myopotentials
Aydin 2012	40	2 (5)	2	0	2	0
Burke 2015	882	14 (2)	Not reported	8	6	Not reported
Eckardt 2011	35	Not reported	Not reported	Not reported	Not reported	Not reported
El-Chami 2015	52 (non-dialysis)	5 (10; non-dialysis)	5 (non-dialysis)	3 (non-dialysis)	1 (non-dialysis)	1 (non-dialysis)
	27 (dialysis)	1 (4; dialysis)	1 (dialysis)	1 (dialysis)	0 (dialysis)	0 (dialysis)
Friedman 2016	3717	Not reported	Not reported	Not reported	Not reported	Not reported
Frommeyer 2016	18	4 (22)	11	4	0	0
Hai 2015	21	0 (0)	0	0	0	0
Jarman 2013	111	17 (15)	51	41/51	4/51	6/51
Kobe 2013	69	3 (4)	3	3	0	0
Koman 2016	68 (non-dialysis)	5 (8; non-dialysis)	Not reported	1 (non-dialysis)	2 (non-dialysis)	2 (non-dialysis)
	18 (dialysis)	2 (11; dialysis)	Not reported	1 (dialysis)	1 (dialysis)	0 (dialysis)
Mithani 2016	71	1 (1)	Not reported	Not reported	Not reported	Not reported
Smith 2013	73	9 (12)	Not reported	Not reported	Not reported	Not reported
Theuns 2015	55	Not reported	Not reported	Not reported	Not reported	Not reported
Torres 2014	73	2 (3)	Not reported	2	Not reported	Not reported
Weinstock 2016	16	1 (6)	1	0	0	0
Willner 2015	22 (submuscular)	1 (5; submuscular)	Not reported	Not reported	Not reported	Not reported
	12 (subcutaneous)	1 (8; subcutaneous)	Not reported	Not reported	Not reported	Not reported
Event rate from combined studies (%)		4.3				