HTA Austria
Austrian Institute for
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Subcutaneous implantable cardioverter-defibrillator (S-ICD)

1. Update 2022
Systematic review

AIHTA Decision Support Document: 109, 1. Update | ISSN-online: 1998-0469

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Vienna, March 2022

Project Team

Project leader: Gregor Goetz, MSSc, MPH

Authors: Sarah Wolf, BSc, MSc
Gregor Goetz, MSSc, MPH

Project Support

Systematic literature search: Tarquin Mittermayr, BA(Hons), MA

Internal Review: Claudia Wild, Priv.-Doz. Dr Phil.

External Review: Bernhard Wernly, Priv.-Doz. Dr., PhD, MD
University Salzburg, General Hospital Oberndorf, Paracelsus Medical University Salzburg, Austria

Correspondence: Sarah Wolf, BSc, MSc; sarah.wolf@aihta.at

This report should be referenced as follows

Wolf S. and Goetz G. Subcutaneous implantable cardioverter-defibrillator (S-ICD). Update 2022. Systematic Review. AIHTA Decision Support Documents No. 109; 2022. Vienna: Austrian Institute for Health Technology Assessment GmbH.

Conflict of interest

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

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

IMPRINT

Publisher:
HTA Austria – Austrian Institute for Health Technology Assessment GmbH
Garnisongasse 7/Top20 | 1090 Vienna – Austria
https://www.aihta.at/

Responsible for content:
Priv.-Doz. Dr Phil. Claudia Wild, managing director

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AIHTA Decision Support Documents No.: 109, 1. Update

ISSN online 1998-0469

Content

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List of abbreviations

ACC ..... American College of Cardiology
AHA ..... American Heart Association
AMSTAR ..... A MeaSurement Tool to Assess systematic Reviews
ATLAS ..... Avoid Transvenous Leads in Appropriate Subjects
ATP ..... Anti-tachycardia pacing
Bzgl ..... Bezüglich
CI ..... Confidence interval
CoI ..... Conflict of interest
CRD ..... Centre for Reviews and Dissemination
CRT ..... Cardiac resynchronisation therapy
DFT ..... Defibrillation threshold testing
ECG ..... Electrocardiogram
ELISIR ..... Experience from the Long-term Italian S-ICD
ESC ..... European Society of Cardiology
EUnetHTA ..... European Network for Health Technology Assessment
FDA ..... Food and Drug Administration

GRADE ..... Grading of Recommendations Assessment, Development and Evaluation
HR ..... Hazard ratio
HRS ..... Heart Rhythm Society
ICD ..... Implantable cardioverter-defibrillator
ICD-10-CM ..... The International Classification of Diseases, Tenth Revision, Clinical Modification
LVEF ..... Left ventricular ejection fraction
MD ..... Mean difference
MeSH ..... Medical Subject Headings
NCDR ..... National Cardiovascular Data Registry
NCT ..... National Clinical Trials
NICE ..... National Institute for Health and Care Excellence
NYHA ..... New York Heart Association
NRCT ..... Non-randomised controlled trial
OR ..... Odds ratio
Pat. ..... Patients
PRAETORIAN ..... Prospective, RAndomized comparison of subcutaneous and tRansvenous ImplANtable cardioverter-defibrillator therapy
PRISMA ..... Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL ..... Quality of life
RCT ..... Randomised controlled trial
RoB ..... Risk of bias
RR ..... Risk ratio
SR ..... Systematischer Review
s.s. ..... Statistisch signifikant
SCD ..... Sudden Cardiac Death
SF-12 ..... Short Form Survey
S-ICD PAS ..... S-ICD Post Approval Study
S-ICD ..... Subcutaneous implantable cardioverter-defibrillator
TV-ICD ..... Transvenous implantable cardioverter-defibrillator
UNTOUCHED ..... Understanding Outcomes With the S-ICD in Primary Prevention Patients With Low Ejection Fraction
VF ..... Ventricular fibrillation
Vs ..... Versus
VT ..... Ventricular tachycardia

Executive Summary

Introduction

Health problem and therapeutic aim

sudden cardiac death: public health issue

Cardiovascular diseases are a significant public health issue. According to the European Society of Cardiology (ESC) guideline (2021), a high proportion of deaths among patients with heart failures, especially in those with milder symptoms, occur suddenly and unexpectedly. Thus, the ESC guideline (2021) recommends implantable cardioverter-defibrillators (ICDs) for primary and secondary prevention of sudden cardiac death.

ESC recommendation (2021): ICD indicated for primary or secondary prevention

Description of the technology

relatively new: ICD with subcutaneous lead

An ICD device detects and terminates life-threatening ventricular tachyarrhythmias by converting the abnormal heart rhythm back to normal. Some years ago, the S-ICD emerged as a promising alternative to the established TV-ICD by placing the lead subcutaneously and thereby leaving the heart and vascular system untouched. As a result, it is deemed to overcome short- and long-term complications associated with the implantation of transvenous leads and direct contact with the heart. Such complications can include pneumothorax, cardiac perforation, lead fracture, lead dysfunction, infections (e.g. lead endocarditis), and venous thrombosis. However, an S-ICD cannot be implanted if there is a need for pacing in bradycardia, anti-tachycardia pacing (ATP), or an indication for cardiac resynchronisation therapy (CRT).

only for pts. with no indication for a pacemaker, ATP or CRT

1. S-ICD generation: CE-marketing in 2009, 2. generation in 2015

The Cameron Health S-ICD system (later acquired by Boston Scientific Inc.) received CE-marking (CE: 623289) in 2009 for the use in eligible patients to prevent sudden cardiac death. The second generations EMBLEM™ S-ICD systems and EMBLEM MRI S-ICD systems received CE-marking in 2015.

Methods

project aim: update of the S-ICD evidence

This assessment presents an update of the evidence comprised in the previous systematic review from 2018 about the effectiveness and safety of the S-ICD compared to the conventional TV-ICD in patients at an increased risk of sudden cardiac death and an ICD indication for primary or secondary prevention.

adapted search strategy & inclusion criteria:

The report's search strategy and inclusion criteria were minimally modified compared with the initial assessment:

systematic search in 4 databases limited to 2017-2021

The systematic search was limited from December 2017 to December 2021 and conducted on the 24th November 2021 in the following databases: Medline via Ovid, Embase, the Cochrane Library and the INAHTA. In addition, a manual search on the internet was performed.

stringent inclusion criteria in terms of controlled observational studies (NRCTs)

Only randomised controlled trials (RCTs) and retrospective and prospective observational studies with a control group (non-randomised controlled trials, NRCTs) of high to moderate quality and with more than 100 patients in the S-ICD cohort were included in the evidence synthesis.

selection, extraction & quality appraisal: conducted by 2 researchers

The study selection, data extraction and assessment of the methodological quality of the studies were performed by two independent researchers. GRADE (Grading of Recommendations Assessment, Development and Evaluation) was further used, and the evidence was qualitatively synthesised.

Domain effectiveness

crucial outcomes for effectiveness

The following effectiveness-related outcomes were used as evidence to derive a recommendation: mortality due to any causes, appropriate ICD shock therapy and ICD shock efficacy.

Domain safety

and crucial safety outcomes

The following safety-related outcomes were used as evidence to derive a recommendation: inappropriate ICD shock therapy and device- and lead-related complications.

Results

Available evidence

available evidence for effectiveness & safety: 1 new RCT & 1 post-hoc analysis of the RCT 2 new & 2 old NRCTs

One new non-inferiority RCT and a post-hoc analysis of the RCT with 849 patients, as well as two new (1 retrospective and 1 prospective) observational studies with propensity score-matched control group and two retrospective observational studies with propensity score-matched control group of the previous assessment with a total of 7.149 patients investigated the effectiveness and safety of S-ICD compared to the TV-ICD. The study populations represented patients with a higher risk for sudden cardiac death and an ICD indication for primary and secondary prevention without the need for pacing.

RoB of the included studies: moderate to high

According to the Cochrane risk of bias tool v.2, the RCT was classified with a moderate risk of bias (RoB) and the post-hoc analysis with a high RoB. According to the ROBINS-I tool, all four NRCTs could be included for the evidence synthesis due to the moderate RoB.

Clinical effectiveness

no statistically significant (s.s.) differences in crucial endpoints: all-cause mortality & shock efficacy; no precise results of appropriate shocks, inappropriate shocks & device-related complications

None of the included studies detected a statistically significant difference in the crucial outcomes, all-cause mortality and shock efficacy. Concerning the crucial outcome, appropriate shocks, a statistically significant difference between patients with S-ICDs and patients with TV-ICDs was detected in the RCT and one NRCT. In the RCT, numerically more appropriate shocks were observed in the S-ICD group. In contrast, fewer appropriate shocks were counted in patients with the S-ICD in the NRCT.

Safety

but S-ICD non-inferior compared to TV-ICD in terms of inappropriate shocks & device-related complications & s.s. lower risk for lead-related complications with S-ICDs

In terms of the crucial composite primary endpoint of inappropriate shocks and device-related complications, moderate-quality evidence (1 RCT) suggests that the S-ICD is non-inferior to TV-ICD. When looking at the endpoint components separately, in the RCT, no statistically significant difference in inappropriate shocks was reported, with numerically less inappropriate shocks occurring in the TV-ICD group. In contrast, one NRCT showed less inappropriate shocks in the S-ICD cohort but was not statistically significantly different. Only in one NRCT a statistically significant difference in inappropriate shocks was reported in favour of the TV-ICD. Regarding the device- and lead-related complications, in the RCT, no statistically significant difference was detected, with a trend towards fewer complications in the S-ICD group. In contrast, in two NRCTs, fewer complications were reported in the TV-ICD cohorts; however, only in one NRCT, the difference was statistically significant. Concerning the complications only related to the lead, statistically significantly lower risk in patients with S-ICDs was detected in the RCT and two NRCTs.

Upcoming evidence

The search for ongoing studies in clinical trial registries yielded one new RCT and one follow-up analysis of the included RCT. The follow-up analysis focuses on the effectiveness of the S-ICD with and without defibrillation testing. The primary completion date of this analysis is estimated at September 2023. The new RCT presents the investigator-initiated ATLAS trial comparing the effectiveness and safety of newer S-ICD generations to TV-ICDs in a selected patient population that may benefit from S-ICD. This RCT is expected to be completed by February 2022.

2 ongoing RCTs: 1 new RCT & one follow-up of the included RCT

Reimbursement

Since 2018, the S-ICD has been included in the Austrian hospital benefit catalogue. Reimbursement for the S-ICD has been coded with DE112 and requires approval by the regional healthcare fund.

reimbursement of the S-ICD with restrictions (code: DE112)

Discussion and conclusion

The certainty of the available evidence was very low to moderate due to the high imprecision (most studies were underpowered to detect a statistically significant difference in most of the crucial outcomes) and the moderate to high RoB of the included studies.

certainty of evidence: very low to moderate

Further, it is noteworthy to state that there are concerns about the non-inferiority analysis of the primary composite endpoint of inappropriate shocks and device-related complications because the same weight was given to severe consequences of inappropriate high-voltage shocks and less severe device-related complications, such as pneumothorax.

RCT: same weight for more & less severe complications

In terms of external validity, the data is considered generalisable to the Austrian context, as the included studies were conducted in several European countries.

generalisability to Austrian context

Overall, the current evidence is insufficient to draw definitive conclusions on the comparative effectiveness and safety of S-ICD in patients with an increased risk of sudden cardiac death and an ICD indication for primary and secondary prevention with no need for pacing. Nevertheless, moderate quality of evidence (1 RCT) suggests that the S-ICD is non-inferior to the TV-ICD in terms of a composite-endpoint of inappropriate shocks and device-related complications. Furthermore, included evidence indicates a statistically significantly lower risk for lead-related complications in patients with S-ICDs.

S-ICD non-inferior in terms of inappropriate shocks & device-specific complications & lower risk for lead-related complications

Recommendation

Based on these results, the recommendation of the previous systematic review from 2018 to reimburse S-ICDs with restrictions should be upheld. Thereby, the existing code (DE112) should be maintained, including reimbursement after approval by the regional healthcare fund. In addition, close monitoring of the use of S-ICDs is recommended.

recommendation: reimbursement of S-ICDs with restriction

Moreover, the results of the ATLAS trial are to be awaited to shed more light on the randomised evidence of S-ICD versus TV-ICD in a selected patient population that may benefit from S-ICD. Thus, a re-evaluation is recommended not before 2024.

results of the ATLAS trial are to be awaited; re-evaluation not before 2024

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

plötzlicher Herztod: Public Health Problem

Herz-Kreislauf-Erkrankungen sind ein großes Public Health Problem. Gemäß der aktuellen Leitlinie (2021) der europäischen Gesellschaft für Kardiologie (engl. ESC) geht ein Großteil dieser Erkrankungen mit dem plötzlichen Herztod aufgrund einer ventrikulären Tachyarrhythmie einher. Für Patient*innen mit einem erhöhten Risiko für einen plötzlichen Herztod empfiehlt die Leitlinie den implantierbaren Kardioverter-Defibrillator (engl. ICD). Einerseits ist der ICD als primäre Präventionsmaßnahme bei Patient*innen mit symptomatischer Herzinsuffizienz (NYHA-Klasse II-III), einer linksventrikulären Ejektionsfraktion von weniger als 35,0 % und einer Lebenserwartung von mehr als einem Jahr in guter körperlicher Verfassung indiziert. Andererseits werden die ICDs auch als sekundäre Präventionsmaßnahme bei Patient*innen empfohlen, die bereits eine ventrikuläre Arrhythmie erlitten haben.

häufigste Ursache: ventrikuläre Tachyarrhythmie

Empfehlung der ESC-Leitlinie (2021): ICD für Primär- & Sekundärprävention

Beschreibung der Technologie

relativ neu: ICD mit subkutaner Sonde

Ein ICD-Gerät hat das Ziel, lebensbedrohliche ventrikuläre Tachyarrhythmien zu erkennen und zu unterbrechen. Seit einigen Jahren gilt der subkutane (S-) ICD als vielversprechende Alternative zum etablierten transvenösen (TV)-ICD, um Kurz- und Langzeitkomplikationen einer transvenösen implantierten Sonde und den direkten Kontakt mit dem Herzen zu vermeiden. Zu den Komplikationen, die mit der Implantation einer transvenösen Sonde einhergehen können, zählen insbesondere Ventrikelperforation, Pneumothorax, Sondenbrüche, isolationsdefekte der Sonden, Infektionen wie Sonden-Endokarditis und venöse Thrombosen. Voraussetzung für die Implantation eines S-ICDs ist jedoch, dass kein Stimulationsbedarf bei Bradykardie, kein Bedarf an anti-tachykarder Stimulation (antitachykardes Pacing, ATP) oder keine Indikation für eine Kardiale-Resynchronisationstherapie (CRT) besteht.

Voraussetzung: keine Indikation für Herzschrittmacher, ATP oder CRT

1. S-ICD Generation: CE-Zulassung in 2009, 2. Generation in 2015

Das S-ICD-System von Cameron Health (später von Boston Scientific Inc. übernommen) erhielt 2009 die CE-Kennzeichnung (CE: 623289) als Präventionsmaßnahme bei geeigneten Patient*innen mit einem erhöhten Risiko für einen plötzlichen Herztod. Die zweite Generation, das EMBLEM™ S-ICD-System und das EMBLEM MRI S-ICD-System, erhielt die CE-Kennzeichnung im Jahr 2015.

Methode

Projektziel: Update der S-ICD-Evidenz

Ziel der vorliegenden Arbeit war es, die in der systematischen Übersichtsarbeit aus dem Jahr 2018 dargelegte Evidenz zur Wirksamkeit und Sicherheit des S-ICDs im Vergleich zum herkömmlichen TV-ICD bei Patient*innen mit erhöhtem Risiko für einen plötzlichen Herztod und einer ICD-Indikation zur Primär- oder Sekundärprävention zu aktualisieren.

angepasste Suchstrategie & Einschlusskriterien

Die Suchstrategie und die Einschlusskriterien des Berichts wurden im Vergleich zum Erst-Assessment minimal verändert:

Die systematische Suche wurde auf den Zeitraum Dezember 2017 bis Dezember 2021 beschränkt und am 24. November 2021 in den folgenden Datenbanken durchgeführt: Medline über Ovid, Embase, die Cochrane Datenbank und die INAHTA-Datenbank. Darüber hinaus wurde eine manuelle Suche im Internet durchgeführt.

systematische Suche in 4 Datenbanken, begrenzt auf Dez. 2017-2021

Es wurden nur randomisierte kontrollierte Studien (engl. RCT), sowie retrospektive und prospektive Beobachtungsstudien mit einer Kontrollgruppe (engl. NRCT) von guter bis moderater Qualität und mit mehr als 100 Patient*innen in der S-ICD-Kohorte in die Evidenzsynthese eingeschlossen.

kontrollierte Beobachtungsstudien (NRCTs): >100 Pat. & guter bis moderater Qualität

Die Auswahl der Studien, die Datenextraktion und die Bewertung der methodischen Qualität der Studien wurden von zwei unabhängigen Wissenschaftern durchgeführt. Darüber hinaus wurde das GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema verwendet und die Evidenz qualitativ zusammengefasst.

Auswahl, Extraktion & Qualitätsbeurteilung von 2 Forschern durchgeführt

Wirksamkeitsendpunkte

Die folgenden Endpunkte wurden für die Bewertung der Wirksamkeit als entscheidend definiert: Gesamtmortalität, angemessene ICD-Schocktherapie und Wirksamkeit der ICD-Schocktherapie.

entscheidungsrelevante Endpunkte für die Wirksamkeit

Sicherheitsendpunkte

Die folgenden Endpunkte wurden für die Bewertung der Sicherheit als entscheidend definiert: unangemessene ICD-Schocktherapie, sowie geräte- und sondenbedingte Komplikationen.

& Sicherheits-endpunkte

Ergebnisse

Verfügbare Evidenz

Für das Update 2022 konnten ein neues RCT und eine post-hoc-Analyse des RCTs mit 849 Patient*innen, sowie zwei neue (1 prospektive und 1 retrospektive) Beobachtungsstudien mit gematchter Kontrollgruppe und zwei retrospektive Beobachtungsstudien mit gematchter Kontrollgruppe aus dem Erst-Assessment mit insgesamt 7.149 Patient*innen eingeschlossen werden. Die Populationen der Studien umfassten Patient*innen mit einem erhöhten Risiko für einen plötzlichen Herztod und einer ICD-Indikation für die Primär- oder Sekundärprävention ohne die Notwendigkeit von Stimulationsbedarf (e.g. ATP).

verfügbare Evidenz für Wirksamkeit & Sicherheit: 1 neues RCT & Post-hoc-Analyse des RCTs 2 neue & 2 alte NRCTs

Gemäß dem Cochrane Risk of Bias Tool 2 wurde das RCT mit einem moderaten und die post-hoc Analyse mit einem hohen Bias-Risiko eingestuft. Alle vier NRCTs konnten aufgrund des moderaten Bias-Risikos gemäß dem ROBINS-I Tool inkludiert werden.

