HTA Austria
Austrian Institute for
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Wearable cardioverter-defibrillator (WCD) therapy for primary and secondary prevention of sudden cardiac arrest

2. Update 2022

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List of abbreviations

AEs ..... adverse events;
CABG ..... coronary artery bypass graft;
CE ..... Conformité Européenne
CMP ..... cardiomyopathy;
DCM ..... dilated cardiomyopathy;
EF ..... ejection fraction;
EUnetHTA ..... European Network for Health Technology Assessment;
HF ..... heart failure;
ICD ..... implantable cardioverter-defibrillator;
ICM ..... ischemic cardiomyopathy;
IQR ..... interquartile range;
LV ..... left ventricular;
LVEF ..... left ventricular ejection fraction;
MI ..... myocardial infarction;
NA ..... not available;
NICM ..... non-ischemic cardiomyopathy;
NYHA ..... New York Heart Association;
OMT ..... optimal medical therapy;
PCI ..... percutaneous coronary intervention;
pt(s) ..... patient(s);
SCA ..... sudden cardiac arrest;
SCD ..... sudden cardiac death;
SD ..... standard deviation;
VA ..... ventricular tachyarrhythmias;
VF ..... ventricular fibrillation;
VS ..... versus;
VT ..... ventricular tachycardia;
WCD ..... Wearable Cardioverter-Defibrillator;
yrs ..... years;

Executive Summary

Introduction

WCD therapy: intended to protect against sudden cardiac death in high-risk patients

The wearable cardioverter defibrillator (WCD) is a device temporarily used in the primary and secondary prevention of sudden cardiac death (SCD) in high-risk patients. The WCD monitors the patient's heart function and automatically delivers electrical therapy when needed. WCD therapy is intended to be used for covering the conservative therapy phase before the definitive indication of an implantable cardioverter-defibrillator (ICD) or protecting patients in other high-risk phases. In this report, the latest available evidence with regard to the comparative effectiveness and safety of WCD therapy is summarized.

Methods

update AGENAS/ LBI-HTA Report 2019

Building on two existing health technology assessment published in 2019, a systematic literature search was conducted in three databases (8/2018-5/2022). Data extraction and quality assessment of the identified studies were performed by two researchers. The evidence was described narratively. The strength of the evidence was assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluation).

Results

1 RCT: no stat. difference in arrhythmic mortality in post myocardial infarction patients and impaired ejection fraction

The current available evidence consists of one RCT (n=2,348) and eleven observational studies (n=5,345). Low certainty evidence derived from one RCT (n=2,348) indicated that WCD therapy might not be associated with a clinical benefit in arrhythmic mortality in post-myocardial infarction (MI) patients with an ejection fraction of ≤35%. In this RCT, a statistically significant difference in the secondary outcome all-cause mortality was found (uncorrected for multiple testing). WCD appropriately shocked 1.3% wearing the WCD in the RCT. Compliance was low, with a mean daily wear-time of 14.0 hours. Further, 0.6% of patients wearing the device received an inappropriate shock, and there were four serious adverse events (0.2%) potentially related to WCD use. WCD use was statistically associated with milder AEs such as rash and itching, occurring in 13% and 14.5% of patients in the WCD group.

11 observational studies: mixed patient population

All observational studies enrolled mixed, broad patient populations and reported a daily wear-time of WCD use ranging from 20 to 23.5 hours. Arrhythmic mortality was measured 0% in two studies and all-cause mortality ranged from 0% to 5.2% across nine studies. The range of patients receiving one or more appropriate shocks was between 1% and 4.8% across nine studies. Further, the first shock success was reported to be 100% in three studies. Inappropriate shocks occurred between 0% and 2% across ten observational studies (range of enrolled patients across studies: 102-2,000). Two studies reported further adverse events: One study (n=102) reported that 2% and 57% of patients were allergic to nickel and received false alarms, respectively. The Austrian registry (n=448) only reported milder adverse events such as dermatitis and pressure marks, occurring in 0.9% and 0.2% of enrolled patients, respectively

Conclusion

unzureichende Evidenz für Zusatznutzen, Compliance mit Defibrillator-Weste in Österreich adäquat

The only available RCT failed to show that an add-on use of the WCD leads to a reduction in sudden cardiac death in patients with a recent myocardial infarction and impaired ejection fraction when compared to medical therapy alone. Observational evidence shows that compliance with WCD is good in Austria, with poor compliance being a major limitation of the only available randomised evidence for WCD use.

keine indikationsspezifischen Aussagen auf Basis der Beobachtungsstudien möglich

Most of the evidence is observational and consists of studies including mixed-populations in the analysis, leading to the inability to draw firm conclusions on indication-specific utility of the WCD. In the absence of comparative effectiveness evidence, more RCT data are needed to justify continuing or expanding the use of WCD therapy in Austria.

Zusammenfassung

Einleitung

Defibrillator-Weste: Schutz vor plötzlichem Herztod bei Hochrisiko-Patient*innen

Die Defibrillator-Weste ist ein tragbarer Kardioverter Defibrillator, welcher einen Schutz vor dem plötzlichen Herztod bei Hochrisiko-Patient*innen ermöglichen soll: Man erwartet, dass die Defibrillator-Weste vor allem zur Überbrückung vor der Implantation eines implantierbaren Defibrillators (ICD) oder zur Überbrückung einer vorübergehenden Hochrisikophase von Nutzen sein kann.

Im folgenden Bericht gingen wir der Frage nach, ob der Einsatz der Defibrillator-Weste als Zusatz zur pharmakologischen Therapie oder als Ersatz für einen Krankenhausaufenthalt bei Hochrisiko-Patient*innen zu einem klinisch relevanten Zusatznutzen führt.

Methoden

Update AGENAS/ LBI-HTA Bericht 2019

Aufbauend auf einem Update-Bericht von AGENAS (Italienische Nationale Agentur für regionale Gesundheitsdienste) und dem LBI-HTA (Ludwig Boltzmann Institut für HTA) aus 2019 und dem Erst-Assessment von EUnetHTA (European Network for Health Technology Assessment) wurde eine systematische Literatursuche in drei Datenbanken (8/2018-5/2022) durchgeführt. Die Datenextraktion und Qualitätsbewertung der identifizierten Studien wurde von zwei Personen durchgeführt. Die Evidenz wurde narrativ beschrieben. Darüber hinaus wurde die Stärke der Evidenz mit GRADE eingeschätzt.

Die Fragestellung, die Einschlusskriterien und die Suchstrategie des HTA-Berichts wurde dabei minimal verändert: Es wurden nur randomisierte kontrollierte Studien (RCTs), prospektive vergleichende Beobachtungsstudien und nicht-vergleichende Registerstudien mit mindestens 100 Studienteilnehmer*innen in die Evidenzsynthese eingeschlossen.

Klinische Wirksamkeit

entscheidende Endpunkte:

Zur Bewertung der vergleichenden Wirksamkeit der Defibrillator-Weste wurde die Mortalität (arrhytmische und Gesamtmortalität) als entscheidend erachtet.

Wirksamkeit: Mortalität

Zusätzlich wurden folgende Endpunkte als wichtig eingestuft: Endpunkte zur Benutzerfreundlichkeit/ Akzeptanz (Compliance, Patient*innenzufriedenheit), Lebensqualität, Hospitalisierungsrate und weitere Endpunkte, die die Funktionalität des Geräts überprüfen (Surrogatendpunkte: adäquate Therapieabgabe, Shock-Erfolgsrate, unterdrückte Shocks).

Sicherheit

Sicherheit: SUE/ UE

Die folgenden Endpunkte wurden für die Bewertung der Sicherheit als entscheidend definiert: schwere unerwünschte Ereignisse (SUE) und unerwünschte Ereignisse (UE)

Ergebnisse

Verfügbare Evidenz

Evidenz: 1 RCT (n=2.302) 11 Beobachtungsstudien (n=5.345)

Für das Update 2022 konnten im Rahmen der Literaturrecherche sieben neue Beobachtungsstudien identifiziert werden. Aus dem letzten Assessment erfüllten ein RCT (die VEST-Studie) und vier Beobachtungsstudien unsere Einschlusskriterien. Einige weitere neu identifizierte Publikationen bezogen sich auf Daten dieser Studien.

RCT: Post-MI mit eingeschränkter Ejektionsfraktion

Ein RCT mit 2.302 Patient*innen untersuchte den Einsatz der Defibrillator-Weste bei Patient*innen mit Post-Myokardinfarkt und Ejektionsfraktion kleiner gleich 35 % zur Primärprävention des plötzlichen Herztodes. Die Patient*innen wurden im 2:1 Verhältnis randomisiert und erhielten eine Defibrillator-Weste in Kombination mit pharmakologischer Therapie (n=1.524) oder eine pharmakologische Therapie alleine (n=778). Die Patient*innen wurden durchschnittlich 84.3 Tage nachbeobachtet.

gemischte Patient*innenkollektive in Beobachtungsstudien, unklar, ob Add-on oder Ersatz für einen Spitalaufenthalt

Elf Fallserien- und Registerstudien mit insgesamt 5.345 Studienteilnehmer*innen untersuchten den Einsatz der Defibrillator-Weste in verschiedensten Indikationen (gemischte Patient*innenkollektive). Ischämische und nicht-ischämische Kardiomyopathien zählten zu den Ätiologien, welche am häufigsten in den Studien vorkamen. In keiner der Beobachtungsstudien wurde in angemessener Weise berichtet, ob die Defibrillator-Weste als Ergänzung zur pharmakologischen Therapie oder als Ersatz für einen Spitalaufenthalt eingesetzt wurde. Das Verzerrungspotenzial war moderat in vier Studien und hoch in den restlichen sechs Studien.

Primär- oder Sekundärprävention in einer Beobachtungsstudie (n=448) berichtet: 52 % vs. 48 %

Nur eine der Beobachtungsstudien berichtete, ob die Defibrillator-Weste zur Primär- oder Sekundärprävention des plötzlichen Herztodes eingesetzt wurde. Die österreichische Registerstudie berichtete, dass 216 Patient*innen (48 %) die Defibrillator-Weste zur Sekundärprävention erhielten, während die restlichen 232 Patient*innen (52 %) die Defibrillator-Weste zur Primärprävention des plötzlichen Herztodes erhielten.

Vertrauenswürdigkeit der Evidenz

Vertrauenswürdigkeit der Evidenz: RCT: niedrig

Die Vertrauenswürdigkeit der RCT-Evidenz war niedrig, was vor allem auf Abweichungen von der beabsichtigten Intervention (niedrige Compliance) innerhalb der Interventionsgruppe zurückzuführen ist. Zusätzlich lag ein Reporting Bias der beschriebenen Ergebnisse vor, da einige erhobene Daten (beispielsweise zur Lebensqualität) nicht berichtet wurden.

Beobachtungsstudien: sehr niedrig

Die Vertrauenswürdigkeit der Evidenz aus Beobachtungsstudien war sehr niedrig: Neben dem inhärenten Verzerrungsrisiko aufgrund der Studiendesigns ist dieser Umstand vor allem auf das erhöhte Risiko eines Selektionsbias bei der Rekrutierung der Patient*innen zurückzuführen. Des Weiteren ist die Übertragbarkeit der Evidenz aus Beobachtungsstudien auf spezifische Indikationen aufgrund der vielen heterogenen Patient*innenkollektive eingeschränkt.

Komparative Wirksamkeit

komparative Wirksamkeit (RCT):

RCT Evidenz

Der RCT fand keinen statistisch signifikanten Unterschied hinsichtlich der **arrhythmischen Mortalität** zwischen 1.524 Patient*innen mit Defibrillator-Weste und 778 Patient*innnen mit pharmakologischer Therapie alleine (arrhythmische Mortalität: 1,6 % vs. 2,4 %; p=0,18). Die beobachtete statistisch signifikante Reduktion der Gesamtmortalität (p=0,04) kann, wie von den Wissenschafter*innen der VEST Studie vermutet, zufällig sein.

arrhythmische Mortalität: kein stat. signifikanter Unterschied

Es wurden Daten zu drei der gewählten fünf wichtigen Endpunkte in der eingeschlossenen Studie berichtet.

kein stat. signifikanter Unterschied bei der Hospitalisierungsrate

- **Gesundheitsbezogene Lebensqualität**: Die gesundheitsbezogene Lebensqualität wurde in dem eingeschlossenen RCT zwar gemessen, jedoch wurden diese Daten in den verfügbaren Publikationen nicht berichtet.
- **Hospitalisierungsrate**: Es wurde kein statistisch signifikanter Unterschied zwischen Interventions- und Kontrollgruppe gefunden (31,2 % vs. 32,5 %; p=0,51).

keine Evidenz zu Patient*innen-zufriedenheit und Lebensqualität

- **Patient*innen-Zufriedenheit**: Es wurde keine RCT-Evidenz zur Patient*innen- Zufriedenheit gefunden.
- **Compliance:** In Summe haben 97,2 % der Interventionsgruppe die Defibrillator-Weste getragen. Durchschnittlich trugen sie die Defibrillator-Weste 14 Stunden pro Tag. Die mediane tägliche Tragezeit betrug 18 Stunden.

Compliance niedrig

- **Surrogat-Endpunkte**: Die Rate der adäquaten Therapieabgaben betrug 1,3 %. Zusätzlich haben 4,5 % der Patient*innen mit Defibrillator-Weste einen Schock erfolgreich unterdrückt.

Surrogatparameter: 1.3 % Pat. mit adäquaten Schocks

Evidenz aus Beobachtungsstudien

Die **Mortalitätsrate** wurde in neun Beobachtungstudien (n=4,992) berichtet und schwankte zwischen 0 % und 5,2 %.

Mortalitätsrate in 9 Studien: 0 % - 5.2 %

Hinsichtlich der **Lebensqualität** wurde eine statistische Assoziation zwischen Defibrillator-Weste und Angst zu Beginn der Therapie innerhalb einer komparativen Beobachtungsstudie (Defibrillator-Weste: n=38, keine Defibrillator-Weste: n=38) gefunden. In einer weiteren nicht-vergleichenden Beobachtungsstudie konnten statistisch signifikante Verbesserungen der Lebensqualität bis 90 Tage nach Therapiestart bei 210 Patient*innen mit einer Defibrillator-Weste gefunden werden (Fragebogen: Kansas City Cardiomyopathy Questionnaire).

Lebensqualität in 2 Studien: stat. Assoziation von Defibrillator-Weste und Angst, Verbesserung der Lebensqualität im Therapieverlauf

Die **Hospitalisierungsrate** wurde von zwei Beobachtungsstudien berichtet: In einer Studie (n=102) wurden 12,7 % aufgrund kardialer Ursachen in das Krankenhaus eingeliefert. In einer weiteren Studie (n=153) betrug die Hospitalisierungsrate 67 %.

Hospitalisierungsrate (2 Studien): 12,5 % bzw. 67 %

Die **Compliance** mit der Defibrillator-Weste wurde in zehn Beobachtungsstudien (n=5,068) mit einem Telemonitoring-System gemessen: Die tägliche mediane/ durchschnittliche Tragezeit betrug über 20 Stunden pro Tag und schwankte zwischen 20 bis 23.5. Die mediane tägliche Tragezeit betrug in der österreichischen Registerstudie 23.5 Stunden.

Compliance in 10 Studien: 20-23.5 Stunden tägliche Tragezeit

Zufriedenheit: keine Evidenz
Anz. an Pat. mit zumindest einem adäquaten Shock: 1,1 % - 4,8 %

Die **Zufriedenheit** wurde in den eingeschlossenen Beobachtungsstudien nicht gemessen.

Folgende Ergebnisse werden zu **Surrogatendpunkten** berichtet: Der Anteil der Patient*innen, die einen oder mehrere adäquate Schocks erhielten, lag zwischen 1 % und 4,8 %. Außerdem wurde in drei Studien berichtet, dass der Erfolg des ersten Schocks bei 100 % lag. Die Anzahl der zurückgehaltenen Schocks wurde in zwei Studien mit 2.000 und 781 Patient*innen berichtet: Es traten dabei 90 Ereignisse bei 22 Patient*innen (1,1 %) bzw. 47 Ereignisse bei 22 Patient*innen (2,8 %) auf.

Sicherheit

Sicherheit

RCT-Evidenz:

RCT Evidenz

SUE: 4 (0,2 %) Geräte-bezogene SUE 9 (0,6 %) Pat. erhielten unangemessene Schocks

In der VEST-Studie traten vier schwerwiegende Ereignisse (0,2 %) auf, die potentiell mit der Defibrillator-Weste assoziiert waren: Ein Patient starb während des Tragens der Defibrillator-Weste und weitere drei Patient*innen wurden wegen abgebrochenem oder unangemessenem Schock ins Krankenhaus eingeliefert. Zusätzlich erhielten neun Patient*innen (0,6 %) unangemessene Schocks.

