Subcutaneous implantable cardioverter defibrillator (ICD)

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

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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
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.

sudden cardiac death: major public health issue
common cause: ventricular tachyarrhythmias due to underlying cardiac conditions

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).

Implantable cardioverter-defibrillator (ICD): established conventional ICD with transvenous lead(s)

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).

promising relatively new alternative: ICD with subcutaneous leads

prerequisite: no indication for pacing therapy for bradycardia, anti-tachycardia, or resynchronization

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].

NICE guidance document: current evidence on efficacy and safety supports the use of the subcutaneous ICD

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.

Research question: comparative effectiveness and safety of subcutaneous ICD vs. transvenous ICD

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

Electronic search in 4 databases

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.

dual study selection, data extraction, risk of bias assessment and rating of the quality of evidence

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

effectivness and safety: 7 observations studies (n = 6,916 patiens) 1 systematic review (n = 6,498 patients)

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].

risk of bias observational studies: high for 3 studies medium for 4 studies

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].

subcutaneous ICD vs. transvenous single-chamber or dual-chamber ICD

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

effectiveness: 7 studies

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].

overall mortality, rate of appropriate shock and mental quality of life: no statistically significant differences

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).

quality of evidence: very low

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.

safety:
5 observational studies:
no statistically significant differences for inappropriate shocks, infections and haematomas,

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].

yet fewer lead complications with subcutaneous ICD

The quality of evidence for safety outcomes is very low.

quality of evidence:
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.

ongoing RCT:
PRAETORIAN trial (ClinicalTrials.gov NCT01296022)
subcutaneous ICD vs. transvenous ICD

planned sample size:
850 patiens

completion estimated:
December 2019

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.

comparative evidence subcutanous ICD vs. transvenous ICD:
7 observational studies and 1 systematic review

The available body of evidence has several limitations.

risk of bias and other 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.

different follow-up duration of included studies from in-hospital up to 5 years.

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.

despite matching baseline characteristics different in some studies

inprecision: only few events for most of the endpoints

Third, for most effectiveness and safety endpoints, only few events occurred, limiting precision of the findings.

results from large RCT are pending

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

current evidence insufficient to conclude about comparative effectiveness, however substantially lower risk for lead complications with subcutaneous ICD

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

plötzlicher Herztod: Public Health Problem

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.

häufigste Ursache: ventrikuläre Tachyarrhythmie aufgrund angeborener oder erworbener Herzerkrankungen

Beschreibung der Technologie

Implantierbarer Kardioverter-Defibrillator (ICD): etablierter konventioneller ICD mit transvenösen Sonden

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

relativ neu: ICD mit subkutaner Sonde

Voraussetzung: keine Indikation für Herzschrittmacher, antitachykarde Stimulation oder kardiale Resynchronisation

Als vielversprechende Alternative zum seit Jahrzenten verwendeten transvenösen ICD steht seit einigen Jahren der subkutane ICD zur Verfügung, um Kurz- und Langzeitkomplikationen einer transvenös implantierten Sonde und den direkten Kontakt mit dem Herzen zu vermeiden. Zu den Komplikationen, die mit der Implantation einer tranvenösen Sonde einhergehen können, zählen insbesondere Ventrikelperforation, Penumothorax, Sondenbrüche, Isolationsdefekte der Sonden, Infektionen wie Sonden-Endokarditis und venöse Thrombosen. Voraussetzung für die Implantation eines subkutanen ICD ist jedoch, dass kein Stimulationsbedarf bei Bradykardie, kein Bedarf an antitachykarder Stimulation (antitachykardes Pacing, ATP) oder keine Indikation für eine Kardiale-Resynchronisationstherapie (CRT) besteht.

NICE Guidance Dokument: derzeitige Evidenz zeigt Wirksamkeit und Sicherheit

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

Forschungsfrage: Vergleich der Wirksamkeit und Sicherheit subkutaner ICD vs. transvenöser ICD

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

systematische Literatursuche in 4 Datenbanken

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.

duale Studienauswahl, Datenextraktion, Bewertung des Bias-Risikos sowie der Qualität der Evidenz nach GRADE

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.

Die verfügbare Evidenz einzelner Studien fassten wir narrativ zusammen. Weiters beschreiben wir die Ergebnisse der Random-Effekts-Meta-Analysen einer systematischen Übersichtsarbeit [3]. Wir führten deshalb keine neuen Meta-Analysen durch.

Ergebnisse

Verfügbare Evidenz

verfügbare Evidenz: Wirksamkeit und Sicherheit : 7 vergleichende Beobachtungsstudien (n = 6.916 PatientInnen) 1 Systematischer Review (n = 6.498 PatientInnen)

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].

Bias-Risiko der eingeschlossenen Beobachtungsstudien: hoch für 3 Studien medium für 4 Studien

Zwei Autoren bewerteten das Bias-Risiko der eingeschlossenen Beobachtungsstudien mit der Newcastle-Ottawa Scale [11]. Drei Studien [4, 6, 8] wurden mit hohem Bias-Risiko, vier Studien mit mittleren Bias-Risiko [5, 7, 9, 10] eingestuft. Den einzigen systematischen Review bewerteten wir mit niedrigem Bias-Risiko mittels der Checkliste AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews) [12].

Matching mit Propensity-Score: 4 Studien

In vier Studien [5, 7, 9, 10] wurde die Kontrollgruppe mittels Propensity Score ausgewählt, um Gruppen zu erhalten, die ein ähnliches Risiko aufweisen, 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].

Subkutaner ICD vs. transvenöser Ein- oder Zweikammer-ICD

Klinische Wirksamkeit

Wirksamkeit: 7 Beobachtungs-studien

Drei Studien mit 6.222 PatientInnen berichten über Mortalität [4, 7, 10]. Der Unterschied zwischen PatientInnen, die einen subkutanen ICD oder einen transvenösen ICD bekommen 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].

Gesamtmortalität, adäquate Schocks und mentale Lebensqualität: kein statistisch signifikanter Unterschied

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 Survery (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).

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.