Bias-Risiko: RCT: moderat Post-hoc: hoch NRCTs: moderat

Klinische Wirksamkeit

In keiner der eingeschlossenen Studien wurde ein statistisch signifikanter Unterschied bezüglich der entscheidungsrelevanten Endpunkte, **Gesamtmortalität** und **Wirksamkeit der Schocktherapie**, nachgewiesen.

keine s.s. Unterschiede bei den Endpunkten: Gesamtmortalität & Schockwirksamkeit

Hinsichtlich des entscheidungsrelevanten Endpunktes, **angemessene Schocktherapie**, wurde ein statistisch signifikanter Unterschied im RCT und in einem NRCT festgestellt. Dabei wurden im RCT nummerisch mehr angemessene Schocks in der S-ICD Gruppe beobachtet. Im Gegensatz dazu wurde im NRCT bei Patient*innen mit dem S-ICD weniger angemessene Schocks gezählt.

keine eindeutigen Ergebnisse zu angemessener Schocktherapie

Sicherheit

S-ICD vs. TV-ICD bzgl. unangemessenen Schocks & gerätbedingten Komplikationen nicht unterlegen

In Bezug auf den entscheidungsrelevanten kombinierten Endpunkt, **unangemessene Schocktherapie und gerätbedingte Komplikationen**, deutete moderate Qualität der Evidenz (1 RCT) auf eine Nichtunterlegenheit des S-ICDs gegenüber dem TV-ICD hin. Bei der Begutachtung der einzelnen Endpunktkomponenten zeigte das RCT jedoch keinen statistisch signifikanten Unterschied bezüglich **unangemessenen Schocks**, wobei in der TV-ICD-Gruppe nummerisch weniger unangemessene Schocks beobachtet wurden. Im Gegensatz dazu, zeigte ein NRCT weniger unangemessene Schocks in der S-ICD-Kohorte. Der Unterschied war jedoch nicht statistisch signifikant. Nur in einem NRCT wurde ein statistisch signifikanter Unterschied bezüglich unangemessenen Schocks (zugunsten des TV-ICDs) berichtet.

keine eindeutigen Ergebnisse zu einzelnen Endpunkten: unangemessene Schocktherapie & gerätbedingte Komplikationen,

aber s.s. geringeres Risiko für sondenbedingte Komplikationen mit S-ICDs

Im Hinblick auf die **geräte- und sondenbezogenen Komplikationen** wurde im RCT kein statistisch signifikanter Unterschied zwischen den Interventionsgruppen beobachtet, wobei in der S-ICD-Gruppe nummerisch weniger Komplikationen auftraten. Im Gegensatz dazu wurden in zwei NRCTs weniger Komplikationen in den TV-ICD-Kohorten gemeldet; allerdings war der Unterschied nur in einem NRCT statistisch signifikant. Hinsichtlich der **Komplikationen, die sich nur auf die Sonden bezogen,** wurde im RCT und in zwei NRCTs ein statistisch signifikant geringeres Risiko bei Patient*innen mit S-ICDs festgestellt.

Laufende Studien

2 laufende RCTs: 1 neues RCT 1 Follow-up des eingeschlossenen RCTs

Die Suche in klinischen Studienregistern ergab ein neues RCT und eine Follow-Up Analyse des eingeschlossenen RCTs. Das Follow-up RCT (n=965) untersucht die Wirksamkeit des S-ICDs mit versus ohne Defibrillationstest. Im September 2023 soll die Analyse fertiggestellt sein. Das neue Forscherinitiierte ATLAS-RCT (n=500) vergleicht die Wirksamkeit und Sicherheit neuerer S-ICD-Generationen mit TV-ICD Systemen und soll im Februar 2022 abgeschlossen werden.

Kostenerstattung

Erstattung des S-ICDs mit Einschränkungen seit 2018 (Code: DE112)

Im Jahr 2018 wurde der S-ICD in den österreichischen Krankenhausleistungskatalog (LKF-Katalog) aufgenommen. Die Kostenerstattung für den S-ICD ist seither mit DE112 kodiert und bedarf einer Genehmigung durch die regionalen Gesundheitsfonds.

Diskussion und Schlussfolgerung

Qualität der Evidenz: sehr niedrig – moderat

Die Qualität der eingeschlossenen Evidenz wurde als sehr niedrig bis moderat eingeschätzt. Gründe dafür waren einerseits die hohe statistische Ungenauigkeit (die meisten Studien waren nicht dafür ausgelegt, einen statistisch signifikanten Unterschied bei den entscheidungsrelevanten Endpunkten festzustellen) und andererseits das moderate bis hohe Bias-Risiko der eingeschlossenen Studien.

RCT: keine Gewichtung des Schweregrades der Komplikationen

Hinsichtlich des kombinierten Endpunktes „unangemessene Schocks und gerätbedingte Komplikationen“ gab es in der Nichtunterlegenheitsanalyse des RCTs keine Gewichtung des Schweregrades der Komplikationen. So wurden z. B. schwerwiegende unangemessene Schocks gleich gewertet als weniger schwerwiegende Komplikationen, wie Pneumothorax.

Übertragbarkeit der Ergebnisse auf den österreichischen Kontext anzunehmen

In Bezug auf die externe Validität kann eine Generalisierbarkeit der Studienergebnisse auf den österreichischen Kontext angenommen werden, da die eingeschlossenen Studien in mehreren europäischen Ländern durchgeführt wurden.

S-ICD gegenüber TV-ICD nicht unterlegen hinsichtlich unangemessenen Schocks & gerätbedingten Komplikationen

s.s. geringeres Risiko für sondenbedingte Komplikationen mit S-ICDs

Insgesamt ist die aktuell verfügbare Evidenz unzureichend, um endgültige Schlussfolgerungen über die Wirksamkeit und Sicherheit des S-ICD im Vergleich zum TV-ICDs bei Patient*innen mit einem erhöhten Risiko für einen plötzlichen Herztod und einer ICD-Indikation für die Primär- und Sekundärprävention ohne die Notwendigkeit von Stimulationsbedarf (z. B. ATP) zu ziehen. Dennoch gibt es Hinweise aus dem RCT, dass das S-ICD gegenüber dem TV-ICD in Bezug auf den kombinierten Endpunkt „unangemessene Schocks und gerätebezogene Komplikationen" nicht unterlegen ist. Darüber hinaus weisen die eingeschlossenen Studien darauf hin, dass bei Patient*innen mit S-ICDs ein statistisch signifikant geringeres Risiko für sondenbezogene Komplikationen besteht.

Empfehlung

Empfehlung: Beibehaltung der Erstattung von S-ICDs mit Einschränkungen

Vor diesem Hintergrund soll die Empfehlung der systematischen Übersichtsarbeit aus dem Jahr 2018, S-ICDs mit Einschränkungen zu erstatten, beibehalten werden. Dabei soll der bestehende Kode (DE112) einschließlich der Erstattung nach einer Genehmigung durch die regionalen Gesundheitsfonds bestehen bleiben. Darüber hinaus wird eine genaue Überwachung der Verwendung von S-ICDs empfohlen.

Ergebnisse eines neuen RCTs stehen noch aus; Re-Evaluierung nicht vor 2024

Für weitere randomisierte Evidenz zur Wirksamkeit und Sicherheit des S-ICDs gegenüber dem TV-ICD sind die Ergebnisse des laufenden, Forscher-initiierten ATLAS-RCTs abzuwarten. Eine Re-Evaluierung ist daher nicht vor 2024 anzudenken.

Summary of the previous assessment (2018)

Zusammenfassung des systematischen Reviews aus 2018

This chapter shortly summarises the systematic review conducted in 2017/2018 on the effectiveness and safety of the subcutaneous implantable cardioverter-defibrillator (S-ICD) compared to the conventional transvenous implantable cardioverter-defibrillator (TV-ICD) in patients at an increased risk of sudden cardiac death [1]. Facts about the health problem and technology were updated.

Overview of the health problem and technology (updated)

Disease, health condition, and target population[1]

ein Großteil der kardiovaskulären Erkrankungen sind mit plötzlichem Herztod verbunden

Cardiovascular diseases are a significant public health issue. According to the European Society of Cardiology (ESC) guideline (2021), a high proportion of deaths among patients with heart failures, especially in those with milder symptoms, occur suddenly and unexpectedly [2, 3].

Current clinical practice[2]

ESC-Leitlinienempfehlung (2021) zu ICDs: Indikation zur primären Prävention

The ESC guideline 2021 recommends an implantable cardioverter-defibrillator (ICD) for primary prevention in patients with [2, 3]

- symptomatic heart failure (NYHA class II-III) of an ischaemic and non-ischaemic aetiology (unless they have had a myocardial infarction in the last 40 days),
- a left ventricular ejection fraction (LVEF) less than 35.0%, despite more than three months of optimal medical therapy provided, and
- if they are expected to survive substantially longer than one year with good functional status.

Indikation zur sekundären Prävention

In addition, the guideline recommends an ICD also for secondary prevention of sudden cardiac death in patients who have

- recovered from a ventricular arrhythmia causing haemodynamic instability, and
- who are expected to survive for more than one year with good functional status, in the absence of reversible causes or unless the ventricular arrhythmia has occurred less than 48 hours after myocardial infarction.

z. B. pädiatrische und jüngere Erwachsene Pat. für S-ICD geeignet

Usually, conventional TV-ICD systems are implanted; however, some experts also recommend considering the S-ICDs [2, 3]. Potential candidates for S-ICDs include paediatric patients with congenital heart disease, difficult ve-

[1] **A0001 –** For which health conditions, and for what purposes is the S-ICD used?
A0002 – What is the disease or health condition in the scope of this assessment?

[2] **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 in this assessment?

nous access (obstruction, venous abnormality), chronic indwelling catheters or high infection risk, as well as younger adult patients with electrical heart disease (e.g. Brugada Syndrome, long QT syndrome, short QT syndrome, and hypertrophic cardiomyopathy) [4].

ESC-Leitlinienempfehlung (2021) zu S-ICD:

In detail, according to the ESC guideline 2021 [2, 3]:

bei Pat. mit ICD-Indikation ohne Pacing

- ✓ S-ICDs should be considered an alternative to TV-ICDs in patients with an indication for an ICD when pacing therapy for bradycardia support, cardiac resynchronisation, or anti-tachycardia pacing (ATP) is not needed (class IIa, level C).

bei Pat. mit ungünstigem Venenzugang; für jüngere Pat. mit längerer Lebenserwartung

- ✓ Further, the S-ICD may be considered a valuable alternative to the TV-ICD system when venous access is difficult, after removing a TV-ICD for infections or in young patients with a long-term need for ICD therapy (class IIa, level C).
- ✗ In contrast, patients requiring bradycardia pacing are not suitable candidates for S-ICDs, unless pacing is only required immediately after shock delivery, as transcutaneous pacing can only be delivered for 30 seconds after the shock. Patients suffering from tachyarrhythmia quickly resolved by ATP and needing cardiac resynchronisation therapy (CRT) are also not candidates for S-ICDs.

AHA/ACC/HRS Leitlinienempfehlung (2017) stimmen mit ESC Empfehlungen überein

The American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (2017) is in line with the ECS guideline [5]:

- ✓ S-ICDs are recommended in patients who meet the criteria for an ICD, who have inadequate vascular access or are at high risk for infection, and in whom pacing for bradycardia or ventricular tachycardia (VT) termination or as part of CRT is neither needed nor anticipated (class I, level B/class IIa, level B).
- ✗ In contrast, S-ICDs cannot achieve adequate arrhythmia sensing for all patients and neither provide bradycardia nor ATP, which are both possible with the TV-ICD.

Features of the intervention[3]

Vorteil des S-ICDs gegenüber des TV-ICDs: keine Implantation einer transvenösen Sonde & kein direkter Kontakt mit kardialen Strukturen

An ICD device detects and terminates life-threatening ventricular tachyarrhythmias by converting the abnormal heart rhythm back to normal [5]. Recently, the S-ICD emerged as a promising alternative to the established TV-ICD by placing the lead subcutaneously, i.e. directly under the skin and thereby leaving the heart and vascular system untouched. Consequently, it is deemed to overcome short- and long-term complications associated with the implantation of transvenous leads and direct contact with the heart [6]. Specifically, such complications are pneumothorax, cardiac perforation, lead fracture, lead dysfunction, infections (e.g. lead endocarditis), and venous thrombosis [5].

S-ICD 1. Generation CE-Kennzeichnung 2009, 2. Generation 2015

The Cameron Health S-ICD system (later acquired by Boston Scientific Inc.) received CE-marking (CE: 623289) in 2009 for the use in eligible patients to prevent sudden cardiac death. The second generations EMBLEM™ S-ICD system and EMBLEM MRI S-ICD system received CE-marking in 2015 [1].

[3] **B0001** – What is the technology and the comparator(s)?
A0020 – For which indications has the S-ICD received marketing authorisation or CE marking?
B0002 – What is the claimed benefit of the S-ICD in relation to the TV-ICD?

Current utilisation[4]

Since 2018, the S-ICD has been included in the Austrian hospital benefit catalogue. Reimbursement for the S-ICD is coded with DE112 and requires approval by the regional healthcare fund [7].

seit 2018 werden S-ICD als genehmigungspflichtige Leistungen refundiert (Code: DE112)

Results

Available evidence

The systematic review from 2018 included seven eligible observational studies with a control group (non-randomised controlled studies, NRCTs) with 6,916 patients comparing the S-ICD with the conventional TV-ICD [8-14]. The largest retrospective observational study 5,760 patients from the National Cardiovascular Data Registry (NCDR) [14]. In addition, a systematic review and meta-analysis [15], which included results from five of the studies mentioned above (6,498 patients) [8, 9, 11, 13, 14], was considered.

7 Beobachtungsstudien mit Kontrolle & insgesamt 6.916 Pat. & 1 systematischer Review (SR) eingeschlossen

The follow-up in the included studies ranged from the duration of the hospital stay to five years after device implantation. In four studies [8, 10, 13, 14], the control cohort was selected by propensity score matching to obtain similar cohorts. Three studies [9, 11, 12] compared S-ICD with a single-chamber TV-ICD. In four studies [8, 10, 13, 14], patients in the control cohort received either single- or dual-chamber TV-ICDs.

variable Nachbeobachtungszeiträume: Krankenhausaufenthalt bis 5 Jahre danach

Based on the Newcastle-Ottawa Scale [16], three included studies [9, 11, 12] were rated with a high risk of bias (RoB), and the remaining four studies [8, 10, 13, 14] with a medium RoB. The included systematic review was rated with a medium RoB based on an assessment with the AMSTAR (A MeaSurement Tool to Assess Systematic Reviews)-2 checklist [17].

Verzerrungsrisiko der eingeschlossenen Studien: moderat bis hoch

Clinical effectiveness

Three observational studies with 6,222 patients reported mortality [9, 13, 14]. The difference between patients receiving S-ICDs or TV-ICDs was not statistically significant regarding overall mortality in all three studies:

- Mortality in the largest retrospective observational registry study: 3/1,920 vs 3/3,840; relative risk (RR) 2.0, 95% confidence interval (CI): 0.4-9.9 [14].
- Mortality in the observational study with the longest follow-up (5 years post-implantation): survival rate 96.0% (95% CI 90.1-100.0) vs 94.8% (95% CI 90.7-99.0), p=0.64 [13].

Gesamtmortalität: 3 Studien (n=6.222): kein statistisch signifikanter (s.s.) Unterschied zwischen S-ICD vs TV-ICD

In three included observational studies with 556 patients [8, 11, 13], the rate of appropriate shocks was lower in patients with S-ICDs than in patients with conventional TV-ICDs; however, the studies did not report a statistically significant difference.

angemessene Schocktherapie: 3 Studien (n=556): numerisch weniger bei Pat. mit S-ICD, jedoch kein s.s. Unterschied

[4] **A0021** – What is the reimbursement status of the S-ICD?

Lebensqualität: 1/2 Studien (n=89): s.s. höhere physische Lebensqualität bei Pat. mit S-ICD beobachtet

Regarding the generic health-related quality of life (QoL), two observational studies with 418 patients [10, 12] found no statistically significant difference for the mental quality of life assessed with the 12-item Short-Form Health Survey (SF-12) after S-ICD and TV-ICD implantation. Nevertheless, one of the two studies (n=84) observed a statistically significantly higher physical QoL in patients with S-ICDs (mean score difference [MD] 6.7, 95% CI 1.88-11.52) [12], whereas the second study with 334 patients did not (MD -0.2, 95% CI -2.67-2.27) [10].

Qualität der Wirksamkeitsevidenz als sehr niedrig eingestuft

Based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scheme, the quality of evidence was graded very low for all effectiveness outcomes considered crucial for the recommendation.

Safety

Sicherheitsdaten: 5 Beobachtungsstudien & 1 SR

In total, five observational studies [8, 9, 11, 13, 14] and one systematic review with random-effects meta-analyses [15] reported data on harms.

keine s.s. Unterschiede bzgl. unangemessene Schocktherapie, Infektionen & Hämatomen

No statistically significant differences were observed in patients with S-ICDs compared to patients with TV-ICDs for

- **inappropriate shocks** (4 studies [8, 9, 11, 13] [n=738]: follow-up from 6 months to 5 years, 29/369 vs 44/369; odds ratio [OR] 0.87, 95% CI 0.51-1.49 [15]),
- **infection rates** (5 studies [8, 9, 11, 13, 14] [n=6,498]: follow-up from hospitalisation to 5 years, 8/2,269 vs 13/4,189; OR 0.75, 95% CI 0.30-1.89 [15]) and
- **haematomas** (3 studies [9, 11, 14] [6,080 patients]: follow-up from hospitalisation to 6 months, 9/2,080 vs 3/4,000).

s.s. weniger sondenbedingte Komplikationen in der S-ICD-Gruppe

However, the included random-effects meta-analyses [15] showed statistically significant *more* inappropriate shocks because of oversensing (sensing of noise, T-wave oversensing), but statistically significantly *fewer* lead-complications (OR 0.13, 95% CI 0.05-0.38) in patients with S-ICDs compared to patients with TV-ICDs [15].

Qualität der Evidenz zur Sicherheit als sehr niedrig eingestuft

Based on the GRADE scheme, the quality of evidence was graded very low for all crucial safety outcomes.

Recommendation

2018: Aufnahme der Intervention in den Leistungskatalog mit Einschränkungen

The seven included observational studies with a control group and one systematic review with meta-analyses were insufficient to determine whether the S-ICD is equally or more effective than the TV-ICD. Based on the available evidence, no statistically significant differences were observed in terms of overall mortality, rate of adequate and inadequate shocks, infections, haematomas, and mental QoL. However, significantly fewer lead-related complications were observed in patients with S-ICDs than patients with TV-ICDs. Thus, in 2018, the inclusion of the S-ICD in the Austrian hospital benefit catalogue was recommended with restrictions for patients with an increased risk of sudden cardiac death and an ICD indication for primary or secondary prevention.

UPDATE 2022

1 Objectives and scope

Update der Evidenz zu S-ICD vs TV-ICD

This assessment represents an update of the evidence comprised in the previous systematic review from 2018 about the effectiveness and safety of the S-ICD compared to the conventional TV-ICD in patients at an increased risk of sudden cardiac death and an indication for an ICD for primary or secondary prevention [1].

1.1 PICO question

PIKO-Frage

Is the S-ICD equally or more effective and/or equally safe or safer than the conventional TV-ICD regarding preventing sudden cardiac death in patients at an increased risk?