UE: Hautausschlag: 13 %, vs. 3,8 %; Jucken: 14,5 % vs. 3,1 % keine Unterschiede: Schwindel, Ohnmacht etc.

Die VEST-Studie berichtete von folgenden UE: Bei Patient*nnen in der Interventionsgruppe trat statistisch signifikant häufiger Hautausschlag (13 % vs. 3,8 %; $p<0,001$) und Jucken (14,5 % vs. 3,1 %; $p<0,001$) auf. Keine statistisch signifikanten Unterschiede waren bei Schwindel, Ohnmacht oder Herzklopfen festzustellen.

Beobachtungsstudien:

Evidenz aus Beobachtungsstudien

SUE: unangemessene Schocks: 0 % - 2 %
UE in 1 Studie: Dermatitis: 0,9 % Druckstellen: 0.2 % Fehlalarme in 1 Studie: 57%

Die eingeschlossenen Beobachtungsstudien berichteten von folgenden SUEs: Inadäquate Shocks schwankten zwischen 0 % und 2 %. Zwei weitere Studien berichteten von UEs: Dermatitis und Druckstellen durch das Tragen der Defibrillator-Weste traten in der österreichischen Registerstudie bei vier (0,9 %) bzw. einem (0,2 %) der 448 eingeschlossenen Patient*innen auf. In einer weiteren Studie traten bei 58 Patient*innen (57 %) Fehlalarme auf und zwei weitere Patient*innen (2 %) bekamen einen Hautauschlag.

Laufende Studien

1 laufende Studie vorzeitig abgebrochen

Insgesamt wurde lediglich eine laufende Studie identifiziert (NCT02481206), welche jedoch frühzeitig aufgrund von Problemen bei der Rekrutierung abgebrochen wurde. Diese Studie untersuchte den Einsatz der Defibrillator-Weste bei Patient*innen im Endstadium einer Nierenkrankheit.

Diskussion

Adoption trotz fehlender Evidenz

Die Defibrillator-Weste ist eine Technologie, die es bereits seit über zwei Dekaden gibt und für die wenig klinische komparative Evidenz verfügbar ist. Trotzdem ist die Adoption der Technologie weiter vorangeschritten und wurde Teil der klinischen Praxis in einigen Ländern.

etwaiger Zusatznutzen mit großer Unsicherheit behaftet

Der etwaige protektive Effekt, wie er in einer Post-hoc Analyse (Per-Protokoll-Analyse) basierend auf einer Hochrechnung der Personenmonate (an tatsächlich getragenen Defibrillator-Weste) setzt sich über die Randomisierung und entsprechende Intention-To-Treat Analyse hinweg (und ist dieser stark unterlegen), indem nur von jenen Patient*innen berichtet wird, die die Weste

auch trugen (durchschnittlich 14 Stunden pro Tag) und in der Studie nachbeobachtet wurden. Die Ergebnisse der VEST Studie sollten daher nicht reinterpretiert werden: In dieser Studie zeigte sich, dass die Defibrillator-Weste bei Post-MI Patient*innen mit eingeschränkter Ejektionsfraktion im Vergleich zur alleinigen pharmakologischen Therapie nicht zu einer signifikanten Reduktion des plötzlichen Hertztodes geführt hat. Die statistisch signifikante Senkung der Gesamtmortalität kann, wie von den Autor*innen der VEST-Studie im Zuge der ersten Publikation vermutet, zufällig sein.

Evidenz aus Beobachtungsstudien stark eingeschränkt: Selektionsbias, gemischte Patient*innenkollektive

Eine große Einschränkung der Evidenz aus Beobachtungsstudien besteht darin, dass die meisten dieser Studien keine Kontrollgruppe haben und gemischte Patient*innenkollektive eingeschlossen wurden. Des Weiteren wurde der genaue Einsatz der Defibrillator-Weste nicht beschrieben: Es ist daher in den meisten der eingeschlossenen Studien nicht ableitbar, ob die Defibrillator-Weste zur Primär- oder Sekundärprävention des plötzlichen Herztodes verwendet wurde bzw. ob diese einen Spitalsaufenthalt ersetzt oder eine pharmakologische Therapie ergänzt.

Schlussfolgerung

Zusatznutzen der Defibrillator-Weste: unzureichende Evidenz

Die beste verfügbare Evidenz ist nach wie vor eine randomisierte Kontrollstudie, welche bereits im ursprünglichen Bericht identifiziert wurde. In dieser Studie hat der Einsatz der Defibrillator-Weste bei Patient*innen mit Post-Myokardinfarkt und eingeschränkter Ejektionsfraktion im Vergleich zur alleinigen pharmakologischen Therapie nicht zu einer signifikanten Reduktion des plötzlichen Hertztodes geführt.

Beobachtungsstudien weisen auf adäquate Compliance hin; belastbare Daten aus kontrollierten Studien vor Indikationsausweitung erforderlich

Evidenz aus Beobachtungsstudien deutet darauf hin, dass die Compliance mit der Defibrillator-Weste in Österreich gut ist. Der Großteil der vorhandenen Evidenz besteht jedoch aus Beobachtungsstudien ohne Kontrollgruppe, die gemischte Patient*innenkollektive in die Analyse einbeziehen, sodass keine eindeutigen Schlussfolgerungen zum indikationsspezifischen Zusatznutzen der Defibrillator-Weste gezogen werden können. Belastbare Daten aus RCTs bzw. gut konzipierten komparativen Studien sind dringend erforderlich, um die Fortsetzung (in Nischenindikationen) oder eine etwaige Indikationsausweitung in Österreich begründen zu können.

1 Introduction

The summary of technical characteristics of the wearable cardioverter defibrillator (WCD) and health problem and current use of the technology is based on the previous assessments [1, 2] with slight modifications.

Technical Characteristics of the Wearable Cardioverter Defibrillator

WCD: Therapie zur Prävention des plötzlichen Herztodes

The WCD is a device temporarily used in the primary and secondary prevention of sudden cardiac death (SCD). It is a defibrillator worn by the patient for most of the day, except when taking a bath/shower when the presence of a caregiver or a family member is recommendable [3, 4].

z.B. vor ICD Indikation bei Patient*innen nach Myokardinfarkt, vor ICD Re-Implantierung

WCD therapy may be indicated as a temporary measure

- **before implantable cardioverter-defibrillator (ICD) implantation** in patients at risk of SCD in the subacute phase of acute myocardial damage,
- those with accepted indicators for **ICD implantation** but also other **contraindications** (e.g., infection),
- those **waiting for a final decision regarding ICD** implantation, or
- in patients who cannot undergo immediate **ICD re-implantation** [4, 5].

WCD soll temporär vor plötzlichem Herztod bei Risikogruppen schützen

The WCD monitors the patient's heart function and automatically delivers electrical therapy. In case a life-threatening rhythm is detected (the WCD is tested for ventricular tachycardia or ventricular fibrillation based on a specific tracking algorithm), the device delivers treatment to restore normal rhythm. If patients are conscious, they can prevent the treatment by using the response buttons when the device alerts them that treatment is coming [1, 6].

LifeVest® CE Mark seit 2011

Currently, the LifeVest® – WCD 4000 (Zoll Medical Corporation, Pittsburg, USA) is the only commercially available WCD in Europe. The WCD is a Class IIb device [1]. In the United States, the ASSURE WCD System Kit (Kestra Medical Technologies, Inc) was recently FDA approved [7].

Alternativen Indikationsabhängig: Krankenhaus-entlassung ohne WCD (Add-on), oder …

Depending on disease severity and exact clinical indications, the alternative to WCD therapy may cover

- discharge home without a WCD
- discharge to a skilled nursing facility (SNF) or
- remaining in the hospital without a WCD [8]

Spitalsaufenthalt (Replacement)

Hence, WCD therapy can be considered an add-on to optical medical therapy (OMT) or an alternative to a hospital stay.

Health problem and current use of WCD therapy in Austria

SCAs treten ohne Vorwarnung auf

und führen unbehandelt zum Tod

The WCD is supposed to reduce the risk of SCD, the health condition in the scope of this assessment. Ventricular fibrillation (VF) and ventricular tachycardia (VT), with a subset of Torsades de Pointes (TdP), are responsible for the majority of sudden cardiac arrests (SCA). Both of these rapid heart rhythms arise in the heart's lower (pumping) chambers, the ventricles. While VT is a fast, but regular heart rhythm, VF is irregular and unsynchronised. When fibrillating, the heart stops pumping blood, which leads to SCA. Further causes of SCA are slow heart rate (extreme bradycardia, A-V III degree block), no cardiac electrical activity (asystole), electromechanical dissociation pulseless electrical activity (PEA), post-acute myocardial infarction (MI) or cardiac tamponade [9-11].

Risikofaktoren in jüngeren und älteren Menschen unterschiedlich

Overall, the risk factors associated with SCD differ in young and older individuals. There is a predominance of myocarditis and substance abuse, channelopathies and cardiomyopathies in young patients, and chronic degenerative diseases in older patients (chronic coronary artery disease, valvular heart diseases, and heart failure) [4]. In older individuals, multiple chronic cardiovascular conditions contribute to the risk of SCD. Hence, it is difficult to determine which contributed the most. In younger individuals, inherited channelopathies or drug-induced arrhythmias devoid of structural abnormalities may make the diagnosis of SCD elusive [4]. Dysfunction of the left ventricle (LV) is a significant determinant of the risk of SCD. Still, family history, diabetes mellitus, obesity, and heart rate profile during exercise make the determinants diverse and multifactorial [12]. Lifestyle behaviour is essential in preventing SCD (e.g., no smoking, sports, healthy diet) [13].

klinische Leitlinien: keine Empfehlung für breite Adoption

Based on current clinical practice guidelines (CPGs), there is no general recommendation for the use of WCD in unselected high-risk patient groups [5]. Instead, there are some narrow indications for which WCD received a "may be used" recommendation based on low-level evidence, mainly for patients who would have otherwise needed extensive and sometimes burdensome hospital observation [5]. That is, ESC guidelines [4, 14] recommend that the WCD may be used in the following narrow indications (all recommendations: IIb/ Grade B or C):

empfohlene enge Indikationen

- **Temporary explantation of an ICD** (e.g., due to infection)
- those with accepted indicators for **ICD implantation but also other contraindications** (e.g., infection)
- Patients on **the waiting list for heart transplantation** (without an ICD)
- Patients with an active **myocarditis**
- **Peripartum cardiomyopathy** (PPCM)
- Patients in the **early postinfarction** phase with "arrhythmias"
- Patients with **post-coronary intervention** (90 days) and impaired LV function

basierend vorwiegend auf Expert*innenkonsens

However, it is noteworthy to state that the usefulness is, per ESC definition, less well established by evidence and/ or opinion [14].

Further, a statement paper by the German Society of Cardiology (DGK) explicitly stated that some of these indications are not realistic for the German setting and that WCD therapy should immediately be terminated if the daily wear time of more than 20 hours per day is not reached by the patient [5].

In Austria, reimbursement of WCD therapy is restricted to hospitals with a strong focus on cardiology and to certain specific indications:

keine breite Refundierung in Ö, Kostenerstattung: enge Indikationen mit Restriktionen (kardiologische Referenzzentren)

- Temporary **explantation of an ICD**
- Patients on **the waiting list for heart transplantation** (without an ICD)
- Patients with **acute myocarditis** and LVEF ≤ 35%
- Patients with **peripartum cardiomyopathy (PPCM)** and LVEF ≤ 35%

Although reimbursement is restricted to the aforementioned indications, some Austrian hospitals use it in other narrow indications replacing hospital stay to reduce costs.

Available knowledge and need for HTA report

bisherige systematische Übersichtsarbeiten: unzureichende Evidenz, die Zusatznutzen belegt

For nearly two decades after the approval of the WCD, mainly observational WCD studies for the prevention of SCD were published that provided conflicting data, yielding to the inability to draw firm conclusions on the comparative effectiveness and safety of WCD therapy [2, 15, 16]. In 2018, the first randomised controlled trial (RCT) was available (VEST/ Prevention of Early Sudden Death Trial), showing no reduction in SCD when compared to medical therapy alone in patients with a recent myocardial infarction (MI) and low ventricular ejection fraction (LVEF) of ≤35% [17]. This trial was the basis of a joint collaborative health technology assessment between AGENAS (Italian National Agency for Regional Health Services) and LBI-HTA (Ludwig Boltzmann Institute for Health Technology Assessment) that concluded that the comparative effectiveness of the device is still not established [1]. The joint systematic review further found low-quality evidence (1 RCT and 10 observational studies) indicating that the WCD could be a relatively safe intervention for patients at risk of SCD. Another comprehensive meta-analysis presented a similar evidence interpretation [16]. However, intensive marketing hampered the scientific debate regarding the appropriateness of the WCD [18, 19].

1 RCT mit verfehltem Studienziel, limitiert durch schlechte Compliance

Due to the fact that the VEST results were limited by poor compliance, it is still unclear whether the anticipated patient-relevant benefits of using the WCD is supported by scientific evidence. Further, the policy question arose whether reimbursement of the aforementioned narrow indications (that are backed mainly by clinical plausibility) for WCD use should be expanded towards broader indications in Austria (incl. WCD therapy as an add-on measure in post-MI patients with LVEF of ≤35%).

Update der Evidenz 2018-2022

The project aims at performing an update evidence synthesis based on a systematic literature search regarding the effectiveness and safety of the WCD for specific indications.

2 Scope

2.1 PICO question

PIKO-Fragen

- What is the evidence that the use of a WCD as a temporary measure (add-on or replacement) for the treatment of patients at risk of sudden cardiac death is more effective and safe than standard care without WCD, or as effective and safe as hospital observation concerning the defined outcomes (see Table 2-1)?
- Which (health-related) effects (if any) does the WCD have on the Quality of Life of patients?
- What is the satisfaction and compliance rate of patients with the WCD?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarized in Table 2-1.

Table 2-1: Inclusion criteria

Population	Population: adults over 18 years of age (according to CE mark) with the following indications: As a temporary intervention prior to the insertion of an ICD for (e.g.): ■ patients immediately after explantation of an ICD, if an immediate reimplantation of an ICD is not possible; ■ patients in whom an immediate implantation of an ICD is indicated, but not possible due to temporary contraindications. As a temporary measure prior to optimal pharmacological therapy, or as a protection during pharmacological therapy optimisation when a heightened risk of SCD is present, but possibly resolvable over time or with treatment of left ventricular dysfunction; for patients with: ■ ischaemic heart disease with envisaged or recent revascularization (90-day waiting period post revascularization with either CABG or PCI); ■ secondary cardiomyopathy (tachycardia mediated, thyroid mediated, etc.) or induced arrhythmias (secondary to hypothermia, electrolyte imbalance, iatrogenic prolongation of the QT interval, etc.) in which the underlying cause is potentially treatable; ■ with certain forms of structural heart disease associated with risk of malignant arrhythmias or primary electric diseases, prior to diagnostic tests such as MRI. Post Myocardial Infarction (MI) and LVEF of ≤ 35%, as a temporary measure during prognostic stratification in situations associated with increased risk of arrhythmic death within 40 d of MI As a temporary measure prior to heart transplantion in patients without ICD
Intervention	WCD (as add-on or replacement): LifeVest® (WCD 4000) from ZOLL (Lifecor) Medical Corporation, Pittsburgh, PA, USA [20] ASSURE™ Wearable Cardioverter Defibrillator (WCD) from Kestra Medical Technologies, Inc.[7]
Control	Hospital observation; Optimal Medical Therapy (OMT)
Outcomes	
Efficacy	**Critical:** ■ Mortality (all-cause mortality, disease-specific mortality) **Important:** ■ Health-related Quality of Life measured using a validated instrument ■ Hospitalisation rate ■ Patient satisfaction measured using a validated instrument ■ Compliance ■ Relevant surrogate endpoints related to the functional performance of the device (appropriate shocks, shock success, withheld shocks)
Safety	■ *Adverse events:* device related and patient related (frequency of AEs, frequency of discontinuation due to AEs, frequency of unexpected AEs), ■ *Serious Adverse events:* device related and patient related (frequency of SAEs, frequency of SAEs leading to death).
Study design	Randomised and prospective observational studies with a control group Observational prospective studies and register studies with at least 100 patients
Publication period	08/2018-05/2022

***Abbreviations: AE** – adverse events; CABG – coronary artery bypass graft; CE – Conformité Européenne; **d** – day(s); ICD – implantable cardioverter-defibrillator; **MRI** – Magnetic resonance imaging; **OMT** – optimal medical therapy; **PCI** – percutaneous coronary intervention; **SAE** – serious adverse events; **SCD** – sudden cardiac death; **WCD** – wearable cardioverter-defibrillator;*

3 Methods

This report represents a systematic review of the comparative effectiveness and safety of the WCD, updating the EUnetHTA report 2017 [2] for the second time [1].

