Tragbare Kardioverter Defibrillator Therapie zur Primär- und Sekundärprävention von plötzlichem Herzstillstand

Deutsche Zusammenfassung des EUnetHTA-Berichts

Ludwig Boltzmann Institut
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neue Therapie zur Prävention des plötzlichen Herzstillstands:

LifeVest® WCD 4000 seit 2011 CE-Kennzeichnung

Indikation: Überbrückung zu einer angemessenen Therapie

Der tragbare Kardioverter-Defibrillator (*wearable cardioverter defibrillator*/WCD) ist eine neue Therapie in der primären und sekundären Prävention des plötzlichen Herzstillstands (*sudden cardiac arrest*/SCA). Der WCD wird in Form einer „LifeVest" von der/dem Patientin/en für den Großteil des Tages, mit Ausnahme beim Duschen/Baden, getragen [1]. Derzeit ist nur ein WCD am Markt verfügbar: die LifeVest® der Firma ZOLL Medical Corporation, welche bereits in der fünften Geräte-Generation produziert wird. Das jüngste Modell, der WCD 4000, wurde 2011 in Europa mit der CE-Kennzeichnung zugelassen. Das Produkt erhielt bereits im Jahr 2001 eine FDA-Zulassung für Erwachsene und im Jahr 2015 auch eine für Kinder mit einem Risiko für SCA, die aufgrund bestimmter Erkrankungen oder fehlender Zustimmung der Eltern keine KandidatInnen für einen implantierbaren Kardioverter-Defibrillator (ICD) sind [2]. Der WCD soll einen vorübergehenden Schutz vor SCA in den Hochrisiko-Perioden zwischen der Diagnose oder Auftreten von ventrikulärer Tachykardie (VT) oder ventrikulärer Fibrillation (VF) und einer angemessenen Behandlung (oder deren Optimierung) bieten.

zwei Komponenten:

Elektrodengürtel + Weste,

Monitor an Taille oder Schultergurt

Der WCD besteht aus zwei Hauptkomponenten:

1. einem Elektrodengürtel und einer Weste, welche die Brust der/des Patientin/en umgeben und
2. einem Monitor, welchen der/die PatientIn an der Taille oder an einem Schultergurt trägt. Der Monitor ist am Elektrodengurt angeschlossen und stellt digitalisierte EKG-Daten zur Verfügung, welche dann auf dem LifeVest® Network beobachtet werden können [3].

Behandlungsschocks bei ventrikulären Tachykardien (VT) und Kammerflimmern (VF)

programmierbar

Der WCD überwacht kontinuierlich das Herz des/der Patienten/in und gibt – wenn ein lebensbedrohlicher Herzrhythmus wie eine VT der VF erkannt wird – einen automatischen Behandlungsschock ab. Vor jedem Behandlungsschock wird ein Alarm ausgelöst, der von dem/der PatientIn durch Drücken von zwei Antworttasten, die sich am tragbaren Monitor befinden, verhindert oder zurückgehalten werden kann. Der WCD kann auf verschiedene VT- oder VF-Zonen programmiert und auf unterschiedliche Zeit und Schock-Energien (zwischen 75 und 150 Joules, biphasisch) eingestellt werden [4]. Ein Einzelschockereignis dauert in der Regel weniger als eine Minute.

in Europa, USA, Australien, Kanada Israel, Japan, Singapur, China zugelassen

Erstattung in Frankreich, Luxemburg, Schweiz; Hochrechnung für Österreich: ca. 160

Das LifeVest® System ist für PatientInnen älter als 18 Jahre indiziert, die ein Risiko für SCA haben und keine KandidatInnen für einen implantierbaren Kardioverter-Defibrillator (ICD) sind, oder diesen ablehnen [3]. Der WCD ist derzeit für den Einsatz in Europa, den Vereinigten Staaten von Amerika, Australien, Israel, Japan und Singapur zugelassen. Weiters ist der WCD in Kanada und China zugelassen, dort aber noch nicht eingeführt. Der WCD wird für bestimmte Indikationen in Frankreich, Luxemburg und der Schweiz vollständig rückerstattet. Die erwarteten jährlichen Anwendungen des WCD, basierend auf den aktuellen US-Daten, betragen 160 Verordnungen pro Jahr in Österreich, wenn die gleiche Verordnungspraxis wie in den USA angenommen wird.

2 Gesundheitsbedrohung plötzlicher Herzstillstand

SCAs treten ohne Vorwarnung auf

und führen unbehandelt zum Tod

Lebensbedrohende Herzrhythmusstörungen (VT/VF) sind für die Mehrheit der SCAs verantwortlich: Diese schnellen Herzrhythmen entstehen in den unteren (Pump-)Kammern des Herzens, den Ventrikeln. Während VT ein schneller, aber regelmäßiger Herzrhythmus ist, ist VF unregelmäßig und unsynchronisiert. Bei VF hört das Herz auf, Blut zu pumpen, was zum SCA und weiters naturgemäß zum Tod führt, wobei ein Überleben mit guter neurologischer Funktion bei einer kleinen Gruppe der PatientInnen möglich ist [3]. SCAs treten ohne Vorwarnung auf, und da die PatientInnen innerhalb von Sekunden das Bewusstsein verlieren, können diese nicht um Hilfe rufen. Weitere Ursachen von SCA sind langsame Herzfrequenz (Bradykardie), keine elektrische Herzaktivität (Asystolie) oder elektromechanische Dissoziation bei post-akutem Herzinfarkt (MI).