1.2 Inclusion criteria

adaptierte Ein- & Ausschlusskriterien für relevante Studien

The inclusion and exclusion criteria of the previous systematic review from 2018 have been slightly adapted regarding the outcomes and the considered studies. The inclusion and exclusion criteria relevant for this updated review are summarised in Table 1-1.

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 guideline, primary and secondary prevention are defined as follows: ■ Primary prevention of sudden cardiac death: Therapies to reduce the risk of sudden cardiac death in individuals at risk of sudden cardiac death but who have not yet experienced an aborted cardiac arrest or life-threatening arrhythmias. ■ Secondary prevention of sudden cardiac death: Therapies reduce the risk of sudden cardiac death in patients who have already experienced an aborted cardiac arrest or life-threatening arrhythmias. 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	**Subcutaneous implantable cardioverter-defibrillator (S-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 (TV-ICD)** *Rationale*: The TV-ICD is an established and broadly used device for primary and secondary prevention in patients at risk of sudden cardiac death. Several randomised controlled trials have demonstrated its benefit.

Outcomes	
*Efficacy**	■ **All-cause mortality** ■ **Appropriate shocks** ■ **Shock efficacy** ■ Hospital re-admissions ■ Quality of life (QoL) ■ Appropriate anti-tachycardia pacing (ATP)
*Safety**	■ **Inappropriate shocks** ■ **Device- and lead-related complications** ■ Inappropriate ATP
Study design	
Efficacy	■ Randomised controlled trials (RCTs)
Safety	■ Retrospective and prospective observational studies with a control group (non-randomised controlled trials, NRCTs)**
Language	German, English
Publication period	From December 2017 onwards *(last systematic search on the 23rd November 2017)*

Abbreviations: ATP – Anti-tachycardia pacing, NRCTs – None-randomised controlled trials, QoL – Quality of life, RCTs – Randomised controlled trials, S-ICD – Subcutaneous implantable cardioverter-defibrillator, TV-ICD – Transvenous implantable cardioverter-defibrillator

** The bold outcomes are considered crucial for the recommendations.*

*** Retrospective and prospective NRCTs were included if more than 100 patients were analysed in the S-ICD cohort and the RoB was low to moderate according to the ROBINS-I tool.*

2 Methods

Assessment elements from the European Network for Health Technology Assessment (EUnetHTA) Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment [18] (see chapter "Research questions". in the Appendix).

EUnetHTA Core Model® Version 4.2. für SR herangezogen

2.1 Systematic literature search

The systematic literature search was conducted on the 24th November 2021 in the following databases:

systematische Literatursuche in 4 Datenbanken

- Medline via Ovid
- Embase
- The Cochrane Library
- HTA-INAHTA

The systematic search was limited to December 2017 (systematic search of the previous systematic review) to December 2021 and in Medline and Embase to articles published in English or German.

Zeitraum: Dezember 2017-2021, deutsche & englische Literatur

A hand-search in the reference lists of three systematic reviews about S-ICD compared to TV-ICD was conducted [19-21]. No further studies were identified.[5]

Handsuche in Referenzlisten von SRs

The manufacturer of the S-ICD (Boston Scientific Inc.) was contacted for further information about publications; however, no answer was received.

keine Rückmeldung vom Hersteller

Overall, after deduplication, a total of 557 citations were identified. The specific search strategy employed can be found in the Appendix (see chapter "Literature search strategies").

insgesamt 557 Hits identifiziert

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trial registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on 29th November 2021, resulting in 35 potentially relevant articles hits.

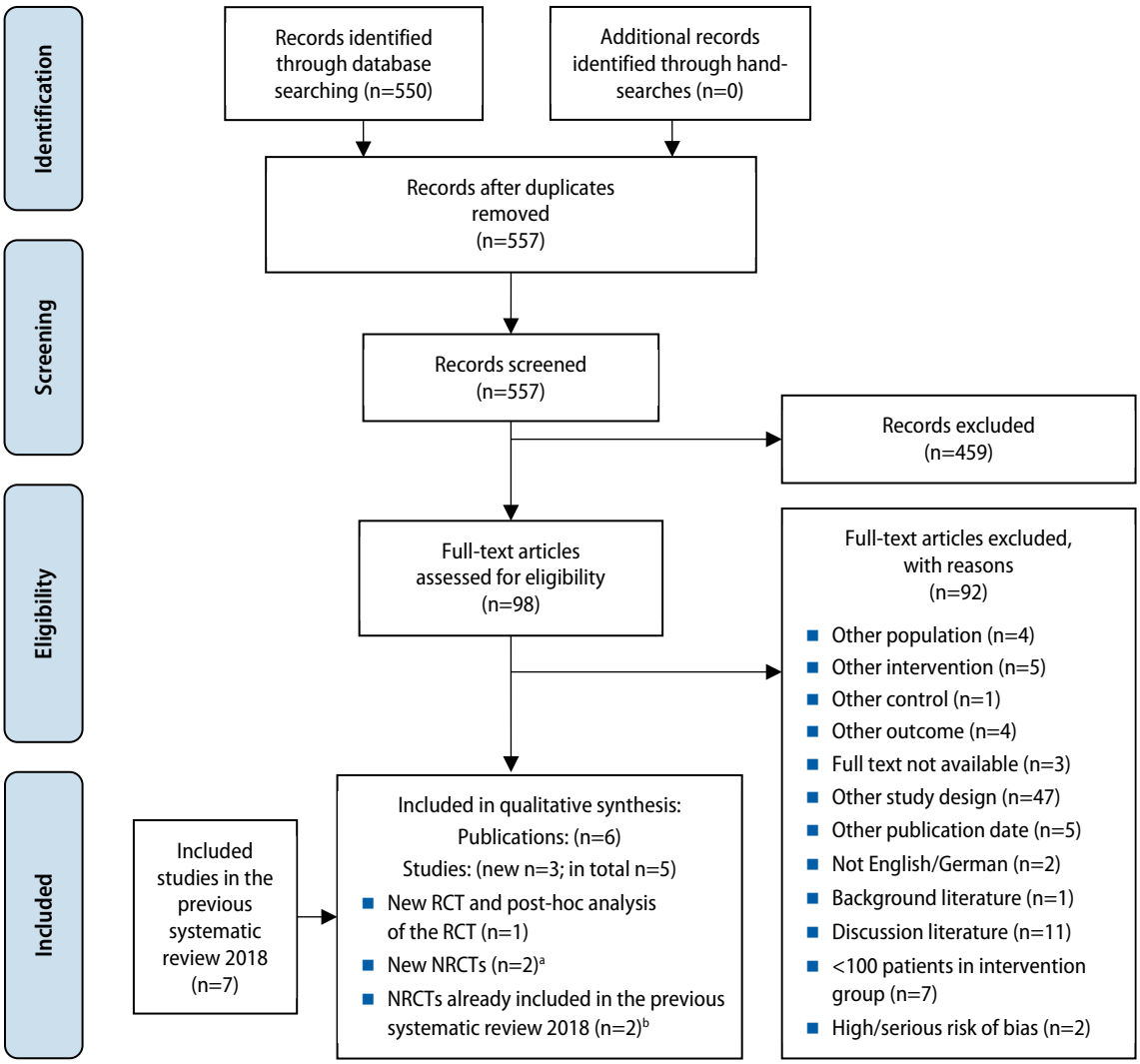
Suche nach laufenden Studien ergab 35 Hits

[5] The seven NRCTs included in the previous systematic review from 2018 were re-assessed taking into account more stringent inclusion criteria regarding the number of patients analysed and the RoB.

2.1.1 Flow chart of study selection

Literaturauswahl: 5 Studien (in 6 Publikationen)

The 557 identified hits were screened by two independent researchers (SW, GG), and in case of disagreement, a third researcher was involved in solving the differences. Out of the 557 hits, a total of five studies (six publications) were selected to be considered for the qualitative synthesis. The six publications consisted of one new RCT, one new post-hoc analysis of the RCT, two new NRCTs, and two NRCTs of the previous systematic review. The selection process is displayed in Figure 2-1.



[a] *Only NRCTs with more than 100 patients analysed in the S-ICD cohort and a low to moderate RoB.*

[b] *In addition, two of the seven NRCTs included in the previous systematic review from 2018 with more than 100 patients analysed in the S-ICD cohort and a low to moderate RoB (according to the ROBINS-I tool) were considered for the update report.*

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

2.2 Analysis

Beurteilung der Studienqualität mit Cochrane RoB Tool (V.2) und ROBINS-I

Two independent researchers (SW, GG) systematically assessed the RoB of the included studies using the Cochrane RoB v.2 tool for RCTs [22] (see Table A-3) and the ROBINS-I tool for NRCTs [23] (see Table A-4).

Datenextraktion aus Studien

Relevant data from eligible primary studies were systematically extracted into data-extraction tables (see Table A-1 & Table A-2). One researcher (SW) extracted the data, and another researcher (GG) checked and verified the extracted data.

All discrepancies were resolved by consensus.

2.3 Synthesis

qualitative Synthese der Evidenz

A qualitative synthesis of the evidence was performed. The research questions were answered in plain text format.

Zusammenfassung der Ergebnisse mit Hilfe des GRADE Schemas

Furthermore, the GRADE scheme was used to synthesise the identified evidence [24]. A GRADE summary of findings table and a GRADE evidence table were compiled (see Table 4-1 & Table A-5 in the Appendix). No inferential statistical analysis was conducted.

3 Results: Clinical effectiveness and safety

3.1 Outcomes

Effectiveness outcomes

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

entscheidungs-relevante Endpunkte für die klinische Wirksamkeit:

- **Mortality**: Mortality was considered a highly patient-relevant outcome measure when assessing the clinical effectiveness of the devices. It was reported as all-cause mortality. **Gesamtmortalität,**
- **Appropriate shocks**: ICD shocks were defined as appropriate if shock therapy is given for either ventricular tachycardia (VT) or ventricular fibrillation (VF)[6]. **angemessene Schocktherapie,**
- **Shock efficacy**: Shock efficacy was defined as the percentage of successful shocks of the total amount of shocks. A shock was considered successful if it could convert ventricular arrhythmia to sinus rhythm or atrial fibrillation within five seconds. **Wirksamkeit der Schocktherapie**

Further effectiveness outcomes were defined as *important*, but not crucial to derive a recommendation:

weitere wichtige Endpunkte:

- **Hospital re-admissions:** Hospital re-admissions involved re-admissions due to general heart failures, device-related complications, or the need for a device upgrade. **Rehospitalisierung &**
- **Quality of life (QoL)**: QoL assessed with validated and standardised questionnaires was considered a patient-relevant outcome measure when evaluating the clinical effectiveness of the devices. **Lebensqualität**

A further effectiveness outcome was defined as *relevant*:

weiterer relevanter Endpunkt:

- **Appropriate anti-tachycardia pacing (ATP)**: ATP can only be performed by the conventional TV-ICD. As ATP may prevent ICD shocks, it was considered an outcome relevant to report even if S-ICDs are not capable of giving ATP. Appropriate ATP therapy was defined if the ATPs were given for either VT or VF. **angemessenes ATP**

Safety outcomes

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

entscheidungsrelevante Endpunkte für Sicherheit:

- **Inappropriate shocks:** An ICD shock was classified as inappropriate when delivered for any rhythm other than VT or VF. **unangemessene Schocktherapie,**
- **Device- and lead-related complications**: ICD complications can occur related to the device or pocket, e.g. pocket haematoma, or lead, e.g. lead perforation, lead repositioning, lead replacement, pneumothorax. Other complications, such as infections, bleeding, pain or discomfort, can be related to the lead or the whole device. **gerät- und sondenbedingte Komplikationen**

[6] VT is defined as >100-250 beats per minute.
VF involves heart beats with >320 beats per minute.

weiterer relevanter Sicherheitsendpunkt: unangemessene ATPs

A further safety outcome was defined as *relevant*:

- **Inappropriate ATP**: ATP can only be performed by the conventional TV-ICD to prevent shock therapy. As ATP may prevent ICD shocks, it was considered as an outcome relevant to report even if S-ICDs are not capable of giving ATP. However, it can also be performed inappropriately when delivered for any rhythm other than VT or VF.

3.2 Included studies for effectiveness and safety

3.2.1 Study and patient characteristics

Studien: 1 non-inferiority RCT, 1 post-hoc Analyse des RCTs, 2 neue NRCTs (retrospektive & prospektive Registerstudie) & 2 retrospektive NRCTs aus vorherigem SR mit Propensity Score Matching

To assess the effectiveness and safety of the S-ICD in comparison to the single- or dual-chamber TV-ICD in patients with a higher risk for sudden cardiac death and an ICD indication for primary and secondary prevention, we identified one non-inferiority RCT [25], a post-hoc analysis of the RCT [26] and two new NRCTs, namely one retrospective observational registry study [27] and one prospective observational registry study [28]. In addition, two NRCTs (namely retrospective observational studies) [13, 14] that have already been included in the previous systematic review from 2018 were also included in this report, as they have met the more stringent inclusion criteria[7]. In all of the included studies, the intervention group received S-ICD compared to the standard care of single-chamber and/or dual-chamber TV-ICDs. In all four NRCTs, the control cohort was selected by propensity score matching to obtain comparable cohorts.

RCT testete non-inferioirty hinsichtlich eines Sicherheitsendpunktes,

weitere primäre Endpunkte: z. B. unangemessene Schocktherapie, gerätbedingten Komplikationen

The PRAETORIAN RCT was powered to test the non-inferiority of S-ICDs over TV-ICDs in terms of a primary composite endpoint of inappropriate ICD shocks and device-related complications (non-inferiority margin: 1.45) [25]. The primary endpoints of the post-hoc analysis of the RCT were appropriate ICD therapy and first shock efficacy [26]. The primary endpoint of three NRCTs [13, 27, 28] was device-related complications. Thereby, two of the three NRCTs [13, 27] considered all system-related complications that require invasive intervention, and the third NRCT [28] considered any device-related adverse events that require surgical revision. The fourth NRCT [14] defined a primary composite endpoint of any complication recorded in the hospital, such as death, cardiac arrest, cardiac perforation, valve injury, haematoma, haemothorax, infection, lead dislodgement, myocardial infarction and pericardial tamponade.

RCT mit 849 Pat. post-hoc Analyse des RCTs selbe ITT-Population; NRCTs mit 7.149 Pat. von unterschiedlichen Registern; Einschlusskriterien: ICD Indikation für primäre & sekundäre Prävention ohne Pacing-Bedarf

The RCT [25] enrolled a total of 849 patients older than 18 years of age with AHA/ACC/HRS class I or IIa ICD indication for primary or secondary prevention. Patients with previous ICD implantation, an indication for either bradycardia pacing, biventricular pacing, or another unsuitability for S-ICD implantation, were excluded from the RCT. In the post-hoc analysis of the RCT, the same intention-to-treat population was considered [26]. Similar inclusion criteria were applied in three NRCTs [14, 27, 28]. Only in one NRCT [13], patients with previous ICD-implantation were also considered; however, this affected only 14.0% of the patients with S-ICDs and 11.0% of the patients with TV-ICDs. Thus, the study was still included for the qualitative

[7] > 100 patients in the S-ICD cohort and low to moderate RoB.

synthesis. The four NRCTs had a total of 7,149 patients (2,620 matched patient pairs), with the biggest NRCT comprising 5,760 patients from the National Cardiovascular Data Registry (NCDR) [14]. The other NRCTs included patients from the Academic Medical Center (S-ICD) and the Leiden University Medical Center (TV-ICD) [13], from the EFFORTLESS (S-ICD) and SIMPLE registry (TV-ICD) [27] and the POINTED registry (S-ICD & TV-ICD) [28].

RCT & NRCTs: Mehrheit der Pat. männlich,

Pat. in NRCTs etwas jünger als Pat. in RCT

In the RCT and the NRCTs, most of the patients were male (RCT S-ICD group: 79.0% vs TV-ICD group: 81.6%; NRCTs range: 60.0-81.7% vs 62.0-81.4%). In the RCT, the median age of the patients was 63 years in the S-ICD group and 69 in the TV-ICD group, while the patients in the NRCTs were slightly younger: mean age ranged from 54 years [14] to 56 years [28] in the S-ICD cohorts and from 54 years [13] to 57 years [28] in the TV-ICD cohorts. However, no statistically significant differences in gender and age balance were reported.

RCT: durchschnittliche LVEF Rate: 30,0 %

3 NRCTs: durchschnittliche LVEF Rate zwischen 31,2-39,4 % vs 31,4-39,5 %

In the RCT, the median LVEF was 30.0% in each treatment group and the most common diagnoses were ischaemic (67.8% vs 70.4%) or non-ischaemic cardiomyopathy (23.2% vs 23.2%) and atrial fibrillation or atrial flutter (27.0% vs 22.1%) [25, 26]. In three NRCTs [14, 27, 28], the mean LVEF rate ranged between 31.2% and 39.4% in patients who received S-ICDs and between 31.4% and 39.8% in the TV-ICD cohorts, while the patients analysed in the fourth NRCT [13] had a median LVEF of 50.0% and 49.0%, respectively. The most commonly reported diagnosis in the NRCTs were genetic arrhythmia syndrome (1 NRCT [13]: 54.0% vs 39.0%), ischaemic diagnosis (3 NRCTs [13, 27, 28]: 19.0%-47.8% vs 29.0%-49.6%) and non-ischemic cardiomyopathy (3 NRCTs [13, 14, 27]: 20.0%-44.1% vs 21.0%-43.3%).

variable Nachbeobachtungs-zeiträume: Krankenhausaufenthalt bis 6 Jahre nach Implantation

The median follow-up of the RCT was 49.1 months (four years). A total of 184 (87 vs 97) patients were lost to follow-up, and 18 patients in the S-ICD group (4.3%) versus 11 patients in the TV-ICD group (2.7%) switched to the other treatment group[8] [25]. The median follow-up in the included NRCTs ranged from the in-hospital stay [14] to 72 months (six years) [28]. Loss to follow-up in the NRCTs was either zero [28] or not applicable due to the retrospective design [13, 14, 27].

Verzerrungsrisiko der eingeschlossenen Studien: moderat – hoch

Overall, the RoB of the RCT was rated with some concerns, while the post-hoc analysis of the RCT was rated with a high RoB. All four included NRCTs were ranked with a moderate RoB and thus included in the evidence synthesis (see chapter 4 and Table A-3 in the Appendix).

Study characteristics and results of included studies are displayed in the Appendix in Table A-1 and Table A-2 and in the evidence profile (Table A-5).

[8] Switch from the S-ICD to the TV-ICD group: 4 patients before the implantation and 14 patients during the implantation; Switch from the TV-ICD to the S-ICD group: 6 patients before the implantation and 5 during the implantation.

3.3 Effectiveness results

Mortality

Gesamtmortalität:

The crucial outcome **mortality** was reported in the RCT [25] and in all four included NRCTs [13, 14, 27, 28]; however, it was not defined as a primary endpoint in any studies[9].

