NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of subcutaneous implantable cardioverter defibrillator insertion for preventing sudden cardiac death

A subcutaneous implantable cardioverter-defibrillator (ICD) is a device that is placed under the skin of the chest. It detects and treats fast irregular heartbeats called arrhythmias. The device uses electrical shocks to help control life-threatening arrhythmias that can cause sudden cardiac death.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in September 2016 and updated in June 2017.

Procedure name

- subcutaneous implantable cardioverter defibrillator insertion for preventing sudden cardiac death

Specialist societies

- Heart Rhythm UK
- Royal College of Physicians
- British Cardiovascular Society.

Description

Indications and current treatment

Sudden cardiac death is often caused by ventricular arrhythmias (ventricular tachycardia or ventricular fibrillation). The most common cause of ventricular arrhythmia is underlying heart disease.

Prevention of sudden cardiac death can be primary, which is defined as preventing a first life-threatening arrhythmic event in someone who is at high risk of such an event. Or, it can be secondary, which refers to preventing further life-threatening events in survivors of previous serious ventricular arrhythmias. Treatment with an implantable cardioverter defibrillator (ICD) is recommended in NICE's technology appraisal guidance on implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure for patients with arrhythmias and those at risk of sudden cardiac death.

An ICD consists of a generator, which contains a battery, capacitor and sophisticated electronic circuitry, and 1 or more leads. The device senses and detects arrhythmias, and delivers pacing impulses or defibrillating shocks to the heart as necessary, to restore normal cardiac rhythm. A conventional transvenous ICD consists of a generator under the skin below the clavicle and 1 or more leads passed through a vein into the heart.

What the procedure involves

An entirely subcutaneous implantable cardioverter defibrillator (ICD) differs from a transvenous ICD in that a single lead is placed subcutaneously. The lead comprises 2 sensing electrodes and a shocking coil. The ICD senses cardiac signals, but the lead is not directly attached to the heart. Also, unlike a conventional transvenous ICD, the subcutaneous device is not designed to provide long-term pacing.

The implantation procedure is carried out with the patient under general anaesthesia, or with local anaesthesia and sedation. Implantation is guided by anatomical landmarks without the use of fluoroscopy or other medical imaging. A subcutaneous pocket for the generator is created on the left side of the chest. The lead is tunnelled subcutaneously from the pocket to a small incision at the lower end of the sternum. Then, it is tunnelled to a second small incision at the upper end of the sternum and secured so that the sensing electrodes and shocking coil lie alongside the sternum. The lead is then connected to the generator in the pocket. Finally, the incisions are closed and the sensing, pacing and recording functions of the ICD are adjusted using an external programmer. Ventricular fibrillation is induced to test that the ICD can appropriately detect and correct it.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to subcutaneous implantable cardioverter defibrillator insertion for preventing sudden cardiac death. The following databases were searched, covering the period from their start to 8th June 2017: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Prevention of sudden cardiac death.
Intervention/test	Subcutaneous implantable cardioverter defibrillator insertion.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on approximately 2,917 patients from 4 matched cohort studies[1-3, 7] and 5 case series[4-6, 8-9].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on subcutaneous implantable cardioverter defibrillator insertion for preventing sudden cardiac death

Study 1 Brouwer T F (2016)

Details

Study type	**Retrospective propensity-matched cohort study**
Country	The Netherlands (2 centres)
Recruitment period	S-ICD patients: 2009-15 TV-ICD patients: 2005-14
Study population and number	n= **280 (140 S-ICD versus 140 TV-ICD)** patients implanted with an ICD
Age and sex	S-ICD: Median 41 years; 60% (84/140) male TV-ICD: Median 42 years; 62% (87/140) male
Patient selection criteria	Patients included in the ongoing PRAETORIAN (Prospective, RAndomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy) trial were excluded from this analysis.
Technique	The devices used were S-ICDs (Boston Scientific) and TV-ICDs (Biotronik, Boston Scientific, Medtronic, and St Jude Medical). The majority of both S-ICD and TV-ICD patients were implanted under local anaesthesia, according to the prevailing local hospital protocol.
Follow-up	**S-ICD: median 3 years** **TV-ICD: median 5 years**
Conflict of interest/source of funding	Dr Wilde serves on the scientific board of Sorin. Dr Knops received personal fees and research grants from Boston Scientific, Medtronic, and St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Analysis

Follow-up issues:

- The follow-up of the S-ICD cohort was statistically significantly shorter than the follow-up of the TV-ICD cohort (p<0.001).

Study design issues:

- Complications were defined as all device-related complications needing surgical intervention. Lead complications were defined as complications needing replacement or repositioning of the lead, without elective pulse generator replacement. Lead survival was defined as the time between lead implantation and lead failure, with or without elective pulse generator replacement. Appropriate therapy consisted of antitachycardia pacing (ATP) only and shocks (whether preceded by ATP or not) for ventricular tachycardia (VT) or ventricular fibrillation (VF). Inappropriate therapy consisted of ATP and shocks for heart rhythms other than VT or VF. Local electrophysiologists adjudicated all arrhythmia episodes.
- Propensity score matching was performed with patients for whom complete baseline variables were available (total n=1,154). Analysis of excluded patients because of missing baseline data did not suggest selection bias. Authors used logistic multivariable regression with device type (S-ICD or TV-ICD) as the dependent variable and 16 baseline variables as independent predictors to calculate the propensity score. The Harrell's C-statistic for the propensity score logistic regression model was 0.89. Patients were 1-to-1 greedy matched using the nearest-neighbour method. There was sufficient overlap in the propensity scores to individually match each S-ICD case to a TV-ICD control.
- Kaplan–Meier method was used to correct for differences in follow-up and estimate the cumulative incidence of outcomes at 5-year follow-up. P values and hazard ratios (HRs) were calculated using conditional proportional hazards models with adjustment for ICD programming. Conditional proportional hazards assumptions were visually inspected by plotting Schoenfeld residuals.

Study population issues:

- In the propensity-matched cohort, S-ICD cases were similar to their TV-ICD controls, with no significant differences in any baseline characteristics**.**
- Compared with the entire cohort, the matched S-ICD cohort was younger, had less comorbidity and had a higher left ventricular ejection fraction, and genetic arrhythmia syndromes as the main diagnosis (53%). In the TV-ICD group, 124 devices (88.6%) were dual-chamber and 16 (11.4%) were single-chamber. The TV-ICD group had ischemic cardiomyopathy as the predominant diagnosis (64%), significant cardiovascular comorbidity, and a median left ventricular ejection fraction of 34%.
- In the S-ICD group, 6 patients (4.3%) had a concomitant transvenous pacemaker

Other issues:

- Only approximately 15% of all TV-ICD patients from 1 of the 2 centres were included in the analysis.

- The authors could not exclude residual confounding of unmeasured variables, such as pacing indication at time of implant, because of the nonrandomised character of the study.
- The match between S-ICD and TV-ICD patients would have been more optimal with a higher rate of single-chamber ICDs, because single-chamber ICDs are associated with an approximately 1% lower rate of major complications compared with dual-chamber ICDs during short-term follow-up.
- The primary analysis included patients with advisory leads.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **280 (140 S-ICD versus 140 TV-ICD)**

Appropriate ICD intervention *

	S-ICD	Rate (KM)	TV-ICD	Rate (KM)
Total	12	17% (95% CI 6% to 26%)	39	31% (95% CI 23% to 40%)
ATP			28	22%
Shock	12	17%	24	21%

** Crude number of patients in the first 5 years and the adjusted Kaplan–Meier rate for the follow-up duration.

Appropriate ICD intervention (antitachycardia pacing and shocks) occurred statistically significantly more often in the TV-ICD group (HR: 2.42; p=0.01).

The incidence of appropriate shocks (TV-ICD HR: 1.46; p = 0.36) was similar in both groups.

Survival analysis

Five-year patient survival was 96% in the S-ICD arm and 95% in the TV-ICD arm; p = 0.42.

Safety

Complications*

Complications	S-ICD	KM rate	TV-ICD	KM rate	p value
Total	14	14%	21	18%	0.80
Lead (total)	1	5%	17	11.5%	0.03
Atrial lead failure			3	3%	
Defibrillation lead failure	0	0	10	8.5%	
Atrial and defibrillation lead failure	-	-	3	3%	
Displacement	1	1%	1	1%	
Infection**	5	4%	4	4%	0.36
Erosion	3	3%	2	1.5%	
DFT failure	1	1%	0	0	
Inappropriate sensing	2	3%	0	0	
Twiddler syndrome	1	1%	1	1%	
Device failure	1	1%	0	0	
Deceased	2	-	6	-	
Noncardiac	1	2%	3	3%	
Cardiac	1	2%	2	2%	
Unknown	0	0	1	1%	

* Crude number of patients in the first 5 years and the adjusted Kaplan–Meier rate for the follow-up duration.

** There were 2 patients with bacteraemia in the TV-ICD group and 1 in the S-ICD group, who also had a concomitant transvenous pacemaker.

Nonlead-related complications: 10% vs 2% (p = 0.047)

Lead survival: 99% versus 85.9% (p = 0.02).

Inappropriate shocks*

	S-ICD	KM rate	TV-ICD	KM rate
Total	20	20.5%	22	19.1%
Oversensing	17	17%	1	1%
Supraventricular tachycardia	3	4%	21	18%

* Crude number of patients in the first 5 years and the adjusted Kaplan–Meier rate for the follow-up duration.

The incidence of inappropriate shocks (TV-ICD HR: 0.85; p =0.64) was similar in both groups.

Pulse generator replacement because of battery depletion did not differ at the 5-year follow-up; p =0.18.

Of S-ICD patients, 1% were upgraded to a TV-ICD or cardiac synchronization therapy device versus 5% in the TV-ICD group; p=0.26.

Abbreviations used: ATP, antitachycardia pacing; CI, confidence interval; DFT, defibrillation threshold testing; HR, hazard ratio; ICD, implantable cardioverter defibrillator; IQR, interquartile range; KM, Kaplan–Meier; S-ICD, subcutaneous implantable cardioverter defibrillator; TV-ICD, transvenous implantable cardioverter defibrillator.

Study 2 Honarbakhsh S (2017)

Details

Study type	**Propensity matched case-control study**
Country	Not reported
Recruitment period	S-ICD: 2010-15 TV-ICD: not reported
Study population and number	n= **138 (69 S-ICD versus 69 TV-ICD)** patients with an ICD indication for primary or secondary prevention of sudden cardiac death
Age and sex	S-ICD: Mean 35 years; 75% (52/69) male TV- ICD: Mean 40 years; 75% (52/69) male
Patient selection criteria	Inclusion criteria for S-ICD patients: all patients who had an S-ICD implanted over a five-year period in a single tertiary centre. Inclusion criteria for TV-ICD patients: all patients who had a TV-ICD implanted over a contemporary period in the same centre. Exclusion criteria: patients with a concomitant pacing indication, biventricular devices, documentation of sustained monomorphic ventricular tachycardia likely to need ATP, and advisory transvenous leads.
Technique	Before S-ICD implantation, all patients had an electrocardiogram screening to ensure suitability for a S-ICD through excluding those susceptible to T-wave over-sensing. S-ICD implantation was done with the patient under general anaesthesia.
Follow-up	**S-ICD: mean 31 months** **TV-ICD: mean 32 months**
Conflict of interest/source of funding	None reported

Analysis
Follow-up issues: Not reported.
Study design issues:

- Single centre study.
- The following factors were used for propensity score matching: age, gender, diabetes, hypertension, chronic kidney disease, left ventricular ejection fraction, cardiac aetiology and indication (primary or secondary prevention).
- All procedures in both groups were done by an electrophysiology consultant with more than 10 years of experience in device implantation.
- After propensity scores were obtained for all eligible patients having ICD implantation, the propensity scores on the S-ICD group were matched 1:1 to the closest TV-ICD patient fulfilling inclusion criteria using the nearest neighbour matching approach. The propensity score was matched to 5 decimals whenever possible. If an S-ICD patient could not be matched to any TV-ICD patient on the second digit of the propensity score, then the S-ICD patient was discarded from the matched analysis.

Study population issues:

- S-ICD: primary prevention, 81% (56/69); secondary prevention, 19% (13/69). Underlying heart disease: ischaemic cardiomyopathy 9% (6/69), dilated cardiomyopathy, 6% (4/69); hypertrophic cardiomyopathy, 59% (41/69); arrhythmogenic right ventricular cardiomyopathy, 10% (7/69); idiopathic ventricular fibrillation, 9% (6/69); Brugada syndrome, 6% (4/69); congenital heart disease, 1% (1/69).Mean left ventricular ejection fraction: 57%.