Sicherheit:
5 Beobachtungsstudien:
kein statistisch signifikanter Unterschied bei inadäquaten Schocks, Infektionen und Hämatomen;
Sondenkomplikationen statistisch signifikant seltener mit subkutanem ICD;
Qualität der Evidenz: sehr niedrig

Laufende Studien

Bei unserer Suche haben wir das Studienprotokoll der randomisiert kontrollierten Multicenter-Studie PRAETORIAN (Prospective, RAndomizEd comparison of subcutaneous and tRansvenous ImplANtable cardioverter-defibrillator therapy) gefunden [13]. Diese Studie plant 850 PatientInnen mit Indikationen für einen ICD, zu einem subkutanen oder transvenösen ICD zu randomisieren (1:1) [14]. Die Fallzahl wurde berechnet um Nichtunterlegenheit und/oder Überlegenheit des subkutanen ICD in Bezug auf einen kombinierten, primären Endpunkt (inadäquater Schock oder ICD-assoziierte Komplikationen innerhalb von 48 Monaten) zu zeigen. Nach dem ClinicalTrials.gov Eintrag (NCT01296022) wird die Studie voraussichtlich im Dezember 2019 beendet [14]. Deshalb liegen derzeit noch keine Resultate vor.

laufender RCT:
PRAETORIAN trial (ClinicalTrials.gov NCT01296022)
Subkutaner vs. transvenöser ICD
Geplante Anzahl an StudienteilnehmerInnen:
850 PatientInnen
Voraussichtliches Ende:
Dezember 2019

Diskussion

Wie dieser Review zeigt, ist die Evidenz bezüglich Vergleichs des subkutanen mit dem transvenösen ICD auf kontrollierte Beobachtungsstudien mit oder ohne Propensity-Score-Matching beschränkt. Ein rezent publizierter Systematischer Review mit Meta-Analysen hat die Ergebnisse einiger dieser Studien zusammengefasst und analysiert. Die vorliegende Evidenz zeigte keinen statistisch signifikanten Unterschied bei PatientInnen, die einen subkutanen ICD oder einen transvenösen Ein- oder Zweikammer-ICD erhielten in Bezug auf Gesamtmortalität, adäquaten und inadäquaten Schocks, Infektionen, Hämatome, und mentaler Lebensqualität. Sondenkomplikationen waren jedoch statistisch signifikant seltener bei PatientInnen, die einen subkutanen ICD erhalten hatten als bei PatientInnen mit transvenösem ICD. Dabei muss berücksichtig werden, dass bei einem subkutanen ICD die Sonde nicht transvenös platziert wird und auch kein direkter Kontakt mit kardialen Strukturen besteht.

Vergleichsstudien subkutaner ICD vs. transvenöser ICD:
7 Beobachtungsstudien und
1 Systematischer Review

Die verfügbare Evidenz hat einige Einschränkungen.

Der Beobachtungszeitraum unterscheidet sich deutlich zwischen den einzelnen Studien und reichte von der Dauer des Krankenhausaufenthaltes bis zu fünf Jahre nach ICD-Implantation. Deshalb könnte es sein, dass in den meisten Studien Langzeitkomplikationen nicht abgebildet wurden. Außerdem sind aufgrund der Variabilität des Follow-Up-Zeitraumes die Ergebnisse der Random-Effects-Meta-Analyse nur eingeschränkt aussagekräftig.

Bias-Risiko und andere Einschränkungen

unterschiedliche Beobachtungs-zeiträume der Studien

Baseline-PatientInnen-Charakteristika trotz Matching unterschiedlich in manchen Studien

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 weiters, dass nicht alle Studien PatientInnen in der Kontrollgruppe mit transvenösem ICD mit Indikation für Herzschrittmacher, antitachykarde Stimulation oder kardialer Resynchronisations-Therapie ausschlossen. Deshalb könnten ungleichmäßig verteilte prognostische Faktoren die Ergebnisse beeinflusst haben.

eingeschränkte Präzision aufgrund weniger Ergebnisse bei einigen Endpunkten

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

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

Empfehlung

Evidenz derzeit unzureichend für den Vergleich der Wirksamkeit, jedoch deutlich geringeres Risiko für Sondenkomplikationen mit subkutanen ICD

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?

PIKO-Frage

1.2 Inclusion criteria

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

Einschlusskriterien für relevante Studien

Table 1-1: Inclusion criteria

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	
Effectiveness	✪ Randomized controlled trials ✪ Observational studies with control group ✪ Systematic reviews **Excluded:** conference abstracts, narrative reviews, letters to the editor, case reports, case series, retrospective and prospective single-arm studies
Safety	✪ Randomized controlled trials ✪ Observational studies with control group ✪ Systematic reviews **Excluded:** conference abstracts, narrative reviews, letters to the editor, case reports, retrospective and prospective single-arm studies

2 Methods

2.1 Research questions

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

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

Clinical Effectiveness	
Element ID	**Research question**
D0001	What is the expected beneficial effect of the subcutaneous ICD on mortality?
D0005	How does the subcutaneous ICD affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of the technology on patients' body functions?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of the subcutaneous ICD on generic health-related quality of life?
D0013	What is the effect of the t subcutaneous ICD on disease-specific quality of life?

Safety	
Element ID	**Research question**
C0008	How safe is the subcutaneous ICD in comparison to the transvenous ICD?
C0002	Are the harms related to dosage or frequency of applying the technology?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the subcutaneous ICD?
C0007	Are the subcutaneous ICD and transvenous ICD associated with user-dependent harms?

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

systematische Literatursuche in 4 Datenbanken

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.

Suche nach laufenden Studien; Kontaktaufnahme mit Herstellern

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.

insgesamt 740 Referenzen identifiziert

2.4 Flow chart of study selection

Literaturauswahl

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.