RCT (n=849): kein s.s. Unterschied nach 4 Jahren: 16,4 % vs 13,1 %

In the RCT (n=849) [25], after a median of four years, no statistically significant difference in all-cause mortality could be detected (hazard ratio [HR] 1.23, 95% CI 0.89-1.70, p=not reported). Deaths due to any cause were reported more frequently in the S-ICD group compared to the TV-ICD group (83 [16.4%] vs 68 [13.1%]). The number of deaths due to sudden cardiac death was similar between the treatment groups (18 [21.7%] vs 18 [26.5%]). The certainty of the RCT evidence for this crucial endpoint was rated as low.

4 NRCTs (n=7.140) kein s.s. Unterschied unabhängig vom Nachbeobachtungs-zeitraum

Similarly, no statistically significant difference in all-cause mortality was detected in the four included NRCTs (n=7,140): During hospitalisation, an almost equal number of patients died in the S-ICD and the TV-ICD cohorts (S-ICD: 3 [0.2%], single-chamber TV-ICD: 2 [0.1%], p>0.99, dual-chamber TV-ICD: 1 [0.05%], p=0.64) [14]. After a median of three and five years, the survival rates were slightly higher in the S-ICD cohort compared to the TV-ICD cohort but still not statistically significantly different [3 years: 93.7% vs 91.5%, p=0.32 [27]; 5 years: 96.0% vs 94.8%, p=0.42 [13]). After a median of six years, three deaths (1.8%) occurred in each cohort (p=1.000) [28]. The overall certainty of the NRCT evidence for the crucial outcome mortality was rated as very low.

Morbidity

Morbidität

The crucial outcomes **appropriate shocks** and **shock efficacy**, the important outcome **hospital re-admissions** and the relevant outcome **appropriate ATPs** were considered when answering the research question about morbidity[10].

angemessene Schocktherapie:

Appropriate shocks were reported in the RCT (n=849) [25] and in two NRCTs (n=1,042) [13, 27] as a secondary outcome.

1 RCT (n=849): s.s. Unterschied *zugunsten S-ICD:* 4 Jahre: 19,2 % vs 11,5 %

In the RCT [25], a statistically significant difference between the S-ICD group and the TV-ICD group with *more* appropriate shocks appearing in the S-ICD group (83 [19.2%] vs 57 [11.5%], HR 1.52, 95% CI 1.08-2.12, p=0.02) was detected after a median of four years. However, the certainty of RCT evidence for this crucial endpoint was rated as low.

2 NRCTs (n=1.042): 3 Jahre: s.s. Unterschied *zugunsten TV-ICD* (9,9 % vs 13,9 %) 5 Jahre: kein s.s. Unterschied

In comparison, only one of two NRCTs (n=782) [27] was showed a statistically significant difference in appropriate shocks between the two cohorts: After a median of three years, the appropriate shock rate was *lower* in the S-ICD compared to the TV-ICD cohort (9.9% [95% CI 7.0-13.9] vs 13.9% [95% CI 10.8-17.8], p=0.003). After a median of five years, the difference was not statistically significant (17.0% [95% CI 6.3-26.4] vs 21.3% [95% CI 12.6-27.3], HR 1.46, p=0.36) [13]. The certainty of the NRCT evidence for the crucial outcome appropriate shocks was rated as very low.

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[9] **D0001** – What is the expected beneficial effect of the S-ICD on mortality?
D0003 – What is the effect of S-ICD on the mortality due to causes other than cardiac diseases with a higher risk for sudden cardiac death?

[10] **D0005** – How does the S-ICD affect symptoms and findings (severity, frequency) of cardiac diseases with a higher risk for sudden cardiac death?

Shock efficacy was reported in the post-hoc analysis of the RCT (n=849) [26] and one NRCT (n=782) [27]; however, only in the post-hoc analysis of the RCT [26], it was defined as a primary endpoint.

Wirksamkeit der Schocktherapie:

In the post-hoc analysis of the RCT [26], after a median of four years, no statistically significant difference in shock efficacy between the S-ICD and the TV-ICD group was detected (first shock efficacy: 93.8% vs 91.6%, p=0.40; final shock efficacy: 97.9% vs 98.4%, p=0.70). The certainty of the RCT evidence for this crucial endpoint was rated as low.

1 post-hoc Analyse des RCTs (n=849) &

Equally, the NRCT [27] showed no statistically significant difference between the two cohorts after a median of three years (88.6% vs 88.6%, p=1.00). The certainty of the NRCT evidence for this crucial endpoint was rated as very low.

1 NRCT (n=782): kein s.s. Unterschied nach 4 bzw. 3 Jahren

Hospital re-admissions were reported in the RCT (n=849) [25] and in four NRCTs (n=7,140) [13, 14, 27, 28] as secondary endpoint.

Rehospitalisierung:

In the RCT [25], no statistically significant difference in re-hospitalisations due to heart failures between the S-ICD and TV-ICD group (79 [17.4%] vs 74 [16.2%], HR 1.08, 95% CI 079-1.49) was detected after a median of four years.

1 RCT (n=849): kein s.s. Unterschied nach 4 Jahren bei Pat. mit Herzversagen (17,4 % vs 16,2 %)

Similarly, no statistically significant difference in the number of re-hospitalisations was detected in three of the four NRCTs (n=6,802) [13, 14, 27]: During the hospitalisation, device revisions were rare (0.3%) and did not vary by device type [14]. After a median of three and five years, slightly more re-interventions due to needed device up-grades were reported in the TV-ICD cohort (3 years: 1.3% vs 2.1%, p=0.48 [27]; 5 years: 1.3% vs 4.6%, p=0.26 [13]). The fourth NRCT (n=338) [28] showed a statistically significant difference in complication-related re-hospitalisations between the cohorts after a median of six years: In the S-ICD cohort *fewer* complication-related re-hospitalisations per patient (mean [range]: 0.3 [0-1] vs 0.9 [0-1], p=0.013) and *fewer* complication-related additional hospital treatment days per patient (mean [range]: 1.0 [0-2] vs 6.5 [0-29], p=0.048) were reported.

3/4 NRCTs (n=6.802): kein s.s. Unterschied der Rehospitalisierungen aufgrund von Device-Upgrades 3 Jahre: 1.3 % vs 2.1 %, 5 Jahre: 1.3 % vs 4.6 %

1/4 NRCTs: s.s. Unterschied *zugunsten S-ICD nach 6 Jahren*

Appropriate ATPs were reported in the RCT and its post-hoc analysis (n=849) [25, 26]. However, it was only defined as a primary endpoint in the post-hoc analysis [26]. Neither the primary analysis [25] nor the post-hoc analysis [26] reported a p-value. After a median of four years, 54 of the 423 patients (12.9%) in the TV-ICD group received appropriate ATP [25]. Of all the patients who received appropriate therapy either in the form of ATP or shock therapy (n=78), ATP was applied as the only treatment in 21 (26.9%) patients in the TV-ICD group [26].[11]

angemessenes ATP: 1 RCT & post-hoc Analyse (n=849): in 54 Pat. mit TV-ICD (12.9 %), in 21 Pat. (26.9 %) als einzige Therapie

Function

None of the included studies reported on the effect of the S-ICD on patients' body functions[12] or how the use of the S-ICD affects the activities of daily living[13].

Funktion: keine Evidenz

[11] In the S-ICD group 6/426 (0.6%) patients received appropriate ATPs, because they had previously crossed over to TV-ICD therapy [25]. Of the patients who received appropriate therapy in the S-ICD group (n=86), 3 (3.5%) patients received ATP as the only treatment [26].

[12] **D0011** – What is the effect of S-ICD on patients' body functions?

Health-related quality of life and patient satisfaction

Lebensqualität: keine Evidenz

None of the included studies reported on the effect of the S-ICD on generic health-related or disease-specific quality of life[14] and whether using the S-ICD was worthwhile for the patients[15].

3.4 Safety results

Sicherheit:

The crucial outcomes **inappropriate shocks** and **device-and lead-related complications** and the relevant outcome **inappropriate ATPs** were considered when answering the research question about patients' safety[16].

Composite endpoint inappropriate shocks and device-related complications

1 RCT (n=849): S-ICD gegenüber TV-ICD nicht unterlegen bzgl. unangemessenen Schocks & Komplikationen (Non-Inferiority-Grenzwert: 1.45)

The composite endpoint of **inappropriate shocks and device-related complications** was reported as the primary outcome in the RCT (n=849) [25]. After a median of four years, the RCT reported non-inferiority of the S-ICD compared to the TV-ICD concerning inappropriate shocks and device-related complications (68 [15.1%] vs 68 [15.7%], HR 0.99, CI 95% 0.71-1.39, non-inferiority margin 1.45, p=0.001), but not superiority (p=0.95). The certainty of the RCT evidence was rated as moderate for this crucial outcome.

Inappropriate shocks

unangemessene Schocktherapie:

Inappropriate shocks were reported as one component of the composite primary endpoint in the RCT (n=849) [25] and as a secondary endpoint in three NRCTs (n=1,380) [13, 27, 28].

1 RCT (n=849): kein s.s. Unterschied nach 4 Jahren: 9,7 % vs 7,3 %

In the RCT [25], no statistically significant difference in inappropriate shocks between the treatment groups was detected after a median of four years. Slightly more inappropriate shocks were reported in the S-ICD group compared to the TV-ICD group (41 [9.7%] vs 29 [7.3%], HR 1.43, 95% CI 0.89-2.30, p=not reported). In the S-ICD group, most inappropriate shocks were caused by cardiac and non-cardiac oversensing. In contrast, most inappropriate shocks in the TV-ICD group were caused by atrial fibrillation or supraventricular tachycardia. The certainty of the RCT evidence for this crucial endpoint was rated as low.

2/3 NRCTs (n=598): kein s.s. Unterschied: 5 Jahre: 20,5 % vs 19,2 % 6 Jahre: 6.5 % vs 8.3 %

Similarly, two NRCTs (n=598) [13, 28] did also not detect a statistically significant difference in inappropriate shocks: After a median of five years, higher inappropriate shock rates were observed in the S-ICD cohort (20.5% vs 19.2%, p=0.64 [13]), while after a median of six years, more inappropriate shocks were reported in the TV-ICD cohort (11 [6.5%] vs 14 [8.3%], p=0.533

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[13] **D0016** – How does the use of S-ICD affect activities of daily living?

[14] **D0012** – What is the effect of the S-ICD on generic health-related quality of life?
D0013 – What is the effect of the S-ICD on disease-specific quality of life?

[15] **D0017** – Was the use of the S-ICD worthwhile?

[16] **C0008** – How safe is the S-ICD in comparison to the TV-ICD?
C0004 – How does the frequency or severity of harms change over time or in different settings?

[28]). Only after a median of three years, another NRCT (n=782) [27] reported a statistically significant difference in inappropriate shocks with higher inappropriate shock rates in the S-ICD cohort (11.9% vs 7.5%, p=0.007). The overall certainty of the NRCT evidence for this crucial endpoint was rated as very low.

1/3 NRCTs (n=782): s.s. Unterschied *zugunsten TV-ICD :* 3 Jahre: 11,9 % vs 7,5 %

Device-and lead-related complications

The **device- and lead-related complications** were reported in the RCT (n=849) as an additional component of the composite primary endpoint [25] and in three NRCTs (n=1,380) as the primary endpoint [13, 27, 28].

gerät- und sondenbedingte Komplikationen:

In the RCT [25], no statistically significant difference in device- and lead-related complications between the S-ICD and the TV-ICD group was detected after a median of four years. Slightly more device-and-related complications occurred in the TV-ICD group (31 [5.9%] vs 44 [9.8%], HR 0.69, 95% CI 0.44-1.09; p=not reported). The most common device-and lead-related complications in the S-ICD group were bleeding (n=8/426), infections (n=4/426), device malfunctions (n=4/426), and sensing issues (n=4/426). In the TV-ICD group lead replacements (n=9/423), infections (n=8/423), lead repositioning (n=7/423) and device malfunctions (n=6/423) occurred most frequently. The certainty of RCT evidence for this crucial endpoint was rated as low.

1 RCT (n=849): kein s.s. Unterschied nach 4 Jahren: 5,9 % vs 9,8 %

die häufigsten Komplikationen: z. B. Blutungen, Fehlfunktion des Geräts, Infektionen

Similarly, no statistically significant difference in device- and lead-related complications was detected in two NRCTs (n=1,042) [13, 27]: After a median of three years, slightly more device-and lead-related complications with a need for invasive intervention were observed in the S-ICD cohort (34 [9.0%] vs 25 [6.5%], p=0.29) [27], while after a median of five years, slightly more complications were reported in the TV-ICD (14 [13.7%] vs 21 [18.0%], p=0.80) [13]. Only after a median of six years, in another NRCT (n=338) [28], a statistically significant difference in device- and lead-related complications with a need for invasive intervention was reported with slightly more complications in the S-ICD cohort (3 [1.8%] vs 17 [0.1%], odds ratio [OR] 0.16, 95% CI 0.05-0.56, p=0.001). The overall certainty of NRCT evidence for this crucial endpoint was rated as very low.

2/3 NRCTs (n=1.042): kein s.s. Unterschied: 3 Jahre: 9,0 % vs 6,5 % 5 Jahre: 13,7 % vs 18,0 %

1/3 NRCTs (n=338): s.s. Unterschied *zugunsten TV-ICD*: 6 Jahre: 1,8 % vs 0,1 %

Lead-related complications only

In the RCT [25], a statistically significant difference in lead-related complications between the treatment groups was reported after a median of four years, including infections, perforations, lead dislodgements, and lead dysfunctions. A *lower* incidence of lead-related complications was observed in patients with S-ICDs (1.4% vs 6.6%, HR 0.24, 95% CI 0.10-0.54, p=not reported). The certainty of RCT evidence for this crucial outcome was rated as moderate.

sondenbedingte Komplikationen:

1 RCT (n=849): s.s. Unterschied nach 4 Jahren *zugunsten S-ICD:* 1,4 % vs 6,6 %

These findings were supported by the results of two NRCTs (n=1,042) [13, 27] that also reported statistically significantly *fewer* lead-related complications in the S-ICD cohort compared to the TV-ICD cohort after a median of three years (1 [0.3%] vs 9 [2.3%], p=0.03) [27] and five years (1 [0.8%] vs 17 [11.5%], p=0.03) [13]. After a median of six years, another NRCT (n=338) [28] did not detected a statistically significant difference in lead failures (0 [0.0%] vs 4 [2.4%], p=0.123) and lead dislodgements (0 [0.0%] versus 5 [3.0%], p=0.61) between the two cohorts. The certainty of the NRCT evidence for this crucial outcome was considered very low.

2/3 NRCTs (n=1.042): s.s. Unterschied *zugunsten S-ICD:* 3 Jahre: 0,3 % vs 2,3 % 5 Jahre: 0,8 % vs 11,5 %

Inappropriate ATPs

unangemessenes ATP: 1 RCT (n=849): in 30 (7.2 %) Pat. mit TV-ICD

As described earlier, ATPs can also be performed inappropriately. In the RCT (n=849) [25], after a median of four years, 30 patients (7.2%) in the TV-ICD group received inappropriate ATPs that were delivered for any rhythm other than VT or VF.[17]

[17] In the S-ICD group 1/426 (0.3%) patient received an inappropriate ATP. This patient had previously crossed over to TV-ICD therapy [25].

4 Quality of evidence

Verzerrungsrisiko mit Cochrane RoB V.2 und ROBINS-I bewertet

The RoB for individual studies was assessed with the Cochrane RoB V.2 tool (for RCTs) [29] and the ROBINS-I tool (for NRCTs) [30]. The included RCT [25] and its post-hoc analysis [26] were ranked as having some concerns and a high RoB, respectively. Across the six NRCTs, which were considered for the RoB assessment, two NRCTs of the previous systematic review [13, 14] and two new NRCTs [27, 28], all with propensity score matching, were ranked as having a moderate RoB and thus included in the evidence synthesis of the present report. The detailed RoB assessments are presented in Table A-3 and Table A-4 in the Appendix.

RCTs: moderates bis hohes Verzerrungsrisiko aufgrund des non-inferiority Studiendesigns & CoI

NRCTs: moderates Verzerrungsrisiko (Einschlusskriterium) aufgrund des retrospektiven Studiendesigns, CoI, etc.

The main reasons for the RoB in the RCT and its post-hoc analysis were the concerns about the non-inferiority design and the S-ICD manufacturer (Boston Scientific Inc.) as one of the study sponsors. Moreover, the post-hoc analysis was not powered for "shock efficacy" as the primary outcome. The use of propensity score matching lowered the RoB in the NRCTs. However, the retrospective data collection (except in one NRCT), the missing blinding of the outcome assessors in some studies and the S-ICD manufacturer (Boston Scientific Inc.) as the study sponsor in one NRCT still resulted in a moderate RoB.

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to the GRADE scheme [31] for each endpoint individually. Thereby, each endpoint was rated by two independent researchers (SW, GG). In case of disagreement, a third researcher solved the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [31].

GRADE uses four categories to rank the strength 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 the evidence profile in Appendix (see Table A-5).

insgesamt sehr niedrige Qualität der Evidenz (S-ICD vs TV-ICD)

Overall, the certainty of the body of evidence for the clinical effectiveness and safety of S-ICD in comparison to standard care (with TV-ICD) was rated as very low for adult patients with a higher risk for sudden cardiac death and an ICD indication for primary and secondary prevention without the need for pacing.

