Subcutaneous implantable cardioverter defibrillator (ICD)

Systematic Review
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Systematic Review
This report should be referenced as follows:

Conflict of interest
All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

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The external reviewers did not co-author the scientific report and do not necessarily all agree with its content. Only the LBI-HTA is responsible for errors or omissions that could persist. The final version and the policy recommendations are under the full responsibility of the LBI-HTA.

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.
Content

Executive Summary ................................................................. 5
Zusammenfassung ................................................................. 9
1 Scope .................................................................................. 13
  1.1 PICO question ............................................................... 13
  1.2 Inclusion criteria .......................................................... 13
2 Methods ............................................................................ 15
  2.1 Research questions ...................................................... 15
  2.2 Sources ......................................................................... 16
  2.3 Systematic literature search ........................................ 16
  2.4 Flow chart of study selection ......................................... 17
  2.5 Analysis ......................................................................... 18
  2.6 Synthesis ....................................................................... 18
3 Description and technical characteristics of technology ......... 19
4 Health Problem and Current Use .......................................... 21
5 Clinical effectiveness .......................................................... 25
  5.1 Outcomes ...................................................................... 25
  5.2 Included studies ........................................................... 25
  5.3 Results .......................................................................... 26
6 Safety ................................................................................ 29
  6.1 Outcomes ...................................................................... 29
  6.2 Included Studies ........................................................... 29
  6.3 Results .......................................................................... 29
7 Quality of evidence ............................................................ 33
8 Discussion .......................................................................... 35
9 Recommendation ............................................................... 37
10 References ......................................................................... 39

Appendix ................................................................................ 43
  Evidence tables of individual studies included for clinical effectiveness and safety ............. 43
  Risk of bias tables and GRADE evidence profile ................................................................. 50
  Applicability table .................................................................................................................. 54
  List of ongoing randomised controlled trials ................................................................. 54
  Literature search strategies .................................................................................................. 55
    Search strategy for Pubmed ................................................................................................. 55
    Search strategy for Embase.com (Elsevier) ................................................................. 55
    Search strategy for Cochrane Library (Wiley) .............................................................. 56
    Search strategy for CRD Databases ............................................................................... 56

List of Figures

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram) ................................................. 17
List of tables

Table 1-1: Inclusion criteria ............................................................................................................................................ 13
Table 7-1: Summary of findings table of subcutaneous ICD compared with transvenous ICD in patients at high risk of sudden cardiac death ........................................................................................ 34
Table 9-1: Evidence based recommendations .................................................................................................................. 37
Table A-1: Subcutaneous versus transvenous ICD: Results from observational studies ......................................... 43
Table A-2: Risk of bias – study level (observational studies) ......................................................................................... 50
Table A-3: Risk of bias – study level (systematic review) ............................................................................................... 51
Table A-4: Evidence profile: comparative effectiveness and safety of the subcutaneous and transvenous ICD in patients at increased risk for sudden cardiac death ........................................ 52
Table A-5: Summary table characterising the applicability of a body of studies ...................................................... 54
Table A-6: List of ongoing randomised controlled trials of subcutaneous ICD ....................................................... 54

List of abbreviations

ACC ....................... American College of Cardiology
AHA ...................... American Heart Association
AMSTAR .............. A MeaSurement Tool to Assess systematic Reviews
ATP ....................... Antitachcardia pacing
ATLAS .................. Avoid Transvenous Leads in Appropriate Subjects
CI ........................... Confidence interval
CRD ...................... Centre for reviews and dissemination
CRT ....................... Cardiac Resynchronization Therapy
ESC ....................... European Society of Cardiology
ECG ....................... Electrocardiogram
EKG ....................... Elektrokardiogramm
GRADE ................. Grading of Recommendations Assessment, Development and Evaluation
HRT ...................... Heart Rhythm Society
HR .......................... Hazard ratio
ICD-10-CM .......... The International Classification of Diseases, Tenth Revision, Clinical Modification
ICD ....................... Implantable Cardioverter-Defibrillator
KI ........................... Konfidenzintervall
LVEF ....................... Left ventricular ejection fraction
MeSH ..................... Medical Subject Headings
MD ......................... Mean difference/mittlere Differenz
NCDR .................... National Cardiovascular Data Registry
NCT ....................... National Clinical Trials
NICE ..................... National Institute for Health and Care Excellence
OR ......................... Odds ratio
PRISMA ................ Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRAETORIAN .... Prospective, RAndomizEd comparison of subcutaneous and tRansvenous ImplANtable cardioverter-defibrillator therapy
QoL ........................ Quality of life
RR .......................... Risk ratio
RCT ........................ Randomized controlled trial
S-ICD .................... Subcutaneous Implantable Cardioverter-Defibrillator
SF-12 ...................... Short Form Survey
SCD ........................ Sudden Cardiac Death
TV .......................... Transvenous
VF .......................... Ventricular fibrillation
VT .......................... Ventricular tachycardia
Executive Summary

Introduction

Health Problem
Cardiovascular disease is a major public health issue accounting for almost 17 million deaths per year globally. According to estimates, 40-50% of them are sudden cardiac deaths. Approximately 6 million sudden cardiac deaths are caused by ventricular tachyarrhythmias [1]. Several underlying acquired or congenital cardiac conditions are associated with an increased risk of ventricular arrhythmias.

Description of Technology
The implantable cardioverter-defibrillator (ICD) device detects and terminates these life-threatening ventricular tachyarrhythmias. Based on evidence from several trials, clinical practice guidelines of cardiological societies recommend the ICD in patients at high risk of developing ventricular tachyarrhythmia (primary prevention), or in patients who have experienced a prior episode of life-threatening ventricular tachyarrhythmias (secondary prevention).

Recently, the subcutaneous implantable ICD emerged as a promising alternative to the established transvenous ICD to overcome short- and long-term complications associated with the implantation of transvenous leads and direct contact with the heart. Specifically, such complications are pneumothorax, cardiac perforation, lead fracture, lead-dysfunction, infections (e.g. lead endocarditis) and venous thrombosis. The subcutaneous ICD leaves the heart and vascular system untouched. It is important to note, however, that the subcutaneous ICD is restricted to patient populations who are not dependent on pacing therapy for bradycardia, anti-tachycardia (ATP), or resynchronization (CRT).

Based on NICE (National Institute for Health and Care Excellence) guidance document, the current evidence on the efficacy and safety of subcutaneous ICD for preventing sudden cardiac death is adequate to support the use of this procedure [2].

Methods
We conducted a systematic literature review to evaluate the effectiveness and safety of the subcutaneous ICD compared to the conventional transvenous ICD in patients at an increased risk for sudden cardiac death due to an underlying acquired or congenital cardiac condition.

We searched four electronic databases: (Medline, Embase, Cochrane Library, CRD [Centre for reviews and dissemination]-Database).

In addition, we searched clinical trial registries and obtained relevant literature from the manufacturer. Two authors independently conducted study selection, data extraction, risk of bias assessment and rating of the quality of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.
We synthesized evidence from identified individual studies narratively. In addition, we presented results from a random-effects meta-analysis from one systematic review [3]. Therefore, we did not perform any new meta-analysis.

Results

Available evidence

We found seven observational studies (6,916 patients) comparing the subcutaneous ICD with the conventional transvenous ICD [4-10], with the largest study including 5,760 patients [10]. In addition, we identified one systematic review and meta-analysis [3] including results from five of the aforementioned observational studies (6,498 patients) [4, 6, 7, 9, 10].

Two reviewers assessed the risk of bias of the included observational studies with the Newcastle-Ottawa Scale [11]. They rated the risk of bias as high for three studies [4, 6, 8] and medium for four studies [5, 7, 9, 10]. The systematic review was medium risk of bias based on our assessment with the AMSTAR (A MeaSurement Tool to Assess Systematic Reviews)-2 checklist [12].

In four studies, the control group was selected by propensity score matching [5, 7, 9, 10] in order to obtain similar groups. Three studies compared subcutaneous ICD only with a single-chamber transvenous ICD [4, 6, 8]. In four studies, patients in the control group received either single- or dual-chamber ICDs [5, 7, 9, 10].

Clinical effectiveness

Three studies with 6,222 patients reported on mortality [4, 7, 10]. The difference between patients receiving subcutaneous ICDs or transvenous ICDs was not statistically significant regarding overall mortality in-hospital (1 study, 5,760 patients, relative risk [RR] 2.0, 95% Confidence interval [CI]: 0.4-9.9) [10], mortality 6 months (1 study, 182 patients; RR 1.0; 95% CI: 0.14-6.95) [4] and mortality up to 5 years (1 study, 280 patients, 5-yearsurvival 96.0% vs. 94.8%, p = 0.42) [7].

Between patients receiving subcutaneous ICDs and transvenous ICDs, no statistical significant differences were observed regarding appropriate shocks during mean follow-up of 7.1 months (1 study, 138 patients, RR 0.33, 95% CI: 0.09-1.18) [6], 2.6 years (1 study, 138 patients, RR 0.60, 95% CI: 0.15-2.14) [9] and 5 years (1 study, 280 patients, hazard ratio [HR] 0.68, p = 0.36) [7].

Two studies with 418 patients found no statistically significant difference for mental quality of life assessed with 12-item Short-Form Health Survey (SF-12) after subcutaneous and transvenous ICD implantation [5, 8]. One study with 84 patients [8] observed statistically significantly higher physical quality of life in patients with subcutaneous ICDs (mean difference [MD] 6.7, 95% CI: 1.88-11.52) but another study with 334 patients [5] did not (MD -0.2, 95% CI: -2.67-2.27).

The quality of evidence is very low for all effectiveness outcomes.
Safety

For inappropriate shocks (4 studies, 738 patients, Odds ratio [OR] 0.87, 95% CI: 0.51-1.49) [3], infections (5 studies, 6,498 patients, OR 0.75, 95% CI: 0.30-1.89) [3] and haematomas (3 studies, 6,080 patients, RR ranged from 3.00 to 3.5) [4, 6, 10] no statistically significant differences were observed in patients with subcutaneous ICD compared to patients with transvenous ICD.

However, random-effects meta-analyses showed statistically significant fewer lead-complications in patients with subcutaneous ICD compared to patients with transvenous ICD (4 studies, 6,316 patients, OR 0.13, 95% CI: 0.05-0.38) [3].

The quality of evidence for safety outcomes is very low.

Upcoming evidence

Our searches yielded the study protocol of an investigator-initiated, multicenter, randomized controlled PRAETORIAN (Prospective, RAndomizEd comparison of subcutaneous and tRansvenous ImplANtable cardioverter-defibrillator therapy) trial [13]. The planned sample size of this study is 850 patients with an indication for ICD therapy and without an indication for pacing, randomized to either the subcutaneous or transvenous ICD (1:1) [14]. This study is powered to claim non-inferiority and/or superiority of the subcutaneous ICD regarding a composite primary endpoint of inappropriate shocks and ICD-related complications (within 48 months). According to the ClinicalTrials.gov (NCT01296022) entry, the estimated completion date is December 2019 [14]. Thus, no results are available yet.

Discussion

The comparative evidence for the subcutaneous and transvenous ICD is limited to controlled observational studies with or without propensity-score matching and a systematic review with meta-analyses summarizing some of these studies. Based on this evidence, no statistically significant differences were observed in terms of overall mortality, rate of adequate and inadequate shocks, infections, and haematomas. Lead complications were statistically significantly less frequent in patients with subcutaneous ICDs compared to those with transvenous ICDs. It has to be considered that the subcutaneous ICD has no contact with vascular and cardiac structures. The quality of evidence is very low for all outcomes.

The available body of evidence has several limitations.

First, the follow-up periods varied considerably among the individual studies, ranging from a few days (duration of the hospital stay) to five years after ICD implantation. Therefore, most of the studies did not reflect long-term complications. Due to the variability of follow-up periods, pooled results from random-effects meta-analysis are limited.