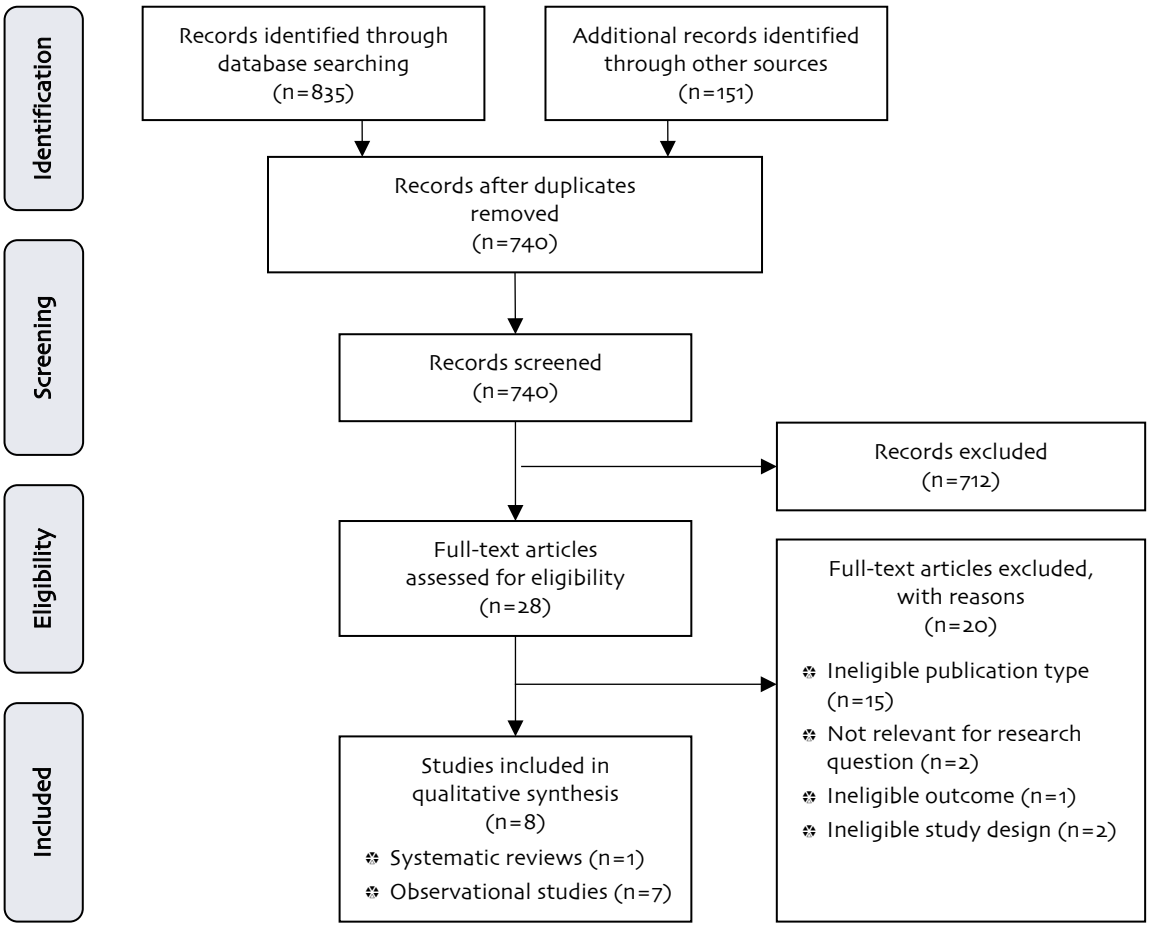

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.5 Analysis

Datenextraktion in Tabellen

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.

Zusammenfassung der Ergebnisse einer Random-Effects Meta-Analyse eines rezent publizierten systematischen Reviews

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.

Risk of Bias Bewertung mit Newcastle-Ottawa Scale und AMSTAR-2

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

Zusammenfassung der Ergebnisse

Bewertung der Qualität der Evidenz mit GRADE

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

B0001 – What is the subcutaneous and the transvenous ICD?

subkutaner und transvenöser 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].

detektieren und beenden lebensbedrohliche Tachyarrhytmien durch Schockabgabe

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].

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

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]

A0020 – For which indications has subcutaneous ICD received marketing authorisation or CE marking?

Indikation: Prävention des plötzlichen Herztodes

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.

B0002 – What is the claimed benefit of the subcutaneous ICD in relation to the transvenous ICD?

Vorteile des subkutanen ICD: keine Implantation einer transvenösen Sonde und dadurch auch kein direkter Kontakt mit kardialen Strukturen

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].

B0003 – What is the phase of development and implementation of the subcutaneous ICD and transvenous ICD?

Subkutaner ICD: 2009 CE-Kennzeichnung 2012 FDA Zulassung 2015 CE Kennzeichnung EMBLEM™ S-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.

Transvenöser ICD: Seit fast 30 Jahren implantiert Wirksamkeit mehrfach in RCTs gezeigt

After first human implantation in 1980 [21], the transvenous ICD has been now 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)

B0004 – Who administers the subcutaneous ICD and transvenous ICD and in what context and level of care are they provided?

Implantation: Erfahrene/r interventionelle/r Kardiologe/In oder HerzchirurgIn

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

B0008 – What kind of special premises are needed to use the subcutaneous and transvenous ICD?

Herzkatheterlabor oder Operationssaal

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

B0009 – What supplies are needed to use subcutaneous ICD and transvenous ICD?

Implantation unter Regionalanästhesie

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

A0021 – What is the reimbursement status of the subcutaneous ICD?

derzeit nicht im Leistungskatalog abgebildet

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?

verschiedene angeborene oder erworbene Herzerkrankungen führen zu einem erhöhten Risiko für plötzlichen Herztod

Subkutaner ICD: Voraussetzung keine Indikation für Herzschrittmacher, antitachykarde Stimulation oder kardiale Resynchronisation

Anwendung des subkutanen ICD zB bei kompliziertem Venenzugang, hohem Infektionsrisiko, junge PatientInnen mit Ionenkanalerkrankungen oder Kardiomyopathie

Primäre und sekundäre Prävention des plötzlichen Herztodes

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, short 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?

junge PatientInnen: Ionenkanalerkrankungen, Myokarditis, Kardiomyopathien
ältere PatientInnen: Koronare Herzkrankheit, Herzklappen erkrankungen, Herzinsuffizienz

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?

sudden cardiac death: major public health issue common cause: ventricular tachyarhythmias due to underlying cardiac conditions

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?

Basisdiagnostik: Anamnese, Physikalische Krankenuntersuchung, EKG, Echokardiographie

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).

weitere Abklärung je nach Verdachtsdiagnose

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?

ESC Leitlinie: Subkutaner ICD sollte bei Patientinnen ohne Notwenigkeit für Schrittmacher, antitachykardes Pacing oder Resynchronisations Therapie erwogen werden (Klasse IIa, Level C) kann bei schwierigem Venenzugang, nach Entfernung eines transvenösen ICDs aufgrund einer Infektion oder bei jungen PatientInnen erwogen werden (Klasse IIa, Level C

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-threating 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)*

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

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

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.

PatientInnen mit angeborenere oder erworberener Herzerkrankung die mit einem erhöhten Risiko des plötzlichen Herztodes assoziiert sind

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]

Primäre oder sekundäre Prävention des plötzlichen Herztodes

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].

Österreich: 2013: 1.296 ICD Implantationen

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].

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).

eingeschlossene Publikationen:
7 Beobachtungsstudien mit 6.916 PatientInnen

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

1 Systematischer Review mit Meta-Analyse aus 5 dieser Beobachtungsstudien

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].

Follow-up Zeitraum der identifizierten Studien sehr variabel:
Krankenhausaufenthalt bis 5 Jahre

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.

größte retrospektive Beobachtungsstudie mit Propensity Score Matching analysierte Daten von 5.760 PatientInnen aus dem NCDR ICD Register

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?

Gesamtmortalität: 3 Beobachtungsstudien, kein statistisch signifikanter Unterschied

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].

Größte Studien mit 5.760 Patientinnen Krankenhausmortalität 0,2 % vs. 0,1 %, p > 0,99

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].