Table 4-1: Summary of findings table of the S-ICD

Outcome	Anticipated absolute effects (95% CI)	Relative effect (95% CI)	Number of participants	Quality	Comments
Effectiveness					
Mortality	**No s.s. difference in the RCT:** **4 yrs:** 83 (16.4%) vs 68 (13.1%)	HR 1.23, 95% CI 0.89-1.70	849	Low[a,b,c,j]	Mortality due to any caused was reported.
	No s.s. difference in 4 NRCTs: **In-hospital:** 3 (0.2%) vs 2 (0.1%), p>0.99; 3 (0.2%) vs 1 (0.05%), p=0.64 **5 yrs:** 2 (1.4%) vs 6 (4.6%), p=NR **6 yrs:** 3 (1.8%) vs 3 (1.8%), p=1.000	NR	6,378 (3 NRCTs)	Low[b,d]	
	3-yr-survival rate: 93.7% vs 91.5%, p=0.32	HR 0.74, 95% CI 0.41-1.35	782 (1 NRCT)	Very low[b,c,g]	
Appropriate shocks	**S.s. difference in the RCT:** **4 yrs:** 83 (19.2%) vs 57 (11.5%), p=0.02	HR 1.52, 95% CI 1.08-2.12	849 (1 RCT)	Low[a,b,c]	Appropriate shock therapy is defined as shock therapy for either VT or VF.
	S.s. difference in 1 NRCT: **3 yrs:** 9.9% (95% CI 7.0-13.9) vs 13.8% (95% CI 10.8-17.8), p=0.03 **5 yrs:** 17.0% (95% CI 6.3–26.4) vs 21.3% (95% CI 12.6–27.3), p=0.36	**3 yrs:** NR **5 yrs:** HR 1.46	1,062 (2 NRCTs)	Very lowg[b,c,g]	
Shock efficacy	**No s.s. difference in the RCT:** **First shock efficacy:** 93.8% vs 91.6%, p=0.40 **Final shock efficacy:** 97.9% vs 98.4%, p=0.70	NR	849 (1 post-hoc analysis of the RCT)	Low[a,f]	Shock efficacy is defined as the percentage of successful shocks of the total amount of shocks. A shock is considered successful when it can convert ventricular arrhythmia to sinus rhythm or atrial fibrillation within 5 seconds.
	No s.s. difference in 1 NRCT: **3 yrs:** 88.6% vs 88.6%, p=1.000	NR	782 (1 NRCT)	Very low[b,d,g]	
Safety					
Composite primary endpoint	**Non-inferiority in the RCT:** **4 yrs:** 68 (15.1%) vs 68 (15.7), non-inferiority margin 1.45, p=0.001	HR 0.99, 95% CI 0.71-1.39	849 (1 RCT)	Moderate[a]	The composite primary endpoint includes inappropriate shocks and device-related complications.
Inappropriate shocks	**No s.s. difference in the RCT:** **4 yrs:** 41 (9.7%) vs 29 (7.3%), p=NR	HR 1.43, 95% CI 0.89-2.30	849 (1 RCT)	Low[a,b,c]	Inappropriate shocks are defined as shocks that were delivered for any rhythm other than VF or VT.
	S.s. difference in 1 NRCT: **3 yrs:** 11.9% (95% CI 8.8-15.9) vs 7.9% (95% CI 5.6-11.1), p=0.07 **5 yrs:** 20.5% (95% CI: 11.5-28.6) vs 19.1% (95% CI: 11.6-26.0), p=0.64	**3 yrs:** NR **5 yrs:** HR 0.85	1,062 (2 NRCTs)	Very low[b,d,g]	
	6 yrs: 11 (6.5%) vs 14 (8.3%), p=0.533	NR	338 (1 NRCT)	Low[b,d]	

Outcome	Anticipated absolute effects (95% CI)	Relative effect (95% CI)	Number of participants	Quality	Comments
Device-and lead-related complications	**No s.s. difference in the RCT:** **4 yrs:** 31 (5.9%) vs 44 (9.8%), p=NR	HR 0.69 95% CI 0.44-1.09	849 (1 RCT)	Low[a,b,c]	-
	S.s. difference in 1 NRCT: **3 yrs:** 34 (9.0%) (95% CI 6.5-12.3) vs 25 (6.5%) (95% CI 4.4-9.4), p=0.29 **5 yrs:** 14 (13.7%) (95% CI 6.4-20.3) vs 21 (18.0%) (95% CI 10.5-24.8), p=0.80 **6 yrs:** 3 (1.8%) (95% CI 0-3.8) vs 17 (10.1%) (95% CI 5.5-14.6), p=0.001	**3 yrs:** NR **5 yrs:** NR **6 yrs:** OR 0.16, 95% CI 0.05-0.56	1,400 (3 NRCTs)	Very low[c,g,h]	
Lead-related complications only	**S.s. difference in the RCT:** **4 yrs:** 1.4% vs 6.6%	HR 0.24, 95% CI 0.10-0.54	849 (1 RCT)	Moderate[a,b]	-
	S.s. difference in 2 NRCTs: **3 yrs:** 1 (0.3%) (95% CI 0.0-1.8) vs 9 (2.3%) (95% CI 1.2-4.4), p=0.03 **5 yrs:** 1 (0.8%) (95% CI: 0.0-2.2) vs 17 (11.5%) (95% CI: 5.3-17.2), p=0.03	NR	1,062 (2 NRCTs)	Very low[c,g]	

Abbreviations: CI -confidence interval, HR – hazard Ratio, n – Number, NRCT -Non-randomised controlled trial, RCT- Randomised controlled trial, s.s. – statistically significant, yrs – years

Explanations

[a.] *Concerns about non-inferiority designs include that non-inferiority testing should also assess efficacy for treatments that have superior safety or some other obvious benefit. Therefore, testing the S-ICD against TV-ICD can also include testing superiority for safety outcomes and non-inferiority for efficacy.*

[b.] *Secondary outcome.*

[c.] *Wide confidence intervals: uncertainty about the magnitude of effect.*

[d.] *No statistically significant difference was detected.*

[e.] *Post-hoc analysis of the RCT with maintaining ITT-population.*

[f.] *The study was not initially designed to determine a difference for the primary outcome of the post-hoc analysis "shock efficacy".*

[g.] *At least 1 study was supported by the manufacturer.*

[h.] *The outcome results did not coincide within the studies.*

[i.] *Sudden cardiac death, n: 18 vs 18.*

[j.] *Requiring invasive interventions.*

5 Discussion

The subcutaneous implantable cardioverter-defibrillator (S-ICD) is deemed to have certain advantages over the conventional transvenous cardioverter-defibrillator (TV-ICD) in patients with an increased risk of sudden cardiac death and who fulfil the ECG criteria defined by the manufacturer, namely no need of bradycardia, biventricular or anti-tachycardia pacing [32]. The publication of the first randomised controlled trial (RCT) in 2020 assessing the effectiveness and safety of the S-ICD compared to the TV-ICD initiated this re-assessment of the evidence on S-ICD.

neues RCT zu S-ICD veranlasste Re-Assessment der Evidenz

Overall, the update report captures evidence from a non-inferiority RCT [25], a post-hoc analysis of the RCT [26], as well as two retrospective observational studies with propensity score matching of the previous systematic review from 2018 [13, 14] and two new NRCTs, one retrospective observational registry study [27] and one prospective observational registry study [28].

verfügbare Evidenz: 1 RCT, 1 post-hoc Analyse des RCTs, 4 NRCTs

Summary of the main findings

All included studies (RCT: n=849; NRCTs: n=7,140) investigated the use of the S-ICD compared to the TV-ICD in patients with an increased risk of sudden cardiac death and an ICD indication for primary and secondary prevention without the need for pacing. The overall certainty of the evidence was very low due to the high imprecision (most studies were underpowered to detect a statistically significant difference in most of the crucial outcomes) and moderate to high risk of bias (RoB) (e.g. study design and conflict of interests) affecting the certainty of the findings.

Gesamtqualität der Evidenz als sehr niedrig eingestuft

moderates bis hohes Verzerrungsrisiko der Studienergebnisse

Effectiveness: None of the included studies tested non-inferiority of the S-ICD compared to the TV-ICD concerning effectiveness outcomes. Also, none of the included studies detected a statistically significant difference in the crucial outcomes all-cause mortality and shock efficacy. Concerning the crucial outcome appropriate shocks, a statistically significant difference between patients with S-ICD and patients with TV-ICD was detected in the RCT (*in favour of the TV-ICD*) [25] and one NRCT (*in favour of the S-ICD*) [26].

keine s.s. Unterschiede bei Wirksamkeitendpunkten: Gesamtmortalitä & Wirksamkeit der Schocktherapie

Safety: The moderate quality of the RCT evidence suggested non-inferiority of the S-ICD over the TV-ICD regarding the crucial composite endpoint of inappropriate shocks and device-related complications considering a non-inferiority margin of 1.45 However, when considering the endpoint components separately, in the RCT, no statistically significant difference in inappropriate shocks was reported, with less inappropriate shocks occurring in the TV-ICD group. [25]. In contrast, one NRCT showed less inappropriate shocks in the S-ICD cohort but was not statistically significantly different [28]. Only in one NRCTs a statistically significant difference in inappropriate shocks (*in favour of the TV-ICD*) was reported [27]. Regarding the device- and lead-related complications, in the RCT, no statistically significant difference was detected with a numerical trend towards fewer complications in the S-ICD group. In contrast, in two NRCTs, slightly fewer complications were reported in the TV-ICD cohorts [27, 28]; however, only in one NRCT, the difference was statistically significant [28]. Concerning the complications only related to the lead, statistically significantly *lower* risk in patients with S-ICDs was detected in the RCT [25] and two NRCTs [13, 27].

keine eindeutigen Ergebnisse zu den Endpunkten:

angemessene & unangemessene Schocks, gerätbedingten Komplikationen, aber s.s. geringes Risiko für sondenbedingte Komplikationen bei S-ICD

S-ICD bzgl. unangemessenen Schocks & gerätbedingte Komplikationen nicht unterlegen

Overall, the available evidence did not show non-inferiority or superiority of the S-ICD compared to the TV-ICD regarding the effectiveness outcomes. Nevertheless, the S-ICD was suggested to be non-inferior in terms of the composite of inappropriate shocks and device-related complications, as well as superior in terms of lead-related complications compared to the conventional TV-ICD in selected patients with an increased risk of sudden cardiac death, an ICD indication for primary and secondary prevention and who fulfilled the ECG criteria defined by the company (e.g. no need for pacing).

Interpretation of the findings

gewählte Definition von angemessener bzw. unangemessener Schocktherapie Einfluss auf Nichtunterlegenheit von S-ICD?

Concerning the crucial outcomes "appropriate and inappropriate shocks", their definitions significantly influence the final result. For example, in the early course of the RCT, the definitions had been changed from "an appropriate shock includes shock therapy for VT of more than 180 beats per minute" to a more general version of "appropriate shock therapy for VT and VF". With the original definition, more shocks would have been rated as inappropriate. Consequently, non-inferiority of the composite endpoint of inappropriate shocks and device-related complications might not have been identified [33-34].

Ergebnisse zur Anzahl der Schocktherpie abhängig von:

Generation des Devices

Funktionsweise des Devices: S-ICD ohne ATP → Effekt von ATP noch unklar?

Moreover, the number of appropriate and inappropriate shocks is also driven by the nature of the device. There are presumptions that older generation S-ICD models might be associated with a higher rate of inappropriate shocks [33-35]. Furthermore, appropriate shocks are deemed to occur more frequently in patients with S-ICDs, as the system is incapable of delivering anti-tachycardia pacing (ATP). On the other hand, there are pathophysiological considerations and anecdotal evidence from clinical practice that an appropriate and inappropriate ATP could accelerate a cardiac arrhythmia and thus necessitate a shock. In the worst case, an ATP could accelerate a tachycardia, which would otherwise have terminated spontaneously and would also have had no hemodynamic consequence [36, 37]. Thus, the role of ATP therapy is still unclear and was additionally addressed in this review as both an effectiveness and a safety endpoint to underline the lack of evidence in this regard.

weniger sondenbedingte Komplikationen auch auf Funktion des S-ICDs zurückzuführen

S-ICD in Zukunft auch für Pat. mit höherem Risiko für Bakteriämie & Endokarditis anzudenken

In addition, the result of fewer lead-related complications in patients with S-ICDs can also be partly explained by the nature of the devices, as the S-ICD has no contact with cardiac structures due to the absence of transvenous lead implantation [38]. On the other hand, ICD complications are worth considering from a patient-centred perspective. While, for example, pneumothorax or local rebleeding is associated with hospitalisation, lead endocarditis may lead to significant morbidity and mortality [39, 40]. Therefore, while S-ICD has been associated primarily with younger patients in clinical practice, S-ICD may also have a place in patients with a high likelihood of bacteremia and endocarditis in the future. Against this background, a patient-centred weighting of endpoints of future trials would also be desirable.

1. FDA Class I Rückruf zur S-ICD-Sonde aufgrund von berichteten Brüchen, die zu unangemessenen Schocks führen können

2. FDA Class I Rückruf zu 2 EBLEM S-ICD Modellen

Further, in February 2021, there was a Class I Food and Drug Administration (FDA) recall concerning the EBLEM S-ICD lead (model 3501) because of an increased risk of lead fractures, leading to inappropriate shocks. According to the FDA, a Class I recall is the most serious type of recall. The use of these devices may cause serious injuries or deaths. The FDA reported 27 complaints about this device issue and 26 reports of serious injuries, including one death. Notwithstanding, compared to TV-ICD leads, the risk of lead failure was estimated to be lower for the S-ICD lead (annual S-ICD lead failure rate: 0.22% vs annual TV-ICD lead failure rate: 0.40%). These esti-

mations, however, need to be interpreted with caution [41, 42]. Besides, the second Class I FDA recall in February 2021 involved two EBLEM S-ICD devices (S-ICD A209 and MRI S-ICD A219). The reason for this recall was the flawed manufacturing process, which can result in a short circuit when the device tries to deliver high-voltage shocks. Consequently, patients may experience less shock than intended or may not receive a shock at all. The FDA reported six complaints about this device issue. There have been no reports of injuries or deaths [41, 43].

RCT: Bias zugunsten der Nicht-unterlegenheit?

Regarding the RCT result about non-inferiority of the S-ICD in terms of the composite endpoint of inappropriate shocks and device-related complication, the single components of the composite endpoint could be expected to go in opposite directions thus might have biased the trial toward reaching non-inferiority. Moreover, there are concerns that the same weight is given to severe consequences of inappropriate high-voltage shocks and possible less severe device-related complications [41].

keine Unterscheidung der Schweregrade der Komplikationen

keine Langzeitkomplikationen berichtet

Furthermore, considering projected battery longevity of approximately 7 and 10 years for the S-ICD and the TV-ICD, respectively [35], none of the included studies with follow-ups ranging from the in-hospital stay to a maximum of six years after the implantation reflected long-term mortality and complications.

Studienergebnisse auf österreichischen Kontext übertragbar

In terms of external validity, the generalisability of the study results to the Austrian context can be assumed, as the included studies were conducted across several European countries (Netherlands, Germany, United Kingdom, Czech Republic, and Italy). Further aspects of the applicability of the included studies are summarised in the Appendix (see Table A-6).

Existing evidence

Einbettung in bestehendes Wissen:

The results of this systematic review are mostly aligned with the results from two other recent systematic reviews, which followed less stringent inclusion criteria for observational studies:

2 SR aus 2021 mit weniger strikten Einschlusskriterien bzgl. Beobachtungsstudien

One recent systematic review and meta-analysis from 2021 [20] identified the same RCT and 12 observational studies comprising 9,073 patients that directly compared clinical outcomes and complications between patients implanted with S-ICDs and those with TV-ICDs. The authors concluded that patients with an ICD indication without the need for pacing, TV-ICD and S-ICD are overall comparable in terms of the composite of clinically relevant device-related complications and inappropriate shocks.

1 Review: s.s. niedrigeres Risiko für sondenbedingte Komplikationen & Gesamtmortalität in Pat. mit S-ICD beobachtet

Another systematic review and meta-analysis from 2021 [19] searched for RCT and retrospective and prospective, non-randomised, cross-sectional, propensity-matched, case-control, longitudinal and observational studies. Twenty-six studies[18] that examined 7,542 patients with S-ICDs and 5,400 patients with TV-ICDs were identified. The results showed that patients with S-ICDs had a statistically significantly lower incidence of lead-related complications. Moreover, in contrast to the results of the present systematic review, the review observed a statistically significant reduction in all-cause mortality in the S-ICD group.

[18] The 26 studies included all studies that have been included in the previous systematic review from 2018 and this update except the post-hoc analysis of the RCT [26].

CoI nur in 1 SR

Both systematic reviews had no funding sources to disclose, and only in one review [20], the corresponding author received modest speaking fees from Boston scientific and abbot Medical.

ESC Leitlinie 2021: S-ICD für Pat. mit ICD-Indikation ohne anti-tachykardiales Pacing (ATP) empfohlen

Besides, it is noteworthy to mention that the international ESC (2021) and AHA/ACC/HRS (2017) guidelines recommended the use of S-ICD only in patients with an ICD indication for primary and secondary prevention when pacing therapy for bradycardia support, cardiac resynchronisation or ATP is not needed [2, 3, 5]. The studies included in this systematic review aligned with these recommendations.

Limitations of the present report

NRCTs unter Berücksichtigung strikter Einschlusskriterien zusätzlich herangezogen

The results of this review should also be seen in the context of its limitations. Although NRCTs are more prone to internal validity concerns when compared to randomised trials, we have included NRCTs additionally. While some may consider this a weakness of the present systematic review, it can also be a strength. To mitigate the concerns, the included NRCTs were selected based on pre-specified design features (i.e., n=>100 patients in the S-ICD group) and the principle of best available NRCTs (i.e., exclusion of NRCTs with high RoB) in line with Cochrane methodology [44].

Ergebnisse von 2 großen einarmigen Studien keinen Einfluss auf Ergebnisse des vorliegenden SR

Consequently, the results of large single-arm registry studies were excluded from this review. For example, the S-ICD Post Approval Study (S-ICD PAS), a prospective registry, included 1,637 de novo patients (68.5% men, mean LVEF of 32.0%, 42.9% ischaemic disease) from 86 US centres. The authors reported a complication-free rate of 92.5% and an appropriate shock rate of 5.3% [45, 46]. Another example presents the extended Experience from the Long-term Italian S-ICD (ELISIR) registry that included a total of 1,254 patients (median age 52.0 years, 77.6% men, 30.9% ischemic disease). In the study, over a mean follow-up of 23.2 months, complications were observed in 9.3% of the patients with a total of 127 device-related complications [40]. The patient populations and the safety results of these studies are in line with the results of the present systematic review.

UNTOUCHED Studie: interessante Ergebnisse zu Sicherheitsdaten müssen noch bestätigt werden

The results of another large registry study, the Understanding Outcomes With the S-ICD in Primary Prevention Patients With Low Ejection Fraction (UNTOUCHED) trial with 1,111 patients (mean age 55.8 years, 25.6% women, 23.4% Black, mean LVEF 26.4%, 53.5% ischaemic heart disease) showed that the rate of inappropriate shocks observed in the PRAETORIAN trial [25] that mostly used generation 1 S-ICD devices could be further reduced by using generation 2 and 3 S-ICD devices [33, 34]. However, these promising safety profiles need to be confirmed by randomised studies.

Evidence gaps and ongoing studies

weiteres Forscher-initiiertes RCT in Zukunft notwendig

In the present systematic review, the comparative evidence regarding the effectiveness and safety of S-ICD compared to TV-ICD was assessed in adult patients with an increased risk of sudden cardiac death and an ICD indication for primary and secondary prevention with no need for pacing. In the future, an additional confirmatory (preferably investigator-initiated) RCT in the indicated patient population is needed.

weitere (kontrollierte) Evidenz zu S-ICD auch bei Kindern – jungen Erwachsenen wichtig, Nov. 2022 AWMF-Leitlinie zu erwarten

Besides, more, preferably controlled evidence on the effectiveness and safety of the S-ICD compared to the TV-ICD is also needed for children, adolescents and young adult patients. Besides future study results, the German AWMF guideline registered a guideline project about the ICD use in children, adolescents and young adults, which is expected to be completed in November 2022 [47].

längere Nachbeobachtungszeiträume wichtig

Against the background of the lifespan of the devices, further RCTs with more extended follow-up periods (10 years) are recommended because lead-related complications tend to occur later in the lifespan of the devices and may also affect long-term mortality [41].

bessere Evidenzqualität (bevorzugt RCTs) zur Lebensqualität gewünscht

The quality of life of patients with S-ICDs compared to patients with TV-ICDs is important to be assessed next to other effectiveness and safety outcomes. One excluded retrospective NRCT with high RoB found no statistically significant differences in physical and mental quality of life and depression, but statistically significantly less anxiety in patients with S-ICDs [48]. Better quality, preferably randomised studies are to be awaited assessing the quality of life in S-ICD compared to TV-ICD patients.

offene Fragen zu neueren S-ICD-Generationen, Wichtigkeit von DFT, etc.