Other issues: Not reported.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **138 (69 S-ICD versus 69 TV-ICD)**

Appropriate therapy (number of patients)

	S-ICD	TV-ICD
Total	4% (3/69)	7% (5/69)
ATP		1
Shock	3	4

Safety

Device-related complications during follow-up

Complications	S-ICD	TV-ICD	p value
Total number of complications including inappropriate shocks, % (n)	9% (6)	29% (20)	0.004
Total number of complications excluding inappropriate shocks, % (n)	4% (3)	20% (14)	0.008
Total number of complications including inappropriate shocks in those with 2 therapy zones programmed, % (n)	9% (6)	23% (17)	0.021
Implant-related complications (<30 days), % (n)	0	3% (2)	0.24
Right ventricular lead perforation resulting in tamponade	0	1% (1)	1
Right ventricular lead displacement	0	1% (1)	1
Device-related infection, % (n)	1% (1)	6% (4)	0.37
Generator and leads explanted	1% (1)	6% (4)	0.37
ICD generator-related complications	1% (1)	1% (1)	1
Generator displacement needing repositioning	1% (1)	0	1
Wound revision	0	1% (1)	1
ICD lead-related complications resulting in lead intervention, % (n)	0	9% (6)	0.028
Drop in RV sensing ± resulting in T-wave oversensing	0	3% (2)	0.50
Raised RV threshold with suspected micro-displacement	0	1% (1)	1
Lead fracture or lead insulation defect	0	4% (3)	0.12
Device failed to cardiovert ventricular arrhythmia, % (n)	1% (1)	1% (1)	1
Generator replaced to a high energy box	0	1% (1)	1
Inappropriate shocks, % (n)	4% (3)	9% (6)	0.49
Sinus tachycardia	0	3% (2)	0.50
Atrial tachycardia	0	1% (1)	1
Atrial fibrillation	0	4% (3)	0.24
T-wave oversensing in context of sinus tachycardia	4% (3)	0	0.24

The S-ICD group had a statistically significantly lower risk of device-related complications compared to the TV-ICD group: HR 0.30, 95% CI 0.12 to 0.76, p=0.01.

In the S-ICD group, there was a higher rate of survival free from device-related complications during follow-up: HR 2.78, 95% CI 1.10 to 7.01, p=0.031.

There were no death in either group.

Abbreviations used: ATP, antitachycardia pacing; CI, confidence interval; HR, hazard ratio; ICD, implantable cardioverter defibrillator; KM, Kaplan–Meier; S-ICD, subcutaneous implantable cardioverter defibrillator; TV-ICD, transvenous implantable cardioverter defibrillator.

Study 3 Kobe J (2013)

Details

Study type	**Matched-controlled study**
Country	Germany (3 centres)
Recruitment period	Not reported
Study population and number	n= **138 (69 S-ICD versus 69 matched conventional transvenous ICD)** patients with an indication for ICD implantation for primary and secondary prevention of cardiac arrhythmias.
Age and sex	S-ICD: Mean 46 years; 72% (50/69) male Tansvenous ICD: Mean 48 years; 72% (50/69) male
Patient selection criteria	Inclusion criteria: patients with an indication for ICD implantation according to the American College of Cardiology/ American Heart Association/ European Society of Cardiology guidelines for primary and secondary prevention of cardiac arrhythmias. Exclusion criteria for S-ICD: indication for stimulation or slow ventricular tachycardias, bradycardia.
Technique	S-ICD (Cameron health) or conventional transvenous ICD implantation. Procedures were done under general or local anaesthesia.
Follow-up	**Mean 217 days (range 213 to 759 days)**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues:

- Patients had a first interrogation of their device 1 day after implantation. Other controls occurred 2 weeks after implantation and every 3 months. In case of shock delivery, patients were asked to come to the clinic before the regular follow-up.
- 78% (54/69) of S-ICD patients were followed-up over at least 2 years. One S-ICD patient has been lost during follow-up and he/she could not be contacted. 3 S-ICDs were explanted: 1 because of an infection (reported in the safety section) and 2 because the patients received a heart transplant (77 and 168 days after the procedure). One patient died of congestive heart failure.
- In the control group, 1 patient died of right heart failure, 1 ICD had to be explanted and 1 transvenous electrode needed revision.

Study design issues:

- All patients who received an S-ICD system at the University Hospitals of Dusseldorf, Munich and Munster were prospectively followed. Each patient was matched by sex and age to 1 control patient with a conventional single-chamber ICD system randomly selected from an ICD database.
- Comparison of the 2 groups focused on conversion rates of induced ventricular fibrillation at the time of implantation, perioperative adverse events and short-term follow-up.
- The test protocols for the S-ICD differed slightly between the 3 centres.

Study population issues:

- S-ICD: primary prevention, 60% (41/69); secondary prevention, 41% (28/69). Underlying heart disease: dilated cardiomyopathy, 36% (25/69); coronary heart disease, 16% (11/69); hypertrophic cardiomyopathy, 14% (10/69); congenital heart disease, 4% (3/69); electrical heart disease, 20% (14/69); other, 10% (7/69). Mean ejection fraction: 46%.
- Transvenous ICD: primary prevention, 50% (34/69); secondary prevention, 50% (35/69). Underlying heart disease: dilated cardiomyopathy, 46% (32/69); coronary heart disease, 19% (13/69); hypertrophic cardiomyopathy, 6% (4/69); congenital heart disease, 4% (3/69); electrical heart disease, 3% (2/69); other, 25% (17/69). Mean ejection fraction: 41%.
- Groups statistically significantly differed for electrical heart diseases.

Other issues: The S-ICD implantation was the first ICD implantation for 77% (53/69) of patients from the S-ICD group. There is a possible overlap of patients with the Kobe (2017) study.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **138 (69 S-ICD versus 69 matched conventional transvenous ICD)**

Conversion rates of induced ventricular fibrillation at the time of implantation

- **S-ICD: 90%** (60/67) for 65 J (15-J safety margin) and 96% (64/67) including reversed shock polarity (15-J safety margin).
- **Transvenous ICD: 91%** (59/65) for 10-J safety margin and initial polarity (twice).
- **p=0.81**

In 1 patient of the S-ICD group, 65 J and the consecutive 80 J failed and external rescue shocks were applied with a short CPR. This patient received a conventional transvenous device with the need for an additional subcutaneous electrode in the same procedure.

1 patient from the control group needed CPR because of ineffective internal and external shocks and a subcutaneous array electrode consecutively.

Appropriate episodes during follow-up

	S-ICD	Control
Appropriate episode[a]	4% (3/69)	13% (9/69)
Software reset	1/69	0

[a] Statistically significant difference between groups, p=0.05.

Safety

Periprocedural adverse events

	S-ICD	Control
Pericardial effusion	0	1/69
Haematoma needing revision	1/69	0
Early lead revision	0	1/69

Follow-up adverse events

	S-ICD	Control
Infection needing revision	1/69**	1/69***
Late lead revision	0	1/69
Late system revision	1/69*	0

*Change to conventional system because of ventricular tachycardia storm.

**The device had to be explanted because of an infection 8 weeks after the procedure and the patient received a conventional transvenous device.

***The device had to be explanted because of endocarditis and infection.

Death

1 patient in the S-ICD group died of congestive heart failure.

1 patient in the control group died of right heart failure

Inappropriate episodes during follow-up

	S-ICD	Control
Inappropriate episode T-wave oversensing	3/69	0
Inappropriate episode oversensing	2/69	1/69
Inappropriate episode supraventricular	0	2/69

No statistically significant difference between groups for inappropriate episodes (p=0.745).

Abbreviations used: CPR, cardiopulmonary resuscitation; ICD, implantable cardioverter defibrillator; S-ICD, subcutaneous implantable cardioverter defibrillator.

Study 4 Burke M (2015)

Details

Study type	**Case series (pooled analysis of the IDE study and the International EFFORTLESS Registry also reported later)**
Country	Worldwide
Recruitment period	Effortless registry: 2009-2013 IDE study: from 2009
Study population and number	n= **889 (560 from the Effortless registry, 308 from the IDE study and 13 from both studies)** patients with an indication for ICD implantation
Age and sex	Mean 50 years; 72% (636/882) male
Patient selection criteria	Patients with an indication for ICD implantation
Technique	S-ICD system
Follow-up	**Mean 22 months**
Conflict of interest/source of funding	The S-ICD IDE study and the EFFORTLESS S-ICD Registry are sponsored in their entirety by Cameron Health, Inc., a subsidiary of Boston Scientific Corporation.

Analysis

Follow-up issues: 7 patients out of 889 had an implantation but they were not discharged with a device in the IDE study because of acute ventricular fibrillation test results.

Study design issues:

- Rhythm classification of treated and untreated sensed events were reported by the site, and appropriateness of therapy or detection was adjudicated by a sponsor committee (EFFORTLESS) or Clinical Events Committee (IDE). Every spontaneous stored episode was also classified as discrete or as a storm event.
- Kaplan–Meier analyses were used to estimate the time to first event for mortality, complications, and appropriate and inappropriate shocks.
- Study combined 2 groups of patients.
- Some of the patients were enrolled retrospectively into the pool for analysis.
- The Effortless registry allowed enrolment post-implantation.

Study population issues:

- Primary prevention, 70% (610/873); secondary prevention, 30% (263/873). Primary cardiac disease: ischaemic cardiomyopathy, 38% (330/872); non-ischaemic cardiomyopathy, 32% (277/872); genetic, 7% (58/872); idiopathic ventricular fibrillation, 5% (40/872); channelopathies, 10% (90/872); other, 9% (77/872). Mean ejection fraction: 39%.
- 14% (120/873) of patients had already had a defibrillator, 3% (19/873) a pacemaker and 2% (19/873) had a concomitant pacemaker at implant.

Other issues: A study effect was noted for a higher rate of inappropriate shocks and complications in the IDE study (early regulatory implantations) compared with the EFFORTLESS trial (post-regulatory commercial implantations).

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 882

Appropriate shock
111 spontaneous VT/VF events were treated in 59 patients.
100 (90%) events were terminated with 1 shock
109 events (98%) were terminated within the 5 available shocks.
Kaplan–Meier incidence of time to first therapy for VT/VF was 5% at 1 year, 8% at 2 years, and 10.5% at 3 years.</td><td>All type I (device-related) to III (procedure-related) complications
<table>
<tr><th>Description</th><th>Number of events</th><th>Patients</th></tr>
<tr><td>Infection needing device removal/revision</td><td>17</td><td>1.7% (14)</td></tr>
<tr><td>Erosion</td><td>12</td><td>1.2% (11)</td></tr>
<tr><td>Discomfort</td><td>8</td><td><1% (8)</td></tr>
<tr><td>Inappropriate shock: oversensing</td><td>8</td><td><1% (8)</td></tr>
<tr><td>Suboptimal electrode position</td><td>7</td><td><1% (7)</td></tr>
<tr><td>Electrode movement</td><td>7</td><td><1% (5)</td></tr>
<tr><td>Inappropriate shock: SVA above discrimination zone (normal device function)</td><td>6</td><td><1% (6)</td></tr>
<tr><td>Premature battery depletion</td><td>5</td><td><1% (5)</td></tr>
<tr><td>Haematoma</td><td>4</td><td><1% (4)</td></tr>
<tr><td>Suboptimal PG and electrode position</td><td>4</td><td><1% (4)</td></tr>
<tr><td>Adverse reaction to medication</td><td>3</td><td><1% (3)</td></tr>
<tr><td>Inability to communicate with the device</td><td>3</td><td><1% (3)</td></tr>
<tr><td>Inadequate/prolonged healing of incision site</td><td>3</td><td><1% (3)</td></tr>
<tr><td>Incision/superficial infection</td><td>3</td><td><1% (3)</td></tr>
<tr><td>Suboptimal PG position</td><td>2</td><td><1% (2)</td></tr>
<tr><td>Other procedural complications</td><td>11</td><td><1% (8)</td></tr>
<tr><td>Other technical complications</td><td>5</td><td><1% (5)</td></tr>
<tr><td>Total</td><td>108</td><td>10% (85)</td></tr>
</table>
4.5% of patients experienced a complication within 30 days.
11% of patients had a complication over 3 years.
The 3-year Kaplan–Meier estimate for patients with a type I complication was 5%.

Extraction of the S-ICD for pacing occurred in 4 patients because of the need for ventricular pacing: 1 patient developed a new bradycardia indication; 1 patient was explanted because of need for ATP; and 1 patient with 3 VT storm events had replacement with a TV-ICD in an attempt to suppress ventricular arrhythmias using overdrive pacing. In addition, 1 device was extracted for a cardiac resynchronisation therapy upgrade.