Studien mit längster Beobachtungszeit und 280 PatientInnen: 5-Jahres-Überleben: 96,0 % vs. 94,8 %, p = 0,42

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

adäquate Schockabgabe: in 3 Studien numerisch weniger bei PatientInnen mit subkutanen ICD als mit transvenösen ICD Unterschiede jedoch statistisch nicht signifikant

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.

z. B.: eine Studie mit 280 PatientInnen: Kaplan-Meier Analyse Adäquate Schockabgabe 5-Jahre: 17,0 % vs. 21,3 % HR 0.68, p = 0,36

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: 6.3–26.4) 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

keine Evidenz vorhanden

Function

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

No evidence was found to answer this research question.

keine Evidenz vorhanden

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

No evidence was found to answer this research question.

keine Evidenz vorhanden

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].

Lebensqualität gemessen mit SF-12: 2 Studien

One study compared the quality of life in patients with subcutaneous ICD from the prospective, multicentre, observational substudy of the EFFORTLESS S-ICD[1] 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].

Darunter 1 Beobachtungsstudie mit Propensity Score Matching und 334 PatientInnen

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].

Physische und mentale Lebensqualität nach subkutanen und transvenösen ICD ähnlich zu Beginn, nach 3 und 6 Monaten

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 statisti-

[1] Evaluation oF FactORs ImpacTing CLinical Outcome and Cost EffectiveneSS of the S-ICD

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:

Kritische Endpunkte zur Sicherheit

- 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.

5 Beobachtungsstudien und
1 systematischer Review

6.3 Results

Patient safety

C0008 – 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].

Inadäquate Schockabgabe:
4 Beobachtungsstudien

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].

Meta-Analyse mit
4 Studien und
738 PatientInnen OR
0,87 (95 % KI: 0,51-1,49)

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

Sonden-Komplikationen: 4 Beobachtungsstudien mit 6.316 PatientInnen

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-Analyse mit 4 Studien: statistisch signifikant weniger Sondenkomplikationenmit subkutanem ICD OR 0,13 (95 % KI: 0,05-0,38)

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

Infektionen: 5 Beobachtungsstudien mit insgesamt 6.498 PatientInnen

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].

Meta-Analyse mit 5 Studien: kein statistisch signifikanter Unterschied OR 0,75 (95 % KI: 0,30-1,89)

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: 0.05% [1 of 1,920], transvenous single-chamber ICD: 0% [0 of 1,920], transvenous dual-chamber ICD 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

Hämatome: 3 Studien selten in beiden Gruppen

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].

Größte Studie: Implantation des subkutanen und transvenösen Einkammer-ICD keine Perikardtamponade, 5 bei Implantation eines Zweikammer-ICD

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

keine Evidenz zu den Endpunkten Schweregrad, sensible PatientInnengruppen

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

und anwenderabhängige Schäden vorhanden

7 Quality of evidence

Qualität der Evidenz nach GRADE

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.

Qualität der Evidenz ist sehr niedrig

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

Bias Risiko ist hoch für 3 und mittel für 4 Beobachtungsstudien

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with transvenous ICD	Risk with subcutaneous ICD				
Mortality (In-hospital) [10]	1 per 1.000	**2 per 1.000** (0 to 8)	**RR 2.0** (0.4 to 9.9)	5760 (1 observational study)	⨁◯◯◯ VERY LOW [a]	
Mortality (up to 6 months) [4]	22 per 1.000	**22 per 1.000** (3 to 153)	**RR 1.00** (0.14 to 6.95)	182 (1 observational study)	⨁◯◯◯ VERY LOW [b,c,d]	
Mortality (up to 5 years) [7]	43 per 1.000	**0 per 1.000** (0 to 0)	not estimable	280 (1 observational study)	⨁◯◯◯ VERY LOW [c,d]	
Appropriate shock/therapy (7.1 months) [6]	130 per 1.000	**43 per 1.000** (12 to 154)	**RR 0.33** (0.09 to 1.18)	138 (1 observational study)	⨁◯◯◯ VERY LOW [b,c,d]	
Appropriate shock/therapy (2.6 years) [9]	72 per 1.000	**43 per 1.000** (11 to 155)	**RR 0.60** (0.15 to 2.14)	138 (1 observational study)	⨁◯◯◯ VERY LOW [c,d]	
Appropriate shock/therapy (up to 5 years) [7]	171 per 1.000	**120 per 1.000** (0 to 0)	**HR 0.68**	280 (1 observational study)	⨁◯◯◯ VERY LOW [d]	
Inappropriate shocks [3] pooled Data of [4, 6, 7, 9]	95 per 1.000	**83 per 1.000** (51 to 135)	**OR 0.87** (0.51 to 1.49)	738 (4 observational studies)	⨁◯◯◯ VERY LOW [a,b]	
Lead complications [3] pooled Data of [6, 7, 9, 10]	10 per 1.000	**1 per 1.000** (1 to 4)	**OR 0.13** (0.05 to 0.38)	6316 (4 observational studies)	⨁◯◯◯ VERY LOW [e]	
Infections [3] pooled Data of [4, 6, 7, 9, 10]	3 per 1.000	**2 per 1.000** (1 to 6)	**OR 0.75** (0.30 to 1.89)	6498 (5 observational studies)	⨁◯◯◯ VERY LOW [b]	
Pericardial tamponade [9, 10]	2 per 1.000	**0 per 1.000** (0 to 1)	**RR ranged from** 0.18 to 0.33	5898 (2 observational studies)	⨁◯◯◯ VERY LOW [c]	
Haematoma [4, 6, 10]	1 per 1.000	**0 per 1.000** (2 to 3)	**RR ranged from** 3.0 to 3.5	6080 (3 observational studies)	⨁◯◯◯ VERY LOW [b,c]	
Quality of life – physical well-being score [8] assessed with: 12-item Short-Form Health Survey (SF-12)		The mean quality of life – physical well-being score [8] in the intervention group was 6.7 higher (1.88 higher to 11.52 higher)	-	84 (1 observational study)	⨁◯◯◯ VERY LOW [b,d]	
Quality of life – physical well-being score [5] assessed with: 12-item Short-Form Health Survey (SF-12)		The mean quality of life – physical well-being score [5] in the intervention group was 0.2 lower (2.67 lower to 2.27 higher)	-	334 (1 observational study)	⨁◯◯◯ VERY LOW [d]	
Quality of life – mental well-being score [8] assessed with: 12-item Short-Form Health Survey (SF-12)		The mean quality of life – mental well-being score [8] in the intervention group was 0.1 higher (4.43 lower to 4.63 higher)	-	84 (1 observational study)	⨁◯◯◯ VERY LOW [b,d]	
Quality of life – mental well-being score [5] assessed with: 12-item Short-Form Health Survey (SF-12)		The mean quality of life – mental well-being score [5] in the intervention group was 0.15 higher (2.44 lower to 2.74 higher)	-	334 (1 observational study)	⨁◯◯◯ VERY LOW [d,f]	

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*

[a] *Effect estimates includes 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] *Medium risk of bias*

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.