Update Rapid Review

The study was conducted in accordance with the PRISMA statement [21, 22]. The EUnetHTA Core Model was used flexibly as a reporting standard [23].

3.1 Systematic literature search

The systematic literature search was conducted on the 28.04.2022 in the following databases:

systematische Literatursuche in drei Datenbanken

- Medline via Ovid
- Embase
- The Cochrane Library

The systematic search was limited to the years 2018 to 2022, updating the evidence of the AGENAS/ LBI-HTA update-report 2019 [1]. After de-duplication, 469 citations were included overall. The specific search strategy employed can be found in the Appendix (see "Literature search strategies").

Zeitraum: 2018-2022

Furthermore, a hand-search in the reference list of one recent systematic review [16] was conducted to strengthen the systematic search and eventually identify potentially further eligible studies: no further studies were hereby identified.

insgesamt 469 Treffer 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 the 1st of May 2022, resulting in 27 potentially relevant hits.

zusätzliche Suche nach laufenden Studien

3.2 Flow chart of study selection

Overall, 469 hits were identified. The references were screened by two independent researchers (GG, BW). The selection process is displayed in Figure 3-1.

Literaturauswahl

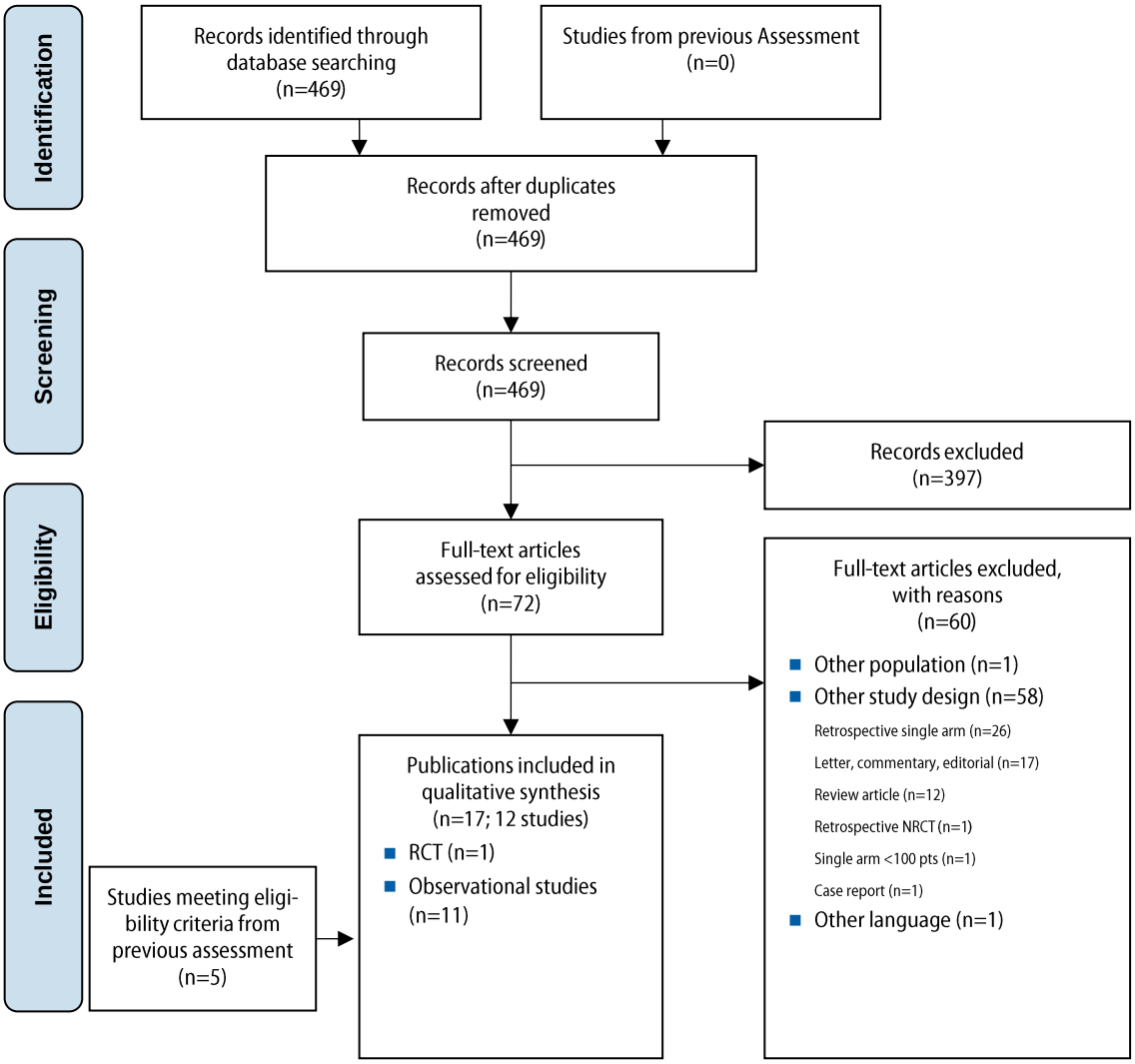

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

3.3 Analysis

Datenextraktion und …

Relevant data from eligible studies were systematically extracted into data-extraction tables. The single-data extraction method with verification by another researcher was utilised: One researcher (GG) extracted the data and another researcher (BW) checked the extracted data.

Einschätzung des Verzerrungspotentials (Risk of Bias/RoB) durch 2 Personen

Two independent researchers (GG, BW) systematically assessed the risk of bias (RoB) of the included studies using the Cochrane RoB tool v.2 [24] and the ROBINS-I tool [25] for RCTs and studies with a control group, respectively. The quality of uncontrolled observational studies was appraised using the Institute of Health Economics (IHE-20) checklist [26].

For assessing the overall RoB of uncontrolled observational studies, pre-defined point scores were utilised (range: 0-20): a high score indicates a low RoB and a low score indicates a higher RoB. The detailed point scoring system and cut-off criteria are presented in Table 3-1 and Table 3-2, respectively.

Table 3-1: Overall risk of bias (RoB) point scores for RoB assessment of uncontrolled observational studies

Answers to specific questions of the IHE-20 checklist	Points
No	0
Partial	0,5
Unclear	0,5
Yes	1

Table 3-2: Cut-off criteria for the risk of bias (RoB) assessment of overall RoB of uncontrolled observational studies

Criteria	Points
Low risk	>18
Moderate risk	16-18
High risk	11.5-15.5
Very high risk	≤11

For eligible observational studies already included in the AGENAS/ LBI-HTA update-report 2019 [1] or in the original EUnetHTA report 2017 [2], we solely retrieved RoB assessment judgements from these reports.

3.4 Synthesis

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

Verwendung von GRADE zur Synthese der Evidenz

We used GRADE (Grading of Recommendations, Assessment, Development and Evaluation) to synthesise the identified evidence [27]. GRADE evidence tables and a GRADE summary of findings tables were hereby created. No inferential statistical analysis was conducted in the absence of high-quality data derived from RCTs.

Evidenz aus Beobachtungsstudien mit gemischten Indikationen: Übersicht

Since all eligible observational studies included mixed populations, we could not synthesise the observational evidence according to specific indications. However, the distribution of enrolled patients (according to indications/ aetiologies) of these studies was presented using a slightly modified structure based on another systematic review [16]. We described the evidence for RCTs and observational studies separately.

4 Clinical Effectiveness and Safety of the wearable cardioverter defibrillator

4.1 Outcomes clinical effectiveness

The following endpoints were selected as the critical endpoints for assessing the comparative effectiveness of WCD-therapy in addition to (or as a replacement of) standard care:

wesentlicher Zielparameter:

- All-cause mortality
- Disease-specific mortality

Mortalität

Further seven outcomes were defined as important for the evaluation of effectiveness of the WCD:

weitere Endpunkte: Lebensqualität, Zufriedenheit, Hospitalisierungsrate, Compliance und angemessene Therapiegabe/ Shock Erfolgsrate

- Health-related Quality of Life measured using a validated instrument
- Hospitalisation rate
- Patient satisfaction measured using a validated instrument
- Compliance
- Relevant surrogate endpoints related to the functional performance of the device (appropriate shocks, shock success, withheld shocks)

Mortality was considered a highly patient-relevant outcome measure when assessing the clinical effectiveness of the device. It was reported as all-cause and disease-specific mortality [17, 28-43].

arrhythmische- und Gesamtmortalität

Patient-reported endpoints such as **health-related quality of life (HRQoL)** and **satisfaction** were seen as further important outcomes: Validated reported instruments to determine HRQoL covered the Kansas City Cardiomyopathy questionnaire [28] and the Short Form-12 (SF-12) questionnaire [43]. One study further used instruments that were related to HRQoL: Beck-Depression Inventory II and State-Trait Anxiety Inventory [43]. Satisfaction measured with a validated instrument was not reported by any of the included studies.

Zufriedenheit und Lebensqualität mittels Fragebögen

The **hospitalisation rate** was measured numerically with the number of hospitalised patients within the time frame of wearing the WCD [17, 30, 33].

Hospitalisierungsrate

Compliance is an intermediate endpoint for assessing the effectiveness of WCD therapy. The endpoint was measured using routine data by all included studies [17, 28-43]: The WCD delivers data on wear time (e.g., hours per day, total days) using remote telemonitoring via the LifeVest® network [44].

Compliance: Tragezeit mittels Remote Monitoring System

The surrogate endpoints **appropriate shocks,** and **shock success** are related to the functional performance and indicate whether the technology under investigation works as anticipated. These outcomes were reported as the number of patients wearing a WCD that received one or more appropriate shocks and how many of the patients presenting with episodes of VT/VF were successfully terminated by WCD shock, respectively [17, 29, 30, 32-42]. Further, **withheld shocks** refer to the number of patients that pressed the response buttons to withhold the shock application [17, 35-37, 41]. These endpoints are reported for patients receiving the WCD and are, hence, descriptive in nature.

angemessene Schockabgabe: Anzahl der Pat. mit zumindest einem Shock (mit erfolgreicher Terminierung von VT/VF)

4.2 Outcomes safety

Sicherheit:

The following outcomes were defined as critical for the evaluation of the comparative safety of the WCD:

- Serious adverse events (SAE)
- Adverse events (AE)

In accordance with the European Commission guidelines for medical devices on SAE reporting, the following definitions are applied [45]:

schwerwiegende unerwünschte Nebenwirkungen (SUE) und …

SAE is any adverse event that led to a) death, b) serious deterioration in the health of the subjected that resulted in any of the following: i) life-threatening illness or injury, ii) a permanent impairment of a body structure or a body function, iii) in-patient hospitalisation or prolongation of existing hospitalisation, iv) medical or surgical intervention to prevent a life-threatening illness or injury, v) chronic disease; c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

unerwünschte Ereignisse (UE)

AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. This includes events associated with the investigational device or related to the procedures involved (any procedure in the clinical investigation plan).

4.3 Included studies

1 RCT (2 Publikationen) und …

No new RCT was identified, but a post-hoc analysis [31] of the only available RCT [17] was published and included in the update review. With regard to observational studies, seven new studies [28, 33, 34, 40-43] met the eligibility criteria. Of these, six studies [33, 34, 40-43] were prospective register studies, and one further study was a sub-study of an ongoing cohort study [28].

11 Beobachtungsstudien (in 15 Publikationen)

Additionally, four newly identified publications [36-39] were related to a multicentre registry study [35] included in the previous assessment. This registry [35] and three case series studies [29, 30, 32] identified by the previous HTA report [1] further met our inclusion criteria.

Hence, the RCT [17, 31] and eleven observational studies [28-30, 32-43] were included in this update systematic review.

4.3.1 Included RCT evidence

Study characteristics

RCT mit hohem Verzerrungspotenzial

The multicentre RCT [17, 31] included sites in the United States (n=76), Poland (n=24), Germany (n=6), and Hungary (n=2). Zoll Medical Corporation and the National Institutes of Health (NIH) /National Heart Lung and Blood Institute (NHLBI) funded the study.

The RoB of the VEST trial [17, 31] was high mainly due to deviations from the intended intervention (cross-overs against study protocol and low compliance). Some concerns were additionally found with bias in the measurement of outcome and selection of reported results. The risk of bias of the per-protocol effect reported in a post-hoc analysis [31] of the VEST trial was further substantially increased as (in addition to the aforementioned sources of biases), bias due to missing data was further high, and the effect of assignment to intervention was not adequately assessable due to the post-hoc analysis. Full RoB assessment can be found in the appendix.

und Post-Hoc Analyse mit sehr hohem Verzerrungspotenzial

Patient characteristics, follow-up and outcomes

In total, 2,348 patients who had been hospitalised with an acute MI (and LVEF≤35%) were enrolled and randomised in a 2:1 ratio in the included study [17]. 46 participants were excluded from the analysis due to irregularities found by the institutional review board at one of the sites. Thus, 2,302 participants were included in the analysis, resulting in 1,524 and 778 patients in the device and control group, respectively. Regarding cross-overs, 20 participants (2.6%) in the control group received the WCD by prescription outside of protocol by treating medical doctors, while 43 participants (2.8%) in the device group, never wore the device after randomization. Patients in the device group received a WCD and OMT, while the control group received OMT solely.

2.302 analysierte Pat.

1.524 Pat. erhielten die Defibrillator-Weste zusätzlich zur pharmakologischen Therapie und

778 Pat erhielten eine pharmakologische Therapie alleine

The inclusion criteria from the VEST trial [17, 31] are: patients who were hospitalised with an acute MI and who had LVEF of ≤35% were enrolled within seven days after hospital discharge. Patients who had/were undergoing one of the following were excluded [17]: ICD or unipolar pacemaker, clinically significant valve disease, long-term haemodialysis, chest circumference being too little or too large to accommodate the WCD, pregnancy or discharge to a nursing facility with an anticipated stay of more than seven days. Previous interventions of the patients included, coronary artery bypass graft (CABG; 8.7% vs 9%) and percutaneous coronary interventions (PCI; 24.6% vs 26%).

Einschlusskriterien: Post Myokardinfarkt und eingeschränkte Ejektionsfraktion (≤35 %)

The mean age of the patients in the device group and control group was 60.9 years (SD: 12.6) and 61.4 years (SD: 12.3), respectively. The mean LVEF was 28.2% (SD: 6.1) for patients in the device group and 28.2% (SD: 5.8) for patients in the control group [17].

durchschnittliches Alter: 60.9 J. vs. 61.4 J.

The percentage of female patients in the sample was 27% and 25% in device and control group, respectively [17].

mehrheitlich männlich

The mean follow-up time of the randomly assigned patients was 84.3 days (SD: 15.6), and further 22 patients were lost to follow-up, with 10 out of 1,524 patients (0.7%) and 12 out of 778 patients (1.5%) in device and control group, respectively [17, 31].

84,3 Tage durchschnittliche Nachbeobachtung

Study characteristics and the results of included studies are displayed in the data extraction table (see Table A - 1) and in the evidence profile (see Table A - 7) that can be found in the Appendix.

4.3.2 Additional included observational evidence

Study characteristics

11 Beobachtungsstudien

In total, eleven observational studies [28-30, 32-43] fulfilled the inclusion criteria. Of these, seven and three studies used a prospective registry [33-43] or a case series design [29, 30, 32], respectively. One further study was a substudy of a prospective ongoing cohort study [28]. Seven studies were conducted in Germany [29, 30, 32-34, 41, 43], and three studies were conducted in France [42], Austria [40] and the USA [35-39], respectively. The remaining study [28] recruited their patients from sites in the USA and Germany.

3 Studien mit moderatem RoB und weitere 8 Studien mit hohem RoB

Overall, the RoB of the included studies was moderate in three studies [33, 40, 41] and high [28-30, 32, 34-39, 41] or critical [43] in the remaining eight studies. It is noteworthy to state that six [28, 34-39, 41-43] out of eight studies reporting on funding were sponsored by the industry.

1 von 11 Studien mit Kontrollgruppe zur Lebensqualität mit WCD

In all of the included studies, the intervention group received a WCD in different indications, and only one of the registry studies [43] investigating the quality of life defined a control group receiving standard care without a WCD.

Patient characteristics, follow-up and outcomes

5.345 Pat.

Overall, the studies [28-30, 32-43] enrolled 5,345 patients (range: 102-2,000), of which 5,307 received WCD therapy primarily in addition to standard care and 38 patients received standard care alone.

unterschiedliche Indikationen Studien berichteten über breite Ätiologien

unklar ob WCD als Zusatz- oder Ersatzmaßnahme

All included observational studies [28-30, 32-43] reported on mixed populations, with the majority of patients suffering from ischemic cardiomyopathies, followed by non-ischemic cardiomyopathies. None of the studies adequately reported whether WCD therapy was used as an add-on to OMT or to replace hospital observation. In most of the enrolled patient groups, WCD therapy is usually used in addition to OMT, although in some indications (e.g. acute infections), WCD therapy may have been used instead of hospital observation. Table 4-1 provides an overview of indications across both observational studies and the VEST trial.

durchschnittliches Alter: 56-66 Jahre

Age was reported differently across studies: eight studies [28-30, 33, 40-43] reported age using the mean as a measure, ranging from 56 to 60 years. The remaining three studies [32, 34-39] reported a median age ranging from 60 to 66 years. In the registry study assessing the quality of life [43], patients with a WCD were statistically significantly younger than the patients in the standard care group, with an average age of 56 ±13 and 64 ±14, respectively.