All-cause mortality:
During follow-up: 3% (n=26/882).
There was only 1 known arrhythmic death because of Loeffler’s syndrome.
3-year Kaplan–Meier estimate: 5% (95% CI 0.9% to 8.5%), with 26 deaths (3%).
Inappropriate shock
Estimated 3-year inappropriate shock rate: 13%.
Causes were SVA above the discrimination zone in 24%, SVA discrimination errors in 1%, T-wave oversensing in 39%, low amplitude signal in 21%, noncardiac oversensing in 8%, oversensing of VT/VF below the rate zone in 4%, other and/or combined types of cardiac oversensing in 2%, and committed shock for VT/VF in 1%.</td></tr>
<tr><td colspan="2">Abbreviations used: ATP, antitachycardia pacing; CI, confidence interval ;ICD, implantable cardioverter defibrillator; PG, pulse generator; S-ICD, subcutaneous implantable cardioverter defibrillator; SVA, supraventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.</td></tr>
</table>

Study 5 Lambiase P D (2014)

Details

Study type	**Case series (international EFFORTLESS registry)**
Country	The Czech Republic, Denmark, Germany, Italy, The Netherlands, New Zealand and the UK.
Recruitment period	2011-13
Study population and number	n= **472** patients with an indication for ICD implantation
Age and sex	Mean 49 years; 72% (323/450) male
Patient selection criteria	Inclusion criteria: patients with an indication for ICD implantation. Exclusion criteria: class I indications for permanent pacing, pace-terminable ventricular tachycardia, and previously implanted functional unipolar pacing system.
Technique	S-ICD system
Follow-up	**Mean 558 days (range 13 to 1342 days)**
Conflict of interest/source of funding	The EFFORTLESS S-ICD Registry is sponsored in its entirety by Cameron Health, Inc., a subsidiary of Boston Scientific Corporation.

Analysis

Follow-up issues:

- Patients were followed as per Institutional standards for up to 60 months post-implant.
- All scheduled and unscheduled follow-ups for the first-year post-implant were recorded, while in years 2 to 5 post-implant there was a minimum annual follow-up data requirement (including all adverse events, spontaneous arrhythmia episodes, and programming changes).
- Of the patients included, six were withdrawn before implantation because of inclusion/exclusion criteria violations (n=3), patient decision, (n=1), and investigator decision (n=2). Nine patients have died during the course of the Registry (2%, 9/450).
- One-year follow-up was completed in 294 patients (189 retrospective; 105 prospective) with 143 and 52 retrospective patients reaching 2- and 3-year follow-up, respectively. Five prospective patients have reached 2-years of follow-up.

Study design issues:

- Patients were enrolled prospectively (51%, 241/472) and retrospectively.

Study population issues:

- Primary prevention: 63% (282/449).
- Clinical disease: ischaemic cardiomyopathy, 37% (166/445); non-ischaemic cardiomyopathy, 31% (139/445); congenital heart disease, 7% (33/445); idiopathic ventricular fibrillation, 8% (34/445); channelopathies, 13% (60/445); other, 3% (13/445). Mean left ventricular ejection fraction: 42% (n=348).
- Previous transvenous ICD: 15% (67/447); concomitant pacemaker: 3% (13/447).

Other issues: There is an overlap of patients with the Burke (2015) paper.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **450**

Conversion test success: 100% (392/393)
7 patients had an initial conversion failure that needed 1 or more procedures to reposition the system to become successful.

Spontaneous episodes recorded and classified by the S-ICD system

S-ICD system performance	Number of episodes	Number of patients (n=456)
Therapy delivered	169	13% (59/456)
Appropriate therapy	**93**	**7% (33/456)**
VT/VF discrete episodes	51	29
VT/VF 'storm' episodes	40	4
VT/VF conversion before shock	2	2
Inappropriate therapy[a]	**73**	**7% (32/456)**
SVT above discrimination zone	10	6
Inappropriate sensing (cardiac)[b]	58	24
Inappropriate sensing (non-cardiac)	4	4
VF/SVT discrimination error	1	1
Rhythm unclassified[c]	3	1
Therapy withheld[d]	145	13% (61/456)
Episode unclassified[e]	3	3
Total	317	19% (85/456)

[a] 3 patients had multiple episodes of different types. 2 patients had episodes of both cardiac and non-cardiac inappropriate sensing and 1 had episodes of cardiac oversensing and discrimination error.

[b]Oversensing because of P-waves, wide QRS, T-waves, low-amplitude signal, and unspecified.

[c]Unclassified episodes where treatment was provided, but no S-ECG source documentation was retained in order to make a full classification of the treated episode.

[d]Appropriate charge with spontaneous termination of VF/VT, inappropriate charge for SVT above discrimination zone or inappropriate sensing.

[e]Unclassified episodes that could not be classified as either treated or un-treated episodes because of incomplete data at the time of data cut.

First shock conversion efficacy for discrete VT/VF episodes: 88%

Overall discrete VT/VF clinical conversion efficacy after a maximum of 5 shocks: 100%

Safety

Death: 2% (9/450)

None of the deaths occurred within 30 days post-implant although 1 remains of unknown cause because of lack of documentation.

4 patients died from pump failure, 1 from kidney disease, 1 from respiratory failure, and 1 from bronchopneumonia and stroke secondary to heart failure. 1 patient died after an apparent extended period of asystole/bradycardia followed by an appropriately detected and treated VF episode that failed to convert.

None of the deaths has been reported to be related to the S-ICD system or implant procedure.

Device explantation: 4% (17/450)

The causes were: infection (n=8), decubitus/erosion (n=1), heart transplant (n=1), failure to convert induced episodes at initial implant (n=1), failure to convert spontaneous episodes (n =1), inappropriate sensing (n=1), elective decision after inappropriate shocks (n=1), replacement of the S-ICD system by a transvenous ICD system because of recurrent VT (n=2) and patient decision because of pain (n=1). One patient had the device turned OFF because of T-wave oversensing and recurrent inappropriate therapy.

Device or procedure-related complications needing intervention

Complication	Number of events	Patients (n)
Erosion or extrusion of implanted electrode or pulse generator	4	4
Haematoma	1	1
Failure to convert spontaneous VF episode	1	1
Inability to communicate with device	1	1
Inappropriate shock: oversensing	2	2
Incision/superficial infection	2	2
Near syncope/dizziness/shortness of breath/confusion	1	1
Pleural effusion	1	1
Pneumothorax	1	1
Premature battery depletion	1	1
Shock delivered for non-VT/VF	1	1
System infection	12	11
Suboptimal electrode position/electrode movement	5	5
Suboptimal pulse generator position	1	1
Suture discomfort	1	1
Total complications (% of 456)	35	**29 (6%)**

360-day post-implant complication-free rate: 94%

Abbreviations used: ICD, implantable cardioverter defibrillator; S-ICD, subcutaneous implantable cardioverter defibrillator; SVT, supraventricular tachyarrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.

Study 6 Weiss R (2013)

Details

Study type	**Prospective case series (S-ICD System Investigational Device Exemption [IDE] study)**
Country	33 sites in the United States, New Zealand, the Netherlands, and the United Kingdom.
Recruitment period	Not reported
Study population and number	n= **321** patients with an indication for ICD implantation
Age and sex	Mean 52 years; 74% male
Patient selection criteria	Inclusion criteria: age ≥18 years and a guideline indication for ICD implantation. Exclusion criteria: patient's circumstances limited his or her ability to comply with the study requirements. Pregnant or lactating and premenopausal women who were unwilling to use adequate birth control for the duration of the study. Participation in any other investigational study was discouraged. Life expectancy of <1 year. Patients with documented spontaneous and frequently recurring VT reliably terminated with antitachycardia pacing were excluded unless the patient was not a candidate for a transvenous ICD system. Existing epicardial patches or subcutaneous electrodes in the left thoracic space. Patients with unipolar pacemakers or pacing devices that revert to unipolar pacing. Estimated glomerular filtration rate ≤29 mL/min per 1.73 m^2.
Technique	S-ICD system
Follow-up	**Mean 11 months**
Conflict of interest/source of funding	The study was sponsored in its entirety by Cameron Health, Inc, a subsidiary of Boston Scientific Corporation.

Analysis

Follow-up issues:

- Follow-up took place and at 30, 90, and 180 days after implantation. After the 180-day follow-up visit, patients were followed semi-annually until study closure.
- Of the 330 enrolments, 321 had an implantation procedure, and 9 were withdrawn before implantation. 98% (314/321) of patients were discharged with the device, and 91% (293/321) remained active in the study at the time of end point analysis.
- A total of 88% (276/314) patients had a follow-up duration of ≥180 days. There were 38 patients with follow-up duration <180 days: 9% (28/314) had their last visit before 180 days, 2% (7/314) withdrew from the study, and 1% (3/314) died.
- During the entire follow-up, 21 patients had had successful device implantation but discontinued participation: 11 patients were withdrawn subsequent to S-ICD System explantation, 8 patients died, 1 patient with limited life expectancy withdrew consent and requested that the S-ICD System be turned off, and 1 patient with congenital heart disease was withdrawn because of a heart transplant.

Study design issues:

- The primary safety end point was the 180-day S-ICD System complication-free rate compared with a pre-specified performance goal of 79%.
- The primary effectiveness end point was the induced ventricular fibrillation conversion rate at implantation compared with a pre-specified performance goal of 88%, with success defined as 2 consecutive ventricular fibrillation conversions of 4 attempts. Detection and conversion of spontaneous episodes were also evaluated.

Study population issues:

- Primary prevention, 79% (n=321).
- Comorbid conditions: congestive heart failure, 61%; atrial fibrillation, 15%; hypertension, 58%.
- Mean ejection fraction: 36% (n=299).
- Previous transvenous ICD: 13%, previous pacemaker: 1%.

Other issues: There is an overlap of patients with the Burke (2015) paper.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **304**

Acute induced ventricular tachycardia/ ventricular fibrillation conversion results

Non-evaluable results	Evaluable results		Estimate (%)	95% Clopper-Pearson interval (%)
	Success	Failure		
16	304	0	100	98.8 to 100

- In most of the 16 non-evaluable tests, the testing protocol was stopped short of completion because of clinical circumstances precluding continued testing (for example haemodynamic instability, sudden change in respiratory status, and inability to induce or reliably convert VF).
- 10/16 non-evaluable patients and 1 patient not tested because of left ventricular thrombus, remained with the device and were followed-up for the safety end point, whereas 7 patients were not implanted with the S-ICD System and were withdrawn from the study.
- When all 17 excluded tests were imputed as failures, the acute VF conversion rate had a success rate of 95% with a 95% lower confidence limit of 92%,

Spontaneous episodes treated: 119 VT/VF episodes in 7% (21/304) of patients (38 discrete VT/VF episodes and 81 occurring during VT/VF storms)

- The S-ICD System converted 35 of 38 episodes (92%) on the first shock and 37 of 38 (97%) with 1 or more shocks.
- There were 81 device episodes associated with 4 VT/VF storm events in 2 patients.
- 3/4 VT/VF storms were ultimately terminated by the S-ICD System, and 1 storm terminated after the emergency department team shocked the patient externally while the S-ICD was charging to deliver the first shock.

Mean time to therapy (interval starting 2000 milliseconds after the last induction artifact and ending at the onset of the shock deflection on a standard ECG): 14.6±2.9 seconds, with a range of 9.6 to 29.7 seconds.

A time to therapy of >18 seconds was noted in 13% of episodes.

Safety

180-day type I (device-related) complication-free rate: 99%

180-day type I through III (not caused by the device but would not have occurred in the absence of the implanted device) complication-free rate: 92%

There was no electrode or pulse generator movement in 99% of implanted patients throughout the follow-up period.

An additional sensitivity analysis showed that the safety performance objective was achieved even when all study exits before 180 days were imputed as complications.

Death: 2% (8/321)

- 5 were noncardiac, nonsudden, and unrelated to the implantation procedure.
- 1 patient died unwitnessed at home; interrogation of the device showed a successfully treated episode of a single ventricular arrhythmia episode.
- 1 unwitnessed, presumed sudden death did not have a final device interrogation because the centre was not notified until 2 months after the patient's death. This patient was diagnosed with atypical pneumonia and hypoxia before his death.
- The last death occurred outside the United States, and repeated attempts to contact the family were unsuccessful. The cause of death remains unknown.

Infection: 6% (18/321)

- 4 infections needed device explantation.
- Superficial or incisional infections were managed without system explantation in 4% (14/321) of patients. 13 patients were treated with antibiotics, and 1 patient had sternal wound revision. Most of these conservatively treated patients continued with their S-ICD Systems through the follow-up period.1 patient had the S-ICD electively explanted after study exit and against medical advice, and 1 patient withdrew consent and elected do-not-resuscitate status at the end of life for reasons unrelated to the infection.

Inappropriate shock rate: 13% (41/321)

Causes of inappropriate shock	Clinical events	Patients (n=314)	Patients managed non-invasively
SVT above discrimination zone (normal device function)	21	5% (16/314)	12/16
Inappropriate sensing	30	8% (25/314)	20/25
Oversensing, cardiac	27	7% (22/314)	17/22
Oversensing, non-cardiac	3	1% (3/314)	3/3
Total	51	13% (41/314)	32/41

Abbreviations used: ECG, electrocardiogram; ICD, implantable cardioverter defibrillator; S-ICD, subcutaneous implantable cardioverter defibrillator; SVT, supraventricular tachyarrhythmias; VF, ventricular fibrillation; VT, ventricular tachycardia.