Second, in several studies, despite matching, there were still differences of baseline characteristics between patients who received subcutaneous ICDs and patients who received conventional transvenous ICDs. In addition, not all studies clearly stated that they excluded patients with indications for pacemakers, anti-tachycardia pacing, or cardiac resynchronization therapy from the control group with transvenous ICDs. Therefore, unevenly distributed prognostic factors could have influenced the outcomes.
Third, for most effectiveness and safety endpoints, only few events occurred, limiting precision of the findings. The PRAETORIAN study, an adequately powered randomized controlled trial (RCT), will provide more reliable information of the comparative effectiveness and harms of subcutaneous and transvenous ICDs.

**Conclusion**

Results from seven observational studies and one systematic review are insufficient to conclude about the comparative effectiveness of subcutaneous and transvenous ICDs. These studies, however, indicate a substantially lower risk for lead complications in patients treated with subcutaneous ICD.
Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Herz-Kreislauferkrankungen sind ein großes Public Health Problem – sie verursachen weltweit jährlich annähernd 17 Millionen Todesfälle. Schätzungen zufolge gelten 40-50 % dieser Todesfälle als plötzlicher Herztod [1]. Ungefähr 80 % davon, also ca. 6 Millionen Todesfälle durch plötzlichen Herztod, sind auf eine ventrikuläre Tachyarrhythmie zurückzuführen. Verschiedenste zugrundeliegende angeborene oder erworbene Herzerkrankungen sind mit einem erhöhten Risiko für das Auftreten von ventrikulären Tachyarrhythmien assoziiert.

Beschreibung der Technologie

Der implantierbare Cardioverter-Defibrillator (ICD) erkennt und unterbricht diese lebensbedrohlichen Herzrhythmusstörungen. Basierend auf den Ergebnissen zahlreicher Studien empfehlen kardiologische Fachgesellschaften dem ICD bei PatientInnen mit erhöhtem Risiko für ventrikuläre Arrhythmien (primäre Prophylaxe) oder bei PatientInnen, die bereits eine Episode einer lebensbedrohlichen ventrikulären Tachyarrhythmie hatten (sekundäre Prophylaxe).


Laut einem NICE (National Institute for Health and Care Excellence) Dokument stützt die derzeitige Evidenz zur Wirksamkeit und Sicherheit die Verwendung des subkutanen ICD zur Prävention des plötzlichen Herztodes [2].

Methoden

Wir führten eine systematische Literatursicht durch. Ziel war es, die Wirksamkeit und Sicherheit des subkutanen ICD zur Verhinderung des plötzlichen Herztodes mit der Wirksamkeit und Sicherheit des herkömmlichen transvenösen ICD zu vergleichen.

Wir führten zur Beantwortung der Forschungsfrage eine systematische Literatursuche in vier Datenbanken durch (Medline, Embase, Cochrane Library, CRD [Centre for reviews and dissemination]-Database). Ergänzend durchsuchten wir Studienregister und sendeten eine Anfrage an den Hersteller mit der Bitte um Zusendung relevanter Literatur.

plötzlicher Herztod: Public Health Problem
häufigste Ursache: ventrikuläre Tachyarrhythmie aufgrund angeborener oder erworberer Herzerkrankungen
Implantierbarer Kardioverter-Defibrillator (ICD): etablierter konventioneller ICD mit transvenös Sonden
relativ neu: ICD mit subkutaner Sonde
Voraussetzung: keine Indikation für Herzschrittmacher, antitachykarder Stimulation oder kardiale Resynchronisation
NICE Guidance Dokument: derzeitige Evidenz zeigt Wirksamkeit und Sicherheit
Forschungsfrage: Vergleich der Wirksamkeit und Sicherheit subkutaner ICD vs. transvenöser ICD systematische Literatursuche in 4 Datenbanken
Zwei AutorenInnen führten unabhängig voneinander die Studienauswahl, die Datenextraktion, die Bewertung der methodischen Qualität der Studien (Bias-Risiko) sowie der Qualität der Evidenz mit GRADE (Grading of Recommendations Assessment, Development and Evaluation) durch.


**Ergebnisse**

**Verfügbare Evidenz**

Wir fanden sieben Beobachtungsstudien mit 6.916 PatientInnen, die subkutane ICD mit herkömmlichen transvenösen ICD verglichen [4-10], wobei die größte Studie 5.760 PatientInnen umfasste [10]. Weiters haben wir einen systematischen Review mit Meta-Analysen identifiziert [3].


In vier Studien [5, 7, 9, 10] wurde die Kontrollgruppe mittels Propensity Score ausgewählt, um Gruppen zu erhalten, die ein ähnliches Risiko aufwiesen, an einem plötzlichen Herztod zu versterben. Drei Studien verglichen den subkutanen ICD mit einem transvenösen Einkammer-ICD [4, 6, 8]. In vier weiteren Studien erhielten die PatientInnen der Kontrollgruppe sowohl Ein- als auch Zweikammer-ICDs [5, 7, 9, 10].

**Klinische Wirksamkeit**

Drei Studien mit 6.222 PatientInnen berichten über Mortalität [4, 7, 10]. Der Unterschied zwischen PatientInnen, die einen subkutanen ICD oder einen transvenösen ICD bekamen hatten, war in Hinblick auf die Mortalität im Krankenhaus (1 Studie, 5.760 PatientInnen, Relatives Risiko [RR] 2,0, 95 % Konfidenzintervall [KI]: 0,4-9,9) [10], Mortalität nach 6 Monaten (1 Studie, 182 PatientInnen, RR 1,0, 95 % KI: 0,14-6,95) [4] und Mortalität bis 5 Jahre (1 Studie, 280 PatientInnen, 5-Jahres-Überleben: 96 % vs. 94,8 %, p = 0,42) statistisch nicht signifikant [7].

Der Unterschied bei adäquaten Schocks zwischen PatientInnen, die einen subkutanen ICD und PatientInnen, die einen transvenösen ICD erhielten, war bei einer mittleren Beobachtungszeit von 7.1 Monaten (1 Studie, 138 PatientInnen, RR 0,33, 95 % KI: 0,09-1,18) [6], 2,6 Jahren (1 Studie, 138 PatientInnen, RR 0,60, 95 % KI: 1,15-2,14) [9] sowie 5 Jahren (1 Studie, 280 PatientInnen, Hazard Ratio [HR] 0,68, p = 0,36) [7] statistisch nicht signifikant.

Die mentale Lebensqualität, die mittels 12-item Short-Form Health Survey (SF-12) erhoben wurde, war in zwei Studien mit 418 PatientInnen nicht statistisch signifikant unterschiedlich [5, 8]. Bei der physischen Lebensqualität zeigte eine Studie mit 84 PatientInnen [8] einen statistisch signifikant höheren Score bei PatientInnen mit subkutanem ICD (mittlere Differenz [MD] 6,7, 95 % KI: 1,88-11,52), eine andere Studie mit 334 PatientInnen [5] jedoch nicht (MD -0,2, 95 % CI: -2,67-2,27).
Zusammenfassung

Die Qualität der Evidenz für die oben genannten Endpunkte ist sehr niedrig.

Sicherheit

Inadäquate Schocks (4 Studien, 738 PatientInnen, Odds Ratio [OR] 0,87, 95 % KI: 0,51-1,49) [3], Infektionen (5 Studien [3], 6.489 PatientInnen, OR 0,75, 95 % KI: 0,30-1,89) und Hämatome (3 Studien, 6.080 PatientInnen, RR von 3,00 bis 3,5) [4, 6, 10] waren nicht statistisch signifikant unterschiedlich bei PatientInnen mit subkutanen im Vergleich zu PatientInnen mit transvenösen ICD.

Jedoch ergab eine Meta-Analyse statistisch signifikant weniger Sondenkomplikationen mit dem subkutanen ICD als mit dem transvenösen ICD (4 Studien, 6.316 PatientInnen, OR 0,13, 95 % KI: 0,05-0,38) [3].

Die Qualität der Evidenz ist sehr niedrig für alle Sicherheits-Endpunkte.

Laufende Studien


Diskussion


Die verfügbare Evidenz hat einige Einschränkungen.

Trotz Matching zeigten sich in einigen Studien teilweise bei den Baseline-Charakteristika Unterschiede zwischen PatientInnen, die einen subkutanen ICD erhielten und PatientInnen, bei denen ein herkömmlicher transvenöser ICD implantiert wurde. Hervorzuheben ist weiteres, dass nicht alle Studien PatientInnen in der Kontrollgruppe mit transvenösem ICD mit Indikation für Herzschrittmacher, antitachykardie Stimulation oder kardialer Resynchronisations-Therapie ausschlossen. Deshalb könnten ungleichmäßig verteilte prognostische Faktoren die Ergebnisse beeinflusst haben.

Beim Großteil der Endpunkte für Wirksamkeit und Sicherheit traten nur wenige Ereignisse auf, was die Präzision der Ergebnisse einschränkt.

Die derzeit laufende randomisierte kontrollierte PRAETORIAN-Studie mit adäquater Power könnte verlässlichere Ergebnisse zum Vergleich des subkutanen ICD mit dem transvenösen ICD liefern.

Empfehlung

Die vorliegenden Ergebnisse aus sieben Beobachtungsstudien sind unzureichend, um eine Aussage über die Wirksamkeit des subkutanen ICDs im Vergleich zum transvenösen ICD treffen zu können. Diese Studien zeigten jedoch statistisch signifikant weniger Sondenkomplikationen bei PatientInnen, die einen subkutanen ICD erhielten.
1 Scope

1.1 PICO question

Is the subcutaneous ICD compared to the conventional transvenous ICD equally or more effective and/or safer for the prevention of sudden cardiac death in patients at an increased risk?

1.2 Inclusion criteria

Table 1-1 summarizes the inclusion criteria for relevant studies.

| Population | Adults (18 years or older) with an underlying cardiac condition/disease associated with an increased risk of sudden cardiac death and indication for an implantable cardioverter-defibrillator for primary or secondary prevention. According to the European Society of Cardiology (ESC) guideline, primary and secondary prevention are defined as follows [15]:
| Primary prevention of sudden cardiac death: Therapies to reduce the risk of sudden cardiac death in individuals who are at risk of sudden cardiac death but have not yet experienced an aborted cardiac arrest or life-threatening arrhythmias [15]
| Secondary prevention of sudden cardiac death: Therapies to reduce the risk of sudden cardiac death in patients who have already experienced an aborted cardiac arrest or life-threatening arrhythmias [15]
| 2018 ICD-10-CM Diagnosis Code: I46.2 Cardiac arrest due to underlying cardiac condition MeSH terms: Death, Sudden, Cardiac (Tree Numbers: C14.280.383.220, C23.550.260.322.250, MeSH Unique ID: D016757)
| Intervention | Subcutaneously implantable cardioverter-defibrillator (ICD)
| 2018 ICD-10-CM Diagnosis Code: Z95.810 Presence of automatic (implantable) cardiac defibrillator MeSH terms: Defibrillators, Implantable (Tree Numbers: E07.305.250.159.175, E07.305.250.319.175, E07.695.202.175, MeSH Unique ID: D017147)
| Control | Single- or dual-chamber, conventional transvenous implantable cardioverter-defibrillator (ICD)
| Rationale: The transvenous ICD is an established and broadly used device for primary and secondary prevention in patients at risk of sudden cardiac death. Several randomized controlled trials have demonstrated its benefit.
| Outcomes | Rationale: For selection of relevant outcomes reflecting benefit and harms, we relied primarily on a recently-published systematic review [3].
| Effectiveness | All-cause mortality
| Appropriate shocks
| Safety | Inappropriate shocks
| Lead complications
| Infections
| Haematoma
| Pericardial tamponade
**Study design**

<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Randomized controlled trials</td>
<td>• Randomized controlled trials</td>
</tr>
<tr>
<td>• Observational studies with control group</td>
<td>• Observational studies with control group</td>
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<tr>
<td>• Systematic reviews</td>
<td>• Systematic reviews</td>
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</tbody>
</table>

*Excluded:* conference abstracts, narrative reviews, letters to the editor, case reports, case series, retrospective and prospective single-arm studies
2 Methods