Mehrheit der Pat. männlich

The percentage of female patients in the sample of the observational studies ranged from 16% to 30% [28-30, 32-43].

3-36,2 Monate Nachbeobachtung:

The length of follow-up ranged from six weeks [43] to 36.2 months [33]. The loss to follow-up rate was insufficiently reported in four studies [28, 34-40] and ranged from 0% to 18% in the remaining studies [29, 30, 32, 33, 41-43].

Study characteristics and the results of included studies are displayed in the data extraction table (see Table A - 2, Table A - 3) and in the evidence profile (see Table A - 7) that can be found in the Appendix.

4.3.3 Indications across included studies

Except for the VEST trial [17, 31], all observational studies [28-30, 32-43] included mixed populations. ICM and NICM were numerically the biggest patient populations across included studies. It is noteworthy that most studies did not adequately report the specific indications for a WCD in these patient populations.

VEST: enge Indikation

Ischemic cardiomyopathy (ICM)

The RCT [17, 31] included a specific indication within ischemic cardiomyopathy: Patients hospitalized with acute MI and with LVEF of ≤35% (assessed ≥8 hours after MI).

Post MI und LVEF ≤35 %

Further, eleven observational studies enrolled ICM patients as part of their study cohorts, accounting for a range of 20% to up to 82% of patients with ICM of the enrolled patients within these studies (range of enrolled patients receiving a WCD: 85-2,000). It is noteworthy to state that this patient population still covers diverse indications, with only eight studies reporting their definition of ICM: Three studies [33, 34, 43] reported enrolling ICM patients with LVEF<35% and another registry study [42] reported on enrolling ICM patients with LVEF<30%. Further, three studies reported more granular ICM indications: One study reported enrolled ICM patients with a recent MI <40 days undergoing PCI and LVEF <35% and/or documented VT/VF [40]. ICM patients in the remaining two studies [32, 41] had either an acute MI and/or revascularisation procedures such as PCI or CABG. The remaining four studies [28-30, 35] did not report more specific characteristics of ICM patients in their samples.

verschiedenste Indikationen bzw. Ätiologien in Studiensamples der Beobachtungsstudien:

ICM in 11 Studien: 20-82 %

Non-ischemic cardiomyopathy (NICM)

Ten studies reported on NICM patients as a subset of their study cohorts, accounting for 32% to up to 54% of patients with NICM within these studies (range of enrolled patients receiving a WCD: 85-2,000). Of these, four studies [32-34, 43] reported enrolling NICM patients with LVEF ≤35%. Another study [40] reported that their enrolled NICM patients were newly diagnosed and had an LVEF of 35% within 90 days of the start/optimization of heart failure therapy and/or documented VT/VF. Only a fragment of these studies reported on the specific NICM subgroups such as idiopathic/ dilated cardiomyopathy [29, 30, 32], peripartum cardiomyopathy [30, 32, 42], myocarditis [29, 30, 32, 33, 40, 42], or Takotsubo cardiomyopathy [29, 30, 32, 42].

NICM in 10 Studien: 32-54 %

ICD explantation

Five studies [32, 33, 40, 42, 43] reported on patients with an ICD explantation as a subset of their study cohorts, accounting for a range of 9% to up to 14% of the enrolled patients within these studies (range of enrolled patients receiving a WCD: 85-1,164).

ICD Explantation in 5 Studien: 9-14 %

Other indications

Other less frequent areas of WCD use within observational studies are the following:

Patients *waiting for heart transplantation (without ICD)* accounted for 8% of enrolled patients in one study (n=1,164). The study did not report on more specific characteristics of this patient subgroup [42].

weniger häufig: 1 Studie mit Pat. auf der Warteliste für Herztransplantation: 8 %

während diagnostischer Abklärung in 2 Studien: 4 bzw. 13 %

Further, two studies reported another sub-population receiving a WCD: *Patients during diagnostic wrap-up* accounted for 4% and 13% of 102 [30] and 781 [41] enrolled patients, respectively. This broad indication area either covered patients suffering from channelopathies/ congenital heart diseases (not further specified) in one study [30] or was only defined as "other risk stratification" in the other study [41].

akute Infektion in 2 Studien: 4 % bzw. 25 %

Patients with an *acute infection* accounted for 18 patients (4%) in one study [40] and 25 patients (25%) in another study [30]. These infections were device-related and systemic acute infections (that delayed ICD implantation), respectively.

verzögerte ICD Implantation in 1 Studie: 12 %
Überbrückung zur Ablation in 1 Studie: 2 %

Patients with a *delayed ICD implantation* due to comorbidities or other reasons accounted for 54 patients (12%) in one study. Further, patients with documented VT events prior or post VT ablation (*bridge to ablation*) accounted for 11 patients (2%) in one study.

Primary vs secondary prevention

WCD zur Primärprävention des plötzlichen Herztodes in RCT
Primär- oder Sekundärprävention in Beobachtungsstudien

Only the RCT and one of the observational studies reported whether the use of the WCD was for primary or secondary prevention of SCD. While the VEST study [17, 31] used the WCD therapy for primary prevention of SCD in a narrow patient population (n=1,524), the Austrian registry [40] reported that 216 patients (48%) received the WCD as secondary prevention as opposed to the remaining 232 patients (52%) receiving the WCD for primary prevention of SCD.

Table 4-1 provides an overview of enrolled patients' indications/ aetiologies and specific use (primary vs secondary prevention) across included studies.

Table 4-1: Overview of indications/ aetiologies across included studies

Study	Study design	N of pts*	Primary vs. secondary prevention	Duration of use, in days**	Daily use, in hours	ICD Explantation	ICM	NICM	NICM Subgroups					WL for heart transplantation	During diagnostic wrap up (e.g., channelopathies)	Acute infection	Bridge to ablation	Delayed ICD Implantation	Other/ data not available
									Idiopathic/ DCM	PPCM	Myocarditis	TCM	Others						
VEST [17, 31]	RCT	1,524	100% vs. 0%	84.3	14,10	0	1524 (100%)	0	0	0	0	0	0	0	0	0	0	0	0
Röger, 2018[32]	OS	105	NR	68.8 ± 50.4	21.5 ± 3.5	15 (14%)	43 (41%)	41 (39%)	38	1	0	2	0	0	0	0	0	0	6 (6%)
Erath, 2018 [29]	OS	130	NR	42 (1-166)	23,00	0	84 (65%)	46 (35%)	25	NR	5	10	5	0	0	0	0	0	0
Erath, 2017 [30]	OS	102	NR	42	20,00	0	27 (27%)	42 (41%)	33	0	9	0	0	0	4 (4%)	25 (25%)	0	0	4 (4%)
WEARIT-II [35-39]	OS	2,000	NR	90	22,5	0	805 (40%)	927 (46%)	NR	NR	NR	NR	NR	0	0	0	0	0	268 (13%)
WEARIT-FR [42]	OS	1,164	NR	62 (37–97)	23.4	119 (10%)	950 (82%)	0	0	0	0	0	0	88 (8%)	0	0	0	0	7 (1%)
WEARIT-II-EU [41]	OS	781	NR	75 ± 47.7	20.3*	0	200 (26%)	249 (32%)	NR	NR	NR	NR	NR	0	102 (13%)	0	0	0	230 (29%)[1]
Odeneg, 2019 [40]	OS	448	52% vs. 48%	54 (1, 436)	23.5	46 (10%)	88 (20%)	139 (31%)[2]	NR	NR	45	NR	NR	0	0	18 (4%)	11 (2%)	54 (12%)	92 (21%
Rosenkaimer, 2020 [33]	OS	153	NR	65.1 ±42	21.45 ± 3.52	16 (10%)	56 (37%)	78 (51%)	NR	NR	8	NR	NR	0	0	0	0	0	3 (2%)
Sinha, 2021 [34]	OS	120	NR	48 (37-62)	22.9 (21.2-23.4)	0	46 (38%)	69 (58%)	NR	NR	NR	NR	NR	0	0	0	0	0	5 (4%)
Weiss, 2019 [43]	cOS	85	NR	59 (40–96)	20 ±5	8 (9%)	20 (24%)	57 (67%)	NR	NR	NR	NR	NR	0	0	0	0	0	0
Burch 2021 [28]	OS	210	NR	NR	NR		91 (43.3%)	113 (53.8%)	NR	NR	NR	NR	NR	0	0	0	0	0	6 (2.9%)

Structure of this table is informed by [16]
**N of patients refers to patents receiving a WCD*
***All values as median (IQR: 1st Quartile-3rd Quartile or range: lowest value, highest value) or Mean ±SD*

***Abbreviations: cOS** – comparative observational study; **DCM** – dilated cardiomyopathy; **ICD** – implantable cardioverter defibrillator; **ICM** – ischemic cardiomyopathy; **NICM** – non-ischemic cardiomyopathy; **NR** – not reported; **OS** – observational study; **PCM** – peripartum cardiomyopathy;* **pts** – patients; **TCM** – tachymyopathy; **WL** – waiting list.

[1] Recent onset/ impairment of heart failure

[2] Severe NICM with LVEF<35%

4.3.4 Results

Effectiveness of the WCD

RCT evidence

RCT Evidenz:

Mortality was reported in the RCT [17, 31]:

arrhythmische Mortalität: kein stat. signifikanter Unterschied

Disease-specific mortality was reported in the VEST study [17]: no statistically significant difference was found within the intention-to-treat (ITT) analysis between the device and control group, with 25 out of 1,524 (1.6%) and 19 out of 778 (2.4%) arrhythmic deaths in those groups, respectively (p = 0.18).

The post-hoc as-treated analysis of the VEST trial [31] showed that nine fatal events occurred in patients wearing the device (2,420 person-months) as opposed to 32 fatal events in patients not wearing the device (3,724 person months), with a relative risk of 0.43 (p=0.026). A per-protocol analysis showed a hazard ratio (HR) of 0.38 (95% CI, 0.17-0.86; p=0.02).

Gesamtmortalität: stat. Signifikanter Unterschied 3,1 % vs. 4,9 %,

All-cause mortality was reported by the VEST trial [17]: The RCT found a statistically significantly lower rate of the secondary outcome deaths from any cause in the device group when compared to the control group, with 48 out of 1,524 (3.1%) and 38 out of 778 (4.9%) deaths from any cause in those groups respectively (p = 0.04).

A post-hoc as-treated analysis of the VEST trial [31] showed that 12 fatal events occurred in patients wearing the WCD (2,320 person-months) as opposed to 71 fatal events in patients not wearing the WCD (3,724 person-months) with an adjusted RR of 0.26 (p<0.005). A per-protocol analysis showed a hazard ratio (HR) of 0.25 (95% CI, 0.13-0.48; p<0.001).

Lebensqualität: keine Evidenz

Regarding **health-related quality of life**, no evidence derived from RCTs is available. The VEST trial gathered data on quality of life without reporting on these data in currently available publications [17, 31].

Hospitalisierungsrate: kein stat. signifikanter Unterschied

The **hospitalisation rate** was reported in the VEST trial: the RCT [17] did not find a statistically significant difference when comparing the rehospitalisation rate between the device group and the control group, with 31.2% and 32.5% rehospitalised patients (any cause) in those groups respectively (p-value = 0.5).

Satisfaction was not reported in the VEST trial [17, 31].

Compliance: durchschnittlich 14 Std. Tragezeit

Compliance was reported in the VEST trial [17]: On average, patients wore the device 14 hours per day (SD: ± 9.3). The median daily use of the WCD was reported to be 18 hours per day, with an interquartile range of 3.8-22.7.

Appropriate shocks were reported in the VEST trial [17]; 20 out of 1,524 patients (1.3%) in the device group received an appropriate shock. Of those, 13 patients received one shock, and seven patients received two or more appropriate shocks. Regarding **withheld shocks**, 69 out of 1,524 patients (4.5%) aborted one or more shocks by pressing the response button. **Shock success** was not reported in the VEST trial [17, 31].

Observational evidence

Mortalität: 0 % - 5,2 %

Mortality was reported in nine uncontrolled observational studies. Two studies [32, 35-39] reported a disease-specific mortality rate of 0%, and nine studies [29, 30, 32-42] reported all-cause mortality, ranging from 0% to 5.2% (range of enrolled patients across studies: 102-2,000).

Lebensqualität: stat. Assoziation zwischen Defibrillator-Weste und Angst zu Beginn der Therapie in 1 Studie

allgemeine Verbesserung der Lebensqualität im Therapieverlauf in 1 Vorher-Nachher Studie

Health-related quality of life was reported in two observational studies [28, 43]: One registry study [43] found a statistical (positive) association between WCD and baseline anxiety when comparing the anxiety score and rate of anxiety between WCD therapy (n=85) to standard care (n=38), with 41 ± 11 vs 39 ± 13 (p = 0.22) and 58.9% vs 29.2% (p = 0.02), respectively (State-Trait Anxiety Inventory). Further, there was a non-statistical trend toward better improvement of depression scores in patients with WCD, with a mean change in score points of -4.1 ±6.1 and -1.8 ±3.9 (p =0.09) in patients receiving WCD and patients receiving no WCD, respectively. The change in anxiousness score was not statistically significantly different between patients enrolled in the WCD registry compared to patients receiving no WCD. The other before-after study [28], enrolling 210 patients with a WCD, found statistically significant improvements in all Kansas City Cardiomyopathy Questionnaire subscales (physical limitation, symptom frequency, quality of life, and social limitation) from baseline to day 90 (p < .001).

Hospitalisierungsrate in 2 Studien: 12,7 % und 67 %

The **hospitalisation rate** was reported in two studies [30, 33]: In one prospective case series study [30], 13 of 102 enrolled patients (12.7%) were hospitalised due to cardiac causes. In the other registry study [33], 102 of 153 enrolled patients (67%) were hospitalised.

Zufriedenheit: -

The **satisfaction** was not reported by the included studies.

20 bis 23.5 Std tägliche Tragezeit

The **compliance** with the WCD was reported by ten observational studies [29, 30, 32-43]: The daily wear time was well above 20 hours in all of the included studies. Six studies [28, 30, 34-40, 42] reported a median daily wear time ranging from 22.5 to 23.5 hours and the other five studies [29, 32, 33, 41, 43] reported a mean wear time ranging from 20 to 23 hours per day (range of enrolled patients across all studies reporting on compliance: 102-2,000).

angemessene Schocks in 9 Studien: 1 % bis 4,8 %

zurückgehaltene Shocks in 2 Studien: 1,1 % und 2,8%

Schockerfolg in 3 Studien: 100 %

Appropriate shocks were reported in nine out of eleven studies [29, 30, 32-42]: The range of patients receiving one or more appropriate shocks was between 1% and 4.8% (range of enrolled patients across studies: 102-2,000). **Withheld shocks** were further reported in two studies enrolling 2,000 and 781 patients: The studies reported 90 events in 22 patients (1.1%) [35-37] and 47 events in 22 patients (2.8%) [41], respectively. **First shock success** was reported in three studies [32, 33, 35-37], with a first shock success rate of 100% in all of these studies.

Safety of the WCD

Sicherheit

RCT evidence

SUE in RCT:

Serious adverse events

gerätebezogene SUE: 0,2 %
unangemessene Schocks: 0,6 %

The only comparative study included [17] reported the safety outcomes described below: four SAEs related or potentially related to the WCD occurred (0.2%). Three were three patient hospitalizations (two due to aborted shocks and one due to an inappropriate shock), and one was a patient who died while wearing the device. The authors state that it was deemed likely not to be an arrhythmic death (the device recorded no tachyarrhythmia and emergency

medical technicians noted pulseless electrical activity on arrival). Other SAEs were *inappropriate shocks* (one was the hospitalized patient already described above) that occurred in 9/1,524 (0.6%) patients in the device group.

UE in RCT:

Adverse events

Hautausschlag und Juckreiz stat. Signifikant häufiger in Interventionsgruppe

Statistically significant differences between the device and control groups were observed for rash and itching in the torso area. Rash occurred in 184 (13.0%) patients in the device group compared to 27 (3.8%) patients in the control group ($p<0.001$). Itch occurred in 205 (14.5%) patients in the device group as opposed to 22 (3.1%) patients in the control group ($p<0.001$).