Study 7 Pedersen S S (2016)

Details

Study type	**Propensity matched case-control study**
Country	S-ICD patients: Czech Republic, Denmark, Germany, Italy, the Netherlands, New Zealand, Portugal and UK (29 sites) TV-ICD patients: the Netherlands (12 site)
Recruitment period	S-ICD: 2011-14 TV-ICD: 2003-10
Study population and number	n= **334 (167 S-ICD [Effortless registry cohort] versus 167 TV-ICD [MIDAS prospective observational study cohort])** patients with an indication for ICD implantation
Age and sex	S-ICD: Mean 54 years; 73% (122/167) male TV-ICD: Mean 55 years; 72% (120/167) male
Patient selection criteria	Inclusion criteria: In the S-ICD group, only prospective and first-time implant patients from the Effortless registry were included. Patients with a first generation S-ICD system per local clinical guidelines because of primary or secondary prevention indication and willing to participate and provide written information consent. The patients from the TV-ICD group were recruited from the MIDAS cohort. Exclusion criteria: In the S-ICD group, patients were excluded if they participated in another study that was considered to interfere with interpretation of the results from the Effortless S-ICD registry, had previously been implanted with an ICD, experienced incessant VT or spontaneous, frequently recurring VT that could reliably be terminated with antitachycardia pacing and if they had a bradycardia indication for cardiac resynchronisation therapy. In the MIDAS cohort, patients who had an indication for bradycardia or cardiac resynchronisation therapy or with a secondary prevention indication because of monomorphic VTs were excluded as these patients were not eligible for an S-ICD system.
Technique	S-ICD system or TV-ICD system
Follow-up	**6 months**
Conflict of interest/source of funding	The EFFORTLESS S-ICD Registry is sponsored in its entirety by Cameron Health, Inc., a subsidiary of Boston Scientific Corporation. The MIDAS study was supported by a VENI grant from the Netherlands Organisation for Scientific Research, the Hague, the Netherlands and a VIDI grant from the Netherlands organisation for health research and development, the Hague, the Netherlands to Dr Pedersen.

Analysis:

Follow-up issues: Not reported

Study design issues:

- Quality of life was assessed with the SF-12 at baseline, 3 and 6 months after implant. The 12 items contribute to a physical component summary and a mental component summary score, with a range from 0 to 100 (0=poorest possible QoL; 100=best possible QoL).
- To control for the potentially confounding influence of personality on QoL, patients completed the Type D Scale (DS14) at baseline (the DS14 is a 14-item measure tapping into negative affectivity and social inhibition). Items are rated on a 5-point Likert scale from 0 to 4 with a score of 10 or greater on both traits indicating a Type D personality. Type D personality is a vulnerability factor for poorer QoL, life-threatening arrhythmias and premature mortality in patients with an ICD.
- Effortless and MIDAS patients were matched 1:1 using propensity score matching on the following a priori selected variables: gender, age, indication for ICD (primary versus secondary), ischemic versus non-ischemic aetiology and baseline physical QoL and mental QoL.
- Propensity score matching was done using the greedy matching algorithm with the recommended calliper width by Austin.
- Of the 419 effortless patients prospectively enrolled, 95% (397/419) consented to participate. Of these patients, 17% (68/397) were excluded because of previous implantation with a TV-ICD system or pacemaker and 20% (80/397) of patients were excluded because of insufficient QoL data.

Study population issues:

- Despite propensity score matching on selected variables, the 2 groups statistically significantly differed on some baseline characteristics: Effortless patients were less likely to have ventricular fibrillation as index arrhythmia and to be prescribed statins, but more likely to have a lower QRS duration, to have VT as index arrhythmia, to be prescribed diuretics, and to have diabetes and heart failure compared with the MIDAS patients.

Other issues: Not reported

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 334 (167 S-ICD versus 167 TV-ICD)

Therapy
S-ICD: 19 episodes were treated with a shock during the 6-month follow-up.
TV-ICD: 29 episodes were treated with a shock during the 6-month follow-up.

Physical and mental QoL during 6-month follow-up
<table>
<tr><th></th><th>Effortless (S-ICD system)
mean (95% CI)</th><th>Midas (TV-ICD systems)
mean (95% CI)</th><th>p value</th></tr>
<tr><td colspan="4">MODEL 1 – adjusted for a priori selected variables</td></tr>
<tr><td colspan="4">Physical QoL (PCS)</td></tr>
<tr><td>Baseline</td><td>39.35 (37.75 to 40.95)</td><td>41.61 (40.02 to 43.19)</td><td>0.032</td></tr>
<tr><td>3 months</td><td>42.42 (40.87 to 43.98)</td><td>44.68 (43.15 to 46.21)</td><td></td></tr>
<tr><td>6 months</td><td>42.33 (40.72 to 43.93)</td><td>44.58 (43.00 to 46.17)</td><td></td></tr>
<tr><td colspan="4">Mental QoL (MCS)</td></tr>
<tr><td>Baseline</td><td>41.60 (40.00 to 43.19)</td><td>42.84 (41.27 to 44.42)</td><td>0.2232</td></tr>
<tr><td>3 months</td><td>45.12 (43.53 to 46.71)</td><td>46.37 (44.80 to 47.93)</td><td></td></tr>
<tr><td>6 months</td><td>44.52 (42.85 to 46.20)</td><td>45.78 (44.12 to 47.41)</td><td></td></tr>
<tr><td colspan="4">MODEL 2 – adjusted for a priori selected variables and baseline differences between the 2 cohorts</td></tr>
<tr><td colspan="4">Physical QoL (PCS)</td></tr>
<tr><td>Baseline</td><td>40.48 (38.69 to 42.27)</td><td>40.77 (39.12 to 42.42)</td><td>0.8157</td></tr>
<tr><td>3 months</td><td>43.56 (41.79 to 45.34)</td><td>43.85 (42.22 to 45.48)</td><td></td></tr>
<tr><td>6 months</td><td>43.45 (41.63 to 45.26)</td><td>43.74 (42.06 to 45.41)</td><td></td></tr>
<tr><td colspan="4">Mental QoL (MCS)</td></tr>
<tr><td>Baseline</td><td>42.39 (40.60 to 44.19)</td><td>42.25 (40.59 to 43.92)</td><td>0.9080</td></tr>
<tr><td>3 months</td><td>45.86 (44.04 to 47.68)</td><td>45.72 (44.04 to 47.40)</td><td></td></tr>
<tr><td>6 months</td><td>45.19 (43.29 to 47.09)</td><td>45.05 (43.28 to 46.81)</td><td></td></tr>
</table>
The evolution in physical (p=0.0503) and mental scores (p=0.3772) during follow-up was similar for both cohorts.
Both patients with an S-ICD system and a TV-ICD system experienced significant improvements in physical and mental QoL between time of implant and 3-month follow-up (p<0.0001) and between time of implant and 6-month follow-up (p<0.0001) but not between 3- and 6-month follow-up (p value not significant).</td><td>No safety event was reported.</td></tr>
<tr><td colspan="2">ATP, antitachycardia pacing; CI, confidence interval; ICD, implantable cardioverter defibrillator; KM, Kaplan–Meier; MCS, mental component summary; PCS, physical component summary; QoL, quality of life; SF-12, short-form health survey 12-item; S-ICD, subcutaneous implantable cardioverter defibrillator; TV-ICD, transvenous implantable cardioverter defibrillator; VT, ventricular tachycardia.</td></tr>
</table>

Study 8 Theuns D A M J (2015)

Details

Study type	**Case series**
Country	Europe and New Zealand
Recruitment period	2008-2009
Study population and number	n= **55** patients at risk of sudden cardiac death
Age and sex	Mean 56 years; 80% (44/55) male
Patient selection criteria	Inclusion criterion: class I, II-a, or II-b indication for ICD therapy. Exclusion criteria: indication for bradycardia pacing, cardiac resynchronisation therapy, ventricular tachycardias with rates <170 beats per minute, or documented monomorphic ventricular tachycardias which could be terminated by antitachycardia pacing.
Technique	S-ICD system
Follow-up	**Median follow-up of 5.8 years**
Conflict of interest/source of funding	Dr Theuns has received institutional grant and consulting fee from Boston Scientific. Dr Hood has received lecture honoraria, institutional grant, and consulting fees from Boston Scientific. Dr Cappato has equity and intellectual property rights from Cameron Health, a subsidiary of Boston Scientific, and lecture honoraria, institutional grant, and consulting fees from Boston Scientific. Dr Knops has institutional grant from Boston Scientific. Dr Maass receives lecture honoraria from Boston Scientific. Dr Boersma receives lecture honoraria and consulting fees from Boston Scientific. The other authors report no conflicts.

Analysis

Follow-up issues:

- End of follow-up with administrative censoring of longevity of devices still in service was set on 1 December 2014.
- Patients who reached the end of follow-up without elective replacement indication (ERI) were censored for administrative reasons. Patients who died before ERI were treated as censored observations.

Study design issues:

- The objective of the study was to evaluate the longevity of the S-ICD system. During follow-up, time and causes of device replacement or explantation were assessed and categorised. Device longevity was estimate using Kaplan–Meier analysis.
- Device longevity was defined as the time from implantation to replacement and thus not the day of detection of ERI. Overestimation of longevity could be neglected because replacement is performed within 1 to 2 weeks after detection of ERI.
- This is the follow-up of the CE mark study.

Study population issues:

- Primary prevention, 78% (43/55); secondary prevention, 22% (12/55).
- Underlying cardiac disease: ischaemic heart disease, 67% (37/55); non-ischaemic cardiomyopathy, 18% (10/55); congenital heart disease, 4% (2/55); other, 11% (6/55).
- Mean left ventricular ejection fraction: 34%.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **55** No data on efficacy were reported.	**Number of deaths before ICD replacement**: 15% (8/55); 3 cardiac and 5 non-cardiac deaths. None of the deaths were related to the S-ICD system or implant procedure. **Devices replaced during follow-up**: 47% (26/55) **Devices explanted (permanent removal) during follow-up**: 9% (5/55) **Indications for device replacement/ explantation**: • Battery depletion: 81% (25/31) • Replacement by transvenous ICD system: 13% (4/31) ✓ 2 patients developed an indication for cardiac resynchronisation therapy because of symptomatic heart failure ✓ 1 patient had an indication for bradycardia pacing because of symptomatic bradycardia ✓ 1 patient received a transvenous ICD system as specified by protocol of the European Regulatory Trial in case of ineffective defibrillation testing. • Infection: 1/31 • Other: 1/31 Premature ERI because of rapid battery depletion was observed in 9% (5/55) of devices with a mean service time of 1.5±0.7 years. Considering the manufacturer-projected device longevity of 5 years, 71% of devices were actually still in service at 5-year follow-up. **Median time for device replacement**: 5 years (Q1–Q3, 4.4–5.6 years). **Event-free rates for device replacement**: • 94% (95% CI, 83%–98%) after 2 years • 89% (95% CI, 76%–96%) after 4 years • 30% (95% CI, 15%–46%) after 6 years **Assessment of relationship between device replacement and shock delivery** • During follow-up, a total of 119 delivered shocks in 16 individual patients (29%) were recorded. Of these patients, the majority (69%) received fewer than 5 shocks. • Proportionally, the occurrence of shock delivery was not different between devices with ERI versus those without ERI (32% versus 27%). • The relation between ICD shocks and elective device replacement was further evaluated by Cox regression analysis. Considering the number of shocks as a time-varying covariate in Cox regression analysis, no association between number of shocks and elective device replacement was found (hazard ratio, 1.01; 95% CI, 0.98–1.04; p=0.29).
Abbreviations used: CI, confidence interval; ERI, elective replacement indication; ICD, implantable cardioverter defibrillator.	

Study 9 NICOR registry data (2017) - *Unpublished*

Details

Study type	**Case series – registry data**
Country	UK
Recruitment period	2015-16 (47 centres)
Study population and number	n= **290**
Age and sex	Mean 47 years
Patient selection criteria	All patients who had the S-ICD implanted in the UK.
Technique	Subcutaneous ICD-SQ
Follow-up	**None**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Not reported

Study design issues: Not reported

Study population issues: Not reported

Other issues: It is likely the patients in this registry overlap with the International registry and IDE clinical study.