2.1 Research questions

<table>
<thead>
<tr>
<th>Description of the technology</th>
<th>Research question</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B0001</strong></td>
<td>What is the subcutaneous ICD and the transvenous ICD?</td>
</tr>
<tr>
<td><strong>A0020</strong></td>
<td>For which indications has the technology received marketing authorisation or CE marking?</td>
</tr>
<tr>
<td><strong>B0002</strong></td>
<td>What is the claimed benefit of subcutaneous ICD in relation to the transvenous ICD?</td>
</tr>
<tr>
<td><strong>B0003</strong></td>
<td>What is the phase of development and implementation of the subcutaneous ICD and the transvenous?</td>
</tr>
<tr>
<td><strong>B0004</strong></td>
<td>Who administers the subcutaneous ICD and transvenous ICD and in what context and level of care are they provided?</td>
</tr>
<tr>
<td><strong>B0008</strong></td>
<td>What kind of special premises are needed to use the subcutaneous ICD and transvenous ICD?</td>
</tr>
<tr>
<td><strong>B0009</strong></td>
<td>What supplies are needed to use the subcutaneous ICD and transvenous ICD?</td>
</tr>
<tr>
<td><strong>A0021</strong></td>
<td>What is the reimbursement status of the subcutaneous ICD?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health problem and Current Use</th>
<th>Research question</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A0001</strong></td>
<td>For which health conditions, and for what purposes is the subcutaneous ICD used?</td>
</tr>
<tr>
<td><strong>A0002</strong></td>
<td>What is the disease or health condition in the scope of this assessment?</td>
</tr>
<tr>
<td><strong>A0003</strong></td>
<td>What are the known risk factors for the disease or health condition?</td>
</tr>
<tr>
<td><strong>A0004</strong></td>
<td>What is the natural course of the disease or health condition?</td>
</tr>
<tr>
<td><strong>A0005</strong></td>
<td>What is the burden of disease for the patients with the disease or health condition?</td>
</tr>
<tr>
<td><strong>A0006</strong></td>
<td>What are the consequences of the disease or health condition for the society?</td>
</tr>
<tr>
<td><strong>A0024</strong></td>
<td>How is the disease or health condition currently diagnosed according to published guidelines and in practice?</td>
</tr>
<tr>
<td><strong>A0025</strong></td>
<td>How is the disease or health condition currently managed according to published guidelines and in practice?</td>
</tr>
<tr>
<td><strong>A0007</strong></td>
<td>What is the target population for this assessment?</td>
</tr>
<tr>
<td><strong>A0023</strong></td>
<td>How many people belong to the target population?</td>
</tr>
<tr>
<td><strong>A0011</strong></td>
<td>How much are the technologies utilised?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Effectiveness</th>
<th>Research question</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D0001</strong></td>
<td>What is the expected beneficial effect of the subcutaneous ICD on mortality?</td>
</tr>
<tr>
<td><strong>D0005</strong></td>
<td>How does the subcutaneous ICD affect symptoms and findings (severity, frequency) of the disease or health condition?</td>
</tr>
<tr>
<td><strong>D0006</strong></td>
<td>How does the technology affect progression (or recurrence) of the disease or health condition?</td>
</tr>
<tr>
<td><strong>D0011</strong></td>
<td>What is the effect of the technology on patients’ body functions?</td>
</tr>
<tr>
<td><strong>D0016</strong></td>
<td>How does the use of technology affect activities of daily living?</td>
</tr>
<tr>
<td><strong>D0012</strong></td>
<td>What is the effect of the subcutaneous ICD on generic health-related quality of life?</td>
</tr>
<tr>
<td><strong>D0013</strong></td>
<td>What is the effect of the subcutaneous ICD on disease-specific quality of life?</td>
</tr>
</tbody>
</table>
2.2 Sources

Description of the technology, health problem and current use

Quellen
- Background publications identified by database search (see Section 2.3) and hand search
- Clinical practice guidelines identified by hand search
- Hand search in the POP (Planned and Ongoing Projects), AdHopHTA (Adopting Hospital-based Health Technology Assessment) and CRD (Centre for Reviews and Dissemination) databases for Health Technology Assessments
- Documentation provided by the manufacturer

2.3 Systematic literature search

The systematic literature search was conducted on November 23, 2017 in the following databases:
- Pubmed
- Embase.com (Elsevier)
- The Cochrane Library (Wiley)
- CRD (Centre for Reviews and Dissemination) Databases:
  - DARE (Database of Abstracts of Reviews of Effects),
  - NHS-EED (National Health System-Economic Evaluation) Database
  - HTA (Health Technology Assessment) Database

The systematic search was limited to the years 2000 to 2017. After deduplication, 569 citations were included overall. The specific search strategy employed can be found in the Appendix p55.

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP [World Health Organization International Clinical Trials Registry Platform]); EU Clinical Trials) was conducted on November 23, 2017, resulting in 20 potential relevant hits after deduplication.
We screened 139 references submitted by the manufacturer of approved subcutaneous ICDs (Boston Scientific).

By hand-search, 12 additional references were found, resulting in 740 citations overall.

### 2.4 Flow chart of study selection

Overall, 740 citations were identified after the removal of duplicates. The references were screened by two independent researchers (GW, AG) and, in case of disagreement, a third researcher was involved to resolve the differences. The selection process is displayed in Figure 2-1.

![Flow chart of study selection](image)

*Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)*
2.5 Analysis

We extracted data from included studies into data extraction tables based on the study design and research question (see Appendix Table A-1). An independent second reviewer (TS, EP) validated the data for accuracy.

In addition to data from seven observational studies, we obtained data from the meta-analysis of one systematic review. We did not conduct any additional meta-analysis. We used mean quality of life scores and standard deviations to calculate mean differences and 95% confidence intervals.

We calculated relative risk for binary outcomes if appropriate.

Two researchers (GW, TS) conducted risk of bias assessments independently. For observational studies they used the Newcastle-Ottawa Scale [11] (see Table A-2); for the systematic reviews, AMSTAR-2 (Assessing the Methodological Quality of Systematic Reviews) [12](see Table A-3). We resolved differences by consensus.

2.6 Synthesis

Based on the data-extraction-table (see Appendix Table A-1), data on each selected outcome were synthesized. Quality of evidence was assessed across studies for each outcome according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [16]. The research questions were answered in plain text format with reference to GRADE evidence tables (see Table A-4).
3 Description and technical characteristics of technology

Features of the technology and comparators

**Bo001 – What is the subcutaneous and the transvenous ICD?**

The subcutaneous ICD and the transvenous ICD continuously monitor heart rate and deliver shock therapy in the event of life-threatening tachycardia, and convert the abnormal heart rhythm back to normal [17].

Subcutaneous ICDs differ from transvenous ICDs in that the lead is placed subcutaneously i.e. directly under the skin rather than transvenously and is not directly attached to the heart [18]. The subcutaneous ICD senses cardiac signals, however, is not designed to provide long-term pacing [2].

Subcutaneous ICDs consist of a pulse generator placed on the left side of the chest at the mid-axillary line between the fifth and sixth intercostal spaces. A lead with two sensing electrodes and a shocking coil, which can defibrillate most patients at 80 Joule, are placed subcutaneously adjacent to the sternum [15]. The pulse generator housing serves as an electrode for defibrillation and can also serve as an optional electrode for sensing.

Patients need to undergo an ECG to assess QRS-T wave morphology prior to implant to check for susceptibility to under-sensing of ventricular tachycardia/ventricular fibrillation and inappropriate shocks [17].

A drawback of the subcutaneous ICD is T-wave oversensing which can lead to inappropriate therapy [19]. Other potential causes of oversensing are electromagnetic interference or myopotentials.

Other limitations are the lack of evidence regarding long-term durability/longevity of subcutaneous ICD leads and experience regarding lead re-interventions.

Transvenous ICDs consist of a generator, which is usually implanted in a pocket in the pectoral region below the left shoulder, and a transvenous right ventricular lead containing the shock coils and pacing electrode. Additional leads may be connected to right atrial or left ventricular pacing, sensing, and defibrillation. The leads are inserted through an incision into a vein and guided to the heart under fluoroscopic guidance. The lead tip is attached to the heart, while the other end of the lead is attached to the pulse generator [17, 20].

**Ao020 – For which indications has subcutaneous ICD received marketing authorisation or CE marking?**

The Cameron Health subcutaneous ICD system (later bought by Boston Scientific) received CE-marking (CE: 623289) in 2009 for use in eligible patients for the prevention of sudden cardiac death. The second generation EMBLEM™ S-ICD System and EMBLEM MRI S-ICD system received CE marking in 2015.

**Subkutaner und transvenöser ICD:**

detektieren und beenden lebensbedrohliche Tachyarrhythmien durch Schockabgabe

implantierbarer Kardioverter-Defibrillator (ICD):

Etablierter konventioneller ICD mit transvenösen Sonden

Subkutaner ICD:

T-Wellen Oversensing

keine Daten zur Langzeithaltbarkeit der Sonde und wenig Erfahrung mit Sonden Re-Interventionen

Indikation:

Prävention des plötzlichen Herztodes
Bo002 – What is the claimed benefit of the subcutaneous ICD in relation to the transvenous ICD?

Subcutaneous ICD technology enables the implantation of a defibrillator system without transvenous ICD leads. The lead is placed subcutaneously rather than transvenously and is not directly attached to the heart, which avoids problems associated with accessing the heart via the vascular system and complications with the transvenous leads of the transvenous ICD system [15]. Specifically, such complications are pneumothorax, cardiac perforation, lead fracture, lead dysfunction, infections (e.g. lead endocarditis) and venous thrombosis. Implantation is done via primarily anatomical landmarks, minimizing the need for fluoroscopy [17].

Bo003 – What is the phase of development and implementation of the subcutaneous ICD and transvenous ICD?

Subcutaneous ICD was introduced in human feasibility trials in 2002 and clinical trials in 2008. Subcutaneous ICD later received CE marking in 2009. Food and Drug Administration (FDA) approval was obtained in September 2012. The second generation EMBLEM™ S-ICD system and EMBLEM™ MRI S-ICD system were introduced in 2015. The use of the subcutaneous ICD in clinical practice is constantly increasing.

After first human implantation in 1980 [21], the transvenous ICD has been in use for almost three decades and is an established and broadly used medical device. Several trials have demonstrated its benefit in primary or secondary prevention patient populations [22-24].

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

Bo004 – Who administers the subcutaneous ICD and transvenous ICD and in what context and level of care are they provided?

The subcutaneous and transvenous ICD is implanted by a cardiologist or a cardiac surgeon experienced in implanting these devices.

Bo008 – What kind of special premises are needed to use the subcutaneous and transvenous ICD?

Both devices, the subcutaneous and transvenous ICDs, are usually implanted at a cardiac catheterisation laboratory or in an operating theater.

Bo009 – What supplies are needed to use subcutaneous ICD and transvenous ICD?

For ICD implantation, patients are monitored by an anaesthesiologist and usually receive regional anaesthesia with analgosedation. The implantation procedure is performed under sterile conditions. The implanting physician is supported by specialized trained assistance/nurses.

Regulatory & reimbursement status

Ao021 – What is the reimbursement status of the subcutaneous ICD?

The subcutaneous ICD does not yet have its own settlement rate and is currently being billed as a transvenous single or dual-chamber ICD.
4 Health Problem and Current Use

Overview of the disease or health condition

A0001 – For which health conditions, and for what purposes is subcutaneous ICD used?

Both transvenous and subcutaneous ICDs are implanted in patients at risk of sudden cardiac death. Ischemic heart disease is the leading structural heart disease, however, non-ischemic cardiomyopathy and other structural abnormalities, such as arrhythmogenic ventricular dysplasia and hypertrophic cardiomyopathy, may also cause sudden cardiac death [2].

Subcutaneous ICDs cannot achieve adequate arrhythmia sensing for all patients, and neither provide bradycardia nor anti-tachycardia pacing, which are both possible with the transvenous ICD [17]. Thus, patients requiring bradycardia pacing are not suitable candidates for subcutaneous ICDs, unless pacing is only required immediately after shock delivery, as transcutaneous pacing can be delivered for 30 seconds after the shock. Patients suffering from tachyarrhythmia that is easily resolved by anti-tachycardia pacing, and patients needing cardiac resynchronization therapy, are also not candidates for subcutaneous ICDs [15].

Potential candidates for subcutaneous ICDs include paediatric patients with congenital heart disease, those with difficult venous access (obstruction, venous abnormality), chronic indwelling catheters, high infection risk, or young patients with electrical heart disease (e.g. Brugada Syndrome, long QT syndrome, and hypertrophic cardiomyopathy) [25].