Resultate für Wirksamkeit: nicht signifikater Unterschied

Lead complications were statistically significantly less frequent in patients with subcutaneous ICDs as compared to transvenous ICDs. Difference 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.

Resultate für Sicherheit: weniger Sondenkomplikationen bei subkutanem ICD

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

Qualität der Evidenz: sehr niedrig

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

Bias Risiko und andere Limitationen

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.

unterschiedliche Beobachtungszeiträume der Studien von Krankenhausaufenthalt bis zu 5 Jahren

Second, in few studies, despite matching, there were still differences of baseline characterises 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.

trotz Matching Baseline Patientencharakteristika unterschiedlich in manchen Studien

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.

bei einigen Endpunkten nur wenige Ereignisse → breite KI die relevante Unterschiede einschließen können

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.

laufender RCT PRAETORIAN trial

Subkutaner vs. Transvenöser ICD geplante Anzahl an Studienteilnehmern: 850 Patienten

Voraussichtliches Ende: Dezember 2019

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

Evidenz derzeit unzureichend für den Vergleich der Wirksamkeit, jedoch deutlich geringeres Risiko für Sondenkomplikationen mit subkutanem ICD

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

	The **inclusion** in the catalogue of benefits is **recommended**.
X	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
	The inclusion in the catalogue of benefits is ***currently*** **not recommended.**
	The **inclusion in** the catalogue of benefits is **not recommended.**

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.

Resultate für Sicherheit: weniger Sondenkomplikationen bei subkutanem ICD; Resultate für Wirksamkeit: kein statistisch signifikanter Unterschied

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.

Ergebnisse eines RCTs werden erwartet

10 References

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

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

Author, year	Köbe, 2013 [6]	Brouwer, 2016 [7]	Friedmann, 2016 [10]	Pedersen, 2016 [5]	Köbe, 2017 [8]	Honoarbakhsh, 2017 [9]	Mithani, 2017 [4]
Country	Germany	Netherlands	Unites States of America	Czech Republic, Denmark, Germany, Italy, the Netherlands, New Zealand, Portugal, and the United Kingdom	Germany	England	Unites States of America
Sponsor	-	-	Supported by the American College of Cardiology's National Cardiovascular Data Registry (NCDR)	Cameron Health Inc.	-	-	-
Intervention	Subcutaneous ICD	Subcutaneous ICD	Subcutaneous ICD	Subcutaneous ICD	Subcutaneous ICD	Subcutaneous ICD	Subcutaneous ICS
Comparator	Single-chamber transvenous ICD	Single-chamber and dual-chamber transvenous ICD	Single-chamber and dual chamber transvenous ICD	Single-chamber and dual-chamber transvenous ICD	Single-chamber transvenous ICD	Single- and dual-chamber transvenous ICD	Single-chamber transvenous ICD
Study design	Observational study Control matched by sex and age (±5 years)	Observational study with propensity score matching	Observational study with propensity score matching	Observational study with propensity score matching	Observational study Control matched by sex and age (±5 years)	Retrospective observational study with propensity score matching	Observational study Control matched by age, sex and dialysis status
Number of patients, total and intervention vs. comparator	138 69 vs. 69	280 140 vs. 140	5760 1920 vs. 1920 vs. 1920	334 167 vs. 167	84 42 vs. 42	138 69 vs. 69	182 91 vs. 91

Author, year	Köbe, 2013 [6]	Brouwer, 2016 [7]	Friedmann, 2016 [10]	Pedersen, 2016 [5]	Köbe, 2017 [8]	Honoarbakhsh, 2017 [9]	Mithani, 2017 [4]
Inclusion criteria	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	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)	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	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 (EFFORTLES 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.	Consecutive patients with subcutaneous ICD implantation and patients with trans-venous 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.	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)	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.
Exclusion criteria	NR	Patients included in the PRAETORIAN trial	Patients with previous ICD, bradycardia or resynchronization indication for permanent pacing Patients under-going ICD implantation during an acute hospitalization	Patients participating in another study that was considered to interfere with interpretation of the results from the EFFORT-LESS 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	NR	Patients who had a concomitant pacing indication, biventricular devices, documentation of sustained mono-morphic ventricular tachycardia (VT) likely to require anti-tachycardia pacing (ATP), and advisory transvenous leads	Dual-chamber transvenous ICD, Cardiac resynchronization therapy (CRT)
Age of patients, yrs	Mean ± SD: 45.7 ± 15.7 vs. 47.7 ± 14.7, p = 0.433	Median (inter-quartile range): 41 (26-52) vs. 42 (32-50), p = 0.33	Mean ± SD: 54.0 (15.1) vs. 53.7 (15.2) vs. 54.1 (15.0), p = NR	Mean ± SD: 54 ± 16 vs. 55 ± 13, p = 0.8831	Mean ± SD: 44.6 ± 12.5 vs. 44.7 ± 12.1, P = 0.96	Mean ± SD: 35 ± 13 vs. 40 ± 10, p = 0.17	Mean ± SD: 54.93 ± 13.61 vs 56.30 ± 12.71, p = 0.017
Female n (%)	19 (27.5) vs. 19 (27.5), p = 1.0	56 (40) vs. 53 (38), p = 0.71	627 (32.7) vs. 598 (31.2) vs. 633 (33), p = NR	45 (27%) vs 47 (28%) p = 0.8065	12 (28.6) vs. 12 (28.6), p = 1.0	17 (25) vs. 17 (25), p = 1.00	40 (44) vs. 41 (55) P = 1.0