SUE in Beobachtungsstudien:

Observational evidence

Serious adverse events

unangemessene Schocks in 10 Studien: 0 % bis 2 %

Ten observational studies reported the rate of *inappropriate shocks* [29, 30, 32-43], ranging from 0% to 2% (range of enrolled patients across studies: 102-2,000). Other SAEs, such as unsuccessful shocks and the frequency of SAEs leading to death, were either not reported or did not occur.

UE in Beobachtungsstudien: 1 Studie: Dermatitis in 0,9 % und Druckstellen in 0,2 % der Pat. hohe Fehlalarmrate in 1 weiteren Studie

Adverse events

The following Aes were reported in observational studies: skin rash and itching, and false alarms.

Skin rash and itching were reported in two studies [30, 40]: The Austrian registry with 448 enrolled patients reported four patients (0.9%) and one patient (0.2%) that developed dermatitis and a pressure mark, respectively. These five Aes were considered device-related [40]. Another study reported on two patients (2%) with skin rash who were allergic to nickel [30].

The occurrence of *false alarms* was reported in one of the included observational studies [30], with 58 patients (57%) receiving vibrations, sirens or bystanders due to incorrect ECG episodes defined as artefacts upon review.

The *discontinuation due to lifestyle and comfort issues* was reported in two further studies: In one study [32], eight patients (7%) returned their WCD during the first hours after initiation because of unwillingness or inability to handle it. In the other study [33], the exact reason for discontinuation was not reported, with 12 patients (8%) and five patients (3%) discontinuing WCD therapy due to incompliance or other reasons.

Table 4-2: GRADE Summary of findings table: Effectiveness and safety of the wearable cardioverter defibrillator in patients at risk of sudden cardiac death

Outcomes	Indication	Anticipated effects	№ of analysed pts (studies)	Certainty of the evidence (GRADE)
Comparative effectiveness (RCT evidence)				
Mortality	Post-MI	Arrhythmic mortality: 25/ 1,524 (1.6%) vs. 19/ 778 (2.4%), p=0.18 All-cause mortality: 48/1,524 (3.1%) vs. 38/778 (4.9%), p = 0.04	2,348 (1 RCT)	⊕⊕◯◯ LOW[a,b,c]
QoL	Post-MI	-	(0 studies)	-
Hospitalisation	Post-MI	31.2% vs. 32.5% (p-value = 0.5)	2,348 (1 RCT)	⊕⊕⊕◯ MODERATE[a]
Satisfaction	Post-MI	-	(0 studies)	-
Compliance	Post-MI	Mean daily wear time, in days: 14 (SD: ± 9.3)	2,348 (1 RCT)	⊕⊕⊕⊕ High
Surrogate endpoints	Post-MI	Appropriate shocks: 1.3%/ Shock success: NR withheld shocks: 4.5%	2,348 (1 RCT)	⊕⊕⊕◯ MODERATE[a]
Effectiveness (observational evidence)				
Mortality	Mixed	Arrhythmic mortality (2 studies): 0% All-cause mortality (9 studies): 0-5.2%	4,992 (9 studies)	⊕◯◯◯ VERY LOW[d]
QoL	Mixed	statistical association between WCD and baseline anxiety (1 controlled study): 41 ± 11 vs. 39 ± 13 (p = 0.22; higher score indicates higher anxiety) *statistically significant improvements* in all Kansas City Cardiomyopathy Questionnaire subscales (1 before-after study; baseline to day 90)	310 (2 studies)	⊕◯◯◯ VERY LOW[d]
Hospitalisation	Mixed	13/102 (12.7%) in 1 prospective case series 102/153 (67%4) in 1 registry	255 (2 studies)	⊕◯◯◯ VERY LOW[d]
Satisfaction	Mixed	-	-	-
Compliance	Mixed	20-23.5 hrs per day[3]	5,092 (10 studies)	⊕⊕◯◯ LOW
Surrogate endpoints	Mixed	N of pts with at least one appropriate shock: 1.1%-4.8% (range of enrolled patients across studies: 102-2,000) First shock success (3 studies): 100% Withheld shocks (2 studies): 90 events in 22 pts (1.1%) and 47 events in 22 pts (2.8%)	4,992 (9 studies)	⊕⊕◯◯ LOW
Safety (RCT evidence)				
(Serious) adverse events (SAE/AE)	Post-MI	SAE: Inappropriate shocks: 9/1,524 (0.6%), SADE[4]: 4/1,524 (0.2%) AE: Rash: 184 (13.0%) vs. 27 (3.8%), p<0.001 Itch: 205 (14.5%) vs. 22 (3.1%), p<0.001	2,348 (1 RCT)	⊕⊕⊕◯ MODERATE[a]

[3] Measured as median or mean

[4] SAEs related or potentially related to the WCD

Outcomes	Indication	Anticipated effects	№ of analysed pts (studies)	Certainty of the evidence (GRADE)
Safety (observational evidence)				
(Serious) adverse events (SAE/AE)	Mixed	SAE: Inappropriate shocks: 0-2% AE (2 studies): 4/448 pts (0.9%) with dematitis, 1/448 pt (0.2%) with pressure mark in one study; 2 pts (2%) were allergic to nickel and 58 (57%) false alarms in another study	5,092 (10 studies)	⊕⊕◯◯ LOW

Abbreviations: AE *– adverse events;* ***GRADE*** *– grading of recommendations assessment development and evaluation;* ***hrs*** *– hours;* ***MI*** *– myocardial infarction;* ***QoL*** *– quality of life;* ***RCT*** *– randomized controlled trial;* ***SADE*** *– serious adverse device effect;* ***SAE*** *– serious adverse events;* ***SD*** *– standard deviation.*

Explanations

a. *The RCT was judged to be at high risk of bias through the Cochrane Risk of Bias tool due to poor compliance (and selective outcome reporting) that could have influenced the comparative effect estimates for effectiveness outcomes and the estimated proportions of adverse events for safety outcomes.*

b*. In the study occurred few events leading to a wide CI around the estimate of the effect estimate.*

c*. The endpoint "death from any-cause" was set as a secondary outcome in the included RCT. In addition, the study did not statistically correct the analysis for multiple testing.*

d*. Selection bias may be the most significant source of bias in observational studies. In addition, reporting on milder Aes was sparse and patients did not enter the study at the same point of disease. Also mixed populations were included, being heterogeneous patient populations.*

5 Discussion

The wearable cardioverter defibrillator (WCD) is a temporary measure aiming at preventing sudden cardiac death in patients at risk. In this report, we aimed to identify the latest studies in order to to synthesise the best available body of evidence regarding the comparative effectiveness and safety of WCD therapy.

2. Update nach 2016, 2019: keine neuen RCTs identifiziert

Summary of evidence

With regard to the comparative effectiveness of WCD therapy, no further RCT has been identified since the last conducted health technology assessment [1].

neue Beobachtungsstudien

The current available evidence consists of one RCT (n=2,348) and eleven observational studies (n=5,345). Low certainty evidence derived from one RCT (n=2,348) indicated that WCD therapy might not be associated with a clinical arrhythmic mortality benefit in post-myocardial infarction patients with an ejection fraction of ≤35%. The WCD appropriately shocked 1.3% wearing the WCD in the RCT. However, compliance was low in the RCT, with a mean daily wear-time of 14.0 hours. In the RCT, 0.6% of patients wearing the device received an inappropriate shock, and there were four serious adverse events (0.2%) potentially related to WCD use. WCD use was statistically associated with milder adverse events, such as rash and itching, occurring in 13% and 14.5% of patients in the WCD group [17, 31].

Evidenz: 1 RCT und 11 Beobachtungsstudien

unzureichende Evidenz für Zusatznutzen als Add-on oder Ersatz

All observational studies enrolled mixed, broad patient populations, and ten of these studies reported a daily wear-time of WCD use ranging from 20 to 23.5 hours [29, 30, 32-43]. The range of patients receiving one or more appropriate shocks was between 1% and 4.8% across nine studies [29, 30, 32-42]. Further, the first shock success was reported to be 100% in three studies [32, 33, 35-37]. Inappropriate shocks occurred in between 0% and 2% [29, 30, 32-43] of enrolled patients across ten observational studies (range of enrolled patients across studies: 102-2,000). One further study reported two patients (2%) who were allergic to nickel and 58 patients (57%) in whom false alarms occurred. Another registry (n=448) reported milder adverse events, such as dermatitis and pressure marks, occurring in 0.9% and 0.2% of enrolled patients, respectively [40].

Beobachtungsstudien: breites Patient*innenkollektiv

While the VEST trial [17, 31] was impacted by poor compliance, with a mean wear-time of 14 hours per day, evidence derived from real-world evidence indicates that daily wear-time is well above 20 hours per day and the Austrian registry [40] reported on a median daily wear time of 23.5 hours. New observational evidence [28, 33, 34, 38, 40-43] further confirms that the WCD may be a safe technology, although reporting on milder adverse events was sparse in the identified studies.

Compliance mit Defibrillator-Weste adäquat

Embedding our evidence into existing knowledge

Our findings complement and are primarily aligned with existing knowledge on the WCD: One recent independent systematic review and meta-analysis [16] using broader inclusion criteria, including 28 studies (27 observational studies and the VEST trial), found that the evidence from observational studies is fraught with poor methodology, selection bias, and confounding. Based on the VEST trial data [17], the review authors concluded that WCD was not

Einbettung in bestehendes Wissen: 1 SR und Meta-Analyse in 2019: unzureichende Evidenz

associated with a decreased risk of sudden cardiac death. Based on these findings, the authors noted that WCD therapy should not be used in primary prevention before RCT data justify its use [16].

adäquate WCD Therapierate in 3-monatigem Zeitraum: 1 in 100 Personen (RCT) 11 in 100 Personen (Beobachtungsstudien)

The same systematic review [16] further investigated the rate of appropriate WCD therapy by using a meta-regression, with an incidence of appropriate WCD therapy (as defined by appropriate shocks) of five per 100 persons over three months. The systematic review further found differences in WCD therapy incidence when comparing the VEST trial (1 per 100 persons over three months, 95% CI 1.0, 2.0) to observational studies (11 per 100 persons over three months, 95% CI 11.0, 20.0, I^2= 93%). The study authors noted that selection bias and the use of mixed patient populations enrolled in observational studies were deemed likely to be the major cause of the higher rate of appropriate treatment in patients receiving a WCD in observational studies as compared to the intervention group in VEST.

1 SR mit Interessenskonflikt in 2020: adäquate WCD Therapierate hervorgehoben, keine Schlüsse zu Zusatznutzen gezogen

Another systematic review published in 2020 [46] included one RCT (VEST trial), one retrospective observational study with a historical control group and forty-four uncontrolled observational studies. Similar to the aforementioned systematic review [16], this review found a high rate of appropriate shocks in mixed patient populations. Although industry-sponsored, the study authors [46] did not conclude on the comparative effectiveness of the WCD more broadly. Instead, it was noted that large registries confirm the device's safety and that the WCD detects and terminates VT/VF reliably.

WCD als Beispiel für Adoption VOR Evidenzgenerierung: Angst vor Rechtsstreitigkeiten?

The WCD is a historical example in which evidence-based decision-making falls short [16], with the WCD use increasing all over the world. An online report [47] showed that over 200,000 WCDs were prescribed until 2015, which was three years before the first RCT was published. Cardiologists who wrote one of the aforementioned systematic reviews [16] see this treatment pattern as likely to be "driven by the finality of SCD and partly by fear of litigation, despite the absence of data to support it".

klinische Evidenz vs. Performance-Daten in Zulassungsprozess

However, fear may only be one factor that led to the assumption-based adoption of this medical device in clinical practice. That is to say; there is no need for proof of clinical effectiveness or long-term safety to receive a CE mark in the European Union. Instead, evidence on the performance (purposes defined by the manufacturer) and safety are sufficient to receive a CE mark from notified bodies [48]. Although the new medical device regulation into force since May 2021 arguably intensifies the focus on clinical benefits of medical devices more broadly [49], the future will show whether this regulation fixes existing problems through strong and consistent support for implementation or whether the status quo is upheld [50].

Spin Bias der VEST-Resultate: Studie mit verfehltem Studienziel im Nachhinein positiv reinterpretiert

The VEST trial results may further be an example of what is sometimes referred to as spin bias [51]: The first publication in the New England Journal of Medicine (NEJM) of the VEST trial was adequately reflecting the results of the primary endpoint using the intention-to-treat (ITT) principle. In contrast, the results of the secondary endpoint (all-cause mortality) were well promoted in scientific meetings and the media, without mentioning that the RCT did not meet its primary endpoint [18, 52].

Per-Protokoll Effekt mit großer Unsicherheit behaftet

Further, the follow-up publication of this trial [31] specifically reporting on the as-treated and per-protocol analysis of the VEST trial appears to be positive with regard to the clinical utility of the device, which is in stark contrast to what has been concluded in the original NEJM-publication of the VEST trial [17]. The protective effect based on the per-protocol analysis [31] is based

on an extrapolation of person-months (on which wearable defibrillator was worn: 14 hours/ day) overriding the randomization of the trial. As per-protocol analysis is strongly inferior to the intention-to-treat (ITT) analysis, the results of the VEST study should, therefore, not be re-interpreted. In this study, the additional use of the wearable cardioverter defibrillator did not lead to a significantly lower rate of the primary outcome of arrhythmic death compared to pharmacological therapy alone in post myocardial infarction patients with impaired ejection fraction. The statistically significant reduction in all-cause mortality could also occurred due to chance, as suggested by the authors of the VEST study in the course of the first publication [17].

plausible (enge) Indikationen für WCD trotz fehlender Evidenz aus RCTs: z.B. um Patient*innen einen Spitalsaufenthalt ersparen zu können

However, the available (absence of) evidence to justify WCD therapy should not be confused with evidence for no effect in all indications. In fact, and although there is insufficient evidence to support widespread use of the WCD, there may be pragmatic and plausible reasons for using the WCD: in some specific clinical settings (e.g., explanted ICD due to infection), the alternative to a WCD therapy may be hospital observation which can be burdensome to patients and simultaneously impose high costs for the health care system. However, the clinical evidence (which is primarily based on observational studies and high uncertainty) should be made clear to both patients and clinicians in order to make an informed and shared decision [53]. It is suffice to say that compliance with WCD and clinical risk for mortality is to be assessed additionally within this clinical decision-making process [5, 54]. Decision-makers in the health sector must also be particularly careful that, once a niche indication has been approved, it is not deliberately expanded in the context of everyday clinical practice. Hence, the use of WCD should still be restricted to cardiological centres in Austria.

ist Nachweis der Nicht-Unterlegenheit ausreichend

It is noteworthy to mention that the evidence requirements also differ depending on the clinical setting and comparator. For instance, if WCD therapy is seen as part of a telemonitoring system [55], replacing hospital observation in specific clinical indications, proof of non-inferiority would arguably suffice as evidence to clearly show the additional benefit of the WCD. There are currently scientific efforts to establish broader telemedical concepts for heart failure patients that incorporate the WCD [56, 57].

Nutzung in vielen Indikationen weiterhin experimentell

The Blue Cross Blue Shield Association [58] in the United States concluded, based on clinical considerations and informed by an evidence review, that WCD therapy may be considered a necessary temporary measure before implantable cardioverter (re-)placement in patients for which ICD placement criteria are met and a temporary contraindication to receiving an ICD placement exists or an ICD was removed due to a concurrent infection or malfunction. In all other clinical scenarios, however, WCD therapy was considered investigational.

Limitations of the evidence

Limitationen der Evidenz: gemischte Patient*innenkollektive

The evidence derived from the observational studies we included is primarily based on broad indication areas or aetiologies, which makes it impossible to assess the indication-specific benefits of WCD. Another clear limitation with regard to the evaluation and interpretation of available data was that study populations are often heterogeneous not only in terms of aetiology but also in whether the WCD was used for primary or secondary prevention of sudden cardiac death. In clinical practice, for instance, there is little difference in the treatment of patients presenting with LVEF of 25%, regardless of whether it is ischemic or non-ischemic in origin. However, a significant difference is the

prior occurrence of an arrhythmic event [14]. Therefore, we believe that the quality of future studies evaluating WCD could be improved if not only aetiologies but also indications were stringently reported.

enge Indikationen ohne Evidenz aus RCTs

For some of the niche indications, it is improbable that randomised trials such as VEST can be conducted [59]. Yet, pragmatic randomised trials [60] may still be feasible in these cohorts of patients, even though slow enrolment does pose a problem regarding the completion of such trials. Well-designed prospective observational studies with concomitant control groups can further be used to shed more light on the additional benefit of WCD therapy in specific (niche) indications. Suffice it to say that evidence generation, following evidence-based medicine principles, needs to be prioritised in light of intensive marketing [19] and the increased risk of bias present in available observational studies.