A0002 – What is the disease or health condition in the scope of this assessment?

Primary and secondary prevention of sudden cardiac death.

The term sudden cardiac death is defined as [15]:

- A congenital, or acquired, potentially fatal cardiac condition known to be present in life; or
- Autopsy results showing cardiac or vascular anomaly as the probable cause of the event; or
- No obvious extra-cardiac causes found during post-mortem examination and therefore an arrhythmic event is likely the cause of death.

A0003 – What are the known risk factors for the disease or health condition?

In younger patients, channelopathies, myocarditis, cardiomyopathies, and substance abuse are the predominant cardiac diseases associated with sudden cardiac death [15].

In older patients, the presence of chronic degenerative diseases, such as valvular heart diseases, coronary artery diseases (CAD), and heart failure (HF), are the main causes of sudden cardiac death [15].
Effects of the disease or health condition on the individual and society

A0005 – What is the burden of disease for patients with the disease or health condition?

Cardiovascular disease is a major public health issue accounting for almost 17 million deaths per year globally. According to estimates, 40-50% of deaths are sudden cardiac deaths, with approximately 80% (6 millions) of them due to ventricular tachyarrhythmias [1].

Several underlying acquired or congenital cardiac conditions are associated with an increased risk of ventricular arrhythmias.

A0006 – What are the consequences of the disease or health condition for the society?

In one observational study with 138 patients, the mean cost per patient including implant and complication costs was £12,601 ± 1,786 for the subcutaneous ICD and £9,967 ± 4,511 for the transvenous ICD (p = 0.0001) [9].

Current clinical management of the disease or health condition

A0024 – How is the disease or health condition currently diagnosed according to published guidelines and in practice?

Clinical history, physical examination and electrocardiogram (ECG) are the first step in diagnostic algorithm of congenital and acquired cardiac disease. Echocardiography is recommended for assessment of left ventricular function and detection of structural heart disease. Coronary angiography is applied in patients with suspected coronary artery disease (CAD).

Additional patient assessment, e.g. stress test, holter 48 hours, cardiovascular magnetic resonance imaging, drug challenges, electrophysiological study or genetic testing is performed according to suspected cardiac condition.

A0025 – How is the disease or health condition currently managed according to published guidelines and in practice?

In general, ICD is recommend for primary prevention of sudden cardiac death in certain patients with ischaemic cardiomyopathy, post myocardial infarction, non-ischaemic cardiomyopathy, inherited arrhythmia syndromes or inherited cardiomyopathies. In patients with history of cardiac arrest or life-threatening ventricular arrhythmia ICD is recommended for secondary prevention of sudden cardiac death if certain criteria are met. Usually transvenous ICDs systems are implanted, however, guidelines recommend to consider the use of the subcutaneous ICD as follows [15]:

- Subcutaneous ICDs should be considered as an alternative to transvenous ICDs in patients with an indication for an ICD when pacing therapy for bradycardia support, cardiac resynchronization or anti-tachycardia pacing is not needed. (Class IIa, Level 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 IIa, Level C)

The 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death state the following recommendations [17]:
In patients who meet criteria for an ICD who have inadequate vascular access or are at high risk for infection, and in whom pacing for bradycardia or VT termination or as part of CRT is neither needed nor anticipated, a subcutaneous implantable cardioverter-defibrillator is recommended (Class I, Level B).

In patients who meet indication for an ICD, implantation of a subcutaneous implantable cardioverter-defibrillator is reasonable if pacing for bradycardia or VT termination or as part of CRT is neither needed nor anticipated (Class IIa, Level B).

Based on NICE (National Institute for Health and Care Excellence) guidance document, current evidence on the efficacy and safety of subcutaneous ICD for preventing sudden cardiac death is adequate to support the use of this procedure [2].

**Target population**

**A0007 – What is the target population in this assessment?**

Patients with congenital or acquired cardiac disease at high risk for sudden cardiac death.

According to the European Society of Cardiology (ESC) guideline, primary and secondary prevention are defined as follows [15]:

- **Primary prevention of sudden cardiac death**: Therapies to reduce the risk of sudden cardiac death in individuals who are at risk of sudden cardiac death but have not yet experienced an aborted cardiac arrest or life-threatening arrhythmias [15]

- **Secondary prevention of sudden cardiac death**: Therapies to reduce the risk of sudden cardiac death in patients who have already experienced an aborted cardiac arrest or life-threatening arrhythmias [15]

**A0023 – How many people belong to the target population?**

**A0011 – How much is the subcutaneous ICD utilised?**

It is estimated that up to 55% of patients with an ICD indication are potential candidates for a subcutaneous device in clinical practice [26].

Based on the statistical report from the European Heart Rhythm Association, in Austria, 1,296 ICDs were implanted in the year 2013 [27].

In the United States, based on the National Cardiovascular Data Registry (ICD Registry), 393,734 ICDs were implanted between September 28, 2012 and March 31, 2015. Among them, 3,717 (0.9%) were subcutaneous ICDs [10].

AHA/ACC/HRS Leitlinie 2017 Empfehlungen: Klasse I, Level B

Klasse IIa, Level B

NICE Guidance Dokument: derzeitige Evidenz zeigt Wirksamkeit und Sicherheit des subkutanen ICDs

Patientinnen mit angeborenener oder erwerberener Herzerkrankung die mit einem erhöhten Risiko des plötzlichen Herzodes assoziiert sind

Primäre oder sekundäre Prävention der plötzlichen Herztodes

Österreich: 2013: 1.296 ICD Implantationen

USA: >390.000 ICD Implantationen in 2,5 Jahren, davon 3.717 (0,9 %) subkutane ICDs
5 Clinical effectiveness

5.1 Outcomes

The following outcomes were defined as crucial to derive a recommendation:

- All-cause mortality
- Appropriate shock

Appropriate shock is usually defined as a shock delivery for ventricular tachycardia or ventricular fibrillation.

5.2 Included studies

We identified seven eligible observational studies with 6,916 patients [4-10] and one systematic review [3] addressing our research question. From the systematic review we obtained results of quantitative analysis (meta-analyses).

Our search also identified a second systematic review, but it did not include recently published studies comparing the subcutaneous with the transvenous ICD [28].

Study characteristics and results of included studies are displayed in Table A-1 and in the evidence profile in Table A-4.

The maximum follow-up in the studies ranged from the duration of the hospital stay to five years after implantation. In four studies, the control group was selected by propensity score matching [5, 7, 9, 10] in order to obtain similar groups. Three studies compared a subcutaneous ICD with a single-chamber transvenous ICD [4, 6, 8]. In four studies, patients in the control group received either single- or dual-chamber ICDs [5, 7, 9, 10].

The largest retrospective observational study involving a total of 5,760 patients from the National Cardiovascular Data Registry (NCDR) ICD Registry compared the effectiveness and safety of the subcutaneous ICD to the single-chamber ICD and dual-chamber ICD for multiple clinical endpoints during hospitalization [10]. Propensity score matching took into account implantation date, patient characteristics, and physician characteristics.

The other retrospective observational studies had longer observation periods but analyzed significantly fewer patients.
5.3 Results

Mortality

d0001 – What is the expected beneficial effect of the subcutaneous ICD on mortality?

All-cause mortality

Three retrospective observational studies with 6,222 patients [4, 7, 10] showed no statistically significant differences in mortality. Two of the studies performed propensity score matching [7, 10].

In all three studies, there were no statistically significant differences in mortality rates between the two groups. In the largest observational study involving a total of 5,760 patients, 0.2% (3 of 1,920) died during hospitalization in the subcutaneous ICD group, 0.1% (2 of 1,920; p > 0.99) in the single-chamber ICD group, and 0.05% (1 of 1,920, p = 0.64) in patients with dual-chamber ICD. No statistically significant differences were found if patients with subcutaneous ICD compared to all patients with transvenous ICD (3 of 1920 vs. 3 of 3840; relative risk [RR] 2.0, 95% confidence interval [CI]: 0.4-9.9, [self-calculated]) [10].

In a smaller study with 280 participants, 5-year survival rate was 96.0% (95% CI: 90.1-100.0%) in the subcutaneous ICD group compared to 94.8% (95% CI: 90.7-99.0%) in the transvenous ICD group (p = 0.42) [7]. Patients with pacemaker indication were not excluded in the group of patients with conventional ICD and the mean observation period of the subcutaneous and transvenous group was different (5 years vs. 3 years) [7].

Morbidity

d0005 – How does the subcutaneous ICD affect symptoms and findings (severity, frequency) of the disease or health condition?

Appropriate shock

In three studies (556 patients), the rate of appropriate shocks was lower in patients with subcutaneous ICDs than in patients with conventional ICDs [6, 7, 9]. However, this difference was not statistically significant in any of the three studies.

For example, the observational study with the longest follow-up [7] showed that adequate shocks were less frequent in patients with subcutaneous ICDs than in patients with transvenous ICD (8.6% [12 of 140] versus 17.1% [24 of 140]. At 5 year, Kaplan-Meier analysis revealed estimated rate of patients with appropriate shocks of 17.0% (95% CI: 63–26.4) in the subcutaneous group and 21.3% (95% CI: 12.6-27.3) in the transvenous group. The hazard ratio (HR) adjusted for ICD programming was 0.68 [self-calculated from HR transvenous vs. subcutaneous ICD], p = 0.36 [7].

In two other observational studies [6, 9] with 276 patients, the incidence of adequate shock deliveries was also lower in the subcutaneous ICD group compared to the transvenous ICD group, but difference did not reach statistical significance.
D0006 – How does the technology affect progression (or recurrence) of the disease or health condition?

No evidence was found to answer this research question.

Function

D0011 – What is the effect of the subcutaneous ICD on patients’ body functions?

No evidence was found to answer this research question.

D0016 – How does the use of the subcutaneous ICD affect activities of daily living?

No evidence was found to answer this research question.

Health-related quality of life

D0012 – What is the effect of the subcutaneous ICD on generic health-related quality of life?

Two observational studies with 418 patients evaluated the quality of life in patients with subcutaneous ICD and transvenous ICD by administration of the generic 12-item Short-Form Health Survey (SF-12). Physical and mental component summary scores of the SF-12 range on a scale from 0 (poorest possible) to 100 (best possible) [5, 8].

One study compared the quality of life in patients with subcutaneous ICD from the prospective, multicentre, observational substudy of the EFFORTLESS S-ICD registry (n = 167) with a propensity score-matched cohort with transvenous ICD of the single-centre MIDAS study (n = 167) [5]. Multivariable model adjusted for prior selected variables and baseline differences between the two cohorts revealed no statistically significant differences at baseline, 3 months and 6 months between patients with subcutaneous ICDs and transvenous ICDs [5].

The mean physical quality of life scores (standard deviation [SD] self-calculated from 95% CI) were similar at baseline (40.5 ± 11.8 vs. 40.8 ± 10.9), 3 months (43.6 vs. 43.9), and 6 months (43.5 ± 12 vs. 43.7 ± 11, mean difference [self-calculated] -0.2; 95% CI: -2.67-2.27). In addition, the mean mental quality of life score was not statistically significantly different at baseline (42.4 ± 11.8 vs. 42.3 ± 11.0), 3 months (45.9 vs. 45.7) and 6 months (45.2 ± 12.5 vs. 45.1 ± 11.6, mean difference [self-calculated] 0.15; 95% CI: -2.44-2.74). Statistically significant improvements in physical and mental quality of life were observed in both groups between the time of implantation and 3 months and between the time of implantation and 6 months, but not between 3 and 6 months [5].

In a second observational study, 42 patients with subcutaneous ICD were matched to 42 patients with single-chamber transvenous ICD and evaluated with respect to posttraumatic stress disorder, psychological disorders and quality of life [8]. Quality of life was assessed after mean duration of 622 days after subcutaneous ICD and 942 days after transvenous implantation. The physical well-being score obtained by the SF-12 questionnaire was statist-
cally significantly higher with subcutaneous than transvenous ICDs (46.6 ± 9.9 vs. 39.9 ± 12.5, mean difference [self-calculated] 6.7; 95% CI: 1.88-11.52). However, the mental well-being score did not statistically significantly differ between groups (51.9 ± 10.4 vs. 51.8 ± 10.8, mean difference [self-calculated] 0.10; 95% CI: -4.43 − 4.63) [8].