Key efficacy and safety findings

Efficacy	Safety
In financial year 2015-16 there were in total 7,168 ICD implants registered. 290 of these were subcutaneous ICDs (ICD-SQ) implanted in 47 centres (range 1-19 per centre). The average age for ICD-SQ patients was 47.4 (range 16-85), compared to 63.4 (range 0.4-93.4) for conventional ICDs.	The complication field was completed in 183 of the 290 ICD-SQ implants. 181 cases had no acute complications. There was 1 **haematoma** and 1 **lead displacement**. This rate is similar to the reported rate of 1.8% in conventional ICD implants.
Abbreviations used: S-ICD, subcutaneous implantable cardioverter defibrillator	

Efficacy

Detection and conversion efficacy of induced arrhythmias

In a matched-controlled study of 138 patients comparing 69 patients with subcutaneous implantable cardioverter defibrillators (ICD) and 69 patients with transvenous ICDs, the conversion rates of induced ventricular fibrillation at implantation were similar (p=0.81): 90% (60/67) for 65 J of energy (15-J safety margin) in the subcutaneous ICD group and 91% (59/65) for a device-dependent 10-J safety margin in the transvenous ICD group.[3]

In an international registry of 472 patients, the conversion test success rate was 100% (392/393); 7 patients had an initial conversion failure that needed 1 or more procedures to reposition the system to become successful.[5]

In a prospective case series of 321 patients (the IDE study), the acute induced ventricular arrhythmia conversion success rates were 100% for the 304 evaluable results and 95% (304/321) when 17 excluded tests were imputed as failures. [6]

Detection and conversion efficacy of spontaneous arrhythmias

In a retrospective propensity-matched cohort study of 280 patients (140 with subcutaneous ICDs and 140 with transvenous ICDs), appropriate ICD intervention rates (shocks and antitachycardia pacing) were lower in the subcutaneous ICD group, at 17% (95% confidence intervals [CI] 6% to 26%) compared with 31% (95% CI 23% to 40%) in the transvenous ICD group (hazard ratio [HR] 2.42; p=0.01). However, the incidence of appropriate shocks was similar in both groups (HR 1.46; p=0.36).[1]

In a propensity-matched case-control study of 138 patients comparing 69 S-ICD patients with 69 TV-ICD patients, appropriate ICD therapy rates were 4% (3/69) and 7% (5/69) in each group respectively. [2]

In a case series of 889 patients, which combined patients from the IDE study and from an international registry (Effortless), 111 episodes of spontaneous ventricular arrhythmias were treated in 59 patients within a mean 22-month follow-up; 90% (100/111) of these events were stopped with 1 shock and 98% (109/111) were stopped within the 5 available shocks.[4]

In the international registry of 472 patients, 93 episodes of spontaneous ventricular arrhythmias were treated in 7% (33/456) of patients within a mean 558-day follow-up. The first shock conversion efficacy for discrete ventricular arrhythmia episodes was 88% and the overall discrete ventricular arrhythmia clinical conversion efficacy after a maximum of 5 shocks was 100% (patients also included in the case series of 889 patients).[5]

In the prospective case series of 321 patients, 119 episodes of spontaneous ventricular arrhythmias were treated in 7% (21/304) of patients within a mean 11-month follow-up (38 discrete ventricular arrhythmia episodes and 81 occurring during VT/VF storms). 92% (35/38) of the discrete episodes were converted on the first shock and 97% (37/38) with 1 or more shocks. The 81 episodes occurring during VT/VF storms were associated with 4 VT/VF storm events in 2 patients. 75% (3/4) of the VT/VF storms were ultimately terminated by the S-ICD device, and 1 storm terminated after the patient was shocked externally while the S-ICD was charging to deliver the first shock (patients also included in the case series of 889 patients).[6]

Mean time to therapy

In the prospective case series of 321 patients, the mean time to therapy (defined as the interval starting 2,000 milliseconds after the last induction artefact and ending at the onset of the shock deflection on a standard ECG) was 14.6 seconds (range 9.6 seconds to 29.7 seconds). A time to therapy of greater than 18.0 seconds was noted in 13% of episodes.[6]

Survival

In the retrospective propensity-matched cohort study of 280 patients comparing 140 patients with subcutaneous ICDs and 140 patients with transvenous ICDs, 5-year patient survival was similar in both groups (96% and 95% respectively, p=0.42).[1]

Quality of life

In a propensity-matched case-control study of 334 patients comparing 167 patients from the Effortless registry with 167 patients with transvenous ICDs from the Midas prospective observational study cohort, there were no statistically significant differences between groups on physical (p=0.8157) and mental quality-of-life scores measured using the SF-12 questionnaire (p=0.9080) at baseline, and 3 months and 6 months after implantation in adjusted analyses. The evolution in physical (p=0.0503) and mental scores (p=0.3772) during 6-month follow-up was similar for both cohorts. Both patients with subcutaneous ICDs and patients with transvenous ICDs experienced statistically significant improvements in physical and mental quality of life between implantation and 3-month follow-up (p<0.0001) and 6-month follow-up (p<0.0001). However, the difference between 3- and 6-month follow-up was not statistically significant. [7]

Safety

Death

Death was reported in 1% (2/140) of patients in the subcutaneous implantable cardioverter defibrillators (ICD) group (1 from a non-cardiac cause and 1 from a cardiac cause) and in 4% (6/140) of patients in the transvenous (TV) ICD group (3 from non-cardiac causes, 2 from cardiac causes and 1 for an unknown reason)

in a retrospective propensity-matched cohort study of 280 patients with a 5-year follow-up. [1]

Death from congestive heart failure was reported in 1 patient in the subcutaneous ICD group in a matched-controlled study of 138 patients comparing 69 patients with subcutaneous ICDs and 69 matched patients with transvenous ICDs (average follow-up 217 days).[3]

All-cause mortality rate was 3% (26/882) in a case series of 889 patients with a mean 22-month follow-up that combined patients from a prospective case series and from an international registry (Effortless). There was only 1 known arrhythmic death because of Loeffler's syndrome. The 3-year Kaplan–Meier estimate was 5% (95% confidence interval [CI] 1% to 9%), with 26 deaths (3%).[4]

Death was reported in 15% (8/55) of patients before subcutaneous ICD replacement in a case series of 55 patients with a median 5.8-year follow-up. None of the deaths were related to the subcutaneous ICD system or implant procedure. [8]

Inappropriate shocks

Inappropriate shock rate was 21% in the subcutaneous ICD group (17% because of oversensing and 4% because of supraventricular tachycardia) compared with 19% in the transvenous ICD group (1% because of oversensing and 18% because of supraventricular tachycardia) in the retrospective propensity-matched cohort study of 280 patients. In the same study, inappropriate sensing rate was 3% in the subcutaneous ICD group and zero in the transvenous ICD group. [1]

Inappropriate shock rate over a mean 31-month follow-up was similar in both groups in a propensity matched case control study of 138 patients: 4% (3/69) in the S-ICD group versus 9% (6/69) in the TV-ICD group (p=0.49). In the S-ICD group, they were all caused by T-wave oversensing in the context of sinus tachycardia. [2]

Inappropriate episode was reported in 7% (5/69) of patients in the subcutaneous ICD group and in 4% (3/69) of patients in the transvenous ICD group in the matched-controlled study of 138 patients with an average follow-up of 217 days (no statistically significant difference between groups, p=0.745). In the S-ICD group, 3 inappropriate episodes were caused by T-wave oversensing and 2 by oversensing, and in the transvenous ICD group, 1 was caused by oversensing and 2 were supraventricular. [3]

The estimated 3-year inappropriate shock rate was 13% in the case series of 889 patients. The causes were T-wave oversensing in 39%, supraventricular arrhythmia above the discrimination zone in 24%, low-amplitude signal in 21%, non-cardiac oversensing in 8%, oversensing of ventricular tachycardia and fibrillation below the rate zone in 4%, other or combined types of cardiac

oversensing in 2%, supraventricular arrhythmia discrimination errors in 1%, and committed shock for ventricular tachycardia and fibrillation in 1%.[4]

There were 73 episodes of inappropriate shocks reported in 7% (32/456) of patients in the international registry of 472 patients. The causes were inappropriate sensing (cardiac) in 24 patients, supraventricular tachycardia above the discrimination zone in 6, inappropriate sensing (non-cardiac) in 4 patients, and ventricular tachycardia and fibrillation discrimination error in 1 patient (patients also included in the case series of 889 patients). [5]

Fifty-one episodes of inappropriate therapy were reported in 13% (41/314) of patients in the prospective case series of 321 patients with a mean 11-month follow-up (patients also included in the case series of 889 patients). The causes were supraventricular tachycardia above the discrimination zone in 5% (16/314) of patients, and inappropriate sensing in 8% (25/314) of patients.[6]

Device malfunction

Premature battery depletion

Pulse generator replacement because of battery depletion did not differ between the groups at 5-year follow-up in the retrospective propensity-matched cohort study of 280 patients (p=0.18).[1]

Premature battery depletion was reported in 5 patients in the case series of 889 patients. [4]

Rapid battery depletion causing premature elective replacement of the device was reported in 9% (5/55) of devices, with a mean service time of 1.5 years, in a case series of 55 patients; 71% of devices were still in service at 5-year follow-up.[8]

Inability to communicate with device

Inability to communicate with the device was reported in 3 patients in the case series of 889 patients. [4]

Twiddler syndrome

Twiddler syndrome rate was 1% in both groups in the retrospective propensity-matched cohort study of 280 patients. [1]

Device failure

Device failure rate was 1% in the subcutaneous ICD group and none in the transvenous ICD group in the retrospective propensity-matched cohort study of 280 patients. [1]

Failure of a device to cardiovert ventricular arrhythmia was reported in 1 patient out of 69 patients in a propensity-matched case-control study of 138 patients within a mean 31-month follow-up. [2]

Device replacement/explantation/re-intervention

Rate of upgrade to a TV-ICD or to a cardiac synchronisation therapy device was 1% in the S-ICD group compared with 5% in the TV-ICD group in the retrospective propensity-matched cohort study of 280 patients over a 5-year follow-up (p=0.26).[1]

Late system revision because of ventricular tachycardia storm was reported in 1 out of 69 patients in the S-ICD group in the matched-controlled study of 138 patients with an average follow-up of 217 days. The S-ICD was replaced by a conventional system. [3]

Explantation of the subcutaneous ICD for pacing was reported in 4 patients because of the need for ventricular pacing in the case series of 889 patients: 1 patient developed a new bradycardia indication; in 1 patient, the device was explanted because of the need for antitachycardia pacing; and 1 patient with 3 ventricular tachycardia storm events had replacement with a transvenous ICD in an attempt to suppress ventricular arrhythmias using overdrive pacing. In addition, 1 device was extracted for a cardiac resynchronisation therapy upgrade.[4]

Device explantation was reported in 4% (17/450) of patients in the international registry of 472 patients with a mean 558-day follow-up. The causes were infection (n=8), decubitus/erosion (n=1), heart transplant (n=1), failure to convert induced episodes at initial implant (n=1), failure to convert spontaneous episodes (n =1), inappropriate sensing (n=1), elective decision after inappropriate shocks (n=1), replacement of the subcutaneous ICD system by a transvenous ICD system because of recurrent VT (n=2) and patient decision because of pain (n=1). One patient had the device turned OFF because of T-wave oversensing and recurrent inappropriate therapy (patients also included in the case series of 889 patients).[5]

Device replacement was reported in 47% (26/55) of patients and device explantation (permanent removal) was reported in 9% (5/55) of patients during a median 5.8-year follow-up in the case series of 55 patients. The indications for device replacement or explantation were battery depletion in 81% (25/31) of patients, replacement with a transvenous ICD system in 13% (4/31), infection in 1 patient and ‘other’ in 1 patient. The median time for device replacement was 5 years (first quartile–third quartile, 4.4 years to 5.6 years) and the event-free rates for device replacement were 94% (95% CI, 83% to 98%) after 2 years, 89% (95% CI, 76% to 96%) after 4 years and 30% (95% CI, 15% to 46%) after 6 years. [8]

Device erosion

Erosion rate was 3% in the subcutaneous ICD group and 2% in the transvenous ICD group in the retrospective propensity-matched cohort study of 280 patients. [1]

Erosion was reported in 1% (11) of patients in the case series of 889 patients. [4]

Infection

Infection rate was similar in the S-ICD group and in the TV-ICD group in the retrospective propensity-matched cohort study of 280 patients over a 5-year follow-up: 4% versus 4% (p=0.36). There were 2 patients with bacteraemia in the TV-ICD group and 1 in the S-ICD group, who also had a concomitant transvenous pacemaker.[1]

Device-related infection rate over a mean 31-month follow-up was similar in both groups in a propensity matched case control study of 138 patients: 1% (1/69) in the S-ICD group versus 6% (4/69) in the TV-ICD group (p=0.37). They all needed generator and lead extraction and implantation of a new system. [2]

Infection was reported in 1 out of 69 patients in the S-ICD group in the matched-controlled study of 138 patients 8 weeks after the procedure. The device had to be explanted and the patient received a conventional transvenous device. [3]

Infection needing device removal or revision was reported in 2% (14) of patients in the case series of 889 patients. In the same study, incision or superficial infection were reported in 3 patients. [4]

Incision or superficial infection were reported in 2 patients and system infection was reported in 11 patients in an international registry of 472 patients with a mean 558-day follow-up (patients also included in the case series of 889 patients). [5]

Infection was reported in 6 % (18/321) of patients in a prospective case series of 321 patients with a mean follow-up of 11 months; incision or superficial infection without device explantation were reported in 4% (14/321) of patients and infection needing device explantation was reported in 4 patients (patients also included in the case series of 889 patients).[6]

Haematoma

Haematoma needing revision was reported in 1 out of 69 patients in the S-ICD group in the matched-controlled study of 138 patients with an average follow-up of 217 days (further details not reported). [3]

Haematoma was reported in 4 patients in the case series of 889 patients. [4]

Discomfort

Discomfort was reported in 8 patients in the case series of 889 patients with a mean 22-month follow-up. [4]

Inadequate or prolonged healing of incision site

Inadequate or prolonged healing of the incision site was reported in 3 patients in the case series of 889 patients. [4]