Apart from that, further uncertainties exist concerning newer algorithms and later-generation S-ICD devices (especially the effect on the number of inappropriate shocks), as well as the importance of defibrillation threshold testing (DFT) [33]. Follow-ups of the PRAETORIAN trial are planned to investigate these questions [33-35].

2 laufende RCTs identifiziert:

The systematic search and the search in clinical trial registries yielded two ongoing RCTs:

PRAETORIAN Follow-up zu DFT

- The follow-up PRAETORIAN-DFT (NCT03495297) will test the hypothesis that implantation of a S-ICD without performing a defibrillation test is non-inferior to S-ICD implant with a defibrillation test with regards to the primary endpoint failed the first shock in a spontaneous arrhythmia episode. The estimated primary completion date is September 2023.

Forscher-initiiertes ATLAS RCT zu neueren S-ICD Generationen

- The randomised prospective investigator-initiated Avoid Transvenous Leads in Appropriate Subjects (ATLAS) study (NCT02881255) will determine if using newer S-ICD generations compared to TV-ICDs reduces the primary composite outcome of perioperative lead-related complications including pulmonary or pericardial perforation, lead dislodgement or dysfunction, tricuspid regurgitation and ipsilateral venous thrombosis. In addition, it will assess mortality and shock efficacy. Five hundred patients younger than 60 will be enrolled from 14 Canadian hospitals, and data will be collected at six and 24 months. The estimated primary completion date was 31st December 2021, and the study completion date is planned for February 2022 [49].

A summary of the identified ongoing RCTs is presented in the Appendix (see Table A-7).

Conclusion

Schlussfolgerung: S-ICD hinsichtlich unangemessenen Schocks & gerätbedingten Komplikationen nicht unterlegen

The current evidence is insufficient to draw definitive conclusions on the comparative effectiveness and safety of S-ICD in patients with an increased risk of sudden cardiac death and an ICD indication for primary and secondary prevention with no need for pacing. However, moderate-quality evidence from the RCT suggests that the S-ICD is non-inferior to TV-ICD in terms of a composite-endpoint of inappropriate shocks and device-related complications. Furthermore, included evidence indicates a statistically significantly lower risk for lead-related complications in patients with S-ICDs.

Ergebnisse eines neuen RCTs werden erwartet

The results of the ATLAS trial are to be awaited to shed more light on the randomised evidence of S-ICD versus TV-ICD in a selected patient population that may benefit from S-ICD.

6 Recommendation

In Table 6-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 6-1: 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:

Empfehlung basierend auf upgedateter Evidenz:

Aufrechterhaltung der Erstattung von S-ICD als genehmigungspflichtige Leistung

The updated evidence is insufficient to determine whether the S-ICD is equally or more effective and safer than the conventional TV-ICD in patients with an increased risk of sudden cardiac death and an ICD indication for primary and secondary prevention without the need for pacing. Nevertheless, moderate-quality evidence from the RCT suggests that the S-ICD is non-inferior to the TV-ICD in terms of a composite of inappropriate shocks and device-related complications. In addition, the available evidence indicates that there is a statistically significantly lower risk for lead-related complications in patients with S-ICDs.

Based on these results, it is recommended to reimburse S-ICDs with restrictions: The existing code (DE112) should be maintained, including reimbursement after the approval by the state healthcare fund [7]. In addition, close monitoring of the use of S-ICDs is recommended.

Ergebnisse des ATLAS RCTs werden erwartet → Re-evaluierung nicht vor 2024

The new randomised evidence results of the investigator-initiated ATLAS trial comparing the effectiveness and safety of more recent S-ICD generations to TV-ICDs (n=500, expected study completion date: February 2022) will potentially influence the effect estimate. Thus, a re-evaluation is recommended not before 2024.

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Subcutaneous versus transvenous implantable cardioverter-defibrillator: Results from randomised controlled trials

Author, year, trial name	Knops et al. 2020 [25], PRAETORIAN trial (Primary analysis)	Knops et al. 2021 [26], PRAETORIAN trial (Post-Hoc analysis)
Study characteristics		
Countries	International (Netherlands, Germany, United Kingdom, Czech Republic, Chicago United States of America)	
Sponsor	■ Academisch Medisch Centrum – Universiteit van Amsterdam (AMC-UvA) ■ Boston Scientific Corporation	
Intervention/Product	Subcutaneous implantable cardioverter-defibrillator (S-ICD): ■ Boston Scientific/Cameron Health 1010 (190) ■ Boston Scientific A209 EMBLEM (191) ■ Boston Scientific A219 EMBLEM MRI (48)	
Comparator/Products	Transvenous implantable cardioverter-defibrillator (TV-ICD): ■ Boston Scientific (149) ■ St. Jude Medical (115) ■ Medtronic (87) ■ Biotronik (66) ■ Sorin (3)	
Study design	Investigator-initiated, international, randomised, non-inferiority trial	Post-hoc analysis of the randomised controlled trial
Primary endpoint(s)	Composite endpoint: device-related complications and inappropriate shocks[19] **(non-inferiority margin 1.45)**	■ Total appropriate ICD therapy[20] ■ First shock efficacy[21]
Number of pts, total (intervention vs comparator)	Modified intention-to-treat analysis[22]: 849 (426 vs 423)	

[19] An ICD shock was classified as inappropriate when it was delivered for any rhythm other than ventricular fibrillation (VF) or ventricular tachycardia (VT).

[20] Appropriate ICD therapy was defined as ATP or shock therapy for either VT or VF.

[21] Shock efficacy was defined as the percentage of successful shocks of the total amount of shocks. A shock is considered successful if it is able to convert the ventricular arrhythmia to sinus rhythm or atrial fibrillation within 5 seconds.

[22] The modified intention-to treat poplation included patients according tot he group to which they had been randomly assigned, regardless of the device they received, whithdrawals, losses to follow-up or crossovers. Patients who did not receive either device after randomisation or who underwent randomisation in error were excluded from the analyses.

Author, year, trial name	Knops et al. 2020 [25], PRAETORIAN trial (Primary analysis)	Knops et al. 2021 [26], PRAETORIAN trial (Post-Hoc analysis)
Inclusion criteria	■ ≥18 years of age ■ Class I or IIa indication for ICD therapy for primary or secondary prevention, according to the guidelines from the American College of Cardiology – American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society or those from the European Society of Cardiology	
Exclusion criteria	■ Previous ICD implantation ■ Unsuitability for S-ICD therapy according to QRS-T–wave sensing analysis and indications for either bradycardia pacing or biventricular pacing ■ Known VT at a rate below 170 beats per minute or with refractory recurrent monomorphic VT that could not be managed with medication or ablation therapy	
Follow-up, median months (IQR)	49.1 (NR)	52 (41.4-68.5)
Loss to follow-up, n	Loss to follow-up: 17 vs 21 Dead before occurrence of primary endpoint event: 70 vs 76	NR
Cross-over ■ **Before initial implantation, n** ■ **During implantation or follow-up, n** ■ **Upgrade to a CRT-D during follow-up, n**	18 (4.3) vs 11 (2.7), HR 1.64, 95% CI 0.77–3.47 ■ 10 (4 vs 6) ■ 19 (14 vs 5) ■ NR	**Of the patients with appropriate therapy (n= 86 vs 78):** ■ 3 (0 vs 3) ■ 5 (5 vs 0) ■ 13 (8 vs 5)
Patient characteristics		
Age of patients, median yrs (IQR)	63 (54-69) vs 64 (56-70)	
Female, n (%)	89 (20.9) vs 78 (18.4)	
Median body mass index, BMI kg/m^2 (IQR)	27.0 (24.5-30.5) vs 27.9 (25.2-31.7)	
Primary prevention, n (%)	346 (81.2) vs 340 (80.1)	
Median LVEF, % (IQR)	30 (25-35) vs 30 (25-35)	
Ischemic cardiomyopathy, n (%)	289 (67.8) vs 298 (70.4)	
Non-ischemic cardiomyopathy, n (%)	99 (23.2) vs 98 (23.2)	
Genetic arrhythmia syndrome, n (%)	20 (4.7) vs 18 (4.3)	
Hyperthrophic cardiomyopathy, n (%)	15 (3.5) vs 7 (1.7)	
Idiopathic ventricular fibrillation, n (%)	11 (2.6) vs 5 (1.2)	
Congential heart disease, n (%)	3 (0.7) vs 3 (0.7)	
Atrial fibrillation or atrial flutter, n (%)	115 (27.0) vs 93 (22.1)	
Effectiveness outcomes		
All-cause mortality, n (4 yrs cumulative incidences %) ■ **Sudden cardiac death (SCD), n**	83 (16.4) vs 68 (13.1), HR 1.23, 95% CI 0.89-1.70 ■ 18 vs 18	NR
Appropriate shocks (AS)[20], n (4 yrs cumulative incidences %)	83 (19.2) vs 57 (11.5), HR 1.52, 95% CI 1.08-2.12, p=0.02[23]	

[23] Including at least 1 shock per patient.

Author, year, trial name	Knops et al. 2020 [25], PRAETORIAN trial (Primary analysis)	Knops et al. 2021 [26], PRAETORIAN trial (Post-Hoc analysis)
Shock efficacy[21]**, %**	NR	■ First shock efficacy: 93.8 vs 91.6, p=0.40 ■ Final shock efficacy: 97.9 vs 98.4, p=0.70
Appropriate anti-tachycardia pacing (ATP)[20, 24]	**Appropriate ATPs, n (4 yrs cumulative incidences %):** ■ 6 (0.6) vs 54 (12.9)	**ITT-population:** ■ S-ICD: 18 ATPs in 5/426 pts. ■ TV-ICD: 328 ATPs in 56/423 pts. (259 of the 328 ATPs [79.0%] were first ATPs). ■ TV-ICD: 234 of the 259 first ATPs (90.3%) were given on monomorphic VTs with an efficacy of 46% (95% CI 39.9-52.6). **ATP as the only treatment in pts. with appropriate therapy, n (%):** ■ S-ICD: 3/86 (3.5) ■ TV-ICD: 21/78 (26.9)[25]
Hospital re-admission, n (4 yrs cumulative incidences %)	Hospitalisation for heart failure: 79 (17.4) vs 74 (16.1), HR 1.08, 95% CI 0.79-1.49	NR
Quality of life (QoL)	NR	
Safety outcomes		
Composite primary endpoint: device-related complications and inappropriate shocks, n (4 yrs cummulative incidence %)	68 (15.1) vs 68 (15.7), HR 0.99, 95% CI 0.71-1.39 non-inferority margin 1.45, p=0.001 (non-inferiority), p=0.95 (superiority)	NR
Inappropriate shocks (IAS), n (4 yrs cumulative incidences %)[19]	41 (9.7) vs 29 (7.3), HR 1.43, 95% CI 0.89-2.30	NR
■ **Atrial fibrillation or supraventricular tachycardia, n (%)**	11 vs 27	
■ **Cardiac oversensing, n (%)**	24 vs 2[26]	
■ **Non-cardiac oversensing, n (%)**	8 vs 0[27]	
Inappropriate ATP[24]**, n (4 yrs cumulative incidences %)**	1 (0.3) vs 30 (7.2)	NR

[24] Patients who received ATP in the S-ICD group had previously crossed over to TV-ICD therapy or had received a cardiac resynchronisation therapy defibrillator (CRT-D).

[25] The first ATP attempt on a monomorphic VT accelerated the tachycardia in 9.4% of all episodes, which affected 15/78 patients (19.2%).

[26] This category included T-wave and P-wave oversensing and included shock on a trial fibrillation or supraventricular tachycardia below the detection limit in 5 patients in the S-ICD group.

[27] This category included myopotential and noise oversensing.

Author, year, trial name	Knops et al. 2020 [25], PRAETORIAN trial (Primary analysis)	Knops et al. 2021 [26], PRAETORIAN trial (Post-Hoc analysis)
Device- and lead-related complications, n (4 yrs cumulative incidences %)	31 (5.9) vs 44 (9.8), HR 0.69, 95% CI 0.44-1.09 Lead-related complications only: 1.4% vs 6.6%, HR 0.24, 95% CI 0.10-0.54	NR
■ Infections, n	4 vs 8[28]	
■ Bleeding, n	8 vs 2	
■ Thrombotic event, n	1 vs 2	
■ Pneumothorax (lead-related), n	0 vs 4	
■ Lead perforation, n	0 vs 4	
■ Lead repositioning, n	2 vs 7	
■ Pericardial tamponade, n	0 vs 2	
Other lead or device-related complications, n	19 vs 20	NR
■ Lead replacement, n	3 vs 9[29]	
■ Device malfunction, n	4 vs 6	
■ Sensing issues, n	4 vs 0	
■ Pacing indication, n	5 vs 1[30]	
■ Implant failure, n	0 vs 3	
■ Defibrillation test failure, n	3 vs 0[31]	
■ Pain or discomfort, n	2 vs 3	

Abbreviations: ATP – Anti-tachycardia pacing, CRT-D – cardiac-resynchronisation therapy device, ICD – Implantable cardioverter-defibrillator, IQR – Interquartile range, LVEF – Left ventricular ejection fraction, pts. – Patients, QoL – Quality of life, SCD – Sudden cardiac death, S-ICD – Subcutaneous ICD, TV-ICD – Transvenous ICD, VF – Ventricular fibrillation, vs – Versus, VT – Ventricular tachycardia, yrs. – Years

[28] Lead-related infection in the S-ICD group (n=1) vs TV-ICD group (n=5), including infection, perforation, lead dislodgement and lead dysfunction.

[29] In the S-ICD group, lead replacements were due to dislocation in 2 patients and to myopotential oversensing in 1.
In the TV-ICD group, lead replacements were due to lead dysfunction in 6 patients and to lead dislodgement in 3.

[30] In the S-ICD group, 3 patients received a pacemaker, 1 received a CRT-D, and 1 crossed over to TV-ICD therapy all for pacing for the treatment of bradycardia.
In the patient in the TV-ICD group who had previously crossed over to S-ICD therapy, sick-sinus syndrome later developed, for which a pacemaker was implanted.

[31] This category included defibrillator test failures that led to surgical re-intervention.

Table A-2: Subcutaneous versus transvenous implantable cardioverter-defibrillator: Results from non-randomised controlled studies with >100 patients in the intervention group and low to moderate risk of bias

Source	LBI-HTA systematic review 2018 [1]		New studies	
Author, year	**Brouwer et al. 2016 [13]**	**Friedmann et al. 2016 [14]**	**Brouwer et al. 2018 [27]**	**Palmisano et al. 2021 [28]**
Study characteristics				
Country	Netherlands	Unites States of America	Netherlands	Italy
Sponsor	NR	Supported by the American College of Cardiology's National Cardiovascular Data Registry (NCDR)	Boston Scientific Incorporation	Azienda Ospedaliera Cardinale G. Panico
Intervention/Product	S-ICD	S-ICD	S-ICD	S-ICD[32]
Comparator/Products	Single-chamber and dual-chamber TV-CD	Single-chamber and dual-chamber TV-ICD	Single- and dual-chamber TV-ICD	Single- and dual-chamber TV-ICD
Study design	Retrospective observational study with propensity score matching	Retrospective observational study with propensity score matching	Retrospective observational study with propensity score matching	Prospective, multicenter, observational study with propensity score matching
Primary endpoint	Device-related complications[33]	Composite outcome of any recorded in-hospital adverse event[34]	Device-related complications[33]	Device related complications[35]
Number of matched pts.	260 (140 vs 140)	5,760 (1920 vs 1920 vs 1920)	782 (391 vs 391 [89% single-chamber])	338 (169 [88.2% two-incision intermuscular technique] vs 169 [81.7% single-chamber])
Inclusion criteria	■ Patients implanted with S-ICDs between 2009 and 2015 at the Academic Medical Center (AMC). ■ Patients implanted with single- and dual-chamber TV-ICDs between 2005 and 2014 at the Leiden University Medical Center (LUMC).	■ All Patients admitted for ICD implantation (September 28, 2012-March 31, 2015). ■ Eligible for an S-ICD, single- or dual-chamber TV-ICD. ■ Patients from the National Cardiovascular Data ICD Registry.	■ Patients from the EFFORTLESS registry (S-ICD) and the SIMPLE study (TV-ICD)[36, 37] ■ Patients who are not expected to benefit from ATP.	■ Patients from the POINTED (Impact on Patient Outcome and healthcare utilization of cardiac ImplaNTble Electronic Devices complications) registry. ■ Age ≥18 years. ■ Ability to provide informed consent. ■ Life expectancy >6 months.

[32] From February 2015, S-ICD implantations were performed using the two-incision technique14 in all participating centers. From January 2016, in the majority of centers, the two-incision intermuscular technique was used.

[33] Defined as all system-related complications requiring invasive intervention.

[34] Including adverse events, such as death, cardiac arrest, cardiac perforation, valve injury, hematoma, hemathorax, infection, lead dislodgement, myocardial infarction, pericardial tamponade, set screw problem, pneumothorax, transient ischemic attack or stroke, or urgent cardiac surgery.

[35] Any device-related adverse event requiring surgical revision that was identified after the implantation procedure. Complications that occurred after the first month post-implantation were defined as late complications.

[36] The EFFORTLESS registry (funding and devices by Boston Scientific) is a multicentre observational study that enrolled patients implanted with an S-ICD both prospective and retrospective (n=798).

[37] The SIMPLE study (funding and devices by Boston Scientific) randomized patients undergoing single, dual or resynchronization defibrillator implantation to periprocedural defibrillation testing vs no defibrillation testing (single chamber: n=1091; dual chamber: n=553).