D0013 – What is the effect of the subcutaneous ICD on disease-specific quality of life?

keine Evidenz vorhanden

No evidence was found to answer this research question.
6 Safety

6.1 Outcomes

The following outcomes were defined as crucial to derive a recommendation:
- Inappropriate shocks
- Lead complications
- Infections
- Haematoma
- Pericardial tamponade

Outcomes were selected based on a recently published systematic review [3].

6.2 Included Studies

Five eligible observational studies [4, 6, 7, 9, 10] and one systematic review [3] reported data on harms. Study characteristics were described above and results of included studies are displayed in Table A-1 and the quality of evidence is presented in Table A-4.

6.3 Results

Patient safety

Coo08 – How safe is the subcutaneous ICD in comparison to the conventional transvenous ICD?

Inappropriate shocks
In four observational studies (N = 738) with a follow-up period ranging from six months to five years, the number of patients with inappropriate shock in the subcutaneous ICD group and the conventional transvenous ICD group were reported [4, 6, 7, 9].

Inappropriate shock was not statistically significantly different between patients with subcutaneous and transvenous ICDs based on a random-effects meta-analysis with four studies [4, 6, 7, 9] and 738 patients (29 of 369 vs. 44 of 369, OR 0.87; 95% CI: 0.51-1.49) [3].

Causes of inappropriate shock delivery differed among groups. Subanalysis of three studies [6, 7, 9] showed that inappropriate therapy due to supraventricular tachycardia was statistically significantly less frequent with subcutaneous ICD (3 of 278 vs. 29 of 278; OR 0.12; 95% CI: 0.04-0.35).

In contrast, statistically significant more inappropriate shocks because of oversensing (sensing of noise, T-wave oversensing) occurred with the subcutaneous ICD [3].
Lead complications

Four observational studies reported data on lead complications [6, 7, 9, 10]. Three studies showed statistically significantly fewer lead complications with subcutaneous ICD than with transvenous ICD [6, 7, 10]. In the study with the longest observation period of five years, 0.7% (1 of 140) of patients with subcutaneous ICD experienced lead complications, while patients with transvenous (single and dual-chamber) ICD experienced complications in 12.1% of cases (17 of 140) [7]. At 5 year, Kaplan-Meier estimates of patients with lead complications were 0.8% (95% CI: 0-2.2) in the subcutaneous compared to 11.5% (95% CI: 5.3-17.2) (p = 0.03) in the transvenous group.

Meta-analysis of four observational studies (6,316 patients) [6, 7, 9, 10] yielded statistically significantly fewer lead complications in the subcutaneous ICD group compared to the transvenous ICD group (odds ratio [OR] 0.13, 95% CI: 0.05–0.38) [3].

Infections

Five eligible observational studies reported data on infections. Different definitions of an infection were used in individual studies: infections requiring explantation [4], infections necessitating removal of the ICD system and/or antibiotic treatment [9], infection requiring revision [6], or any infection [7, 10].

All five studies showed no statistically significant difference in the rate of infections between patients with subcutaneous ICDs and patients with conventional transvenous ICDs. In the largest observational study (N = 5,760), infections were rare in all three groups. During the hospital stay, which lasted an average of one day, 0 to 0.1% of the patients had an infection (subcutaneous ICD: 0.0% [1 of 1,920], transvenous single-chamber ICD: 0% [0 of 1,920], transvenous dual-chamber ICD: 0.1% [2 of 1,920]) [10]. In one study with a follow-up to five years, the rate of infections in both groups were similar (Kaplan-Meier estimates 4.1% [95% CI: 0.5-7.7] vs. 3.6% [95% CI: 0.0-7.1], p = 0.36) [7].

Random-effects meta-analysis (5 studies 6,498 patients) [4, 6, 7, 9, 10] support findings of individual studies, with no statistically significant difference of risk for infections between the subcutaneous ICD group compared with the transvenous ICD group (8 of 2,269 vs. 13 vs. 4,189; OR 0.75, 95% CI: 0.30-1.89) [3].

Haematoma

Overall, haematomas were rare (subcutaneous ICD: 9 of 2,080 vs. 3 of 4,000). Both a larger study (N = 5,760) [10] (subcutaneous ICD vs. dual-chamber transvenous ICD: RR 3.5, 95% CI: 0.7-19.8) and two smaller retrospective observational studies (N = 320) [4, 6] found no statistically significant difference between subcutaneous ICDs and transvenous single- or dual-chamber ICDs.
**Pericardial tamponade**

Two studies (N = 5,898) reported the rate of pericardial tamponade [9, 10]. In the largest study involving 5,760 patients, no pericardial tamponades occurred during hospital stay in the group with subcutaneous ICDs and the single-chamber ICD group. However, in the dual-chamber ICD group, five pericardial tamponades were observed [10].

_C0004 – How does the frequency or severity of harms change over time or in different settings?_

No evidence was found to answer this research question

_C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of the subcutaneous ICD?_

No evidence was found to answer this research question

_C0007 – Are the subcutaneous ICD and transvenous ICD associated with user-dependent harms?_

No evidence was found to answer this research question
7 Quality of evidence

The quality of evidence was rated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme [16] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved to resolve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [16].

GRADE uses four categories to rank the quality of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and in the evidence profile in Appendix Table A-4.

The quality of evidence for the effectiveness and safety of subcutaneous ICD in comparison to transvenous ICD is very low for all outcomes.

Risk of Bias of included observational studies was assessed with the Newcastle-Ottawa Scale [11] and is presented in Table A-2 in the Appendix. Three studies were considered as high [4, 6, 8] and four as medium risk of bias [5, 7, 9, 10]. Main reasons for downgrading refer to selection of control group, comparability of cohorts and follow-up duration.

The only systematic review was rated as medium risk of bias, since assessment with the AMSTAR-2 checklist [12] revealed moderate overall confidence in the results of the review (see Table A-3).
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>№ of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (in-hospital) [10]</td>
<td>Risk with transvenous ICD: 1 per 1.000 (0 to 8)</td>
<td>Risk with subcutaneous ICD: 2 per 1.000 (0 to 8)</td>
<td>RR 2.0 (0.4 to 9.9)</td>
<td>5760 (1 observational study)</td>
<td>☀️☀️☀️ ☀️ VERY LOW a</td>
</tr>
<tr>
<td>Mortality (up to 6 months) [4]</td>
<td>Risk with transvenous ICD: 22 per 1.000 (3 to 153)</td>
<td>Risk with subcutaneous ICD: 22 per 1.000 (3 to 153)</td>
<td>RR 1.00 (0.14 to 6.95)</td>
<td>182 (1 observational study)</td>
<td>☀️☀️☀️ ☀️ VERY LOW b,c,d</td>
</tr>
<tr>
<td>Mortality (up to 5 years) [7]</td>
<td>Risk with transvenous ICD: 43 per 1.000 (0 to 0)</td>
<td>Risk with subcutaneous ICD: 0 per 1.000 (0 to 0)</td>
<td>not estimable</td>
<td>280 (1 observational study)</td>
<td>☀️☀️☀️ ☀️ VERY LOW b,d</td>
</tr>
<tr>
<td>Appropriate shock/therapy (7.1 months) [6]</td>
<td>Risk with transvenous ICD: 130 per 1.000 (12 to 153)</td>
<td>Risk with subcutaneous ICD: 43 per 1.000 (12 to 153)</td>
<td>RR 0.33 (0.09 to 1.18)</td>
<td>138 (1 observational study)</td>
<td>☀️☀️☀️ ☀️ VERY LOW b,c,d</td>
</tr>
<tr>
<td>Appropriate shock/therapy (2.6 years) [9]</td>
<td>Risk with transvenous ICD: 72 per 1.000 (11 to 155)</td>
<td>Risk with subcutaneous ICD: 43 per 1.000 (11 to 155)</td>
<td>RR 0.60 (0.15 to 2.14)</td>
<td>138 (1 observational study)</td>
<td>☀️☀️☀️ ☀️ VERY LOW b,c,d</td>
</tr>
<tr>
<td>Appropriate shock/therapy (up to 5 years) [7]</td>
<td>Risk with transvenous ICD: 171 per 1.000 (o to o)</td>
<td>Risk with subcutaneous ICD: 120 per 1.000 (o to o)</td>
<td>HR 0.68</td>
<td>280 (1 observational study)</td>
<td>☀️☀️☀️ ☀️ VERY LOW b,c,d</td>
</tr>
<tr>
<td>Inappropriate shocks [3] pooled Data of [4, 6, 7, 9]</td>
<td>Risk with transvenous ICD: 95 per 1.000 (51 to 135)</td>
<td>Risk with subcutaneous ICD: 83 per 1.000 (51 to 135)</td>
<td>OR 0.87 (0.51 to 1.49)</td>
<td>738 (4 observational studies)</td>
<td>☀️☀️☀️ ☀️ VERY LOW b,c,d</td>
</tr>
<tr>
<td>Lead complications [3] pooled Data of [4, 6, 7, 9, 10]</td>
<td>Risk with transvenous ICD: 10 per 1.000 (1 to 4)</td>
<td>Risk with subcutaneous ICD: 1 per 1.000 (1 to 4)</td>
<td>OR 0.13 (0.05 to 0.38)</td>
<td>6316 (4 observational studies)</td>
<td>☀️☀️☀️ ☀️ VERY LOW e</td>
</tr>
<tr>
<td>Infections [3] pooled Data of [4, 6, 7, 9, 10]</td>
<td>Risk with transvenous ICD: 3 per 1.000 (1 to 6)</td>
<td>Risk with subcutaneous ICD: 2 per 1.000 (1 to 6)</td>
<td>OR 0.75 (0.30 to 1.89)</td>
<td>6498 (5 observational studies)</td>
<td>☀️☀️☀️ ☀️ VERY LOW b,c,d</td>
</tr>
<tr>
<td>Pericardial tamponade [9, 10]</td>
<td>Risk with transvenous ICD: 2 per 1.000 (0 to 1)</td>
<td>Risk with subcutaneous ICD: 0 per 1.000 (0 to 1)</td>
<td>RR ranged from 0.18 to 0.33</td>
<td>5898 (2 observational studies)</td>
<td>☀️☀️☀️ ☀️ VERY LOW b,c,d</td>
</tr>
<tr>
<td>Haematoma [4, 6, 10]</td>
<td>Risk with transvenous ICD: 1 per 1.000 (2 to 3)</td>
<td>Risk with subcutaneous ICD: 0 per 1.000 (2 to 3)</td>
<td>RR ranged from 3.0 to 3.5</td>
<td>6080 (3 observational studies)</td>
<td>☀️☀️☀️ ☀️ VERY LOW b,c,d</td>
</tr>
</tbody>
</table>

**Explanations:** *The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

**Abbreviations:** CI = Confidence interval; RR = Risk ratio; HR = Hazard Ratio; OR = Odds ratio; MD = Mean difference

- Effect estimates includes appreciable benefit and harms
- Small number of events
- Two studies with high risk of bias [4, 6]
- Studies with high or medium risk of bias
- Sample size does not meet optimal information size
- Medium risk of bias

---

Table 7-1: Summary of findings table of subcutaneous ICD compared with transvenous ICD in patients at high risk of sudden cardiac death
8 Discussion

Based on the available evidence of seven observational studies [4-10] and one systematic review [3], comparing patients receiving subcutaneous ICDs or transvenous ICDs, no statistically significant differences were observed in terms of overall mortality, rate of adequate and inadequate shocks, infections, and haematomas. Some of these results, however, have wide confidence intervals and encompass differences that would be clinically relevant.

Lead complications were statistically significantly less frequent in patients with subcutaneous ICDs as compared to transvenous ICDs. Differences regarding lead complications, however, are expected by the nature of these devices, as subcutaneous ICDs have no contact with cardiac structures due to the absence of transvenous lead implantation.

The quality of evidence of all outcomes is very low due to risk of bias and imprecision, indicating substantial uncertainty about these findings.