Limitations of the report

Limitationen des Berichts: Einschluss von Beobachtunggsstudien in Ermangelung an randomisierter Kontrollstudien

The results of this report should be seen in light of its limitations. First, we have included observational studies to evaluate both safety and gain insights into real-world performance concerning, inter alia, compliance. Although such studies are generally more prone to internal validity concerns when compared to randomised controlled trials, we carefully selected the included observational studies in line with Cochrane methodology [61] to mitigate concerns. We further reported all data based on observational studies separately from RCT data and noted that causal inference based on these observational data is not possible.

Übersicht über Ätiologien als Sample der Gesamtevidenz (Fokus auf große, prospektive Studien)

Second, our depicted indications across observational studies are only a sample of indications from all clinical studies. In fact, some smaller/ retrospective case series studies reported solely on narrow indications. However, the risk that these studies would have changed the synthesis of observational studies is low. Some of these studies reported on peripartum cardiomyopathy [62], sarcoidosis [63], explanted ICD [64, 65], myocarditis [66], and tachymyopathy [29]. Although these studies would not have changed the picture regarding aetiologies within observational evidence, they may help in patient selection for future studies.

Merhfachpublikationen

Third, some of the publications refer to studies that used databases from ZOLL Medical®. Although most of these publications were clearly referable to the respective study, there may still be some overlapping data within the included studies if the authors did not adequately disclose the name or identifier of the study they reported on.

Ongoing studies

derzeit keine laufende Studien

The search for ongoing studies revealed that there are currently no ongoing comparative studies: the only other ongoing randomised controlled trial is likely to be terminated. The WCD in Haemodialysis Patients (WED-HED) study aimed to enrol up to 2,600 patients to test whether there is an additional benefit of using the WCD in end-stage renal disease patients beginning haemodialysis. The primary endpoint was defined as the number of participants experiencing sudden cardiac death mortality as assessed by ITT analysis, with a follow-up of six months. However, this study should have been completed in December 2016.

Conclusion

unzureichende Evidenz für Zusatznutzen, Compliance mit Defibrillator-Weste in Österreich adäquat

The only available RCT failed to show that an add-on use of the WCD leads to a reduction in sudden cardiac death in patients with a recent myocardial infarction and impaired ejection fraction when compared to medical therapy alone. Observational evidence shows that compliance with WCD is good in Austria, with poor compliance being a major limitation of the only available randomised evidence for WCD use.

keine Indikationsspezifischen Aussagen auf Basis der Beobachtungsstudien möglich

Most of the evidence is observational and consists of studies including mixed populations in the analysis, leading to the inability to draw firm conclusions on the indication-specific utility of the WCD. In the absence of comparative effectiveness evidence, more RCT data are needed to justify continuing or expanding the use of WCD therapy in Austria.

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A - 1: Wearable cardioverter defibrillator for primary or secondary prevention of sudden cardiac death: Results from randomised controlled trials

Study name	**Vest Prevention of Early Sudden Death Trial (VEST)**	
Author, year	**Olgin, 2018 (primary analysis) [17]**	**Olgin, 2020 (secondary analysis) [31]**
STUDY CHARACTERISTICS		
Study registration number	NCT01446965	
Countries of recruitment	USA., Poland, Germany, and Hungary[5]	
Sponsor	National Institutes of Health (NIH) / National Heart Lung and Blood Institute (NHLBI)[6] and Zoll Medical	
Comparator	Guideline-directed medical therapy	
Study design	Multicenter, randomized, controlled trial	
Methods	Randomisation: 2:1 fashion, Intention to treat analysis, further use of monitoring data of the LifeVEST	Secondary analysis: as-treated: event rates per person-month; sensitivity analysis based on a) effect-cause and b) confounding by propensity to adhere bias. Per-protocol analysis based on Kaplan Meier statistics[7] Subgroup analysis:
Study duration (start and completion date)	07/2008 - 04/2017	
Objectives	To determine the efficacy of a Wearable Cardioverter–Defibrillator during the period before ICDs are indicated in patients who have had a myocardial infarction and have a reduced ejection fraction.	To explore the impact of WCD compliance and hospitalizations on outcomes, including additional on-treatment analyses and effect modification analyses to determine factors that identify those most likely to benefit from the WCD.
PATIENTS CHARACTERISTICS		

[5] 76 sites in the United States, 24 in Poland, 6 in Germany, and 2 in Hungary

[6] NIH/NHLBI stopped funding the study.

[7] Kaplan-Meier plots for time from randomization to death or censoring for implantable cardioverter-defibrillator (ICD) implant, by treatment assignment, with follow-up and events censored in the WCD group at the last day the WCD was worn (defined as all subsequent days with 0 hours wear-time)

Study name	Vest Prevention of Early Sudden Death Trial (VEST)	
Author, year	**Olgin, 2018 (primary analysis) [17]**	**Olgin, 2020 (secondary analysis) [31]**
Number of pts	2,302[8] (1,524[9] device group and 778[10] control group).	
Age in yrs (range) ± SD	Device group, mean ± SD: 60.9 ± 12.6. Control group, mean ± SD: 61.4 ± 12.3.	
Sex (female/male)	Device group: 27%/73%. Control group: 25%/75%[11]	
EF in % (range) ± SD	Device group, mean ± SD: 28.2 ± 6.1. Control group: 28.2 ± 5.8.	
Inclusion criteria	Patients who had been hospitalized with an acute myocardial infarction and who had an ejection fraction of ≤35% were enrolled within 7 days after hospital discharge.	
Exclusion criteria	Patients were excluded if they had an ICD or unipolar pacemaker, had clinically significant valve disease, were undergoing long-term hemodialysis, or had a chest circumference that was too small or too large to accommodate the Wearable Cardioverter-Defibrillator. Patients were also excluded if they were pregnant or had been discharged to a nursing facility with an anticipated stay of more than 7 days.	
Follow-up time in months (range), mean ± SD	Mean ± SD: 84.3 ± 15.6 days.	
Loss to follow-up, n (%)	68 pts (2.9%)[12]	-
Diagnosis	Patients with acute myocardial infarction and who had an ejection fraction of ≤35%	-
Previous treatments	Previous CABG Device group: 133/1521 (8.7), Control group: 70/776 (9.0); Previous PCI Device group: 374/1520 (24.6), Control group: 202/776 (26.0).	-
OUTCOMES: CLINICAL EFFECTIVENESS		
Mortality, n (%) • **All-cause mortality**[13]	**Intention to Treat:** Device group: 48 (3.1); control group: 38 (4.9). Relative risk (RR): 0.64 (95% CI, 0.43–0.98); p=0.04.	**As-treated analysis:** 12 (2320 person months) vs. 71 (3724 person months); adjusted RR: 0.26 (p<0.005)[14] Per protocol analysis HR: 0.25 (95% CI, 0.13-0.48); p<0.001

[8] 2,348 patients were initially randomized. 46 participants at one U.S.A. site were excluded after randomization, owing to irregularities found by the institutional review board at that site; therefore, 2,302 participants were included in the analyses.

[9] 43/1524 (2.8%) patients in the device group never wore the WCD after randomization.

[10] 20/778 (2.6%) patients in the control group wore the WCD (2.6%) outside the protocol. Cross-overs were considered to be a protocol deviation.

[11] From the Table 1, 3 pts from the device group and 6 pts from the control group were missing in the male/female data.

[12] 46 (2%) from the U.S.A. site excluded; 10/1524 pts (0.7%) in the device group; 12/778 (1.5%) in the control group.

[13] All-cause mortality was a secondary outcome.

[14] Adjusted for diabetes and PCI, the only variables that remained after backwards stepwise variable deletion.

Study name	Vest Prevention of Early Sudden Death Trial (VEST)	
Author, year	Olgin, 2018 (primary analysis) [17]	Olgin, 2020 (secondary analysis) [31]
• **Disease-specific mortality**[15]	Device group: 25 (1.6); Control group: 19 (2.4). RR: 0.67 (95% CI, 0.37–1.21); p=0.18.	**As treated analysis:** 9 (2420 person months) vs. 32 (3724 person months); RR: 0.43 (p=0.026)[16] **Per-protocol analysis:** HR: 0.38 (95% CI, 0.17-0.86); p=0.02
Appropriate shocks **Withheld shocks**[19]	Device group: 20 (1.3%)[17]. Control group: 1 (0.1%)[18]. P=0.008 Device group: 69 (4.5%)[20]. Control group: 1 (0.1%)[21].	 -
First shock success (%)	NA	-
Health-Related Quality of Life (HRQL)	NA[22]	
Hospitalisation rate	Rehospitalisation by any cause, n (%): Device group: 475 (31.2), Control group: 253 (32.5). RR: 0.96 (95% CI, 0.85–1.09). P=0.51.	-
Satisfaction with technology	NA	-
Compliance/ patient adherence • **WCD wear-time in days (range), median** • **WCD daily use in hours (range), median**	NA[23] Device group[24], mean ± SD: 14.0 ± 9.3 [Median (IQR): 18.0 (3.8–22.7)]; Control group[25], mean ± SD: 0.4 ± 2.7 [Median (IQR): 0.0 (0.0–0.0)].	-

[15] Disease-specific mortality was the primary outcome.

[16] Adjusted for diabetes and PCI, the only variables that remained after backwards stepwise variable deletion.

[17] 13 pts had 1 shock; 7 pts had ≥ 2 shocks.

[18] This patient had ≥2 shocks.

[19] Due to patients using the response button to delay therapy.

[20] 1 shock 43 (2.8%), 2-5 shocks 11 (0.7%), ≥5 shocks 15 (1.0%).

[21] 1 shock (0.1%).

[22] Quality of life was a planned secondary outcome in the study protocol, but it was not reported in neither of the available publications of the VEST trial.

[23] Over the course of the 90 days, the proportion of participants who wore the WCD on a given day fell from 80.8% (CI: 78.8-82.8) just after randomization to 41.3% (CI 37.5, 44.9) at 90 days.

[24] 1481/1524 (97.2%) worn the device.

[25] 20/778 (2.6%) worn the device.

Study name	Vest Prevention of Early Sudden Death Trial (VEST)	
Author, year	Olgin, 2018 (primary analysis) [17]	Olgin, 2020 (secondary analysis) [31]
OUTCOMES: SAFETY		
AEs in n (%) of pts: • **Skin rash and itching** • **False alarms**	Rash on torso, n (%): Device group: 184 (13.0%), Control group: 27 (3.8%). RR: 3.42 (95% CI, 2.31-5.08), p<0.001[26]. Itch on torso, n (%): Device group: 205 (14.5%), Control group: 22 (3.1%). RR: 4.68 (95% CI, 3.04-7.20), p<0.001[27]. NA[28]	-
Frequency of discontinuation due to AEs in n (%) of pts: • **Discontinuation due to comfort and lifestyle issues**	NA	-
Frequency of unexpected AEs in n (%) of pts	NA	-
Hospitalisation related to WCD use	3/1524 (0.2%)[29]	-
Serious Adverse Events (SAEs), n (%) • **Inappropriate shocks** • **Unsuccessful shock**	9 (0.6%) [7 pts had 1 shock; 2 pts had ≥ 2 shocks] NA[30]	-
Frequency of SAEs leading to death in n (%) of pts	NA[31]	-
Effect modifiers		

[26] Rash in any location, n (%): Device group: 216 (15.3%), Control group: 50 (7.1%), p<0.001.

[27] Itch in any location, n (%): Device group: 243 (17.2%), Control group: 45 (6.4%), p<0.001.

[28] Among 41 participants with an alarm indicating asystole, 6 events (all in the device group) were adjudicated as having had a true asystole event.

[29] Two due to aborted shocks and one due to an inappropriate shock.

[30] The shock delivered sometime caused a cardioversion into complex and repeated other cardiac conduction problems which the WCD was not programmed to deal with.

[31] One patient died while he was wearing the device. The authors state that this death could be possibly related to the WCD use. The authors also state that it was deemed likely to not be an arrhythmic death.

Study name	Vest Prevention of Early Sudden Death Trial (VEST)	
Author, year	Olgin, 2018 (primary analysis) [17]	Olgin, 2020 (secondary analysis) [31]
Method of identifiying potential effect modifiers & Results	-	Backward stepwise deletion of potential predictors with P < .05 to select a parsimonious model No interaction was found. A trend for participants with a cardiac arrest (interaction P = .08), pulmonary edema (interaction P = .07), and Cr < 1.5 (interaction P = .06) toward lower mortality in the WCD group in the intention-to-treat analysis

Abbreviations: USA *– United States of America;* ***ICD(s)*** *– implantable cardioverter-defibrillator(s);* ***pt(s)*** *– patient(s);* ***yrs*** *– years;* ***SD*** *– standard deviation;* ***EF*** *– ejection fraction;* ***CABG*** *– coronary artery bypass graft;* ***PCI*** *– percutaneous coronary intervention;* ***NIH*** *– National Institute of Health;* ***RR*** *– relative risk;* ***CI*** *– confidence intervals;* ***VT*** *– ventricular tachycardia;* ***VF*** *– ventricular fibrillation;* ***NA*** *– not available;* ***HRQL*** *– Health-Related Quality of Life;* ***WCD*** *– Wearable Cardioverter-Defibrillator;* ***IQR*** *– interquartile range;* ***AEs*** *– adverse events;* ***SAEs*** *– serious adverse events.*

Table A - 2: Wearable cardioverter defibrillator for primary or secondary prevention of sudden cardiac death: Results from observational studies (Part 1)

First author, year	Röger 2018 [32]	Erath 2018 [29]	Erath 2017 [30]
Source	**AGENAS/ LBI-HTA Report [1]**		
Study name	NA	NA	NA
Study registration number	NA	NA	NA
Country/ies of recruitment	GER	GER	GER
Sponsor	NA	NA	NA
Intervention	WCD (+ SoC)	WCD (+ SoC)	WCD (+ SoC)
Comparator	None	None	None
Study design	Prospective case series	Prospective case series	Prospective case series
Study duration (start and completion date)	4/2012 - 9/2016	NA	2012-2015
Objectives	To determine the value of the WCD for therapy optimization of heart failure pts.	To evaluate the clinical development of tachymyopathy pts protected with a WCD in a single-center non-randomized pt cohort.	To evaluate the efficacy, safety, and compliance of/to WCD use and subsequent medium-term outcome of pts in a single-center.
Number of pts	114[32]	130[33]	102[34]
Age in yrs [mean (range) ± SD; median (IQR)]	All pts (n. 105): Median (IQR): 60 (26–79).	All pts, mean ± SD: 58 ± 16 • Cases: 62 ± 9 • Controls: 58 ± 16 (ns)	All pts, mean ± SD: 59 ± 11.
Sex: female / male	All pts: 22% / 78%	All pts: 22% / 78% • Cases: 20% / 80% • Controls: 22% / 78%	All pts: 28% / 72%.
EF in % [mean (range) ± SD; median (IQR)]	mean ± SD: 28.3 ± 9.8.	All pts, mean ± SD: 28 ± 11 • Cases: 26 ± 6 • Controls: 29 ± 12 (ns)	All pts, mean ± SD: 30 ± 11.

[32] 8 patients returned their WCD during the first hours after initiation because of unwillingness or inability to handle it; one more patient was lost to follow up, leaving 105 patients considered for data analysis. 43/105 patients had ICM.

[33] 20 pts in cases group, and 110 pts in control group.

[34] ICM patients: 27/102.

First author, year	Röger 2018 [32]	Erath 2018 [29]	Erath 2017 [30]
Source	**AGENAS/ LBI-HTA Report [1]**		
Inclusion criteria	All consecutive pts receiving a WCD at a tertiary care University Center	• Cases: consecutive pts with clinically suspect tachymyopathy and high risk of ventricular arrhythmias • Controls: consecutive pts with high risk of ventricular arrhythmias and another option for use of vests	Pts at high risk of VT/VF
Exclusion criteria	NA	NA	NA
Follow-up time in months [mean (range) ± SD; median (IQR)]	Mean ± SD: 18.6 ± 12.3	12 months of follow-up (1, 3 and 12 months)	Mean ± SD: 11 ± 8
Loss to follow-up, n (%)	9 (8)	0 (0)	0 (0)
Diagnosis	Newly diagnosed ICM, LVEF ≤ 35% (n=43); Newly diagnosed NICM, LVEF ≤ 35% (n=41); ICD explant (n=15); Newly diagnosed CMP (n=6).	Pts with symptomatic congestive HF with impaired LV function	Newly diagnosed HF
Previous treatments	Medications (betablocker, ACE-I/ARB, MRA, ARNI, procoralan, diuretic, amiodarone)	Medications (betablocker, amiodarone, ACE inhibitors/ARB, aldosterone antagonists, diuretics, statin, NOAC, VKA)	Medications (β-blocker, amiodarone)
Mortality, n (%) • **All-cause mortality** • **Disease-specific mortality**	 3 (3%) 0 (0)	 No deaths during the use of vest[35]. NA	 No deaths during the use of vest[36]. NA[37]
• **Appropriate shocks** • **Withheld shocks**[39]	5 (4.8%) NA	2 pt in the control group (2%) NA	4 pts (4%)[38] NA
First shock success (%)	100%	NA	NA
Health-Related Quality of Life	NA	NA	NA
Hospitalisation rate	NA	NA	13 pts hospitalised pts due to cardiac causes
Satisfaction with technology	NA	NA	NA

[35] Deaths after the use of the vest: All pts: 5 (4%)

[36] 6 (6 %) after the end of treatment with vest [of these, 2/27 (7%) were ICM pts]: 5 ICD and 1 not-ICD.