Author, year	Köbe, 2013 [6]	Brouwer, 2016 [7]	Friedmann, 2016 [10]	Pedersen, 2016 [5]	Köbe, 2017 [8]	Honoarbakhsh, 2017 [9]	Mithani, 2017 [4]
Primary prevention n (%)	41 (59.4) vs. 34 (50.0), p = 0.268	93 (66) vs. 86 (61), p = 0.38	NR	123 (74) vs. 115 (69), p = 0.3334	26 (61.9) vs. 23 (54.8), p = 0.66	56 (81) vs. 56 (81), p = 1.0	74 (81.3) vs. 70 (76.9), p = 0.585
First ICD implantation n (%)	53 (76.8) vs. NR, p = NR	121 (86) vs. 125 (89), p = 0.47	1920 (100) vs. 1920 (100) vs. 1920 (100)	167 (100) vs. 167 (100)	NR	NR	NR
LVEF, %	Mean ± SD: 46.2 ± 15.6 vs. 40.6 ± 15.9, p = 0.084	Median: 50 vs. 49 p = 0.91	Mean ± SD: 31.2 ± 13.7 vs. 31.4 ± 13.8 vs. 31.2 ± 13.9, p = NR	NR	Mean ± SD: 49.0 ± 13.7 vs. 44.8 ±16.6 p = 0.28	Mean ± SD: 57 ± 15 vs. 58 ±13, p = 0.80	Mean ± SD 26.79 ± 12.08 vs. 27.78 ± 11.66, p = 0.534
Atrial fibrillation or Atrial flutter n (%)	NR	13 (9) vs. 21 (15), p = 0.14	322 (16.8) vs. 323 (16.8) vs. 370 (19.3), p = NR	36 (22) vs. 30 (18), p = 0.4097	NR	NR	14 (15.4) vs. 15 (16.5), p = 1.00
Ischemic heart disease or Coronary artery disease n (%)	11 (15.9) vs. 13 (18.8), p = 0.653	NR	879 (45.8) vs. 890 (46.4) vs. 857 (44.6), p = NR	NR	3 (7.1) vs. 6 (14.3) p = 0.48	NR	NR
Ischemic cardio-myopathy n (%)	NR	26 (19) vs. 41 (29), p = NR	NR	12 (7) vs. 12 (7), p = 1.00	NR	6 (9) vs. 5 (7), p = 1.0	NR
Nonischemic cardiomyopathy n (%)	NR	28 (20) vs. 30 (21), p = NR	846 (44.1) vs. 832 (43.3) vs. 845 (44), P = NR	NR	NR	NR	57 (62.6) vs. 51 (56), p = 0.451
Dilated cardio-myopathy n (%)	25 (36.2) vs. 32 (46.4), p = 0.226	NR	846 (44.1) vs. 832 (43.3) vs. 845 (44), p = NR	25 (15) vs. 39 (23), p = 0.0516	7 (16.7) vs. 12 (28.6), p = 0.30	4 (6) vs. 5 (7), p = 1.0	NR
Hyperthrophic cardiomyopathy n (%)	10 (14.5) vs. 4 (5.8), p = 0.091	NR	123 (6.4) vs. 122 (6.4) vs. 120 (6.3), p = NR	22 (13) vs. 18 (11), p = 0.5002	10 (23.8) vs. 3 (7.1), p = 0.07	41 (59) vs. 42 (61), p = 1.0	NR
Congenital heart disease n (%)	3 (4.4) vs. 3 (4.4), p = 1.0	5 (4) vs. 12 (9), p = NR	Ebstein anomaly: 3 (0.2) vs. 1 (0.1) vs. 1 (0.1) Transposition of the great vessels: (0.2) vs. 2 (0.1) vs. 1 (0.1) Tetralogy of Fallot 6 (0.3) vs. 5 (0.3) vs. 9 (0.5) Arrhythmogenic right ventricular dysplasia: 11 (0.6) vs. 11 (0.6) vs. 6 (0.3) Common ventricle: 2 (0.1) vs. 0 vs. 0	NR	4 (9.5) vs. 5 (11.9), p = 1.0	1 (1) vs. 1(1), p = 1.0	NR

Author, year	Köbe, 2013 [6]	Brouwer, 2016 [7]	Friedmann, 2016 [10]	Pedersen, 2016 [5]	Köbe, 2017 [8]	Honoarbakhsh, 2017 [9]	Mithani, 2017 [4]
Electrical heart disease or Syndromes associated with sudden cardiac death or Genetic arrhythmia syndrome n (%)	Electrical heart disease: 14 (20.3) vs. 2 (2.9), p = 0.002	Genetic arrhythmia syndrome: 75 (54) vs. 54 (39), p = NR	Syndromes associated with sudden cardiac death: Long QT syndrome: 66 (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) Catecholeminergic 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)	NR	Electrical heart disease: 7 (16.7) vs. 2 (4.8), p = 0.16	Arrhythmogenic right ventricular cardiomyopathy: 7 (10) vs. 6 (9), p = 0.79 Idiopathic ventricular fibrillation: 6 (9) vs. 6 (9), p = 1.0 Brugada Syndrome: 4 (6) vs. 4 (6), p = 1.0	NR
Follow-up (months)	Mean ± SD: 7.1 ± 4.5 months Max: 24 months	Median: 36 vs. 60 months, p < 0.001 Max: 50 months	Max: In-hospital	Max: 6 months	Time since ICD implantation Mean ± SD: Subcutaneous ICD: 20.7 ± 10.6 months Single-chamber ICD: 31.4 ± 10.4 7 months	Mean ± SD: Subcutaneous ICD: 31 ±19 months Transvenous ICD: 32± 21 months Max: 60 months	Max: 6 months
Loss to follow-up, n (%)	1 (1.4)	NR	0	0	NR	-	-
Outcome							
Effectiveness							
All-cause mortality n (%)	**Mean 7.1 months:** Subcutaneous ICD: 1/69 (1.4) vs. Single-chamber ICD: 1/69 (1.4), p = NR	**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	**In-Hospital:** Subcutaneous ICD: 3/1920 (0.2) vs. Single-chamber ICD: 2/1920 (0.1) p > 0.99 Subcutaneous ICD: 3/1920 (0.2) vs. Dual-chamber ICD: 1/1920 (0.05), p = 0.64	NR	NR	**Mean 2.6 years:** Subctanous ICD: 0/69 (0) vs. Single-/dual-chamber ICD: 0/69 (0)	**6 months:** Subcutaneous ICD: 2/91 (2.2) vs. Single-chamber ICD: 2/91 (2.2) p = NR

Author, year	Köbe, 2013 [6]	Brouwer, 2016 [7]	Friedmann, 2016 [10]	Pedersen, 2016 [5]	Köbe, 2017 [8]	Honoarbakhsh, 2017 [9]	Mithani, 2017 [4]
Appropriate shocks n (%)	**Mean 7.1. months:** Subcutaneous ICD: 3/69 (4.3) vs. Single-chamber ICD: 9/69 (13.0), p = 0.05	**5 years:** Subcutaneous ICD: 12/140 (8.6) vs. Single/dual-chamber ICD: 24/140 (17.2) Kaplan-Meier analysis: 17,0% (95% CI: 6.3–26.4) vs.21,3% (95% CI: 12.6–27.3) Single/dual-chamber ICD: HR with adjustment for ICD programming: 1.46; p = 0,36	NR	NR	Subcutaneous ICD: 1/42 (2.4) vs. Single-chamber ICD: 7/42 (16.7) p = 0.06	**Mean 2.6 years:** Subcutaneous ICD: 3/69 (4.3) vs. Single-/dual-chamber ICD: 5/69 (7.2), p = NR	**6 months:** Subcutaneous ICD: 1/91 (1,1) vs. Single-chamber ICD: 0/91 (0), p = NR
Quality of life	NR	NR	NR	**12-Item Short-Form Health Survey (SF-12)** 0 = poorest possible, 100 = best possible **Physical QoL:**[a] Mean (95% CI): *Baseline:* 40.48 (38.69-42.27) vs. 40.77 (39.12-42.42), p = 0.8157 *3 months:* 43.56 (41.79-45.34) vs. 43.85 (42.22-45.48), p = 0.8157 *6 months:* 43.45 (41.63-45.26) vs. 43.74 (42.06-45.41), p = 0.8157 **Mental QoL:** [a] Mean (95% CI): *Baseline*: 42.39 (40.60-44.19) vs. 42.25 (40.59-43.92), p = 0.9080 *3 months*: 45.86 (44.04-47.68) vs. 45.72 (44.04-47.40), p = 0.9080 *6 months:* 45.19 (43.29-47.09) vs. 45.05 (43.28-46.81), p = 0.9080	**12-Item Short-Form Health Survey(SF-12)** 0 = poorest possible 100 = best possible **Physical QoL:** Mean ± SD: *Baseline:* NR *Follow-up*: 46.6 ± 9.9 vs. 39.9 ± 12.5, p = 0.01 **Mental QoL:** Mean ± SD: *Baseline:* NR *Follow-up*: 51.9 ± 10.4 vs. 51.8 ± 10.8, p = 0.95	NR	NR