Electrode, pulse generator and lead problems

Suboptimal pulse generator and/or electrode position

Generator displacement needing repositioning was reported in 1 patient out of 69 in the propensity matched case control study of 138 patients within a mean 31-month follow-up. [2]

Suboptimal electrode position was reported in 7 patients in the case series of 889 patients. In the same study, suboptimal pulse generator position was reported in 2 patients and, suboptimal pulse generator and electrode position were reported in 4 patients. [4]

Electrode movement

Electrode movement was reported in 7 patients in the case series of 889 patients.[4]

Lead complications

The lead complication rate was statistically significantly lower in the subcutaneous ICD group than in the transvenous ICD group in the retrospective propensity-matched cohort study of 280 patients (5% versus 12%; p=0.03). The only lead complication reported in the subcutaneous ICD group was lead displacement, which occurred in 1 patient out of 140.[1]

Syncope

Near syncope, dizziness, shortness of breath or confusion were reported in 1 patient in the international registry of 472 patients. [5]

Pleural effusion

Pleural effusion was reported in 1 patient in the international registry of 472 patients. [3]

Pneumothorax

Pneumothorax was reported in 1 patient in the international registry of 472 patients. [5]

Total complications

In the retrospective propensity-matched cohort study of 280 patients (140 S-ICD compared with 140 TV-ICD), the Kaplan–Meier complication rates were similar in both groups: 14% in the S-ICD group versus 18% in the TV-ICD group (p=0.80).[1]

In the propensity matched case control study of 138 patients, there was a statistically significantly lower rate of complications in the S-ICD group than in the TV-ICD group both when including and excluding inappropriate shocks over a 31-month follow-up: 9% (6/69) compared with 29% (20/69) (p=0.004) when including inappropriate shocks and 4% (3/69) versus 20% (14/69) (p=0.008) when excluding inappropriate shocks.[2]

In the case series of 889 patients, 4.5% of patients had a complication within 30 days of the procedure and 11% of patients had a complication over 3 years. In the same study, the 3-year Kaplan–Meier estimate for patients with a device-related complication was 5%.[4]

In the international registry of 472 patients, 6% (29/456) of patients had 35 complications within a mean 558-day follow-up. The 360-day post-implant complication-free rate was 94% (patients also included in the case series of 889 patients). [5]

In the prospective case series of 321 patients, the 180-day type I (device-related) complication-free rate was 99% and the 180-day type I through III (not caused by the device but would not have occurred in the absence of the implanted device) complication-free rate was 92% (patients also included in the case series of 889 patients).[6]

Validity and generalisability of the studies

- There are no prospective comparisons between the subcutaneous ICD and the transvenous ICD with long-term follow-up.
- The longest follow-up was 5.8 years[8].
- There is likely to have some patient overlap between the studies included in table 2.
- A new generation of subcutaneous ICD device is available.
- One paper included in table 2 reported on quality of life outcomes[7].

Existing assessments of this procedure

The Canadian cardiovascular society/ Canadian Heart Rhythm Society published guidelines on implantable cardioverter defibrillators in 2016[10]. They stated:

- *''We recommend an S-ICD be considered in patients with limited vascular access or pocket sites in whom an ICD is recommended (Strong recommendation; low-quality evidence).''*

- *''The implantation of an S-ICD might be considered in patients in whom an ICD is recommended who have 1 of the following conditions: (1) congenital heart disease with no access to the ventricles; (2) congenital heart disease with right to left shunt resulting in increased risk of*

thromboembolic complications with transvenous ICD system: and (3) absence of a pocket site because of either previous device-related infection and/or chronic indwelling catheters. ‘’

- *‘’Although S-ICD systems have been shown to be effective at terminating life-threatening arrhythmias and might have some advantages compared with transvenous ICD systems, we believe that the use of S-ICDs should be limited because of concerns regarding the risk of inappropriate shocks with present devices and the lack of long-term studies and randomised trials that compared transvenous vs S-ICDs.”*

The European Society of Cardiology published guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death in August 2015[11]. It stated:

- *‘’Subcutaneous defibrillators should be considered as an alternative to transvenous defibrillators in patients with an indication for an ICD when pacing therapy for bradycardia support, cardiac resynchronization or antitachycardia pacing is not needed (Class of recommendation IIa, level of evidence C).”*

- *‘’ The subcutaneous ICD may be considered as a useful alternative to the transvenous ICD system when venous access is difficult, after the removal of a transvenous ICD for infections or in young patients with a long-term need for ICD therapy (Class of recommendation IIb, level of evidence C).”*

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Technology appraisals

- Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure. NICE technology appraisal 314 (2014). Available from http://www.nice.org.uk/guidance/TA314

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Five Specialist Advisor Questionnaires for subcutaneous implantable cardioverter defibrillator insertion for preventing sudden cardiac death were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- IPAC previously considered this procedure in 2013 and gave it special arrangements guidance stating that "*Current evidence on the efficacy of the insertion of a subcutaneous implantable cardioverter defibrillator (ICD) for the prevention of sudden cardiac death in the short and medium term is adequate. Evidence on its safety in the short term is adequate but there are uncertainties about long-term durability. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research*."

- On-going studies:
  - NCT02787785: Multicentre Automatic Defibrillator Implantation Trial With Subcutaneous Implantable Cardioverter Defibrillator (MADIT S-ICD); RCT; estimated enrolment: 1800; location: not reported; start date: September

2016; estimated study completion date: October 2021; status: not yet recruiting.

- NCT01296022: A PRospective, rAndomizEd Comparison of subcuTaneOous and tRansvenous ImplANtable Cardioverter Defibrillator Therapy (PRAETORIAN); RCT/ non-inferiority study; estimated enrolment: 850; location: United States, Czech Republic, Denmark, Germany, Netherlands, United Kingdom; estimated study completion date: December 2019; status: recruiting; 48-month follow-up.

- NCT02344277: Evaluation of Subcutaneous Implantable Cardiac Defibrillator in Brugada Patients (S-ICD Brugada); Prospective cohort; estimated enrolment: 200; location: Denmark, France, Germany, Italy, Spain; estimated study completion date: April 2022; status: recruiting.

- NCT02433379: Understanding Outcomes With the EMBLEM™ S-ICD in Primary Prevention Patients With Low Ejection Fraction (UNTOUCHED); prospective case series; estimated enrolment: 1000; location: United States, Belgium, Canada, Germany, Italy, Netherlands, Spain, United Kingdom; estimated completion date: April 2020; status: recruiting; 18-month follow-up.

- NCT01736618: S-ICD® System Post Approval Study; Observational registry; enrolment: 1766; start date: March 2013; estimated primary completion date: October 2021; status; ongoing; 60-month follow-up.

- NCT01085435: Boston Scientific Post Market S-ICD Registry (EFFORTLESS); observational study; estimated enrolment: 1000; start date: October 2010; estimated completion date: December 2020; status: ongoing.

- Unpublished evidence:
  The latest data from the EFFORTLESS registry were presented at the 2016 Heart Rhythm Society congress in May 2016 (Boersma et al. Performance and outcomes in patients with the Subcutaneous Implantable Cardiac Defibrillator through Mid Term Follow-Up. May 6 2016 HRS LBCT). This registry is the largest post-market registry for the S-ICD System and the data presented included 985 patients across 42 study sites across Europe and New Zealand who were followed for up to 5 years (average 3.1 years). Results focused on long-term safety and efficacy including complication-free rates at various time points, inappropriate shock incidence and spontaneous shock efficacy.

- A few studies which analyse new algorithms with the aim of reducing inappropriate shock rates have been published.

References

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2. Honarbakhsh S, Providencia R, Srinivasan N et al. (2017) A propensity matched case-control study comparing efficacy, safety and costs of the subcutaneous vs. transvenous implantable cardioverter defibrillator. International Journal of Cardiology 228, 280-285.
3. Kobe J, Reinke F, Meyer C et al. (2013) Implantation and follow-up of totally subcutaneous versus conventional implantable cardioverter-defibrillators: a multicenter case-control study. Heart rhythm: the official journal of the Heart Rhythm Society 10(1), 29-36.
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9. David Cunningham, Senior strategist for National cardiac Audits. (2016) Personal communication. NICOR. Centre for Cardiovascular Prevention and Outcomes. University College London.
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11. European society of cardiology (2015) 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. European Heart Journal doi:10.1093/eurheartj/ehv316.

Appendix A: Additional papers on subcutaneous implantable cardioverter defibrillator insertion for preventing sudden cardiac death

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies. Only studies with more than 10 patients were included.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Aydin Ali, Hartel Friederike, Schluter Michael et al. (2012) Shock efficacy of subcutaneous implantable cardioverter-defibrillator for prevention of sudden cardiac death: initial multicenter experience. Circulation. Arrhythmia and electrophysiology 5(5), 913-9	Case series n=40 FU=median 229 days	Ineffective shock delivery may occur in patients with S-ICD, even after successful intraoperative testing. Multicentre trials are needed with close monitoring of safety and efficacy end points to identify patients who may be at risk for shock failure	Larger studies or studies with longer follow-up are already included in table 2. This study was included in the original overview.
Bardy GH, Smith WM, Hood MA et al. (2010) An entirely subcutaneous implantable cardioverter-defibrillator. New England Journal of Medicine 363: 36–44.	Case series n=53 FU=mean 10 months	In small, nonrandomized studies, an entirely subcutaneous ICD consistently detected and converted ventricular fibrillation induced during electrophysiological testing. The device also successfully detected and treated all 12 episodes of spontaneous, sustained ventricular tachyarrhythmia.	Larger studies or studies with longer follow-up are already included in table 2. This study was included in the original overview.
Boersma L, Burke M C, Neuzil P et al. (2016) Infection and mortality after implantation of a subcutaneous ICD after transvenous ICD extraction. Heart Rhythm 13(1), 157-164	Retrospective sub-group analysis n=866 FU=mean 651 days	The S-ICD is a suitable alternative for TV-ICD patients whose devices are explanted for any reason. Post-implantation risk of infection remains low even in patients whose devices were explanted for prior TV-ICD infection.	It is a retrospective analysis of the patients included in the S-ICD IDE Study and EFFORTLESS Registry with a prior TV-ICD explantation, as well as those with no prior ICD. These patients are already included in Table 2.

Boersma L V, Barr C S, Burke M C et al. (2017) Performance of the subcutaneous implantable cardioverter-defibrillator in patients with a primary prevention indication with and without a reduced ejection fraction versus patients with a secondary prevention indication. Heart Rhythm 14, 367-375	Retrospective sub-group analyses n=856 FU=mean 644 days	The S-ICD performs well in protecting patients with either PP or SP implant indications from sudden cardiac death. Within PP patients, device performance was independent of EF.	Retrospective analyses of the patients included in the S-ICD IDE Study and EFFORTLESS registry. These patients are already included in Table 2.
Boveda S, Lenarczyk R, Haugaa K et al. (2016) Implantation of subcutaneous implantable cardioverter defibrillators in Europe: Results of the European Heart Rhythm Association survey. Europace 18, 1434-1439	European survey n=52 centres	This survey provides a contemporary insight into S-ICD implantation and management in the European electrophysiology centres, showing different approaches, depending on local policies. Cost issues or lack of reimbursement strongly influence the dissemination of the device. However, most respondents retain that S-ICD use will significantly increase in a very short time.	Overview of the use of S-ICDs across Europe.
Brouwer T F, Driessen A H. G, Olde Nordkamp et al. (2016) Surgical Management of Implantation-Related Complications of the Subcutaneous Implantable Cardioverter-Defibrillator. JACC: Clinical Electrophysiology 2, 89-96	Retrospective case series n=123 FU=median 2 years	In most patients with a complication, S-ICD therapy could be continued after intervention, avoiding the need to convert to a transvenous system. Bridging to recovery with a WCD and submuscular implantation of the pulse generator are effective treatment strategies to manage S-ICD complications.	Larger studies or studies with longer follow-up are already included in table 2
Chan J Y. S, Lelakowski J, Murgatroyd F D et al. (2017) Novel Extravascular Defibrillation Configuration With a Coil in the Substernal Space. The ASD Clinical Study. JACC: Clinical Electrophysiology. 28	Prospective case series n=16 FU= none	These preliminary data demonstrate that substernal defibrillation is feasible and successful defibrillation can be achieved with the shock energy available in current transvenous ICDs. This may open new alternatives to extravascular ICD therapy.	Larger studies or studies with longer follow-up are already included in table 2
Dabiri Abkenari L, Theuns DA, Valk SD et al. (2011) Clinical experience with a novel subcutaneous implantable defibrillator system in a single center. Clinical Research in Cardiology 100: 737–744.	Case series n=31 FU= median 286 days	52 episodes of VF induced. Sensitivity was 100% and conversion efficacy was 100%. Mean time to therapy was 13.9 ± 2.5 s. Late procedure-related complications observed in 2 of the first 11 implantations (lead migration). During follow-up, spontaneous ventricular arrhythmias occurred in 4 patients, with accurate detection of all episodes. Inappropriate therapy was observed in five patients. Recurrences were prevented with reprogramming.	Larger studies or studies with longer follow-up are already included in table 2
D'Souza B A, Epstein A E, Garcia F C, Kim Y et al. (2016) Outcomes in Patients With	Retrospective pooled analysis	The S-ICD is a safe option in CHD patients deemed to be at high risk for sudden cardiac death who do	Retrospective analysis of patients