[37] Arrhythmic mortality after WCD therapy: 4 pts (4%)

[38] Patients were adequately shocked for ventricular fibrillation (seven episodes) or for ventricular tachycardia (one episode).

[39] Due to patients using the response button to delay therapy.

First author, year	Röger 2018 [32]	Erath 2018 [29]	Erath 2017 [30]
Source	**AGENAS/ LBI-HTA Report [1]**		
Compliance/ pt adherence • **WCD wear-time in days [mean (range) ± SD; median (IQR)]** • **WCD daily use in h/day [mean (range) ± SD; median (IQR)]**	mean ± SD: 68.8 ± 50.4 mean ± SD: 21.5 ± 3.5	All pts, median (IQR): 42 (1-166) All pts, mean: 23 h/day	median: 54 days (1-166) 23.0 h/day (7-24)
AEs in n (%) of pts: • **Skin rash and itching** • **False alarms**	NA NA	NA NA	2 pts (2%) are allergic to nickel 58 (57%)
Discontinuation due to comfort and lifestyle issues	8 pts (7%)[40]	NA	NA
Serious Adverse Events (SAEs), n (%) • **Inappropriate shocks** • **Unsuccessful shock**	1 (1%) (ICM pt) NA	2 in the control group (2%) NA	2 (2%) NA
Frequency of SAEs leading to death in n (%) of pts	NA	NA	NA

Abbreviations: AEs – *adverse events;* ***CABG –*** *coronary artery bypass graft;* ***CMP –*** *cardiomyopathy;* ***DCM –*** *dilated cardiomyopathy;* ***EF –*** *ejection fraction; FR – France;* ***GER –*** *Germany;* ***HF –*** *heart failure;* ***ICD –*** *implantable cardioverter-defibrillator;* ***ICM –*** *ischemic cardiomyopathy;* ***INSERM –*** *Institut national de la santé et de la recherche médicale;* ***IQR – i****nterquartile range;* ***LV –*** *left ventricular;* ***LVEF –*** *left ventricular ejection fraction;* ***MI –*** *myocardial infarction;* ***NA –*** *not available;* ***NICM –*** *non-ischemic cardiomyopathy;* ***Ns –*** *not significant;* ***NYHA –*** *New York Heart Association; OMT – optimal medical therapy;* ***PCI –*** *percutaneous coronary intervention;* ***pt(s) –*** *patient(s);* ***SCA –*** *sudden cardiac arrest;* ***SCD –*** *sudden cardiac death;* ***SD –*** *standard deviation;* ***SoC*** *– standard of care;* ***VA –*** *ventricular tachyarrhythmias;* ***VF –*** *ventricular fibrillation;* ***VS –*** *versus;* ***VT –*** *ventricular tachycardia;* ***WCD –*** *Wearable Cardioverter-Defibrillator;* ***yrs –*** *years.*

[40] They returned their WCD during the first hours after initiation because of unwillingness or inability to handle it.

Table A - 3: Wearable cardioverter defibrillator for primary or secondary prevention of sudden cardiac death: Results from observational studies (Part 2)

Study name or first author, year	WEARIT-II [35-39]	WEARIT-FR [42]	WEARIT-EU [41]	Odeneg, 2019 [40]	Rosenkaimer, 2020 [33]	Sinha, 2021 [34]	Weiss, 2019 [43]	Burch, 2021 [28]
Source	**EUnetHTA Report 2017 [2] and new publications**	**New Studies**						
Study name	WEARIT-II Registry[41]	WEARIT-FR	WEARIT-EU	AT-Registry	NA	NA	CRED[42]	HF-Opt[43]
Study registration number	NA	NCT03319160	NA	NA	NA	NA	NA	NCT03016754
Country/ies of recruitment	USA	FR	GER	AT	GER	GER	GER	USA and GER
Sponsor	ZOLL Medical Corporation	ZOLL + INSERM	ZOLL Medical Corp	Public academic funding	Public academic funding	ZOLL Medical Corp	ZOLL Medical Corp	ZOLL Medical Corp
Intervention	WCD (+ SoC)	WCD (+ SoC)	WCD (+ SoC)	WCD + interactive nurse-based training (+ SoC)	WCD (+ SoC)	WCD (+ SoC)	WCD (+ SoC)	WCD (+ SoC)
Comparator	None	None	None	None	None	None	SoC	None
Study design	Multi-centre, prospective register	Multi-centre, prospective register	Multi-centre, prospective register	Multi-centre, prospective register	Prospective registry study	Prospective register	Multi-centre, prospective register	Prospective sub study of a prospective cohort study
Study duration (start and completion date)	08/2011 – 02/2014	05/2014 – 12/2016 and 2017-2018	01/2014-09/2015	2010-2016	2012-2019	2012-2017	NA	2017-2022
Objectives	1. Characterise pts currently prescribed with WCD. 2. Assess the risk for sustained VT events among WCD pts by disease aetiology. 3. Identify the rate of EF improvement and the need for subsequent ICD implantation. Post-Hoc analyses: ■ Describe 1-year FU data	To evaluate contemporary real-world data on WCD use in France, not only in terms of effectiveness and safety but also compliance and acceptability.	To analyze the clinical outcome and mode of death after WCD prescription	To provide real-world data on patients receiving this therapy in a nurse-based wearable cardio-	To assess long-term all-cause mortality and 3-year survival of patients with or without ventricular tachyarrhythmias during WCD use and subsequent device implantation	To investigate WCD use in community-based acute care centers	To prospectively compare baseline characteristics and clinical outcome of patients with a WCD to those without a WCD in order to provide insight on	To examine the change in patient-reported outcomes in newly diagnosed patients with heart failure and reduced ejection fraction (HFrEF) prescribed a wearable cardioverter defibrillator

[41] One out of four publications related to this study was already available in the previous report.

[42] Cologne registry of external defibrillation

[43] Heart Failure Optimization Study

Study name or first author, year	WEARIT-II [35-39]	WEARIT-FR [42]	WEARIT-EU [41]	Odeneg, 2019 [40]	Rosenkaimer, 2020 [33]	Sinha, 2021 [34]	Weiss, 2019 [43]	Burch, 2021 [28]
Source	**EUnetHTA Report 2017 [2] and new publications**	**New Studies**						
	■ Analyse extended use (>90 days with WCD) and ■ describe age differences with regard to WCD use			verter-defibril-lator training programme.			decision criteria of physicians.	
Number of pts	2,000[44] Extended use in 1,019 pts	1,164	781	448	153	120	123 (85 vs. 38)	210
Age in yrs [mean (range) ± SD; median (IQR)]	All pts, median (IQR): 62 (16). ICM pts, median (IQR): 65 (14).	60 ± 12	59.3 ± 13.4	59 ± 14	60 ± 14	66 (56-75)	56 ±13 vs. 64 ±14; s. s. with p<0.05	58 (SD: 13.6)
Female sex, n (%)	All pts: 30% /70%. ICM pts: 23% / 77%.	183 (16)	182 (23.3)	107 (24)	35 (23)	25 (21)	18 (20) vs. 13 (34); diff. n. s. (p=0.18)	54 (25.7)
LVEF in % [mean (range) ± SD; median (IQR)]	All pts, median (IQR): 25 (10). ICM pts, median (IQR): 26 (15).	27 ± 9	26.9 ± 10.3 LVEF ≤ 35%: 700 (90)	33 ± 15	28.61 ± 10.15	26 (20-30)	26 ±8 vs. 25 ±7; diff. n. s. (p=0.73)	23 (SD: 6.9)
Inclusion criteria	Low EF and high risk of SCA post MI or post coronary revas-cularization or new onset nonischaemic DCM or high risk for SCA until stabilisation or in-herited or congenial heart dis-ease	Patients with a prescribed WCD according to the criteria for WCD prescription in FR	WCD pre-scription	All patients prescribed with a WCD	All patients receiving a WCD	Patients with car-diomyopathy LVEF ≤ 35%.	All patients re-ceiving a WCD	Adults hospitalized for new-onset heart failure, with ischemic or nonis-chemic cardiomyopathy, and prescribed a wearable cardioverter defibrillator within 10 days post dis-charge were approached for inclusion

[44] ICM pts: 805 (40%). NICM pts: 927 (46%). Congenital/Inherited pts: 268 (14%).

Study name or first author, year	WEARIT-II [35-39]	WEARIT-FR [42]	WEARIT-EU [41]	Odeneg, 2019 [40]	Rosenkaimer, 2020 [33]	Sinha, 2021 [34]	Weiss, 2019 [43]	Burch, 2021 [28]
Source	**EUnetHTA Report 2017 [2] and new publications**	**New Studies**						
Exclusion criteria	NA	NA	NA	NA	NA	NA	NA	patients with an active unipolar pacemaker, a first hospitalization for heart failure that occurred more than 30 days before enrollment, and patients with a psychological or physical condition that would inhibit interaction with the wearable defibrillator
Follow-up time in months [mean (range) ± SD; median (IQR)]	Original study: Median (IQR): 3.0 (2.1)[45] Post-hoc: Up to one year	NA	12 months	NA	36.2 ± 15.6	90 days (measure of central tendency: NA)	6 weeks	180 days
Loss to follow-up, n (%)	NA 1-year FU: 148 (7)	7 (0.6)	7 (9)	NA	4 (2.6)	NA	23 (18)	NA
Previous treatments	NA Beta-blockers: 1730 (87%) ACE-I/ARBs: 1482 (74%) Amiodarone: 259 (13%)	Beta-blockers: 1,038 (89%) Amiodarone: 189 (16%) ACE-I/ARBs: 1,004 (86%)	NA	NA	Former CIED explanted: 7 (5) History of CABG: 11 ±7	Beta blocker: 111 (92) ACE inhibitor: 96 (80) Diuretic: 103 (86) Digitalis: 2 (2)	No stat. significant diff. in previous treatment	β-Blockers: 198 (94.3) ACE-I/ARB: 152 (72.4) Aldosterone antagonists: 100 (47.6)
CLINICAL EFFECTIVENESS								
Mortality, n (%)								
All-cause mortality	3 (0.2)[46] 1-year FU: 70 (4%)	24 (2.1%)	40 (5.2)	4 (1)	4-year: 15 (1) During WCD use: 2 (1)	0 (0)	NA	NA
Disease-specific mortality	0 (0)	NA	NA	NA	NA	NA	NA	NA

[45] Patients were sent follow-up questionnaires at 1, 3, and 12 months.

[46] 2 patients (8.3%) had a fatal non-arrhythmic event within 3 months after MI

Study name or first author, year	WEARIT-II [35-39]	WEARIT-FR [42]	WEARIT-EU [41]	Odeneg, 2019 [40]	Rosenkaimer, 2020 [33]	Sinha, 2021 [34]	Weiss, 2019 [43]	Burch, 2021 [28]
Source	**EUnetHTA Report 2017 [2] and new publications**	**New Studies**						
Appropriate shocks	30 events/22 pts (1.1) 1-year FU: NA	19 events/ 18 pts (1.6%)	13 events/ 10 pts (1.3)	19 events / 9 pts (1%)	6 (4)	3 (2.5) pts [47]	NA	NA
Withheld shocks[48]	90 events/22 pts (1.1) 1-year FU: NA	NA	47 events/ 22 pts	NA	NA	NA	NA	NA
First shock success (%)	100% 1-year FU: NA	NA	NA	NA	100%	NA	NA	NA
Health-Related Quality of Life	NA	NA	NA	NA	NA	NA	**Association between WCD and baseline anxiety**: anxiety score: 41 ± 11 vs. 39 ± 13, p = 0.22), rate of anxiety: 58.9% vs. 29.2%, p = 0.02 Statistical **trend toward better improvement of depression scores in patients with WCD** (mean [SD] change in score points: -4.1 [6.1] vs -1.8 [3.9]; p =0.09), whereas change of the anxiousness score was not different (-4.6 [9.5]) vs -3.7 [9.1], p = 0.68).	All Kansas City Cardiomyopathy Questionnaire subscales (physical limitation, symptom frequency, quality of life, and social limitation) showed improvement from baseline to day 90 (all Ps < .001)

[47] All shocked patients survived at least 24 hours.

[48] Due to patients using the response button to delay therapy.

Study name or first author, year	WEARIT-II [35-39]	WEARIT-FR [42]	WEARIT-EU [41]	Odeneg, 2019 [40]	Rosenkaimer, 2020 [33]	Sinha, 2021 [34]	Weiss, 2019 [43]	Burch, 2021 [28]
Source	**EUnetHTA Report 2017 [2] and new publications**	**New Studies**						
Hospitalisation rate	NA	NA	NA	NA	102 (67)	NA	NA	NA
Satisfaction with technology	NA	NA[49]	NA	NA	NA	NA	NA	NA
Compliance/ pt adherence								
• **WCD wear-time in days [mean (range) ± SD; median (IQR)]**	Median (IQR): 90 (65) n. s. diff. between age groups 1-year FU: NA	62 (37–97)	75.0 ± 47.7	54 (1–436)	65.1 ± 42	48 (37-62)	59 (40–96)	NA
• **WCD daily use in h/day [mean (range) ± SD; median (IQR)]**	Median (IQR): 22.5 (2.7)[50] Slight s. s. diff. between age groups: ≥65 y. o.: 22.8 (21.5 -23.2) <65 y. o.: 22.3 (19.5 - 23.0) 1-year FU: NA	23.4 (22.2–23.8) younger age associated with lower compliance [odds ratio (OR) 0.97, 95% CI: 0.95–0.99; P< 0.01]	20.3 ± 4.6	23.5 (range: 1–24)	21.5 ± 3.5	22.9 (21.2-23.4)	20 (±5)	NA
AEs, n (%) of pts:	NA	NA	NA	NA	NA	NA	NA	NA
Device related AEs	NA	NA	NA	5 (1)	NA	NA	NA	NA
• **Skin rash and itching**	NA	NA	NA	Dermatitis: 4 pts Pressure mark: 1 pt	NA	NA	NA	NA
• **False alarms**	NA	NA	NA	NA	NA	NA	NA	NA
Discontinuation due to comfort and lifestyle issues	NA	NA	NA	NA	Not specified, discontinuation due to: Incompliance 12 (8) Other reasons 5 (3)	NA	NA	NA

[49] Self-defined 5-point likert scale questionnaire was used to evaluate acceptability. This data was not extracted in the absence of the use of a validated questionnaire.

[50] No significant difference in the daily use among the subgroups of ischemic, nonischemic, or congenital/inherited heart disease.

Study name or first author, year	WEARIT-II [35-39]	WEARIT-FR [42]	WEARIT-EU [41]	Odeneg, 2019 [40]	Rosenkaimer, 2020 [33]	Sinha, 2021 [34]	Weiss, 2019 [43]	Burch, 2021 [28]
Source	**EUnetHTA Report 2017 [2] and new publications**	**New Studies**						
Serious Adverse Events (SAEs), n (%)	NA	NA	NA	NA	NA	NA	NA	NA
• **Inappropriate shocks**	10 (0.5)[51] 1-year FU: NA	8 in 8 pts (0.7%)	2 in 2 pts (0.3%)	3 inappropriate shocks in 2 pts (0.4%)	1 (0.7)	0 (0)	0 (0)	NA
• **Unsuccessful shock**	0 (0)	0 (0)	NA	NA	0 (0)	NA	NA	NA
Frequency of SAEs leading to death in n (%) of pts	0 (0)	0 (0)	NA	0 (0)	NA	NA	NA	NA

Abbreviations: AEs – *adverse events;* ***CABG –*** *coronary artery bypass graft;* ***CMP –*** *cardiomyopathy;* ***DCM –*** *dilated cardiomyopathy;* ***EF –*** *ejection fraction; FR – France;* ***HF –*** *heart failure;* ***ICD –*** *implantable cardioverter-defibrillator;* ***ICM –*** *ischemic cardiomyopathy;* ***INSERM –*** *Institut national de la santé et de la recherche médicale;* ***IQR –*** ***i****nterquartile range;* ***LV –*** *left ventricular;* ***LVEF –*** *left ventricular ejection fraction;* ***MI –*** *myocardial infarction;* ***NA –*** *not available;* ***NICM –*** *non-ischemic cardiomyopathy;* ***Ns –*** *not significant;* ***NYHA –*** *New York Heart Association;* ***OMT*** *– optimal medical therapy;* ***PCI –*** *percutaneous coronary intervention;* ***pt(s) –*** *patient(s);* ***SCA –*** *sudden cardiac arrest;* ***SCD –*** *sudden cardiac death;* ***SD –*** *standard deviation;* ***SoC*** *– standard of care;* ***VA –*** *ventricular tachyarrhythmias;* ***VF –*** *ventricular fibrillation;* ***VS –*** *versus;* ***VT –*** *ventricular tachycardia;* ***WCD –*** *Wearable Cardioverter-Defibrillator;* ***yrs –*** *years.*

[51] Due to ECG artefacts. Inappropriate shocks did not induce VT or VF.