When interpreting the results of our evidence summary, several limitations related to risk of bias and to study design have to be considered:

First, the follow-up period varied considerably among individual studies ranging from the duration of the hospital stay to five years after ICD implantation. Therefore, most of the studies do not reflect long-term complications. Due to this limitation, pooled results from random-effects meta-analysis are limited.

Second, in few studies, despite matching, there were still differences of baseline characteristics between patients who received subcutaneous ICDs and patients who had a conventional transvenous ICDs implanted. In particular, differences in patient characteristics may have influenced outcomes. It should be emphasized that not all studies clearly stated that they excluded patients with an indication for a pacemaker, anti-tachycardia pacing or cardiac resynchronization therapy from the control group with transvenous ICD. Therefore, unevenly distributed prognostic factors could have influenced the outcomes.

Third, due to the small sample size (ranging from 138 to 334 patients), power of most of the studies is low to detect differences. However, this was overcome by the meta-analysis of the included systematic review.

Finally, the most important limitation is that for most effectiveness and safety endpoints, only few events occurred, limiting precision of the findings. Most of the non-significant results are generally indeterminate. The confidence intervals are wide and include important differences.

Applicability of included studies is summarized in Table A-5.

Our review focused on comparative effectiveness and safety of the subcutaneous and transvenous ICD. For that reason, findings of two large cohort studies without control group, the IDE (Investigational Device Exemption) study [29, 30] and the EFFORTLESS (Evaluation of FactORs Impacting CLinical Outcome and Cost EffectiveneSS of the S-ICD) study [30, 31] are not included in this review.
Subcutaneous implantable cardioverter defibrillator (ICD)

Our searches yielded the study protocol of an investigator-initiated, multicentre, randomized controlled PRAETORIAN (Prospective, RAndomizEd comparison of subcutaneous and tRansvenous ImplAnTable cardioverter-defibrillator therapy) trial [13]. Planned sample size of this study is 850 patients with an indication for ICD therapy and without an indication for pacing, randomized to either the subcutaneous or transvenous ICD (1:1) [14]. This study is adequately powered to claim non-inferiority and/or superiority of the subcutaneous ICD regarding a composite primary endpoint of inappropriate shocks and ICD-related complications (within 48 months). According to the ClinicalTrials.gov (NCT01296022) entry, estimated completion date is December 2019 [14]. Thus, no results are available yet.

In addition, we found the ongoing randomized controlled ATLAS (Avoid Transvenous Leads in Appropriate Subjects) S-ICD trial (ClinicalTrials.gov, NCT02881255). Details of this trial are provided in Table A-6.

Conclusion

The results from seven observational studies and one systematic review are inadequate to draw conclusions about the comparative effectiveness of subcutaneous and transvenous ICDs.

These studies, however, indicate substantially lower risk for lead complications in patients with subcutaneous ICD.

The ongoing randomized controlled PRAETORIAN study will provide more reliable results to answer this question.
9 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 9-1: Evidence based recommendations

<table>
<thead>
<tr>
<th>Inclusion in the catalogue of benefits</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>The <strong>inclusion</strong> is <strong>recommended</strong>.</td>
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<tr>
<td>The <strong>inclusion</strong> is <strong>recommended with restrictions</strong>.</td>
<td></td>
</tr>
<tr>
<td>The <strong>inclusion</strong> is <strong>currently not recommended</strong>.</td>
<td></td>
</tr>
<tr>
<td>The <strong>inclusion</strong> is <strong>not recommended</strong>.</td>
<td></td>
</tr>
</tbody>
</table>

Reasoning:
The current evidence is not sufficient to determine whether the subcutaneous ICD is equally or more effective than the transvenous ICD. Based on the available evidence no statistically significant differences were observed in terms of overall mortality, rate of adequate and inadequate shocks, infections, and haematomas. However, lead complications were statistically significantly less frequent in patients with subcutaneous ICDs as compared to transvenous ICDs. Thus, inclusion in the benefit catalogue is recommended with restrictions.

New study results will potentially influence the effect estimate considerably. The re-evaluation is recommended in year 2020 when results of an ongoing randomized controlled trial are published.
10 References