Congenital Heart Disease Receiving the Subcutaneous Implantable-Cardioverter Defibrillator: Results From a Pooled Analysis From the IDE Study and the EFFORTLESS S-ICD Registry. JACC: Clinical Electrophysiology 2, 615-622	n=865 Effortless patients, FU=567 days IDE study, FU=639 days	not have pacing indications. Further research to accurately define sudden cardiac death risk in the diverse anatomic substrates of CHD patients is warranted.	included in the S-ICD IDE Study and EFFORTLESS registry. These patients are already included in Table 2.
El-Chami Mikhael F, Levy Mathew, Kelli Heval M et al. (2015) Outcome of Subcutaneous Implantable Cardioverter Defibrillator Implantation in Patients with End-Stage Renal Disease on Dialysis. Journal of cardiovascular electrophysiology 26(8), 900-4	Retrospective comparative study n=79 (27 dialysis versus 52 non-dialysis) FU= mean 514 days for patients on dialysis and mean 227 days for the non-dialysis patients	S-ICD implantation in dialysis patients is not associated with an excess risk of implant related complications or inappropriate.	Larger studies or studies with longer follow-up are already included in table 2.
Ertugrul I, Karagoz T, Aykan H et al. (2015) Subcutaneous defibrillator implantation in pediatric patients. Anatol J Cardiol. doi: 10.5152/AnatolJCardiol.2015.6589	Retrospective case series n=13 FU= median 32 months	Subcutaneous defibrillator systems are safe and effective in pediatric patients when the transvenous method is risky and contraindicated. Because the high growth rate in this population leads to lead failures, a close follow-up of this population is essential.	Larger studies or studies with longer follow-up are already included in table 2.
Essandoh Michael K, Portillo Juan G, Weiss Raul et al. (2016) Anesthesia care for subcutaneous implantable cardioverter/defibrillator placement: a single-center experience. Journal of clinical anesthesia 31, 53-9	Retrospective case series n=73 FU=2 days	Refractory hypotension was a major adverse event in only 2 patients. The mean baseline SBP was 132.5 +/- 22.0 mm Hg, and the mean minimum SBP during the procedure was 97.3 +/- 9.2 mm Hg (P <0.01). There was also a mean 13-beats per minute decrease in heart rate (P < 0.01), but no pharmacologic intervention was needed. Eight patients developed "severe" pain at the lead tunnelling and generator insertion sites and were adequately managed with intravenous morphine.	Larger studies or studies with longer follow-up are already included in table 2.
Ferrari Paola, Giofre Fabrizio, De Filippo Paolo (2016) Intermuscular pocket for subcutaneous implantable cardioverter defibrillator: Single-center experience. Journal of arrhythmia 32(3), 223-6	Case series n=14 FU=mean 9 months	During a mean follow up of 9 months, no dislocations, infections, hematoma formations, or skin erosions were observed. Intermuscular implantation of the S-ICD could be a reliable, safe, and appealing alternative to the	Larger studies or studies with longer follow-up are already included in table 2.

		standard subcutaneous placement.	
Friedman D J, Parzynski C S, Varosy P D et al. (2016) Trends and In-Hospital Outcomes Associated With Adoption of the Subcutaneous Implantable Cardioverter Defibrillator in the United States. JAMA Cardiol;1(8):900-911. doi: 10.1001/jamacardio.2016.2782.	Retrospective propensity matched analysis n=5,760 (1920 S-ICD vs 1920 SC-ICD vs DC-ICD) National Cardiovascular Data Registry ICD Registry No follow-up	Of the 393 734 ICD implants evaluated during the study period, 3717 were S-ICDs (0.9%). Among 2791 patients with S-ICD who had DFT testing, 2588 (92.7%), 2629 (94.2%), 2635 (94.4%), and 2784 (99.7%) were successfully defibrillated (≤65, ≤70, ≤75, and ≤80 J, respectively). In the propensity-matched analysis of 5760 patients, in-hospital complication rates associated with S-ICDs (0.9%) were comparable to those of SC-ICDs (0.6%) (P = .27) and DC-ICD rates (1.5%) (P = .11). Mean (SD) length of stay after S-ICD implantation was comparable to that after SC-ICD implantation (1.1 [1.5] vs 1.0 [1.2] days; P = .77) and less than after DC-ICD implantation (1.1 [1.5] vs 1.2 [1.5] days; P < .001).	Prospective comparative studies with longer follow-up are already included in Table 2.
Frommeyer G, Dechering D G, Kochhauser S et al. (2016) Long-time "real-life" performance of the subcutaneous ICD in patients with electrical heart disease or idiopathic ventricular fibrillation. J Interv Card Electrophysiol ,	Case series n=24 FU=mean 30 months	Ventricular arrhythmias were adequately detected in 4 patients (17 %). In 3 patients (13 %) oversensing was noticed and led to at least 1 inappropriate shock in 2 patients (8 %). Further adverse events included surgical revision due to a mobile pulse generator as well as explantation of 1 system and switch to a transvenous ICD system because of several ineffective shocks.	Larger studies or studies with longer follow-up are already included in table 2.
Frommeyer Gerrit, Dechering Dirk G, Zumhagen Sven et al. (2016) Long-term follow-up of subcutaneous ICD systems in patients with hypertrophic cardiomyopathy: a single-center experience. Clinical research in cardiology : official journal of the German Cardiac Society 105(1), 89-93	Case series n=18 FU=mean 32 months	Patients with hypertrophic cardiomyopathy and S-ICD systems have an increased risk of T-wave oversensing and inappropriate shock delivery. Thorough monitoring as well as exercise tests may help to improve device settings and thereby prevent T-wave oversensing.	Larger studies or studies with longer follow-up are already included in table 2.
Galvao Pedro, Cavaco Diogo, Adragao Pedro et al. (2014) Subcutaneous implantable cardioverter-defibrillator: Initial experience. Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of Cardiology 33(9), 511-7	Case series n=21 FU=mean 14 months	S-ICD implantation can be performed by cardiologists with a high success rate. Initial experience appears favorable, but further studies are needed with longer follow-up times to assess the safety and efficacy of this strategy compared to conventional devices.	Larger studies or studies with longer follow-up are already included in table 2.
Gold Michael R, Weiss Raul, Theuns Dominic A. M. J et al.	Case series	The addition of a second shock zone with an active discrimination	The patient population is

(2014) Use of a discrimination algorithm to reduce inappropriate shocks with a subcutaneous implantable cardioverter-defibrillator. Heart rhythm : the official journal of the Heart Rhythm Society 11(8), 1352-8	n=314 FU=mean 661 days	algorithm was strongly associated with a reduction in inappropriate shocks with the S-ICD system and did not result in prolongation of detection times or increased syncope. These data support the use of dual zone programming as a standard setting for S-ICD patients.	from the S-ICD IDE Study. These patients are already included in Table 2.
Griksaitis Michael J, Rosengarten James A, Gnanapragasam James P et al. (2013) Implantable cardioverter defibrillator therapy in paediatric practice: a single-centre UK experience with focus on subcutaneous defibrillation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 15(4), 523-30	Case series n=23 (only 3 S-ICD implantations) FU= max 1.33 years	Innovative shock delivery systems can be used in children needing an ICD. The insertion technique and device used need to accommodate the age and weight of the child, and concomitant need for pacing therapy. We have demonstrated effective defibrillation with shocks delivered via configurations employing subcutaneous coils in children.	Larger studies or studies with longer follow-up are already included in table 2.
Hai Jo Jo, Lim Eric Tien-Siang, Chan Chin-Pang et al. (2015) First clinical experience of the safety and feasibility of total subcutaneous implantable defibrillator in an Asian population. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and and cardiac cellular electrophysiology of the European Society of Cardiology 17 Suppl 2, ii63-8	Retrospective case series n=21 FU= mean 107 days	S-ICD is a feasible treatment for ventricular tachyarrhythmias among an Asian population with smaller body-build. There was nonetheless a relatively high rate of wound complications.	Larger studies or studies with longer follow-up are already included in table 2.
Jarman Julian W. E, and Todd Derick M (2013) United Kingdom national experience of entirely subcutaneous implantable cardioverter-defibrillator technology: important lessons to learn. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and and cardiac cellular electrophysiology of the European Society of Cardiology 15(8), 1158-65	Retrospective case series n=111 FU=mean 13 months	The S-ICD is an important innovation in ICD technology. However, these data indicate that adverse event rates are significant during early clinical adoption. Important lessons in patient selection, implant technique, and device programming can be learnt from this experience.	Larger studies or studies with longer follow-up are already included in table 2.
Jarman JW, Lascelles K, Wong T et al. (2012) Clinical experience of entirely subcutaneous implantable	Non-randomised	The S-ICD is an important new option for some patients. However, these data give cause for caution in light of the limited	Larger studies or studies with longer follow-up are already

cardioverter-defibrillators in children and adults: cause for caution. European Heart Journal 33: 1351–1359.	comparative study n= 16 subcutaneous ICD vs 16 TV-ICD FU=median 9.5 months	published data regarding clinical sensing capabilities, particularly among younger patients.	included in table 2. This study was included in the original overview.
Knops R E, Brouwer T F, Barr C S et al. (2016) The learning curve associated with the introduction of the subcutaneous implantable defibrillator. Europace 18, 1010-1015	Retrospective pooled cohort of patients from the IDE study and the Effortless registry n=882 FU=6 months	There is a short and significant learning curve associated with physicians adopting the S-ICD. Performance stabilizes after 13 implants.	Retrospective analysis of patients included in the S-ICD IDE Study and EFFORTLESS registry. These patients are already included in Table 2.
Knops Reinoud E, Olde Nordkamp Louise R A, de Groot Joris R et al. (2013) Two-incision technique for implantation of the subcutaneous implantable cardioverter-defibrillator. Heart rhythm : the official journal of the Heart Rhythm Society 10(8), 1240-3	Prospective case series n=39 FU= mean 18 months	The two-incision technique is a safe and efficacious alternative for S-ICD implantations and may help to reduce complications. The two-incision technique offers physicians a less invasive and simplified implantation procedure of the S-ICD.	Larger studies or studies with longer follow-up are already included in table 2.
Kobe J, Hucklenbroich K, Geisendorfer N et al. (2017) Posttraumatic stress and quality of life with the totally subcutaneous compared to conventional cardioverter-defibrillator systems. Clinical Research in Cardiology 106, 317-321	Matched-controlled study n= 84 (42 consecutive S-ICD versus 42 TV-ICD matched patients) FU not reported	PDS revealed a PTSD in n = 6 tv-ICD and n = 6 S-ICD patients (14.3%) equally. In the PHQ-D questionnaire, n = 4 tv-ICD and n = 2 S-ICD patients fulfilled criteria for a major depression (p = 0.68). Panic disorders (n = 2 tv, n = 0 S-ICD, p = 0.5), and anxiety disorders (n = 3 S-ICD, n = 0 tv-ICD, p = 0.24) did not differ between groups. The physical well-being score was 39.9 +/- 12.5 in patients with a tv-ICD compared to 46.6 +/- 9.9 in S-ICD (p = 0.01). The mental well-being score was comparable in both groups (tv-ICD 51.8 +/- 10.8 vs. S-ICD 51.9 +/- 10.4, p = 0.95).	Larger studies or studies with longer follow-up are already included in table 2.
Koman Eduard, Gupta Ashwani, Subzposh Faiz et al. (2016) Outcomes of subcutaneous implantable cardioverter-defibrillator implantation in patients on hemodialysis. Journal of interventional cardiac electrophysiology : an international journal of	Retrospective comparative case series n=86 (18 hemodialysis versus 68 non-hemodialysis)	Despite representing a sicker patient population, HD patients implanted with S-ICD had similar procedural outcomes and inappropriate shocks. There was no device or blood stream-related infection in HD patients. All appropriate shocks for ventricular	Larger studies or studies with longer follow-up are already included in table 2.