Author, year	Köbe, 2013 [6]	Brouwer, 2016 [7]	Friedmann, 2016 [10]	Pedersen, 2016 [5]	Köbe, 2017 [8]	Honoarbakhsh, 2017 [9]	Mithani, 2017 [4]
Safety							
Inappropriate shocks n (%)	**Mean 7.1. months:** Subcutaneous ICD: 5/69 (7.2) vs. Single chamber ICD: 3/69 (4.3) p = NR	**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	NR	NR	NR	**Mean 2.6 years:** Subcutaneous ICD: 3/69 (4.3) vs. Single-/dual-chamber ICD: 6/69 (8.7), p =0.49	**6 months:** Subcutanous ICD: 1/91 (1.1) vs. Single-chamber ICD: 2/91 (2.2), p = NR
Lead complications n (%)	**Mean 7.1. months:**[b] Subcutaneous ICD: 0/69 (0) vs. Single chamber ICD: 2/69 (2.9) p = NR	**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	**In-Hospital:**[c] 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	NR	NR	**Mean 2.6 years:**[d] Subcutaneous ICD: 0/69 (0) vs. Single-/dual-chamber ICD: 6/69 (8.7), p = 0.028	NR
Infections n (%)	**Mean 7.1. months:**[e] Subcutaneous ICD: 1/69 (1.4) vs. Single-chamber ICD: 1/69 (1.4), p = NR	**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	**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	NR	NR	**Mean 2.6 years:**[f] Subcutaneous ICD: 1/69 (1.4) vs. Single-/dual-chamber ICD: 4/69 (5.8) p = 0.37	**6 months:**[g] Subcutaneous ICD: 3/91 (3.3) vs. single-chamber ICD: 1/91 (1.1), p = NR

Author, year	Köbe, 2013 [6]	Brouwer, 2016 [7]	Friedmann, 2016 [10]	Pedersen, 2016 [5]	Köbe, 2017 [8]	Honoarbakhsh, 2017 [9]	Mithani, 2017 [4]
Haematoma n (%)	**Mean 7.1. months:**[h] Subcutaneous ICD: 1/69 (1.4) vs. Single-chamber ICD: 0/69 (0) p = NR	NR	**In-Hospital:** Subcutaneous ICD: 7/1920 (0.4) vs. Single-chamber ICD: 1/1920 (0.05), p = 0.07 Subcutaneous ICD: 7/1920 (0.4) vs. Dual-Chamber ICD: 2/1920 (0.1), p = 0.18	NR	NR	NR	**6 months:**[i] Subcutaneous ICD: 1/91 (1.1) vs. Single-chamber ICD: 0/91 (0), p = NR
Pericardial tamponade n (%)	**NR**	NR	**In-Hospital:** Subcutaneous ICD: 0/1920 (0) vs. Single-chamber ICD: 0/1920(0), p = NR Subcutaneous ICD: 0/1920 (0) vs. Dual-chamber ICD 5/1920 (0.3), p = NR	NR	NR	**<30 days:** Subcutaneous ICD: 0/60 (0) vs. Single-/dual-chamber ICD: 1/69 (1.4), p = 1.0	**NR**

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:

[a] *Adjusted for confounders*

[b] *Reported as lead revision*

[c] *Reported as lead dislodgement*

[d] *Reported as lead-related complications resulting in lead intervention*

[e] *Reported as infection requiring revision*

[f] *Reported as device infection*

[g] *Reported as infection requiring explant*

[h] *Reported as Haematoma requiring revision*

[i] *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]**

	Selection				Comparability	Outcome			
Study Author, Year	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Overall Risk of Bias
Köbe, 2013 [6]	1	1	1	1	0	1	1	0	**High**
Brouwer, 2016, [7]	1	0	1	1	2	1	1	0	**Medium**
Friedman, 2016, [10]	1	0	1	1	2	1	0	1	**Medium**
Pedersen, 2016 [5]	1	0	0	1	2	0	1	1	**Medium**
Mithani, 2017 [4]	1	1	1	1	0	1	1	1	**High**
Honarbakhs, 2017 [9]	1	1	1	1	2	1	1	0	**Medium**
Köbe, 2017 [8]	1	1	0	1	1	0	1	0	**High**

** 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]

AMSTAR-2	Basu-Ray, 2017 [3]
Research question and inclusion criteria include the components of PICO	Yes
Explicit statement that the review methods were established prior to the conduct of the review	No
Explain their selection of the study designs for inclusion in the review	Yes
Comprehensive literature search strategy	Yes
Perform study selection in duplicate	Yes
Perform data extraction in duplicate	Yes
Provide a list of excluded studies and justify the exclusions	No
Describe the included studies in adequate detail	Yes
Satisfactory technique for assessing the risk of bias (RoB) in individual studies	Yes
Report on the sources of funding for the studies included in the review	No
Appropriate methods for statistical combination of results	Yes
Assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis	No
Account for RoB in individual studies when interpreting/discussing the results of the review	No
Satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	No
Adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
Rating for overall confidence in the results of the review	**Moderate***