Source	LBI-HTA systematic review 2018 [1]		New studies	
Author, year	**Brouwer et al. 2016 [13]**	**Friedmann et al. 2016 [14]**	**Brouwer et al. 2018 [27]**	**Palmisano et al. 2021 [28]**
Exclusion criteria	Patientsincluded in the ongoing PRAETORIANtrial.	■ Patients with previous ICD, bradycardia, or resynchronisation indication for permanent pacing. ■ Patients under-going ICD implantation during acute hospitalisation.	Patients implanted with a CRT-D, history of pacemaker, ICD or CRT-P/D at baseline or paced rhythms at baseline or post-implant.	■ Expected heart transplantation within 6 months. ■ Upgrade of an existing device or a new implantation procedure after removal of a previous pacing system. ■ Patients implanted with a TV-ICD with a concomitant pacing indication and/or documentation of sustained monomorphic VT likely to require ATP as they are generally not candidates for S-ICD implantation and may have significantly different clinical characteristics compared with other patients.
Follow-up (months)	Median: 36 vs 60 months, p <0.001	Max: Duration of hospital stay	Median years (SD): 2.9 ± 1.4 vs 3.3 ± 0.8, p=NR	Median months (IQR): 30.3 (16.1–46.0) vs 31.3 (19.1–53.4), p=0.201
Loss to follow-up, n (%)	NA	NA	NA	0
Patient characteristics				
Age of patients, yrs	Median (IQR): 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=0.21	Mean ± SD: 55.6 ± 13.0 vs 57.4 ± 15.5 p=0.248
Female, n (%)	56 (40) vs 53 (38) p=0.71	627 (32.7) vs 598 (31.2) vs 633 (33) p=NR	92 (23.5) vs 72 (18.4) p=0.08	31 (18.3) vs 42 (24.9) p=0.146
Body mass index, BMI kg/m²	NR	NR	Mean ± SD: 28 ± 6 vs 28 ± 5, p=0.57	NR
Primary prevention, n (%)	93 (66) vs 86 (61) p=0.38	NR	272 (69.6) vs 279 (71.4) p=0.58	142 (84.0) vs 130 (76.9) p=NR
First ICD implantation, n (%)	121 (86) vs 125 (89) p=0.47	1920(100)vs1920 (100)vs1920(100)	391 (100) vs 391 (100)	NR
LVEF, %	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	Mean ± SD: 39.4 ± 17.3 vs 39.8 ± 16.9, p=0.71	Mean ± SD: 37.9 ± 14.7 vs 37.9 ± 14.4, p=0.985
Ischemic heart disease or coronary artery disease, n (%)	NR	879 (45.8) vs 890 (46.4) vs 857 (44.6) p=NR	Coronary artery bypass graft: 51 (13.0) vs 42 (10.7) p=0.32	NR
Ischemic cardiomyopathy, n (%)	26 (19) vs 41 (29) p=NR	NR	Ischemic diagnosis: 187 (47.8) vs 194 (49.6), p=0.62	71 (42.0) vs 60 (35.5) p=0.219
Dilated cardiomyopathy, n (%)	NR	846 (44.1) vs 832 (43.3) vs 845 (44) p=NR	41 (10.5) vs 33 (8.4) p=NR	Idiopathic dilated cardiomyopathy: 51 (30.2) vs 56 (33.1), p=0.559
Non-ischemic cardiomyopathy, n (%)	28 (20) vs 30 (21) p=NR	846 (44.1) vs 832 (43.3) vs 845 (44) p=NR	91 (23.3) vs 91 (23.3)[38]	NR

[38] Including **non-ischaemic cardiomyopathy**, valvular disease, structural defect, syncope of unknown origin, myocarditis, cardiac sarcoidosis, and unknown.

Source	LBI-HTA systematic review 2018 [1]		New studies	
Author, year	**Brouwer et al. 2016 [13]**	**Friedmann et al. 2016 [14]**	**Brouwer et al. 2018 [27]**	**Palmisano et al. 2021 [28]**
Non-ischemic channelopathy, n (%)	NR	NR	35 (9.0) vs 34 (8.7) p=0.90	NR
Genetic arrhythmia syndrome, n (%)	75 (54) vs 54 (39) p=NR	■ 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)	Heart failure: 155 (39.6) vs 153 (39.1) p=0.88	NR
Hyperthrophic cardiomyopathy, n (%)	NR	123 (6.4) vs 122 (6.4) vs 120 (6.3) p=NR	37 (9.5) vs 39 (10.0) p=NR	17 (10.1) vs 20 (11.8) p=0.601
Idiopathic ventricular fibrillation, n (%)	NR	17 (0.9) vs 14 (0.7) vs 18 (0.9)	NR	7 (4.1) vs 11 (6.5) p=0.333
Congential heart disease, n (%)	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	Arrhythmogenic right ventricular dysplasia: 11 (6.5) vs 13 (7.7) p=0.672
Atrial fibrillation or atrial flutter, n (%)	13 (9) vs 21 (15) p=0.14	322 (16.8) vs 323 (16.8) vs 370 (19.3) p=NR	Atrial fibrillation: 80 (20.5) vs 77 (19.7), p=0.79	39 (23.1) vs 50 (29.6) p=0.174
Effectiveness outcomes				
All-cause mortality, n (%)	**5 years:** 2 (1.4) vs 6 (4.6) Kaplan-Meier analysis for survival: 96% vs 94,8%, p=0.42	**In-Hospital:** 3/1920 (0.2) vs single- chamber ICD: 2/1920 (0.1) p > 0.99 3/1920 (0.2) vs dual-chamber ICD: 1/1920 (0.05) p=0.64	**3-year survival rate:** 93.7% vs 91.5%, HR 0.74, 95% CI 0.41-1.35 p=0.32	**72 months (6 years):** 3 (1.8) vs 3 (1.8)[39] p=1.000
Appropriate shocks[20], %	**5 years:** Kaplan Meier analysis: 17.0 (95% CI 6.3–26.4) vs 21.3 (95% CI 12.6–27.3), HR 1.46, p=0.36	NR	**3 years:** 9.9 (95% CI 7.0-13.9) vs 13.8 (95% CI 10.8-17.8) p=0.03	NR
Appropriate anti-tachy-cardia pacing (ATP), n %	NR	NR	72.2% of appropriately treated episodes prior to shock therapy in the TV-ICD group.	NR
Shock efficacy, %	NR	NR	**3 years:**[40] 88.6 vs 88.6, p=1.00	NR

[39] The 3 deaths in the S-ICD group were 1 heart failure death, 1 other non-sudden cardiac death and 1 other non-cardiac death. In the TV-ICD group there were 2 heart failure deaths and 1 cerebrovascular death.

[40] Shock efficacy was evaluated in the same manner as the SIMPLE trial where the first appropriate therapy was used, in ordert o exclude multiple episodes per patient where subsequent shocks would be correlated to the first event. The first shock in the first appropriately treated VT/VF episode was considered failed if the shock did not terminate the arrhythmia.

Source	LBI-HTA systematic review 2018 [1]		New studies	
Author, year	**Brouwer et al. 2016 [13]**	**Friedmann et al. 2016 [14]**	**Brouwer et al. 2018 [27]**	**Palmisano et al. 2021 [28]**
Hospital re-admission, %	**5 years:** Re-intervention due to needed device upgrade: [41] Kaplan Meier analysis: 1.3 (95% CI 0.0-3.7) vs 4.6 (95% CI 0.5-8.5) p=0.26	Device revisions during the hospitalisation were rare (0.3%) and did not vary by device type.	**3 years:** Re-intervention due to needed device upgrade:[41] Kaplan Meier analysis: 1.3 (95% CI 0.5-3.6) vs 2.1 (95% CI 1.0-4.4) p=0.48	**72 months (6 years):** ■ Around 90% of patients with lead-related complications needed hospitalisation to solve the issue. ■ Nr. of complication-related re-operations per patient, mean ± SD: 1.0 ± 0.0 vs 1.0 ± 0.0, p=1.000 ■ Nr. of complication-related rehospitalisations per patient, mean (range): 0.3 (0–1) vs0.9 (0–1), p=0.013 ■ Number of complication- related additional hospital treatment days per patient, mean ± SD (range): 1.0 ± 1.0 (0-2) vs 6.5 ± 4.4 (0-29), p=0.048
Quality of life (QoL)	NR	NR	NR	NR
Safety outcomes				
Inappropriate shock[19], n (%)	**5 years:** Kaplan Meier analysis: 20.5% (95% CI 11.5-28.6) vs 19.1% (95% CI 11.6-26.0), HR 0.85, p=0.64	NR	**3 years:** Kaplan Meier analysis: 11.9% (95% CI 8.8-15.9) vs 7.9% (95% CI 5.6-11.1)[42] p=0.07	**72 months (6 years):** 11 (6.5) vs 14 (8.3)[43] p=0.533
Inappropriate ATPs, n (%)	NR	NR	NR	NR
Device- and lead-related complications requiring invasive interventions, n (%)	**5 years:** Kaplan Meier analysis: 14 (13.7) (95% CI 6.4-20.3) vs 21 (18.0) (95% CI 10.5-24.8) p=0.80	NR	**3 years:** Kaplan Meier analysis: 34 (9.0) (95% CI 6.5-12.3) vs 25 (6.5) (95% CI 4.4-9.4) p=0.29	**72 months (6 years):** Kaplan Meier analysis: 3 (1.8) (95% CI 0-3.8) vs 17 (10.1) (95% CI 5.5-14.6)[44] OR 0.16, 95% CI 0.05-0.56, p=0.001 ■ Early complications (<30 days after implantation): 2 (1.2) vs 8 (4.7), p=0.104 ■ Late complications (>30 days after implantation): 1 (0.6) vs 9 (5.3), OR 0.11, 95% CI 0.01-0.84, p=0.010

[41] Upgrade for the S-ICD patients to single, dual-chamber or resynchronisation defibrillator; upgrade for single-chamber TV-ICD patients to dual-chamber TV-ICD or resynchronisation defibrillator.

[42] The majority (77%) of inappropriate shocks in TV-ICD patients were due to supraventricular tachycardia vs 17% in S-ICD patients. In the S-ICD group, the majority of inappropriate shocks (67%) were due to oversensing, of which 48% was cardiac and 19% non-cardiac oversensing.

[43] Patients with at least one inappropriate shock. The majority (2.4%) of inappropriate shocks in the S-ICD group were T-wave oversensing and inappropriate sensing. The majority (5.3%) of inappropriate shocks in the TV-ICD group were due to supraventricular tachyarrhythmias/sinus tachycardia.

[44] Patients with at least one complication requiring surgical revision.

Source	LBI-HTA systematic review 2018 [1]		New studies	
Author, year	**Brouwer et al. 2016 [13]**	**Friedmann et al. 2016 [14]**	**Brouwer et al. 2018 [27]**	**Palmisano et al. 2021 [28]**
Device-related complications, n (%)	5 years: Non-lead related complications:[45] Kaplan Meier analysis: 9.9% (95% CI 2.0-15.4) vs 2.2% (95% CI 0.0-4.6), p=0.047	NR	**3 years:** Pocket-related complications:[46] Kaplan Meier analysis: 14 (3.8) (95% CI 2.2-6.3) vs 7 (1.8) (95% CI 0.9-3.8) p=0.14	NR
Pocket haematoma, n (%)	NR	**In-Hospital:** 7 (0.4) vs single-chamber ICD: 1 (0.05), p=0.07 7 (0.4) vs dual-Chamber ICD: 2 (0.1), p=0.18	**3 years:** 2 (0.5) vs 3 (0.8)	**72 months (6 years):** 1 (0.6) vs 3 (1.8), p=0.663
Lead-related complications, n (%)	**5 years:** Kaplan Meier analysis: 1 (0.8) (95% CI 0.0-2.2) vs 17 (11.5) (95% CI 5.3-17.2) p=0.03	NR	**3 years:** Kaplan Meier analysis: 1 (0.3) (95% CI 0.0-1.8) vs 9 (2.3) (95% CI 1.2-4.4)[47] p=0.03	**72 months (6 years):** Most of the complications observed requiring surgical revision were lead-related (65%), e.g.: ■ Lead failure: 0 (0) vs 4 (2.4), p=0.123 ■ Lead dislodgement: 0 (0) vs 5 (3.0), p= 0.061
Infections, n (%)	**5 years:** Kaplan Meier analysis: 5 (4.1) (95% CI 0.5-7.7) vs 4 (3.6) (95% CI 0.0-7.1), p=0.36	**In-Hospital:** 1 (0.05) vs single- chamber ICD: 0 (0), p=NR 1 (0.05) vs dual-chamber ICD: 2 (0.1), p=NR	**3 years:** Device-infection requiring invasive intervention: Kaplan Meier analysis: 10 (2.6) (95% CI 1.4-4.7) vs 2 (0.5) (95% CI 0.1-2.0) p=0.09	**72 months (6 years):** Device-infection requiring surgical revision: 1 (0.6) vs 2 (1.2)[48] p=1.000
Cardiac tamponade, n (%)	NR	**In-Hospital:** 0 (0) vs single-chamber ICD: 0 (0), p=NR 0 (0) vs dual-chamber ICD: 5 (0.3), p=NR	**3 years:** Implant-related myocardial perforation with tamponade: 0 (0) vs 1 (0.3)	**72 months (6 years):** Cardiac tamponade requiring surgical revision: 0 (0) vs NR p=NR

Abbreviations: ATP – Anti-tachycardia pacing, CI – Confidence Interval, CRT – Cardiac Resynchronization Therapy, HR – Hazard ratio, ICD – implantable cardioverter-defibrillator, LVEF – Left ventricular ejection fraction, PRAETORIAN – Prospective, RAndomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy trial, pts – Patients, NR – not reported, QoL – Quality of life, S-ICD – Subcutaneous ICD, TV – transvenous, TV-ICD – Transvenous ICD, VF – ventricular fibrillation, VT – ventricular tachycardia

[45] Including pocket erosion, defibrillation threshold testing failure and device failure.

[46] Including haematoma, erosion, movement, wound discomfort or pocket seroma.

[47] There were a total of 9 lead complications in the TV-arm, of which 1 was related to the atrial lead and 8 were ventricular lead complications.

[48] Both TV-ICD patients presented systemic infection and underwent complete removal of the pacing system with transvenous leads extraction. After removal of the infected CIED, the implantation of an S-ICD was performed during subsequent re-hospitalisation in one of the 2 patients. The management of device infection in the 2 patients required respectively 29 and 20 additional hospital treatment days.

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. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA [2] and the Guidelines of EUnetHTA [3].

Table A-3: Risk of bias – endpoint level (randomised studies), see [1]

Trial	Endpoints	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Knops et al. 2020 [25], PRAETORIAN trial, NCT01296022	SCD, AS, IAS, device- and lead-related complications	Low	Low[49]	Low[50]	Some concerns[51, 52, 53]	Low[54, 55]	**Some concerns**
Knops et al. 2021 [26], post-hoc analysis of the PRAETORIAN trial	Shock efficacy, appropriate ATP	Low[56]	Low[49]	Some concerns[57]	High[58]	Some concerns[55, 59]	**High**

Abbreviations: AS – Appropriate shocks, ATP – Anti-tachycardia pacing, IAS – Inappropriate shocks, QoL – Quality of life, SCD – Sudden cardiac death

49 Analyses for all the endpoints were performed in the modified intention-to-treat population, which included patients according to the group to which they had been randomly assigned, regardless of the device they received. Patients who did not receive either device after randomisation or who underwent randomisation in error were excluded from the analyses [25]. However, nearly 5.0% of the patients (n=38) were lost to follow-up, and more patients crossed over from the S-ICD group to the TV-ICD group than vice versa (14 vs 5) [41].

50 For all endpoints, the sample included all the patients in the trial group. Sensitivity analyses confirm that plausible values of the missing outcome data could make no important difference to the estimated intervention effect [25].

51 There are concerns about the equivalency of inappropriate shocks with device-related complications, given the negative inotropic consequences of high-voltage shocks [41].

52 Concerns about the non-inferiority design include that non-inferiority testing should assess efficacy for treatments that have a superior safety or some other obvious benefit. Therefore, a better design for testing the S-ICD against TV-ICD would have included testing superiority for safety outcomes and non-inferiority for efficacy [41].

53 The upper bound of the 95% confidence interval of the primary composite endpoint (1.39) was close to the threshold of non-inferiority of 1.45. The authors acknowledge that the magnitude of this non-inferiority margin is debatable on clinical grounds [50].

54 The number of appropriate shocks was higher in the S-ICD group; however, it needs to be considered that ATPs in the TV-ICD group also prevented shock therapy, whereas the S-ICD device is not capable of giving ATPs [41].

55 The trial was partly funded by the S-ICD manufacturer (Boston Scientific Corporation).

56 The intention-to-treat analysis was maintained in the post-hoc analysis [26].

57 The majority of missing electrograms occurred in the TV-ICD group, as this device often overwrites previously stored episodes to preserve storage capacity. These episodes could not be adjudicated and lead to an underestimation of the amount and nature of appropriate therapy in the TV-ICD group and subsequently in shock efficacy [26].

58 The primary endpoint of the post-hoc analysis is "shock efficacy"; however, the study was not powered for "shock efficacy" as the primary endpoint.

59 The endpoints „appropriate and inappropriate ATPs" defined for the post-hoc analysis were not defined in a pre-specified analysis. In contrast, the endpoint „shock efficacy" was already defined in the pre-specified analysis [50].

Table A-4: Risk of bias of non – randomised controlled studies (>100 patients in the intervention group) comparing subcutaneous implantable cardioverter-defibrillator (S-ICD) with transvenous implantable cardioverter-defibrillator (TV-ICD), see [3]

Study reference/ ID	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of intervention	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Assessment of the studies of the LBI-HTA systematic review 2018									
Brouwer et al. 2016 [13]	Moderate[a]	Moderate[b]	Low	NI	Low	Low	Moderate[c]	**MODERATE**	[a] *Propensity score matching (reducing baseline confounding bias), residual confounding of unmeasured variables potentially present.* [b] *Retrospective analysis of intervention group with a matched control group.* [c] *There is no clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses, and sub-cohorts.*
Friedman et al. 2016 [14]	Moderate[a]	Moderate[b]	Low	NI	Low	Low	Moderate[c]	**MODERATE**	[a] *The control groups were sufficiently matched by propensity score matching.* [b] *Retrospective analysis of intervention group with a matched control group.* [c] *There is no clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses, and sub-cohorts.*
Pedersen et al. 2016 [10][60]	Moderate[a]	Moderate[b]	Low	NI	NI	Serious[c]	Moderate[d]	**SERIOUS**[e]	[a] *Confounding expected, all known important confounding domains appropriately measured and controlled for by propensity score matching (greedy matching algorithm).* [b] *Retrospective analysis and start of follow-up and start of intervention do not coincide for all participants: data of two different trials (MIDAS [TV-ICD] & single-arm multicentre EFFORTLESS study [S-ICD]) was matched.* [c] *The outcome measure was subjective (i.e. vulnerable to influence by knowledge of the intervention received by study participants). The outcome was assessed by assessors aware of the intervention received by study participants.* [d] *There is no clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses, and sub-cohorts.* [e] *The corresponding author has served as a consultant for Boston Scientific (manufacturer); a second author is an employee of Boston Scientific.*

[60] 6-months follow-up (n= 167 vs 167).

Study reference/ ID	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of intervention	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Assessment of the new studies									
Brouwer et al. 2018 [27]	Low	Moderate[a]	Moderate[b]	NI	Moderate[c]	Moderate[d]	Moderate[e]	**MODERATE**[f]	[a] *Start of follow-up and start of intervention may not coincide for all participants, because the data of two different trials (randomised multicentre SIMPLE trial [TV-ICD] & single-arm multicentre EFFORTLESS study [S-ICD]) was matched.* [b] *Retrospective analysis of intervention group with a matched control group.* [c] *Exclusion of 285/798 pts in the S-ICD arm vs 126/1644 pts. in the TV-ICD arm for the primary matched cohort analysis.* [d] *All complications and therapy endpoints were adjudicated by a single internal adjudication committee of the sponsor prior to the current analysis.* [e] *There is no clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses, and sub-cohorts.* [f] *This study was supported by Boston Scientific Incorporation.*
Pedersen 2019 [48][61]	Moderate[a]	Moderate[b]	Low	NI	NI	Serious[c]	Moderate[d]	**SERIOUS**[e]	[a] *Confounding expected, all known important confounding domains appropriately measured and controlled for; Reliability and validity of measurement of important domains were sufficient, such that we do not expect serious residual confounding.* [b] *Retrospective analysis and start of follow-up and start of intervention do not coincide for all participants: data of two different trials (MIDAS [TV-ICD] & single-arm multicentre EFFORTLESS study [S-ICD]) was matched.* [c] *The outcome measure was subjective (i.e. vulnerable to influence by knowledge of the intervention received by study participants). The outcome was assessed by assessors aware of the intervention received by study participants.* [d] *There is no clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses, and sub-cohorts.* [e] *The corresponding author has served as a consultant for Boston Scientific (manufacturer); a second author is an employee of Boston Scientific.*
Palmisano et al. 2021 [28]	Moderate[a]	Low	Low	NI	Low	Moderate[b]	Low	**MODERATE**	[a] *Although there were no differences in baseline characteristics in the matched cohort, residual confounding of unmeasured variables due to the observational nature of the study cannot be excluded.* [b] *It is not clear if the electrophysiologists analysing the EGMs were blinded.*

Abbreviations: BMI – Body Mass Index, NA – Not appropriate, NI – No information, Pts. – Patients, S-ICD – Subcutaneous cardioverter-defibrillator, TV-ICD – Transvenous cardioverter-defibrillator.