arrhythmias and pacing 45(2), 219-23	FU= mean 205 days for hemodialysis and mean 242 days for non-hemodialysis	arrhythmias in HD patients were successful.	
Kooiman Kirsten M, Knops Reinoud E, Olde Nordkamp, Louise et al.(2014) Inappropriate subcutaneous implantable cardioverter-defibrillator shocks due to T-wave oversensing can be prevented: implications for management. Heart rhythm : the official journal of the Heart Rhythm Society 11(3), 426-34	Retrospective case series n=69 FU=mean 14 months	Inappropriate shocks (IASs) due to T-wave oversensing (TWOS) in the S-ICD can be managed by reprogramming the sensing vector and/or the therapy zones of the device using a template acquired during exercise. Exercise-optimized programming can reduce future IASs, and standard exercise testing shortly after the implantation of an S-ICD may be considered in patients at an increased risk for TWOS.	Larger studies or studies with longer follow-up are already included in table 2.
Lambiase Pier D, Gold Michael R, Hood Margaret et al. (2016) Evaluation of subcutaneous ICD early performance in hypertrophic cardiomyopathy from the pooled EFFORTLESS and IDE cohorts. Heart rhythm : the official journal of the Heart Rhythm Society 13(5), 1066-74	Retrospective comparative study n=872 (99 hypertrophic cardiomyopathy versus 773 non-hypertrophic cardiomyopathy) FU=median 637 days	These initial data indicate the S-ICD is safe and effective in patients with hypertrophic cardiomyopathy who are at high risk of ventricular arrhythmias and pass preimplantation electrocardiogram screening. Inappropriate shocks were mainly due to T-wave oversensing, but there were no lead complications needing re-intervention.	The patient population is from the S-ICD IDE Study and the EFFORTLESS Registry. These patients are already included in Table 2.
Maurizi N, Tanini I, Olivotto I et al. (2017) Effectiveness of subcutaneous implantable cardioverter-defibrillator testing in patients with hypertrophic cardiomyopathy. International Journal of Cardiology 231, 115-119	Prospective case series n=55 No follow-up	Acute DT at 65 J at the implant showed the effectiveness of S-ICD in the recognition and termination of VT/VF in all HCM patients except one. Extreme LVH did not affect the performance of the device, whereas severe obesity was likely responsible for the single 65 J failure.	Larger studies or studies with longer follow-up are already included in table 2.
Mesquita J, Cavaco D, Ferreira A et al. (2017) Effectiveness of subcutaneous implantable cardioverter-defibrillators and determinants of inappropriate shock delivery. International Journal of Cardiology 232, 176-180	Prospective case series n=54 FU=mean 2.6 years	In this selected population of patients, the S-ICDs proved effective in preventing sudden cardiac death. Tiered-therapy was independently associated with a lower rate of inappropriate shock delivery.	Larger studies or studies with longer follow-up are already included in table 2.
Migliore F, Allocca G, Calzolari V et al. (2017) Intermuscular Two-Incision Technique for Subcutaneous Implantable Cardioverter Defibrillator Implantation: Results from a Multicenter Registry. PACE -	Case series n=36 FU=10 months	Our experience suggests that the two-incision intermuscular technique is a safe and efficacious alternative to the current technique for S-ICD implantation that may help reducing complications including	Larger studies or studies with longer follow-up are already included in table 2.

Pacing and Clinical Electrophysiology 40, 278-285		inappropriate interventions and offer a better cosmetic outcome, especially in thin individuals.	
Moore J P, Modeser B, Lloyd M S et al. (2016) Clinical experience with the subcutaneous implantable cardioverter-defibrillator in adults with congenital heart disease. Circulation: Arrhythmia and Electrophysiology 2016;9:e004338	Retrospective case series n=21 FU=median 14 months	Ventricular arrhythmia was induced in 81% (17/21) of patients and was converted in all. There was 1 complication related to infection, not needing device removal. Over the follow-up, 21% (4/21) of patients received inappropriate shocks and 1 received appropriate shock. There was 1 arrhythmic death related to asystole in a single ventricle patient.	Larger studies or studies with longer follow-up are already included in table 2.
Olde Nordkamp Louise R A, Brouwer Tom F, Barr Craig et al. (2015) Inappropriate shocks in the subcutaneous ICD: Incidence, predictors and management. International journal of cardiology 195, 126-33	Case series n=581 FU=mean 21 months	Inappropriate shocks, mainly due to cardiac oversensing, occurred in 8% of the S-ICD patients. Patients with hypertrophic cardiomyopathy or a history of atrial fibrillation were at increased risk, warranting specific attention for sensing and programming in this population.	The patient population is from the S-ICD IDE Study. These patients are already included in Table 2.
Olde Nordkamp, L. R, Dabiri, Abkenari L et al. (2012) The entirely subcutaneous implantable cardioverter-defibrillator: initial clinical experience in a large dutch cohort. Journal of the American College of Cardiology 60 (19): 1933-1939.	Retrospective case series n=118 FU= mean 18 months	8 patients experienced 45 successful appropriate shocks (98% first shock conversion efficacy). No sudden deaths occurred. Fifteen patients (13%) received inappropriate shocks, mainly due to T-wave oversensing, which was mostly solved by a software upgrade and changing the sensing vector of the S-ICD. Sixteen patients (14%) experienced complications. Adverse events were more frequent in the first 15 implantations per centre compared with subsequent implantations.	Larger studies or studies with longer follow-up are already included in table 2. This study was included in the previous overview.
Pettit Stephen J, McLean Andrew, Colquhoun Ian et al. (2013) Clinical experience of subcutaneous and transvenous implantable cardioverter defibrillators in children and teenagers. Pacing and clinical electrophysiology : PACE 36(12), 1532-8	Comparative study n=15 (9 S-ICD versus 8 transvenous-ICD) FU=median 20 months for S-ICD, 36 months for transvenous-ICD.	In real-world use in children and teenagers, S-ICD may offer similar survival benefit to transvenous ICD, with a lower incidence of complications needing reoperation. In the absence of randomised trials, S-ICD should be compared prospectively with transvenous ICD in large multicenter registries with comparable periods of follow-up.	Larger studies or studies with longer follow-up are already included in table 2.
Weinstock Jonathan, Bader Yousef H, Maron Martin S et al. (2016) Subcutaneous Implantable Cardioverter	Case series n=23	In a high-risk Hypertrophic Cardiomyopathy cohort without a pacing indication referred for consideration of an ICD, the	Larger studies or studies with longer follow-up are already

Defibrillator in Patients With Hypertrophic Cardiomyopathy: An Initial Experience. Journal of the American Heart Association 5(2),	FU=median 17.5 months	majority were eligible for S-ICD. The S-ICD is effective at recognizing and terminating VF at implant with a wide safety margin.	included in table 2.
Winter J, Siekiera M, Shin D I et al. (2016) Intermuscular technique for implantation of the subcutaneous implantable cardioverter defibrillator: long-term performance and complications. Europace	Case series n=82 FU=mean 3.6 years	Our intermuscular technique and implant methodology is successful for placement of the subcutaneous defibrillator pulse generator. Our technique leads to an excellent cosmetic result and high levels of patient satisfaction. Rates of first shock conversion during defibrillation testing, inappropriate shocks, and complications during follow-up compare favourably with previous published case series. There were no left arm movement limitations post-operatively.	Larger studies or studies with longer follow-up are already included in table 2.

Appendix B: Related NICE guidance for subcutaneous implantable cardioverter defibrillator insertion for preventing sudden cardiac death

Guidance	Recommendations
Interventional procedures	**Insertion of a subcutaneous implantable cardioverter defibrillator for prevention of sudden cardiac death. NICE interventional procedure guidance 454 (2013) [Current guidance]** 1.1 Current evidence on the efficacy of the insertion of a subcutaneous implantable cardioverter defibrillator (ICD) for the prevention of sudden cardiac death in the short and medium term is adequate. Evidence on its safety in the short term is adequate but there are uncertainties about long-term durability. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to insert a subcutaneous ICD for the prevention of sudden cardiac death should take the following actions: • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for the public is recommended. 1.3 Patient selection and treatment should only be done by teams with extensive experience in the insertion of ICDs. 1.4 Clinicians should enter details about all patients undergoing insertion of a subcutaneous ICD for the prevention of sudden cardiac death onto the Central Cardiac Audit Database. Audit should be carried out locally and should include clinical outcomes and their relationship to patient characteristics. 1.5 NICE encourages further data collection, particularly on the efficacy of the procedure for converting spontaneous arrhythmias, on the durability of the devices used and on the need for procedures to revise or replace defibrillators.
Technology appraisals	**Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure. NICE technology appraisal 314 (2014).**

	1.1 Implantable cardioverter defibrillators (ICDs) are recommended as options for:
	• treating people with previous serious ventricular arrhythmia, that is, people who, without a treatable cause:
	  ○ have survived a cardiac arrest caused by either ventricular tachycardia (VT) or ventricular fibrillation **or**
	  ○ have spontaneous sustained VT causing syncope or significant haemodynamic compromise **or**
	  ○ have sustained VT without syncope or cardiac arrest, and also have an associated reduction in left ventricular ejection fraction (LVEF) of 35% or less but their symptoms are no worse than class III of the New York Heart Association (NYHA) functional classification of heart failure.
	• treating people who:
	  ○ have a familial cardiac condition with a high risk of sudden death, such as long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or arrhythmogenic right ventricular dysplasia **or**
	  ○ have undergone surgical repair of congenital heart disease.
	1.2 Implantable cardioverter defibrillators (ICDs), cardiac resynchronisation therapy (CRT) with defibrillator (CRT-D) or CRT with pacing (CRT-P) are recommended as treatment options for people with heart failure who have left ventricular dysfunction with a left ventricular ejection fraction (LVEF) of 35% or less as specified in table 1.
	Table 1 Treatment options with ICD or CRT for people with heart failure who have left ventricular dysfunction with an

LVEF of 35% or less (according to NYHA class, QRS duration and presence of LBBB)

	NYHA class			
QRS interval	**I**	**II**	**III**	**IV**
<120 milliseconds	**ICD if there is a high risk of sudden cardiac death**			**ICD and CRT not clinically indicated**
120–149 milliseconds without LBBB	ICD	ICD	ICD	CRT-P
120–149 milliseconds with LBBB	ICD	CRT-D	CRT-P or CRT-D	CRT-P
≥150 milliseconds with or without LBBB	CRT-D	CRT-D	CRT-P or CRT-D	CRT-P

LBBB, left bundle branch block; NYHA, New York Heart Association

Appendix C: Literature search for subcutaneous implantable cardioverter defibrillator insertion for preventing sudden cardiac death

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	08/06/2017	Issue 6 of 12, June 2017
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	08/06/2017	Issue 5 of 12, May 2017
HTA database (Cochrane Library)	08/06/2017	Issue 4 of 4, October 2016
MEDLINE (Ovid)	08/06/2017	1946 to June Week 1 2017
MEDLINE In-Process (Ovid)	08/06/2017	June 07, 2017
EMBASE (Ovid)	08/06/2017	1974 to 2017 Week 23
PubMed	08/06/2017	n/a
JournalTOCS	08/06/2017	n/a

Trial sources searched on 18/09/2016

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched on 18/09/2016 and 01/09/2016

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 death, sudden, cardiac/

2 (sudden* adj4 cardi* adj4 (death* or arrest*)).ti,ab.

3 commotio cordis/

4 "commotio cordis".ti,ab.

5 Tachycardia/

6 exp Tachycardia, Ventricular/

7 tachycard*.tw.

8 tachyarrhy*.tw.

9 (heart adj4 hyperfunction).tw.

10 Heart Diseases/

11 (disease* adj4 (heart or cardiac)).tw.

12 exp Arrhythmias, Cardiac/

13 (arrhythmia* or arrythmia*).tw.

14 (dysrhythmia* adj4 cardia*).tw.

15 ((rapid* or fast* or quick* or irregular* or abnormal or ectopic) adj4 (heartbeat* or heart beat* or heart-beat* or heart rhythm* or heart-rhyth* or heart rate* or heart-rate* or heartrate* or cardia*)).tw.

16 (aberrant adj4 conduction*).tw.

17 heart rhythm disorder.tw.

18 Ventricular Flutter/

19 (ventricul* adj4 (flutt* or fibrillation*)).tw.

20 Ventricular Fibrillation/

21 exp Cardiomyopathy, Hypertrophic/

22 (hypertroph* adj4 cardiomyopath*).tw.

23 (asymmetric adj4 septal adj4 hypertroph*).tw.

24 (idiopathic adj4 hypertroph* adj4 subaortic adj4 stenos*).tw.

25 ihss.tw.

26 hocm.tw.

27 (idiopathic adj4 hypertroph* adj4 subvalvular adj4 stenos*).tw.

28 or/1-27

29 electrodes, implanted/

30 (electrode* adj4 implant*).ti,ab.

31 Defibrillators, Implantable/

32 ((internal or implant*) adj6 (cardioverter* or cardio-verter* or defibrillator*)).tw.

33 ICD*.tw.

34 Electric Countershock/

35 (electric* adj4 (countershock* or defibrillat*)).tw.

36 (electroversion* adj4 (therap* or cardiac)).tw.

37 cardioversion*.tw.

38 or/29-37

39 S-ICD.tw.

40 Cameron Health.tw.

41 SQ-RX Pulse Generator.tw.

42 Q-TRAK Subcutaneous Electrode.tw.

43 Q-GUIDE Electrode Insertion Tool*.tw.

44 Q-TECH Programmer.tw.

45 or/39-44

46 subcutaneous.tw.

47 non-transvenous.tw.

48 (non adj1 transvenous).tw.

49 or/46-48

50 45 or 49

51 28 and 38 and 50

52 animals/ not humans/

53 51 not 52

54 limit 53 to ed=20121123-20160831

55 (201608* or 201609* or 20161* or 2017*).ed.

56 53 and 55