## Appendix

### Evidence tables of individual studies included for clinical effectiveness and safety

**Table A-1: Subcutaneous versus transvenous ICD: Results from observational studies**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Sponsor</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Study design</th>
<th>Number of patients, total and intervention vs. comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Köbe, 2013 [6]</td>
<td>Germany</td>
<td>-</td>
<td>Subcutaneous ICD</td>
<td>Single-chamber transvenous ICD</td>
<td>Observational study Control matched by sex and age (± 5 years)</td>
<td>138 (69 vs. 69)</td>
</tr>
<tr>
<td>Brouwer, 2016 [7]</td>
<td>Netherlands</td>
<td>-</td>
<td>Subcutaneous ICD</td>
<td>Single-chamber and dual-chamber transvenous ICD</td>
<td>Observational study Control matched by sex and age (± 5 years)</td>
<td>280 (140 vs. 140)</td>
</tr>
<tr>
<td>Friedmann, 2016 [10]</td>
<td>Unites States of America</td>
<td>Supported by the American College of Cardiology’s National Cardiovascular Data Registry (NCDR)</td>
<td>Subcutaneous ICD</td>
<td>Single-chamber and dual-chamber transvenous ICD</td>
<td>Observational study with propensity score matching</td>
<td>5760 (1920 vs. 1920 vs. 1920)</td>
</tr>
<tr>
<td>Pedersen, 2016 [5]</td>
<td>Czech Republic, Denmark, Germany, Italy, the Netherlands, New Zealand, Portugal, and the United Kingdom</td>
<td>Cameron Health Inc.</td>
<td>Subcutaneous ICD</td>
<td>Single-chamber and dual-chamber transvenous ICD</td>
<td>Observational study with propensity score matching</td>
<td>134 (167 vs. 167)</td>
</tr>
<tr>
<td>Köbe, 2017 [8]</td>
<td>Germany</td>
<td>-</td>
<td>Subcutaneous ICD</td>
<td>Single-chamber transvenous ICD</td>
<td>Observational study Control matched by sex and age (± 5 years)</td>
<td>84 (42 vs. 42)</td>
</tr>
<tr>
<td>Mithani, 2017 [4]</td>
<td>Unites States of America</td>
<td>-</td>
<td>Subcutaneous ICD</td>
<td>Single-chamber transvenous ICD</td>
<td>Observational study Control matched by age, sex and dialysis status</td>
<td>182 (91 vs. 91)</td>
</tr>
<tr>
<td>Author, year</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>Age of patients, yrs</td>
<td>Female n (%)</td>
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</tr>
<tr>
<td>Köbe, 2013 [6]</td>
<td>Indication for ICD implantation according to ACA/AHA and ESC guidelines for primary and secondary prevention, no indication for stimulation or slow ventricular tachycardias (VTs). Implantation at the University Hospitals of Düsseldorf, Munich and Münster, Germany.</td>
<td>NR</td>
<td>Mean ± SD: 45.7 ± 15.7 vs. 47.7 ± 14.7, p = 0.433</td>
<td>19 (27.5) vs. 19 (27.5), p = 1.0</td>
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</tr>
<tr>
<td>Brouwer, 2016 [7]</td>
<td>Patients implanted with single- and dual-chamber TV-ICDs between 2005 and 2014 at the Leiden University Medical Center (LUMC), and patients implanted with S-ICDs between 2009 and 2015 at the Academic Medical Center (AMC).</td>
<td>Patients included in the PRAETORIAN trial</td>
<td>Mean ± SD: 54.0 ± 15.1 vs. 54.1 ± 15.0, p = NR</td>
<td>56 (40) vs. 53 (38), p = 0.71</td>
<td></td>
<td></td>
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<tr>
<td>Friedmann, 2016 [10]</td>
<td>All Patients admitted for ICD implantation (September 28, 2012-March 31, 2015) and eligible for an S-ICD, SC TV-ICD or DC TV-ICD.</td>
<td>Patients with previous ICD, bradycardia or resynchronization indication for permanent pacing. Patients undergoing ICD implantation during an acute hospitalization.</td>
<td>Mean ± SD: 54 ± 16 vs. 55 ± 13, p = 0.8831</td>
<td>627 (32.7) vs. 598 (31.2), p = NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pedersen, 2016 [5]</td>
<td>Patients implanted with a first generation S-ICD system due to a primary or secondary prevention indication according to local clinical guidelines. The intervention cohort (EFFORTLESS S-ICD QoL substudy) included prospective and first time implant patients from 29 sites (Czech Republic, Denmark, Germany, Italy, Netherlands, New Zealand, Portugal, United Kingdom) from March 2011 to July 2014. Comparison cohort were patients from the MIDAS study recruited at the Erasmus Medical Center in Rotterdam, Netherlands from August 2003 to February 2010.</td>
<td>Patients participating 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 and/or spontaneously, frequently recurring VT, or if they had a bradycardia indication or cardiac resynchronization therapy.</td>
<td>Mean ± SD: 44.6 ± 12.5 vs. 44.7 ± 12.1, p = 0.06</td>
<td>45 (27%) vs. 47 (28%), p = 0.8065</td>
<td></td>
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<tr>
<td>Köbe, 2017 [8]</td>
<td>Consecutive patients with subcutaneous ICD implantation and patients with transvenous single-chamber ICD implantation from hospital database, capable of responding to standardized questionnaire, previously implanted at Department of Cardiology and Angiology, University Hospital München, Germany and attended the outpatient clinic regularly for device follow-up.</td>
<td>NR</td>
<td>Mean ± SD: 35 ± 13 vs. 40 ± 10, p = 0.17</td>
<td>12 (28.6) vs. 12 (28.6), p = 1.0</td>
<td></td>
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</tr>
<tr>
<td>Honoarbakhsh, 2017 [9]</td>
<td>Indication for ICD implantation for primary and secondary prevention. Patients implanted with subcutaneous ICD between 2010 and 2015 in a single tertiary centre, patients implanted a transvenous ICD over a contemporary time in the same centre (Barts Heart Center, London).</td>
<td>Patients who had a concomitant pacing indication, biventricular devices, documentation of sustained monomorphic ventricular tachycardia (VT) likely to require anti-tachycardia pacing (ATP), and advisory transvenous leads.</td>
<td>Mean ± SD: 54.93 ± 13.61 vs 56.30 ± 12.71, p = 0.017</td>
<td>17 (25) vs. 17 (25), p = 1.00</td>
<td></td>
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</tr>
<tr>
<td>Mithani, 2017 [4]</td>
<td>All patients who had a subcutaneous ICDs implanted between October 22, 2012 and September 22, 2015 at the Cooper University Hospital, Camden, USA. Ninety-one patients who received subcutaneous ICD were consecutively identified and they were then matched to single-chamber transvenous ICD patients during this time frame.</td>
<td>Dual-chamber transvenous ICD, Cardiac resynchronization therapy (CRT)</td>
<td>Mean ± SD: 54.93 ± 13.61 vs 56.30 ± 12.71, p = 0.017</td>
<td>40 (44) vs. 41 (55), p = 1.0</td>
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<tr>
<td><strong>Primary prevention n (%)</strong></td>
<td>41 (59.4) vs. 34 (50.0), p = 0.268</td>
<td>93 (66) vs. 86 (61), p = 0.38</td>
<td>NR</td>
<td>123 (74) vs. 115 (69), p = 0.3334</td>
<td>26 (61.9) vs. 23 (54.8), p = 0.66</td>
<td>56 (81) vs. 56 (81), p = 1.0</td>
</tr>
<tr>
<td>First ICD implantation n (%)</td>
<td>53 (76.8) vs. NR, p = NR</td>
<td>121 (86) vs. 125 (89), p = 0.47</td>
<td>1920 (100) vs. 1920 (100)</td>
<td>167 (100) vs. 167 (100)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>LVEF, %</strong></td>
<td>Mean ± SD: 46.2 ± 15.6 vs. 40.6 ± 15.9, p = 0.084</td>
<td>Median: 50 vs. 49, p = 0.91</td>
<td>Mean ± SD: 31.2 ± 13.7 vs. 31.4 ± 13.8, p = NR</td>
<td>NR</td>
<td>Mean ± SD: 49.0 ± 13.7 vs. 44.8 ± 16.6, p = 0.28</td>
<td>Mean ± SD: 57 ± 15 vs. 58 ± 13, p = 0.80</td>
</tr>
<tr>
<td><strong>Atrial fibrillation or Atrial flutter n (%)</strong></td>
<td>NR</td>
<td>13 (9) vs. 21 (15), p = 0.14</td>
<td>322 (16.8) vs. 323 (16.8) vs. 370 (19.3), p = NR</td>
<td>36 (22) vs. 30 (18), p = 0.4097</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Ischemic heart disease or Coronary artery disease n (%)</strong></td>
<td>11 (15.9) vs. 13 (18.8), p = 0.653</td>
<td>NR</td>
<td>870 (45.8) vs. 890 (46.4) vs. 857 (44.6), p = NR</td>
<td>NR</td>
<td>3 (7.1) vs. 6 (14.3), p = 0.48</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Ischemic cardiomyopathy n (%)</strong></td>
<td>NR</td>
<td>26 (19) vs. 41 (29), p = NR</td>
<td>NR</td>
<td>12 (7) vs. 12 (7), p = 1.00</td>
<td>NR</td>
<td>6 (9) vs. 5 (7), p = 1.0</td>
</tr>
<tr>
<td><strong>Nonischemic cardiomyopathy n (%)</strong></td>
<td>NR</td>
<td>28 (20) vs. 30 (21), p = NR</td>
<td>846 (44.1) vs. 832 (43.3) vs. 845 (44), p = NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Dilated cardiomyopathy n (%)</strong></td>
<td>25 (36.2) vs. 32 (46.4), p = 0.326</td>
<td>NR</td>
<td>846 (44.1) vs. 832 (43.3) vs. 845 (44), p = NR</td>
<td>25 (15) vs. 39 (23), p = 0.0516</td>
<td>7 (16.7) vs. 12 (28.6), p = 0.30</td>
<td>4 (6) vs. 5 (7), p = 1.0</td>
</tr>
<tr>
<td><strong>Hyperthrophic cardiomyopathy n (%)</strong></td>
<td>10 (14.5) vs. 4 (5.8), p = 0.091</td>
<td>NR</td>
<td>123 (6.4) vs. 122 (6.4) vs. 120 (6.3), p = NR</td>
<td>22 (13) vs. 18 (11), p = 0.5002</td>
<td>10 (23.8) vs. 3 (7.1), p = 0.07</td>
<td>41 (59) vs. 42 (61), p = 1.0</td>
</tr>
<tr>
<td><strong>Congenital heart disease n (%)</strong></td>
<td>3 (4.4) vs. 3 (4.4), p = 1.0</td>
<td>5 (4) vs. 12 (9), p = NR</td>
<td>Ebstein anomaly: 3 (0.2) vs. 1 (0.1) vs. 1 (0.1), Transposition of the great vessels: 0 (0.2) vs. 2 (0.1) vs. 1 (0.1), Tetralogy of Fallot: 6 (0.3), vs. 5 (0.3) vs. 9 (0.5), Arythymogenic right ventricular dysplasia: 11 (0.6) vs. 11 (0.6) vs. 6 (0.3), Common ventricle: 2 (0.1) vs. 0 vs. 0, p = NR</td>
<td>4 (9.5) vs. 5 (11.9), p = 1.0</td>
<td>1 (1) vs. 1 (1), p = 1.0</td>
<td>NR</td>
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<tr>
<td><strong>Electrical heart disease or Syndromes associated with sudden cardiac death or Genetic arrhythmia syndrome n (%)</strong></td>
<td>Electrical heart disease: 14 (20.3) vs. 2 (2.9), p = 0.002</td>
<td>Genetic arrhythmia syndrome: 75 (54) vs. 54 (39), p = NR</td>
<td>Syndromes associated with sudden cardiac death: Long QT syndrome: 68 (3.4) vs. 41 (2.1) vs. 77 (4) Short QT syndrome: 1 (0.1) vs. 0 vs. 1 (0.1) Brugada syndrome: 21 (1.1) vs. 28 (1.5) vs. 6 (0.3) Catecholaminergic polymorphic VT: 1 (0.1) vs. 3 (0.2) vs. 3 (0.2) Idiopathic VF: 17 (0.9) vs. 14 (0.7) vs. 18 (0.9)</td>
<td>NR</td>
<td>Electrical heart disease: 7 (16.7) vs. 2 (4.8), p = 0.16</td>
<td>Arrhythmogenic right ventricular cardiomyopathy: 7 (10) vs. 6 (9), p = 0.79</td>
</tr>
<tr>
<td><strong>Follow-up (months)</strong></td>
<td>Mean ± SD: 7.1 ± 4.5 months Max: 24 months</td>
<td>Median: 36 vs. 60 months, p &lt; 0.001 Max: 50 months</td>
<td>Max: In-hospital</td>
<td>Max: 6 months</td>
<td>Time since ICD implantation Mean ± SD: Subcutaneous ICD: 20.7 ± 10.6 months Single-chamber ICD: 31.4 ± 10.7 months</td>
<td></td>
</tr>
<tr>
<td><strong>Loss to follow-up, n (%)</strong></td>
<td>1 (1.4)</td>
<td>NR</td>
<td>0</td>
<td>0</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td><strong>Effectiveness</strong></td>
<td><strong>All-cause mortality n (%)</strong></td>
<td>Mean 7.1 months: Subcutaneous ICD: 1/69 (1.4) vs. Single-chamber ICD: 1/69 (1.4), p = NR</td>
<td>5 years: Subcutaneous ICD: 2/140 (1.4) vs. Single-dual-chamber ICD: 6/140/4.6 Kaplan-Meier analysis for survival: 96% vs. 94.8%, p = 0.42</td>
<td>In-Hospital: Subcutaneous ICD: 3/1920 (0.2) vs. Single-chamber ICD: 2/1920 (0.1), p &gt; 0.99 Subcutaneous ICD: 3/1920 (0.2) vs. Dual-chamber ICD: 1/1920 (0.05), p = 0.64</td>
<td>NR</td>
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<tr>
<td><strong>Appropriate shocks n (%)</strong></td>
<td>Mean 7.1. months: Subcutaneous ICD: 3/69 (4.3) vs. Single-chamber ICD: 9/69 (13.0), p = 0.05</td>
<td></td>
<td></td>
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<td></td>
<td>Mean 2.6 years: Subcutaneous ICD: 1/42 (2.4) vs. Single-chamber ICD: 7/42 (16.7), p = 0.06</td>
</tr>
<tr>
<td>5 years: Subcutaneous ICD: 12/140 (8.6) vs. Single/dual-chamber ICD: 24/140 (17.2)</td>
<td>Kaplan-Meier analysis: 17.0% (95% CI: 6.3–26.4) vs. 21.3% (95% CI: 12.6–27.3)</td>
<td>Single/dual-chamber ICD: HR with adjustment for ICD programming: 1.46; p = 0.36</td>
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<tr>
<td><strong>Quality of life</strong></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>12-item Short-Form Health Survey (SF-12)</td>
<td>0 = poorest possible, 100 = best possible</td>
<td>Physical QoL*: Mean (95% CI): Baseline: 40.48 (38.69–42.27) vs. 40.77 (39.12–42.42), p = 0.8157</td>
<td>7 months: 43.56 (41.79–45.34) vs. 43.85 (42.22–45.48), p = 0.8157</td>
<td>Mental QoL*: Mean (95% CI): Baseline: 42.39 (40.60–44.19) vs. 42.25 (40.59–43.92), p = 0.9080</td>
<td>3 months: 45.86 (44.04–47.68) vs. 45.72 (44.04–47.40), p = 0.9080</td>
<td>6 months: 45.19 (43.29–47.09) vs. 45.05 (43.28–46.81), p = 0.9080</td>
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<td>---------------------</td>
<td>------------------</td>
<td>----------------</td>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inappropriate shocks n (%)</strong></td>
<td>Mean 7.1 months: Subcutaneous ICD: 5/69 (7.2) vs. Single chamber ICD: 3/69 (4.3), p = NR</td>
<td>5 years: Subcutaneous ICD: 20/140 (14.3) vs. Single/dual-chamber ICD: 22/140 (15.7) Kaplan-Meier analysis: 20.5% (95% CI: 11.5-28.6) vs. 19.1% (95% CI: 11.6-26.0) Single/dual-chamber ICD HR with adjustment for ICD programming: 0.85, p = 0.64</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Mean 2.6 years: Subcutaneous ICD: 3/69 (4.3) vs. Single/dual-chamber ICD: 6/69 (8.7), p = 0.49</td>
</tr>
<tr>
<td><strong>Lead complications n (%)</strong></td>
<td>Mean 7.1 months: Subcutaneous ICD: 0/69 (0) vs. Single chamber ICD: 2/69 (2.9), p = NR</td>
<td>5 years: Subcutaneous ICD: 1/140 (0.7) vs. Single/dual-chamber ICD: 17/140 (12.1) Kaplan-Meier analysis: 0.8% (95% CI: 0.0-2.2) vs. 11.5% (95% CI: 5.3-17.2), p = 0.03</td>
<td>In-Hospital: Subcutaneous ICD: 2/1920 (0.1) vs. Single-chamber ICD: 4/1920 (0.2), p = NR Subcutaneous ICD: 2/1920 (0.1) vs. Dual-chamber ICD: 12/1920 (0.6), p = NR</td>
<td>NR</td>
<td>NR</td>
<td>Mean 2.6 years: Subcutaneous ICD: 0/69 (0) vs. Single/dual-chamber ICD: 6/69 (8.7), p = 0.028</td>
</tr>
<tr>
<td><strong>Infections n (%)</strong></td>
<td>Mean 7.1 months: Subcutaneous ICD: 1/69 (1.4) vs. Single-chamber ICD: 1/69 (1.4), p = NR</td>
<td>5 years: Subcutaneous ICD: 5/140 (3.6) vs. Single/dual-chamber ICD: 4/140 (2.9) Kaplan-Meier analysis: 4.1% (95% CI 0.5-7.7) vs. 3.6% (95% CI: 0.0-7.1), p = 0.36</td>
<td>In-Hospital: Subcutaneous ICD: 1/1920 (0.05) vs. Single-chamber ICD: 0/1920 (0), p = NR Subcutaneous ICD: 1/1920 (0.05) vs. Dual-chamber ICD: 2/1920 (0.1), p = NR</td>
<td>NR</td>
<td>NR</td>
<td>Mean 2.6 years: Subcutaneous ICD: 1/69 (1.4) vs. Single/dual-chamber ICD: 4/69 (5.8), p = 0.37</td>
</tr>
</tbody>
</table>

6 months: Subcutaneous ICD: 3/91 (3.3) vs. Single-chamber ICD: 1/91 (1.1), p = NR
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<thead>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haematoma n (%)</strong></td>
<td>Mean 7.1 months:&lt;sup&gt;h&lt;/sup&gt;</td>
<td>NR</td>
<td>In-Hospital: Subcutaneous ICD: 7/1920 (0.4) vs. Single-chamber ICD: 1/1920 (0.05), p = 0.07</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>&lt;6 months:&lt;sup&gt;i&lt;/sup&gt; Subcutaneous ICD: 1/91 (1.1) vs. Single-/dual-chamber ICD: 0/91 (0), p = 1.0</td>
</tr>
<tr>
<td><strong>Pericardial tamponade n (%)</strong></td>
<td>NR</td>
<td>NR</td>
<td>In-Hospital: Subcutaneous ICD: 0/1920 (0), p = NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Abbreviations:** AHA = American Heart Association, ACC = American College of Cardiology, ATP = antitachycardia pacing, HR = Hazard ratio, ICD = implantable cardioverter-defibrillator, ESC = European Society of Cardiology, LVEF = Left ventricular ejection fraction, pts = Patients, NR = not reported, VF = ventricular fibrillation, VT = ventricular tachycardia, TV = transvenous, SC = single chamber, S-ICD = Subcutaneous ICD, PRAETORIAN = Prospective, RAndomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy) trial, QoL = Quality of life, CI = Confidence Interval, CRT = Cardiac Resynchronization Therapy, TV-ICD = Transvenous ICD, SF-12 = 12-Item Short Form Health Survey,

**Explanations:**
- <sup>a</sup> Adjusted for confounders
- <sup>b</sup> Reported as lead revision
- <sup>c</sup> Reported as lead dislodgement
- <sup>d</sup> Reported as lead-related complications resulting in lead intervention
- <sup>e</sup> Reported as infection requiring revision
- <sup>f</sup> Reported as device infection
- <sup>g</sup> Reported as infection requiring explant
- <sup>h</sup> Reported as Haematoma requiring revision
- <sup>i</sup> Reported as Haematoma requiring intervention
Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement, a third researcher was involved to solve the differences.