[61] 12-months follow-up (n= 167 vs 167).

Table A-5: Evidence profile: efficacy and safety of S-ICD in adult patients with a higher risk for sudden cardiac death

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**S-ICD**	**TV-ICD**	**Absolute (95% CI)**	**Relative (95% CI)**		
Effectiveness (RCT evidence)												
Mortality *(all-cause mortality)* (follow-up: median 49.1 months, assessed with: n [%]) [25]												
1	RCT (non-inferiority)	serious[a]	not serious	not serious	serious[b,c]	none	426	423	83 (16.4%) vs 68 (13.1%), p=NR[i]	HR 1.23, 95% CI 0.89-1.70	⨁⨁◯◯ Low	CRITICAL
Appropriate shocks *(appropriate shock therapy for either VT or VF)* (follow-up: median 49.1 months; assessed with: n [4-year cumulative incidence %]) [25, 26]												
1	RCT (non-inferiority)	serious[a]	not serious	not serious	serious[b,c]	none	426	423	83 (19.2%) vs 57 (11.5%), p=0.02	HR 1.52, 95% CI 1.08-2.12	⨁⨁◯◯ Low	CRITICAL
Shock efficacy *(percentage of successful shocks of the total amount of shocks)* (follow-up: range 41.4 months to 68.5 months; assessed with: %) [26]												
1	RCT (post-hoc analysis)[e]	serious[a]	not serious	not serious	serious[f]	none	426	423	**First shock efficacy:** 93.8% vs 91.6%, p=0.40 **Final shock efficacy:** 97.9% vs 98.4%, p=0.70		⨁⨁◯◯ Low	CRITICAL
Effectiveness (NRCT evidence)												
Mortality *(all-cause mortality)* (assessed with: n [%]) [13, 14, 28]												
3	NRCTs	not serious	not serious	not serious	serious[b,d]	none	2,229	4,149	**In-hospital** (1 study: n=3,840): 3 (0.2%) vs 2 (0.1%), p>0.99 3 (0.2%) vs 1 (0.05%), p=0.64 **5 yrs** (1 study: n=280): 2 (1.4%) vs 6 (4.6%), p=NR **6 yrs** (1 study: n=338): 3 (1.8%) vs 3 (1.8%), p=1.000	**NR**	⨁⨁◯◯ Low	CRITICAL
Mortality *(survival)* (assessed with: 3-year survival rate %) [27]												
1	NRCT	serious[g]	not serious	not serious	serious[b,c]	none	391	391	93.7% vs 91.5%, p=0.32	HR 0.74, 95% CI 0.41-1.35	⨁◯◯◯ Very low	CRITICAL
Appropriate shocks *(appropriate shock therapy for either VT or VF)* (assessed with: %) [13, 27]												
2	NRCTs	serious[g]	not serious	not serious	serious[b,c]	none	531	531	**3 yrs** (1 study: n=782): 9.9% (95% CI 7.0-13.9) vs 13.8% (95% CI 10.8-17.8), p=0.03 **5 yrs** (1 study: n=280): 17.0% (95% CI 6.3–26.4) vs 21.3% (95% CI 12.6–27.3), p=0.36	**3 yrs:** NR **5 yrs:** HR 1.46	⨁◯◯◯ Very low	CRITICAL
Shock efficacy *(percentage of successful shocks of the total amount of shocks)* (follow-up: up to 3 years; assessed with: %) [27]												
1	NRCT	serious[g]	not serious	not serious	serious[b,d]	none	391	391	88.6% vs 88.6%, p=1.000	NR	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	S-ICD	TV-ICD	Absolute (95% CI)	Relative (95% CI)		
Safety (RCT evidence)												
Composite primary endpoint: inappropriate shocks and device-related complications (follow-up: median 49.1 months; assessed with: n [4-year cumulative incidence %]) [25]												
1	RCT (non-inferiority)	serious[a]	not serious	not serious	not serious	none	426	423	68 (15.1%) vs 68 (15.7), non-inferiority margin 1.45, p=0.001 (non-inferiority), p=0.95 (superiority)	HR 0.99, 95% CI 0.71-1.39	⨁⨁⨁◯ Moderate	CRITICAL
Inappropriate shocks *(shock was delivered for any rhythm other than VF or VT)* (follow-up: median 49.1 months; assessed with: n [4-year cumulative incidence %]) [25]												
1	RCT (non-inferiority)	serious[a]	not serious	not serious	serious[b,c]	none	426	423	41 (9.7%) vs 29 (7.3%), p=NR	HR 1.43, 95% CI 0.89-2.30	⨁⨁◯◯ Low	CRITICAL
Overall device- and lead-related complications (follow-up: median 49.1 months; assessed with: n [4-year cumulative incidence %]) [25]												
1	RCT (non-inferiority)	serious[a]	not serious	not serious	serious[b,c]	none	426	423	31 (5.9%) vs 44 (9.8%), p=NR	HR 0.69, 95% CI 0.44-1.09	⨁⨁◯◯ Low	CRITICAL
Lead-related complications (follow-up: median 49.1 months; assessed with: %) [25]												
1	RCT (non-inferiority)	serious[a]	not serious	not serious	not serious[b]	None	426	423	1.4% vs 6.6%, p=NR	HR 0.24, 95% CI 0.10-0.54	⨁⨁⨁◯ Moderate	CRITICAL
Safety (NRCT evidence)												
Inappropriate shocks *(shock was delivered for any rhythm other than VF or VT)* (assessed with: %) [13, 27]												
2	NRCTs	serious[g]	not serious	not serious	serious[b,d]	none	531	531	**3 yrs** (1 study: n=782): 11.9% (95% CI 8.8-15.9) vs 7.9% (95% CI 5.6-11.1), p=0.07 **5 yrs** (1 study: n=280): 20.5% (95% CI: 11.5-28.6) vs 19.1% (95% CI: 11.6-26.0), p=0.64	**3 yrs:** NR **5 yrs:** HR 0.85	⨁◯◯◯ Very low	CRITICAL
Inappropriate shocks *(shock was delivered for any rhythm other than VF or VT)* (follow-up: up to 6 years, assessed with: n [%]) [28]												
1	NRCT	not serious	not serious	not serious	serious[b,d]	none	169	169	11 (6.5%) vs 14 (8.3%), p=0.533	NR	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	S-ICD	TV-ICD	Absolute (95% CI)	Relative (95% CI)		
Overall device- and lead-related complications (assessed with: n [%]) [13, 27, 28]j												
3	NRCTs	serious[g]	serious[h]	not serious	serious[c]	none	700	700	**3 yrs** (1 study: n=782): 34 (9.0%) (95% CI 6.5-12.3) vs 25 (6.5%) (95% CI 4.4-9.4), p=0.29 **5 yrs** (1 study: n=280): 14 (13.7%) (95% CI 6.4-20.3) vs 21 (18.0%) (95% CI 10.5-24.8), p=0.80 **6 yrs** (1 study: n=: 338): 3 (1.8%) (95% CI 0-3.8) vs 17 (10.1%) (95% CI 5.5-14.6), p=0.001	**3 yrs:** NR **5 yrs:** NR **6 yrs:** OR 0.16, 95% CI 0.05-0.56	⨁◯◯◯ Very low	CRITICAL
Lead-related complications (assessed with: n [%]) [13, 27]j												
2	NRCTs	serious[g]	not serious	not serious	serious[c]	none	531	531	**3 yrs** (1 study: n=782): 1 (0.3%) (95% CI 0.0-1.8) vs 9 (2.3%) (95% CI 1.2-4.4), p=0.03 **5 yrs** (1 study: n=280): 1 (0.8%) (95% CI: 0.0-2.2) vs 17 (11.5%) (95% CI: 5.3-17.2), p=0.03	**3 yrs:** NR **5 yrs:** NR	⨁◯◯◯ Very low	CRITICAL

Abbreviations: CI -confidence interval, HR – hazard ratio, n – Number, NRCT -Non-randomised controlled trial, RCT- Randomised controlled trial, yrs – years

Explanations

[a.] *Concerns about non-inferiority designs include that non-inferiority testing should also assess efficacy for treatments that have superior safety or some other obvious benefit. Therefore, testing the S-ICD against TV-ICD can also include testing superiority for safety outcomes and non-inferiority for efficacy.*

[b.] *Secondary outcome.*

[c.] *Wide confidence intervals: uncertainty about the magnitude of effect.*

[d.] *No statistically significant difference was detected.*

[e.] *Post-hoc analysis of the RCT with maintaining ITT-population.*

[f.] *The study was not initially designed to determine a difference for the primary outcome of the post-hoc analysis "shock efficacy".*

[g.] *At least 1 study was supported by the manufacturer.*

[h.] *The outcome results did not coincide within the studies.*

[i.] *Sudden cardiac death, n: 18 vs 18.*

[j.] *Requiring invasive interventions.*

Applicability table

Table A-6: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	Within the included studies, this patient population was covered by one RCT and four NRCTs. The inclusion criteria of these studies reflect the intended patient population for the technology. Moreover, the patient populations of included studies reflect real-world conditions concerning age, sex, underlying cardiac disease, and comorbidities.
Intervention	Included studies evaluated the subcutaneous implantable cardioverter-defibrillators (S-ICD) produced by one manufacturer. Device generations used may vary between the studies (e.g. Boston Scientific Cameron Health 1010, Boston scientific A209 EMBLEM, Boston Scientific A219 EMBLEM MRI).
Comparators	A transvenous implantable cardioverter-defibrillator (TV-ICD) is considered an established medical device, which is available from different manufacturers (Boston Scientific, St. Jude Medical, Medtronic, Biotronik, Sorin) as single- or dual-chamber ICDs.
Outcomes	For effectiveness outcomes, the crucial outcomes mortality, appropriate shocks were reported by the RCT (all three outcomes), all four NRCTs (all-cause mortality), two NRCTs (appropriate shocks), and one NRCT (shock efficacy). However, in non of the included studies, these outcomes were reported as the primary outcome measure. Regarding safety outcomes, the crucial outcomes inappropriate shocks and device-and lead-related complications were reported in the RCT as the primary outcome measure. In three NRCTs, inappropriate shocks were reported, but not as the primary outcome measure. The same three NRCTs reported on device- and lead-related complications as the primary outcome measure. However, the definitions of device-and lead-related complications were not standardised in the studies. The fourth NRCT reported any recorded in-hospital adverse events. In all included studies, it was not distinguished between severe and moderate complications. Hence, the applicability for safety is limited and must be interpreted with caution. Moreover, follow-up duration considerably differs among the included studies (min: in-hospital stay, max: 6 years). Nevertheless, long-term complications (follow-up ≥3 years) are reflected by 4/5 included studies.
Setting	The included RCT was conducted as multicenter studies in different geographical regions (Netherlands, Germany, United Kingdom, Czech Republic, Chicago United States of America). The included NRCTs were based on registries from Europe and the United States of America. Thus, it is not expected that the applicability of the results is limited by geographic settings.

List of ongoing randomised controlled trials

Table A-7: List of relevant ongoing randomised controlled trials of the S-ICD

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Estimated completion date	Sponsor
NCT02881255 ATLAS trial	(n=500) Pat. ≥ 18-60 years old AND standard indication for ICD Pat. ≥ 18 years old AND 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) OR chronic obstructive pulmonary disease (with FEV1 < 1.5 L)	S-ICD	TV-ICD	Composite of lead-related perioperative complications	February 2022	Population Health Research Institute
NCT03495297 PRAETORIAN-DFT	(n=965) Pat. over 18 years of age, willing and capable to give informed consent, who meet current guidelines for ICD therapy and intent to undergo a de novo implant procedure for an S-ICD, must pass S-ICD screening per local routine, willing and capable of complying to follow up visits & eligible for either DFT strategy per physician discretion	S-ICD with DFT	S-ICD without DFT	Failed first appropriate shock in a spontaneous episode	September 2023	Academisch Medisch Centrum – Universiteit van Amsterdam (AMC-UvA), Boston Scientific Corporation

Research questions

Table A-8: Health problem and Current Use

Element ID	Research question
A0001	For which health conditions, and for what purposes is the S-ICD used?
A0002	What is the disease or health condition in the scope of this assessment?
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 in this assessment?

Table A-9: Description of the technology

Element ID	Research question
B0001	What is the S-ICD and the TV-ICD?
A0020	For which indications has the S-ICD received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the S-ICD in relation to the TV-ICD?
A0021	What is the reimbursement status of the S-ICD?

Table A-10: Clinical Effectiveness

Element ID	Research question
D0001	What is the expected beneficial effect of the S-ICD on mortality?
D0003	What is the effect of S-ICD on the mortality due to causes other than cardiac diseases with a higher risk for sudden cardiac death?
D0005	How does the S-ICD affect symptoms and findings (severity, frequency) of the disease or health condition?
D0011	What is the effect of the S-ICD on patients' body functions?
D0016	How does the use of S-ICD affect activities of daily living?
D0012	What is the effect of the S-ICD on generic health-related quality of life?
D0013	What is the effect of the S-ICD on disease-specific quality of life?
D0017	Was the use of the S-ICD worthwhile?

Table A-11: Safety

Element ID	Research question
C0008	How safe is the S-ICD in comparison to the comparator(s)?

Literature search strategies

Search strategy for Cochrane

Search Name: Subcutaneous implantable cardioverter-defibrillators_MEL-Update 2022	
Last saved: 24/11/2021 18:23:31	
Comment: SW/GG	
ID	Search
#1	MeSH descriptor: [Defibrillators, Implantable] explode all trees
#2	(cardioverter*):ti,ab,kw (Word variations have been searched)
#3	(defibrillator*):ti,ab,kw (Word variations have been searched)
#4	(ICD):ti,ab,kw (Word variations have been searched)
#5	#1 OR #2 OR #3 OR #4
#6	(subcutaneous*):ti,ab,kw (Word variations have been searched)
#7	#5 AND #6
#8	(subcutaneous* NEAR/4 (defibrillator* OR cardioverter* OR icd)) (Word variations have been searched)
#9	(S-ICD):ti,ab,kw (Word variations have been searched)
#10	#7 OR #8 OR #9
#11	(conference abstract):pt (Word variations have been searched)
#12	(abstract):so (Word variations have been searched)
#13	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#14	#11 OR #12 OR #13
#15	#10 NOT #14 with Cochrane Library publication date Between Nov 2017 and Nov 2021
#16	#10 NOT #14 with Publication Year from 2017 to 2021, in Trials
#17	#15 OR #16
Total: 22 Hits	

Search strategy for Embase

Search Name: Subcutaneous implantable cardioverter-defibrillators_MEL-Update 2022		
Comment: SW/GG		
No.	Query Results	Results
#19	#18 AND [23-11-2017]/sd AND ([english]/lim OR [german]/lim)	456
#18	#17 AND [23-11-2017]/sd	466
#17	#15 NOT #16	794
#16	'conference abstract':it	4,254,398
#15	#10 NOT #14	1,680
#14	#11 OR #12 OR #13	2,934,181
#13	(case* NEAR/3 (report* OR series)):ti	530,059
#12	'case report'/exp	2,763,124
#11	'case study'/exp	82,116
#10	#6 NOT #9	2,211
#9	#7 NOT #8	5,694,704
#8	'human'/exp	24,084,185
#7	'animal'/exp	29,778,889
#6	#3 OR #4 OR #5	2,276
#5	's-icd':ti,ab	1,085
#4	(subcutaneous* NEAR/4 (defibrillator* OR cardioverter* OR icd)):ti,ab	1,574

#3	#1 AND #2	1,680
#2	subcutaneous*	467,297
#1	'implantable cardioverter defibrillator'/exp	43,698
Search date: 24 Nov 2021		

Search strategy for Medline

Search Name: Subcutaneous implantable cardioverter-defibrillators_MEL-Update 2022		
Comment: SW/GG		
ID	Search	Results
1	exp Defibrillators, Implantable/	21,975
2	cardioverter*.ti,ab.	19,265
3	defibrillator*.ti,ab.	29,158
4	ICD.ti,ab.	54,112
5	1 or 2 or 3 or 4	78,457
6	subcutaneous*.mp.	241,362
7	5 and 6	2,010
8	S-ICD.mp.	866
9	7 or 8	2,049
10	exp Animals/	28,673,746
11	exp Humans/	23,205,354
12	10 not 11	5,468,392
13	9 not 12	1,978
14	case reports.pt.	2,604,137
15	(case* and (report* or series)).ti.	573,559
16	14 or 15	2,773,527
17	13 not 16	1,439
18	limit 17 to dt=20171123-20211124	816
19	limit 18 to (english or german)	797
20	remove duplicates from 19	408
Search date: 24 Nov 2021		

Search strategy for INAHTA

Search Name: Subcutaneous implantable cardioverter-defibrillators_MEL-Update 2022	
Comment: SW/GG	
ID	Search
#9	(((((s-icd))[title]) OR (subcutaneous* cardioverter* defibrillator*) OR (subcutaneous* AND (defibrillator* OR cardioverter*)) OR ((subcutaneous*) AND ("Defibrillators Implantable"[mhe])))) FROM 2017 TO 2021) AND (English OR German)[Language],"2","2021-11-24T17:49:24.000000Z"
#8	((((s-icd))[title]) OR (subcutaneous* cardioverter* defibrillator*) OR (subcutaneous* AND (defibrillator* OR cardioverter*)) OR ((subcutaneous*) AND ("Defibrillators Implantable"[mhe])))) FROM 2017 TO 2021,"2","2021-11-24T17:48:33.000000Z"
#7	(((s-icd))[title]) OR (subcutaneous* cardioverter* defibrillator*) OR (subcutaneous* AND (defibrillator* OR cardioverter*)) OR ((subcutaneous*) AND ("Defibrillators Implantable"[mhe])),"16","2021-11-24T17:45:31.000000Z"
#6	((s-icd))[title],"14","2021-11-24T17:45:18.000000Z"
#5	subcutaneous* cardioverter* defibrillator*,"6","2021-11-24T17:37:10.000000Z"
#4	subcutaneous* AND (defibrillator* OR cardioverter*),"7","2021-11-24T17:36:04.000000Z"
#3	(subcutaneous*) AND ("Defibrillators Implantable"[mhe]),"6","2021-11-24T17:34:12.000000Z"
#2	subcutaneous*,"125","2021-11-24T17:33:45.000000Z"
#1	"Defibrillators Implantable"[mhe],"65","2021-11-24T17:32:57.000000Z"
Hits	2 (search date: 24 Nov 2021)

HTA Austria
Austrian Institute for
Health Technology Assessment
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