Risk of bias tables and GRADE evidence profile

Table A - 4: Risk of bias – randomised controlled trials comparing the wearable cardioverter defibrillator and standard care with standard care alone, see [24]

Trial	Bias arising from the randomisation proces	Bias due to deviations from intended intervention	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported results	Overall Bias	Comments
VEST [17, 31]	Low	High[52]	Low	Some concerns[53]	Some concern[54]	High	This bias judgement applies the results of intention to treat analysis For the per-protocol effect, the following further biases arise: high bias due to missing data[55] and further bias due to deviations from intended intervention[56]

[52] Although adequate methods were used (ITT), cross-over and low compliance in intervention group may have lead to bias with regard to deviations from intended interventions.

[53] Outcome assessors may have been aware of the intervention received

[54] Several secondary outcomes planned in the study protocol were not reported in the final study (incl. quality of life). This represents a source of bias more broadly.

[55] Since person months was used as the denominator for the as-treated analysis, the missing data rate was not estimable. However, at a mean wear time of 18.0 (3.8–22.7), missing data represents a significant source of bias.

[56] Per-protocol/ as-treated analysis represents an inadequate method to fully estimate the effect of assignment to intervention.

Table A - 5: Risk of bias of non–randomised controlled studies comparing the wearable cardioverter defibrillator and standard care with standard care alone, see [25]

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
Weiss, 2019 [43]	Serious[57]	Serious[58]	Moderate	Low	Critical[59]	Serious[60]	Low	**Critical**

[57] There is a potential for confounding. No analysis was used to adequately control for all important confounding domains (incl. time-varying confounding).

[58] No adjustment techniques were used to correct for the presence of selection bias.

[59] Missing data: 21%

[60] Outcome assessors were likely aware of intervention received.

Table A - 6: Risk of bias – study level (uncontrolled observational studies), see [26]

	Included in AGENAS/ LBI-HTA Report 2019 [1] or EUnetHTA Report 2017 [2]				Newly identified studies					
Study reference/ID	**Erath 2017 [30]**	**Erath 2018 [29]**	**WEARIT-II [35-39]**	**Röger 2018 [32]**	**WEARIT FR[42]**	**Odeneg, 2019 [40]**	**Rosenkaimer, 2020[33]**	**Sinha, 2021[34]**	**WEARIT-II-EU [41]**	**Burch, 2021 [28]**
Study objective										
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study design										
2. Was the study conducted prospectively?	Yes	Yes	Yes	Yes	Yes[61]	Yes	Yes	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	No	No	Yes	No	Yes	Yes	No	No	Yes	No
4. Were patients recruited consecutively?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study population										
5. Were the characteristics of the patients included in the study described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Partial	Partial	Partial	No	Yes	Yes	Yes	Yes	Yes	Yes
7. Did patients enter the study at a similar point in the disease?	No	No	No	No	No	No	No	No	No	No
Intervention and cointervention										
8. Was the intervention of interest clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were additional interventions (co- interventions) clearly described?68	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome measures										
10. Were relevant outcome measures established a priori?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[61] >100 pts prospectively enrolled

11. Were outcome assessors blinded to the intervention that patients received?	No	No	No	No	No	No	No	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes	Yes	Partial[62]	Yes	Yes	Yes	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Statistical Analysis										
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Results and Conclusions										
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16. Were losses to follow-up reported?	No	No	No	Yes	No	No	Yes	No	Yes	No
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes	Yes	Yes	Yes	Yes[63]	Yes	Yes	Yes	No
18. Were the adverse events reported?	Yes	No	Partial[72]	Partial[72]	Partial[64]	Yes	Partial	Partial	Partial	No
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Partial	Yes	Partial
Competing interests and sources of support										
20. Were both competing interests and sources of	Yes	Yes	Yes	Yes	Partial	Partial	Yes	Yes	Yes	No
Points	15.5	14.5	14.5	15.5	15.5	16.5	16.0	15.0	17.5	12.5
Overall Risk of Bias	**High**	**High**	**High**	**High**	**High**	**Moderate**	**Moderate**	**High**	**Moderate**	**High**

[62] For some secondary outcomes (e.g., acceptability), five point likert agreement response scale was used. It appears that this the questions were self-defined instead of using questions based on a validated tool to assess acceptance of therapy.

[63] Random variability was reported. However, for median values only the range (minimum-maximum) was reported that only partially describes the the exact distribution of data (e.g., interquartile ranges would have been useful).

[64] Adverse events were not sufficiently reported (e.g., low grade adverse events such as a rash etc. was not reported).

GRADE Evidence Profiles Table

Table A - 7: GRADE evidence profile: Effectiveness and safety of the wearable cardioverter defibrillator in patients at risk of sudden cardiac death

Certainty assessment						№ of analysed patients		Effect	Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WCD	No WCD			
Effectiveness (RCT evidence)										
Mortality										
1 RCT [17, 31]	serious [a]	not serious	not serious	serious [b]	none	1,524	778	Arrhythmic mortality: 25/ 1,524 (1.6%) vs. 19/ 778 (2.4%), p=0.18 All-cause mortality[c]: 48/1,524 (3.1%) vs. 38/778 (4.9%), p = 0.04	⊕⊕◯◯ LOW	CRITICAL
QoL										
-	-	-	-	-	-	-		-	-	
Hospitalisation										
1 RCT [17, 31]	serious[a]	not serious	not serious	not serious	none	1,524	778	31.2% vs. 32.5% (p-value = 0.5)	⊕⊕⊕◯ MODERATE	IMPORTANT
Compliance										
1 RCT [17, 31]	Not serious	not serious	not serious	not serious	None	1,524	778	Mean daily wear time, in days: 14 (SD: ± 9.3)	⊕⊕⊕⊕ High	IMPORTANT
Satisfaction										
-	-	-	-	-	-	-	-	-	-	-
Surrogate endpoints (appropriate shocks, shock success, withheld shocks)										
1 RCT [17, 31]	serious [a]	not serious	not serious	not serious	none	1,524	778	Appropriate shocks: 1.3% Shock success: NR Withheld shocks: 69/1524 (4.5%)	⊕⊕⊕◯ MODERATE	IMPORTANT
Effectiveness (observational evidence)										
Mortality										
9 PCS/ registries [29, 30, 32-42]	serious [d]	not serious	not serious	not serious	none	4,992	0	Arrhythmic mortality (2 studies): 0% All-cause mortality (9 studies): 0-5.2%	⊕◯◯◯ VERY LOW	CRITICAL
QoL										

Certainty assessment						№ of analysed patients		Effect	Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WCD	No WCD			
2 registries [28, 43]	serious[d]	not serious	not serious	not serious	none	286	24	statistical association between WCD and baseline anxiety (1 controlled study): 41 ± 11 vs. 39 ± 13 (p = 0.22; higher score indicates higher anxiety) *statistically significant improvements* in all Kansas City Cardiomyopathy Questionnaire subscales (1 before-after study; baseline to day 90)	⊕◯◯◯ VERY LOW	IMPORTANT
Hospitalisation										
2 PCS/ registries [30, 33]	serious[d]	not serious	not serious	not serious	none	255		13/102 (12.7%) in 1 prospective case series 102/153 (67%) in 1 registry	⊕◯◯◯ VERY LOW	IMPORTANT
Satisfaction										
0	-	-	-	-	-	-	-	-	-	-
Compliance										
10 PCS/ registries [29, 30, 32-43]	not serious	not serious	not serious	not serious	none	5,068	24	20-23.5 hrs per day	⊕⊕◯◯ LOW	IMPORTANT
Surrogate endpoints (appropriate shocks, shock success, withheld shocks)										
9 PCS/ registries[29, 30, 32-42]	not serious	not serious	not serious	not serious	none	4,992	0	N of pts with at least one appropriate shock: 1%-4.8% (range of enrolled patients across studies: 102-2,000) First shock success (3 studies): 100% Withheld shocks (2 studies): 90 events in 22 pts (1.1%) and 47 events in 22 pts (2.8%)	⊕⊕◯◯ LOW	IMPORTANT
SAFETY (RCT evidence)										
1 RCT [17, 31]	serious[a]	not serious	not serious	not serious	none	1,524	778	SAE: Inappropriate shocks: 9/1,524 (0.6%), SADE[65]: 4/1,524 (0.2%) AE: Rash on torso: 184 (13.0%) vs. 27 (3.8%), p<0.001 Itch on torso: 205 (14.5%) vs. 22 (3.1%), p<0.001	⊕⊕⊕◯ MODERATE	CRITICAL
SAFETY (observational evidence)										

[65] 3 WCD related hospitalisations, 1 death potentially related to WCD

Certainty assessment						№ of analysed patients		Effect	Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WCD	No WCD			
10 PCS/ registries [29, 30, 32-43]	not serious[d]	not serious	not serious	not serious	none	5,068	24	SAE: Inappropriate shocks: 0-2% AE (2 studies): 4/448 pts (0.9%) with dematitis, 1/448 pt (0.2%) with pressure mark in one study; 2 pts (2%) were allergic to nickel and 58 (57%) false alarms in another study	⊕⊕◯◯ LOW	CRITICAL

Abbreviations: AE – *adverse events****; CI –*** *Confidence interval;* ***WCD –*** *Wearable Cardioverter-Defibrillator;* ***OMT*** *– optimal medical therapy;* ***PCS*** *– prospective case series studies;* ***ICD*** *– implantable cardioverter defibrillator;* ***SAEs*** *– serious adverse events.*

Explanations

a. The RCT was judged to be at high risk of bias through the Cochrane Risk of Bias tool due to poor compliance (and selective outcome reporting) that could have influenced the comparative effect estimates for effectiveness outcomes and the estimated proportions of adverse events for safety outcomes.

b. In the study occurred few events leading to a wide CI around the estimate of the effect estimate.

c. The endpoint "death from any-cause" was set as a secondary outcome in the included RCT. In addition, the study did not statistically correct the analysis for multiple testing.

d. Selection bias may be the most significant source of bias in observational studies. In addition, reporting on milder AEs was sparse and patients did not enter the study at the same point of disease. Also mixed populations were included, being heterogeneous patient populations.

Applicability table

Table A - 8: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	Study population represented a diverse spectrum of patients at risk for SCA. The reason being that indications for LifeVest® are manifold (see scope) and risk factors for SCA are not well defined and might vary based on and within the respective indication. RCT evidence is applicable to post-MI patients with impaired ejection fraction. Highly mixed patient populations were enrolled within observational studies, signifcantly impacting on the applicability of the evidence to specific indications.
Intervention	The WCD was used autonomously by patients outside of the hospital in the RCT in addition to optimal medical therapy. In observational studies, the specifics of the intervention (e.g., primary prevention or secondary prevention; add-on use vs. potential replacement of hospital stay) were hardly reported.
Control	RCT evidence is applicable to patients receiving guideline directed medical therapy alone, representing the standard care of post-MI patients with impaired ejection fraction. Observational evidence consisted mainly of uncontrolled studies. One registry study with a control group investigating quality of life insufficiently reported on the specifics of standard care within the study, hindering an adequate applicability assessment in this context.
Outcomes	The RCT chose arrhythmic mortality as the primary endnpoint. No applicability concerns are hereby present, as this represents the most direct evidence for patient-relent effects. The observational studies emphasised mainly on endpoints such as appropriate shocks and other endpoints related to the functional performance of the device. It is to be noted that, although relevant, these may only be considered as surrogate endpoints for direct patient-relevant endpoints such as mortality. Further, some observational studies chose important endpoints with regard to the usability of the device such as compliance and quality of life. These were measured using a direct remote-monitoring system and validated instruments, respectively. Hence, no applicability concerns were identified.
Setting	Clinical settings were not described in any of the observational studies. However, it is likely that all patients received-standard care at university hospitals or cardiac units. Therefore, it can be assumed that the setting of the studies reflects the clinical setting in which the technology is intended to be used. It needs to be stated that patients are introduced to the technology in the hospital at the beginning and then the technology is used outside of the hospital, yet the patients are monitored throughout.

Informed by [2]. ***Abbreviations: SCA*** *– sudden cardiac arrest;* ***MI*** *– myocardial infarction;* ***RCT*** *– randomized controlled trial;* ***WCD*** *– wearable cardioverter defibrillator.*

List of ongoing studies

Table A - 9: List of ongoing randomised controlled trials of the WCD

Identifier/Trial name	Indication	Intervention	Comparison	Primary Outcomes	Type of Study	No of pts planned	Estimated study completion date	Sponsor
NCT02481206/WED-HED	Hemodialysis	WCD +SoC	SoC	Number of Participants Experiencing Sudden Cardiac Death (SCD) Mortality as Assessed by Intention-to-Treat Analysis [Time Frame: 6 months]	RCT	2,600	2017	Zoll Medical Corp.

Abbreviations: ***RCT*** *– randomised controlled trial;* ***SoC*** *– standard of care;* ***WCD*** *– wearable cardioverter defibrillator;* ***WED-HED*** *- wearable cardioverter defibrillator in hemodialysis patients.*

Literature search strategies

Search strategy for Cochrane

Search Name: LifeVest Update 2022

Last Saved: 28/04/2022 16:43:56

Comment: GG/BW

ID Search

#1 "life vest" (Word variations have been searched)

#2 lifevest* (Word variations have been searched)

#3 lifecor

#4 (wearable or portable) near (cardioverter* or defibrillator*) (Word variations have been searched)

#5 (defibrillat* NEAR (jacket* OR vest*))

#6 wcd:ti,ab,kw (Word variations have been searched)

#7 (wcds):ti,ab,kw

#8 zoll:ti,ab,kw (Word variations have been searched)

#9 (kestra) (Word variations have been searched)

#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 with Cochrane Library publication date Between Aug 2018 and Apr 2022

#12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 with Publication Year from 2018 to 2022, in Trials

#13 #11 OR #12

#14 (conference abstract):pt

#15 (abstract):so

#16 (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

#17 #14 OR #15 OR #16

#18 #13 NOT #17

21 Hits

Search strategy for Embase

Session Results

.....

No. Query Results Results Date

#16. #14 NOT #15 404 28 Apr 2022

#15. #14 AND 'Conference Abstract'/it 166 28 Apr 2022

#14. #13 AND ([english]/lim OR [german]/lim) 570 28 Apr 2022

#13. #12 AND [27-08-2018]/sd NOT [29-04-2022]/sd 574 28 Apr 2022
#12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR 1,340 28 Apr 2022
#9 OR #10 OR #11
#11. kestra 7 28 Apr 2022
#10. assure:dn 52 28 Apr 2022
#9. zoll:df 403 28 Apr 2022
#8. wcds:ab,ti 71 28 Apr 2022
#7. wcd:ab,ti 500 28 Apr 2022
#6. defibrillat* NEAR/2 (jacket* OR vest*) 29 28 Apr 2022
#5. (wearable OR portable) NEAR/2 (cardioverter* OR 659 28 Apr 2022
defibrillator*)
#4. 'wearable cardioverter defibrillator'/exp 125 28 Apr 2022
#3. lifecor 20 28 Apr 2022
#2. lifevest* 255 28 Apr 2022
#1. 'life vest*' 114 28 Apr 2022

Search strategy for Ovid Medline

Database: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to April 27, 2022>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2018 to April 27, 2022>
Search Strategy:
---
1 life vest*.mp. (57)
2 lifevest*.mp. (62)
3 lifecor.mp. (2)
4 ((wearable or portable) adj5 (cardioverter* or defibrillator*)).mp. (528)
5 (defibrillat* adj3 (jacket* or vest*)).mp. (25)
6 wcd.ti,ab. (384)
7 wcds.ti,ab. (77)
8 zoll.mp. (212)
9 kestra.mp. (2)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (908)
11 limit 10 to dt=20180827-20220428 (418)
12 limit 10 to ed=20180827-20220428 (396)
13 11 or 12 (517)
14 limit 13 to (english or german) (504)
15 remove duplicates from 14 (262)
****
28.04.2022

HTA Austria
Austrian Institute for
Health Technology Assessment
GesmbH