Table A-2: Risk of bias – study level (observational studies) [11]*

<table>
<thead>
<tr>
<th>Study Author, Year</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Representative ness of the exposed cohort</td>
<td>Selection of the non exposed cohort</td>
<td>Ascertainment of exposure</td>
</tr>
<tr>
<td>Köbe, 2013 [6]</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Brouwer, 2016, [7]</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Friedman, 2016, [10]</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pedersen, 2016 [5]</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mithani, 2017 [4]</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Honarbakhs, 2017 [9]</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Köbe, 2017 [8]</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

* A study can be awarded a maximum of one point (= star) for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.
## Table A-3: Risk of bias – study level (systematic review), see [12]

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Research question and inclusion criteria include the components of PICO</td>
<td>Yes</td>
</tr>
<tr>
<td>Explicit statement that the review methods were established prior to the conduct of the review</td>
<td>No</td>
</tr>
<tr>
<td>Explain their selection of the study designs for inclusion in the review</td>
<td>Yes</td>
</tr>
<tr>
<td>Comprehensive literature search strategy</td>
<td>Yes</td>
</tr>
<tr>
<td>Perform study selection in duplicate</td>
<td>Yes</td>
</tr>
<tr>
<td>Perform data extraction in duplicate</td>
<td>Yes</td>
</tr>
<tr>
<td>Provide a list of excluded studies and justify the exclusions</td>
<td>No</td>
</tr>
<tr>
<td>Describe the included studies in adequate detail</td>
<td>Yes</td>
</tr>
<tr>
<td>Satisfactory technique for assessing the risk of bias (RoB) in individual studies</td>
<td>Yes</td>
</tr>
<tr>
<td>Report on the sources of funding for the studies included in the review</td>
<td>No</td>
</tr>
<tr>
<td>Appropriate methods for statistical combination of results</td>
<td>Yes</td>
</tr>
<tr>
<td>Assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis</td>
<td>No</td>
</tr>
<tr>
<td>Account for RoB in individual studies when interpreting/discussing the results of the review</td>
<td>No</td>
</tr>
<tr>
<td>Satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review</td>
<td>No</td>
</tr>
<tr>
<td>Adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?</td>
<td>Yes</td>
</tr>
<tr>
<td>Report any potential sources of conflict of interest, including any funding they received for conducting the review?</td>
<td>Yes</td>
</tr>
<tr>
<td>Rating for overall confidence in the results of the review</td>
<td>Moderate*</td>
</tr>
</tbody>
</table>

Moderate – More than one non-critical weakness*: The systematic review has more than one weakness, but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review. [12].
Table A-4: Evidence profile: comparative effectiveness and safety of the subcutaneous and transvenous ICD in patients at increased risk for sudden cardiac death

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
</tr>
<tr>
<td>№ of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>Mortality (in-hospital) [10]</td>
<td>1</td>
<td>observational studies</td>
<td>not serious</td>
</tr>
<tr>
<td>Mortality (up to 6 months) [4]</td>
<td>1</td>
<td>observational studies</td>
<td>serious b</td>
</tr>
<tr>
<td>Mortality (up to 5 years) [7]</td>
<td>1</td>
<td>observational studies</td>
<td>not serious</td>
</tr>
<tr>
<td>Appropriate shocks (7.1 months) [6]</td>
<td>1</td>
<td>observational studies</td>
<td>serious b</td>
</tr>
<tr>
<td>Appropriate shocks (up to 5 years) [7]</td>
<td>1</td>
<td>observational studies</td>
<td>not serious</td>
</tr>
<tr>
<td>Inappropriate shocks [3] pooled Data of [4, 6, 7, 9]</td>
<td>4</td>
<td>observational studies</td>
<td>serious b</td>
</tr>
<tr>
<td>Lead complications [3] pooled Data of [6, 7, 9, 10]</td>
<td>4</td>
<td>observational studies</td>
<td>serious b</td>
</tr>
<tr>
<td>Infections [3] pooled Data of [4, 6, 7, 9, 10]</td>
<td>5</td>
<td>observational studies</td>
<td>serious b</td>
</tr>
</tbody>
</table>
## Quality assessment

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Subcutaneous ICD</th>
<th>Transvenous ICD</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial tamponade [9, 10]</td>
<td>2</td>
<td>observational studies</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>0/1989 (0.0%)</td>
<td>6/3909 (0.2%)</td>
<td>RR ranged from 0.18 to 0.33</td>
<td>not estimable</td>
</tr>
<tr>
<td>Haematoma [4, 6, 10]</td>
<td>3</td>
<td>observational studies</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>9/2080 (0.4%)</td>
<td>3/4000 (0.1%)</td>
<td>RR ranged from 3.0 to 3.5</td>
<td>not estimable</td>
</tr>
<tr>
<td>Quality of life – physical well-being score [8] (assessed with: 12-item Short-Form Health Survey (SF-12))</td>
<td>1</td>
<td>observational studies</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>42</td>
<td>42</td>
<td>MD 6.7 higher (1.88 higher to 11.52 higher)</td>
<td>⬤ ◯◯◯ ◯◯◯ ◯ ◯</td>
</tr>
<tr>
<td>Quality of life – physical well-being score [5] (assessed with: 12-item Short-Form Health Survey (SF-12))</td>
<td>1</td>
<td>observational studies</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>167</td>
<td>167</td>
<td>MD 0.2 lower (2.67 lower to 2.27 higher)</td>
<td>⬤ ◯◯◯ ◯◯◯ ◯ ◯</td>
</tr>
<tr>
<td>Quality of life – mental well-being score [8] (assessed with: 12-item Short-Form Health Survey (SF-12))</td>
<td>1</td>
<td>observational studies</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>42</td>
<td>42</td>
<td>MD 0.1 higher (4.43 lower to 4.63 higher)</td>
<td>⬤ ◯◯◯ ◯◯◯ ◯ ◯</td>
</tr>
<tr>
<td>Quality of life – mental well-being score [5] (assessed with: 12-item Short-Form Health Survey (SF-12))</td>
<td>1</td>
<td>observational studies</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>167</td>
<td>167</td>
<td>MD 0.15 higher (2.44 lower to 2.74 higher)</td>
<td>⬤ ◯◯◯ ◯◯◯ ◯ ◯</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI = Confidence interval; RR = Risk ratio; HR = Hazard Ratio; OR = Odds ratio; MD = Mean difference

**Explanations:**

- **a** Effect estimates include appreciable benefit and harms
- **b** Two studies with high risk of bias [4, 6]
- **c** Small number of events
- **d** Sample size does not meet optimal information size.
- **e** Studies with high or medium risk of bias
- **f** Sample size does not meet optimal information size.
**Applicability table**

Table A-5: Summary table characterising the applicability of a body of studies

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description of applicability of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Patients populations of included studies reflect real-world conditions with respect to age, sex, underlying cardiac condition and comorbidities.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Included studies evaluated the subcutaneous ICD, produced by one manufacturer.</td>
</tr>
<tr>
<td>Comparator</td>
<td>Transvenous ICDs is considered as an established medical device, which is available from different manufacturers as single- or dual-chamber ICD.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Included studies reported several efficacy and safety outcomes, however, follow-up duration considerably differs among studies. Thus, long-term complications are only reflected by one study.</td>
</tr>
<tr>
<td>Setting</td>
<td>Studies were conducted in real-world settings.</td>
</tr>
</tbody>
</table>

**List of ongoing randomised controlled trials**

Table A-6: List of ongoing randomised controlled trials of subcutaneous ICD

<table>
<thead>
<tr>
<th>Identifier/Trial name</th>
<th>Patient population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Primary Outcome</th>
<th>Primary completion date</th>
<th>Sponsor and Collaborator:</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01296022 PRAETORIAN</td>
<td>Patients 18 years and older with class I or IIa indication for ICD therapy according to the ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death Estimated enrollment: 850 patients</td>
<td>Subcutaneous ICD</td>
<td>Transvenous ICD</td>
<td>Number of participants with implantable cardioverter defibrillator (ICD) related adverse events (48 months)</td>
<td>Estimated: December 2019</td>
<td>Academisch Medisch Centrum-Universiteit van Amsterdam (AMC-UvA) Boston Scientific Corporation</td>
</tr>
<tr>
<td>NCT02881255 ATLAS S-ICD</td>
<td>Patient is ≥18-60 years old AND has a standard indication for ICD; OR Patient is ≥18 years old AND has any one of the following present: An inherited arrhythmia syndrome (i.e. Long QT, Brugada, ARVC, hypertrophic or dilated cardiomyopathy, early repolarization syndrome, idiopathic ventricular fibrillation, etc.), prior pacemaker or ICD removal for infection, need for hemodialysis, prior heart valve surgery (repair or replacement), Chronic obstructive pulmonary disease (with FEV1 &lt; 1.5 L) Estimated enrollment: 500 patients</td>
<td>Subcutaneous ICD (Boston Scientific EMBLEM™)</td>
<td>Single-chamber, transvenous ICD</td>
<td>Composite of lead-related perioperative complications (6 months) Additional safety composite (6 months)</td>
<td>Estimated: August 2018</td>
<td>Population Health Research Institute Boston Scientific Corporation</td>
</tr>
</tbody>
</table>

**Abbreviations:** ATALS = Avoid Transvenous Leads in Appropriate Subjects, PRAETORIAN = Prospective, RAnomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy, ICD = Implantable cardioverter defibrillator
## Literature search strategies

### Search strategy for Pubmed

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<td>Search (#1 OR #8)</td>
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<td>Search #9 NOT #10</td>
</tr>
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Total: 410 Hits

### Search strategy for Embase.com (Elsevier)

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<td>'implantable cardioverter defibrillator'/exp AND subcutaneous*</td>
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<td>#1 OR #2 OR #3</td>
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<td>'animal'/exp NOT 'human'/exp</td>
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<td>#6</td>
<td>#4 NOT #5</td>
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<td>#7 NOT #8</td>
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Total: 341 Hits
### Search strategy for Cochrane Library (Wiley)

Search Name: Subcutaneous ICD  
Search Date: November 23rd, 2017  

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<td>#2</td>
<td>subcutaneous* near/4 (defibrillator* or Cardioverter* or ICD)</td>
</tr>
<tr>
<td>#3</td>
<td>subcutaneous*:ti,ab,kw</td>
</tr>
<tr>
<td>#4</td>
<td>[mh &quot;Defibrillators, implantable&quot;]</td>
</tr>
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<td>#5</td>
<td>cardioverter*:ti,ab,kw</td>
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<tr>
<td>#6</td>
<td>defibrillator*:ti,ab,kw</td>
</tr>
<tr>
<td>#7</td>
<td>ICD:ti,ab,kw</td>
</tr>
<tr>
<td>#8</td>
<td>{or, #4~#7}</td>
</tr>
<tr>
<td>#9</td>
<td>#3 and #8</td>
</tr>
<tr>
<td>#10</td>
<td>#1 or #2 or #9</td>
</tr>
<tr>
<td>#11</td>
<td>#10 Publication Year from 2000 to 2017</td>
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### Search strategy for CRD Databases

Search Name: Subcutaneous ICD  
Search Date: November 23rd, 2017  

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<tbody>
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</tr>
<tr>
<td>#2</td>
<td>(Subcutaneous*)</td>
</tr>
<tr>
<td>#3</td>
<td>#1 AND #2</td>
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<td>(S-ICD)</td>
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</tr>
<tr>
<td>#6</td>
<td>#3 OR #4 OR #5</td>
</tr>
<tr>
<td></td>
<td>Total: 5 Hits</td>
</tr>
</tbody>
</table>