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

Quality assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Subcutaneous ICD	Transvenous ICD	Relative (95% CI)	Absolute (95% CI)	
Mortality (In-hospital) [10]											
1	observational studies	not serious	not serious	not serious	serious [a]	none	3/1920 (0.2%)	3/3840 (0.1%)	**RR 2.0** (0.4 to 9.9)	**1 more per 1.000** (from 0 fewer to 7 more)	⊕◯◯◯ VERY LOW
Mortality (up to 6 months) [4]											
1	observational studies	serious [b]	not serious	not serious	serious [c,d]	none	2/91 (2.2%)	2/91 (2.2%)	**RR 1.00** (0.14 to 6.95)	**0 fewer per 1.000** (from 19 fewer to 131 more)	⊕◯◯◯ VERY LOW
Mortality (up to 5 years) [7]											
1	observational studies	not serious	not serious	not serious	serious [c,d]	none	2/140 (1.4%)	6/140 (4.3%)	-		⊕◯◯◯ VERY LOW
Appropriate shocks (7.1 months) [6]											
1	observational studies	serious [b]	not serious	not serious	serious [c,d]	none	3/69 (4.3%)	9/69 (13.0%)	**RR 0.33** (0.09 to 1.18)	**87 fewer per 1.000** (from 23 more to 119 fewer)	⊕◯◯◯ VERY LOW
Appropriate shocks (2.6 years) [9]											
1	observational studies	not serious	not serious	not serious	serious [c,d]	none	3/69 (4.3%)	5/69 (7.2%)	**RR 0.60** (0.15 to 2.14)	**29 fewer per 1.000** (from 62 fewer to 83 more)	⊕◯◯◯ VERY LOW
Appropriate shocks (up to 5 years) [7]											
1	observational studies	not serious	not serious	not serious	serious [d]	none	12/140 (8.6%)	24/140 (17.1%)	**HR 0.68**	**51 fewer per 1.000** (from -- to --)	⊕◯◯◯ VERY LOW
Inappropriate shocks [3] pooled Data of [4, 6, 7, 9]											
4	observational studies	serious [b]	not serious	not serious	serious [a]	none	29/369 (7.9%)	33/369 (8.9%)	**OR 0.87** (0.51 to 1.49)	**11 fewer per 1.000** (from 40 more to 44 fewer)	⊕◯◯◯ VERY LOW
Lead complications [3] pooled Data of [6, 7, 9, 10]											
4	observational studies	serious [e]	not serious	not serious	not serious	none	3/2198 (0.1%)	42/4118 (1.0%)	**OR 0.13** (0.05 to 0.38)	**9 fewer per 1.000** (from 6 fewer to 10 fewer)	⊕◯◯◯ VERY LOW
Infections [3] pooled Data of [4, 6, 7, 9, 10]											
5	observational studies	serious [b]	not serious	not serious	not serious	none	8/2289 (0.3%)	13/4209 (0.3%)	**OR 0.75** (0.30 to 1.89)	**1 fewer per 1.000** (from 2 fewer to 3 more)	⊕◯◯◯ VERY LOW

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

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

Explanations:

[a] *Effect estimates includes 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] *Medium risk of bias*

Applicability table

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

Domain	Description of applicability of evidence
Population	Patients populations of included studies reflect real-world conditions with respect to age, sex, underlying cardiac condition and comorbidities.
Intervention	Included studies evaluated the subcutaneous ICD, produced by one manufacturer.
Comparators	Transvenous ICDs is considered as an established medical device, which is available from different manufacturers as single- or dual-chamber ICD.
Outcomes	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.
Setting	Studies were conducted in real-world settings.

List of ongoing randomised controlled trials

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

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor and Collaborator:
NCT01296022 PRAETORIAN	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	Subcutaneous ICD	Transvenous ICD	Number of participants with implantable cardioverter defibrillator (ICD) related adverse events (48 months)	Estimated: December 2019	Academisch Medisch Centrum-Universiteit van Amsterdam (AMC-UvA) Boston Scientific Corporation
NCT02881255 ATLAS S-ICD	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 < 1.5 L) Estimated enrollment: 500 patients	Subcutaneous ICD (Boston Scientific EMBLEM™)	Single-chamber, transvenous ICD	Composite of lead-related perioperative complications (6 months) Additional safety composite (6 months)	Estimated: August 2018	Population Health Research Institute Boston Scientific Corporation

Abbreviations: *ATALS = Avoid Transvenous Leads in Appropriate Subjects, PRAETORIAN = Prospective, RAndomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy, ICD = Impantable cardioverter defibrillator*

Literature search strategies

Search strategy for Pubmed

Search Name: Subcutaneous ICD	
Search Date: November 23rd, 2017	
ID	Search
#1	Search S-ICD[tw]
#2	Search subcutaneous*[tw]
#3	Search "Defibrillators, Implantable"[Mesh]
#4	Search cardioverter*[tiab]
#5	Search defibrillator*[tiab]
#6	Search ICD[tiab]
#7	Search (#3 OR #4 OR #5 OR #6)
#8	Search (#2 AND #7)
#9	Search (#1 OR #8)
#10	Search "Animals"[Mesh] NOT "Humans"[Mesh]
#11	Search #9 NOT #10
#12	Search (#11) AND ("2000"[Date - Publication] : "3000"[Date - Publication])
#13	Search "Case Reports" [Publication Type] OR (case*[ti] AND (report*[ti] OR series[ti]))
#14	Search (#12 NOT #13)
Total: 410 Hits	

Search strategy for Embase.com (Elsevier)

Search Name: Subcutaneous ICD	
Search Date: November 23rd, 2017	
ID	Search
#1	's icd':ti,ab
#2	(subcutaneous* NEAR/4 (defibrillator* OR cardioverter* OR icd)):ti,ab
#3	'implantable cardioverter defibrillator'/exp AND subcutaneous*
#4	#1 OR #2 OR #3
#5	'animal'/exp NOT 'human'/exp
#6	#4 NOT #5
#7	#6 AND [2000-2017]/py
#8	'case study'/exp OR 'case report'/exp OR ((case* NEAR/3 (report OR series)):ti)
#9	#7 NOT #8
#10	#9 NOT 'conference abstract'/it
Total: 341 Hits	

Search strategy for Cochrane Library (Wiley)

Search Name: Subcutaneous ICD	
Search Date: November 23rd, 2017	
ID	Search
#1	S-ICD:ti,ab,kw
#2	subcutaneous* near/4 (defibrillator* or Cardioverter* or ICD)
#3	subcutaneous*:ti,ab,kw
#4	[mh "Defibrillators, Implantable"]
#5	cardioverter*:ti,ab,kw
#6	defibrillator*:ti,ab,kw
#7	ICD:ti,ab,kw
#8	{or, #4-`#7}
#9	#3 and #8
#10	#1 or #2 or #9
#11	#10 Publication Year from 2000 to 2017
Total: 79 Hits	

Search strategy for CRD Databases

Search Name: Subcutaneous ICD	
Search Date: November 23rd, 2017	
ID	Search
#1	MeSH DESCRIPTOR Defibrillators, Implantable EXPLODE ALL TREES
#2	(Subcutaneous*)
#3	#1 AND #2
#4	(S-ICD)
#5	(subcutaneous* NEAR4 (defibrillator* OR Cardioverter* OR ICD))
#6	#3 OR #4 OR #5
Total: 5 Hits	

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