Risikofaktoren in jüngeren und älteren Menschen unterschiedlich

Screening bei Angehörigen von SCA Betroffenen

Risikofaktoren, die mit SCA assoziiert sind, unterscheiden sich in jungen und älteren Menschen. Bei jungen Menschen überwiegen Myokarditis, Drogenmissbrauch, Kanalopathien und Kardiomyopathien als Risikofaktoren; chronisch degenerative Erkrankungen (koronare Herzerkrankung, Herzklappenerkrankungen und Herzversagen) sind dagegen Risikofaktoren in älteren Menschen [5]. Eine Dysfunktion des linken Ventrikels ist ein wichtiger Bestimmungsfaktor für das Risiko von SCA, wobei die Familiengeschichte, Diabetes Mellitus, Übergewicht und ein Herzfrequenz-Profil während des Trainings die SCA-Bestimmungsfaktoren vielfältig und multifaktoriell machen [6]. Spezifische Risikofaktoren für VT/VF, welche SCA verursachen, werden von den jeweiligen Indikationen bestimmt. Landesweite Screenings für das Risiko von SCA sind selten, aber das Screening von Familien von SCA Betroffenen ist wichtig. In Europa kommt es etwa zu 350.000 SCAs pro Jahr, welche außerhalb des Krankenhauses auftreten [7]. In Österreich sterben rund 15.000 Menschen pro Jahr an plötzlichem Herztod [8].

Österreich: 15.000 Menschen plötzlicher Herztod p.a.

Behandlungsalternativen

4 Standard-Behandlungen

Abhängig von der Indikation kommen vier Arten von Standardbehandlungen bei ventrikulären Arrhythmien (VA) und zur Verhinderung von SCA zum Einsatz [5, 9]:

ICD

- ICDs haben die Befähigung, die meisten Arrhythmien zu korrigieren und Schrittmacherfunktion auszuüben. Die Akkulaufzeit von ICDs beträgt sechs bis zehn Jahre, und ICDs können transvenös oder subkutan implantiert werden [10].

pharmakologische Therapie

- (Guideline-basierte) Pharmakologische Therapien (antiarrhythmische Medikamente) zum Management von VAs sind a) Antiarrhythmika, b) Elektrolyte, oder c) andere Medikamente, die das Reverse-Remodeling verbessern und/oder welche zur Verringerung der Häufigkeit koronarer thrombotischer Verschlüsse beitragen [5].

RFA

- (Guideline-basierte) Katheter-(Radiofrequenz)Ablation ist ein Verfahren, das eine Reihe von dünnen und flexiblen Kathetern (Drähten) umfasst, welche über den Hals, die Leiste oder den Arm in ein Blutgefäß zum Herzen des/der Patienten/in geführt werden. Die Katheter führen Wärmeenergie, welche jene Bereiche des Herzens zerstören, wo abnorme Herzschläge Arrhythmien verursachen [5].

- Automatisierte externe Defibrillatoren (AEDs) können sowohl zu Hause, als auch an öffentlichen Orten und/oder von medizinischem Notfallpersonal bei der Reanimation benutzt werden [5].

AED

3 Methoden

Ziel und Forschungsfrage

Das Ziel des vorliegenden Berichts ist, die Evidenz über die Wirksamkeit und Sicherheit von WCD in der Primär- und Sekundärprävention von SCA bei Erwachsenen über 18 Jahren (gemäß CE-Kennzeichnung) und pädiatrischen PatientInnen (außerhalb der CE-Kennzeichnung) zusammenzufassen. Spezifische Indikationen sind im Scope des englischsprachigen Berichts zu finden.

systematische Literatursuche, Handsuche, Scopus Suche

Dossier vom Hersteller, Suche in Studienregistern und nach klinischen Leitlinien

Die Evidenzsynthese wurde im Rahmen eines „Collaborative Assessments“ im Projekt EUnetHTA durchgeführt: Die Auswahl der „Assessment Elements“ für diesen Bericht basierte auf der EUnetHTA Core Model® Applikation für „Rapid Relative Effectiveness Assessments (REA) (4.2)“ [11]. Eine systematische Literatursuche erfolgte am 14. Juli 2016 in den Datenbanken Medline über Ovid, Embase, Cochrane Library und CRD (DARE, NHS-EED, HTA). Zum Zeitpunkt der systematischen Literatursuche wurde keine Einschränkung bezüglich Studiendesign angewandt. Darüber hinaus wurde eine Handsuche nach Literatur (Web-Suche) durchgeführt. Die systematische Literatursuche wurde des Weiteren durch eine „Scopus-Suche“ ergänzt. Zusätzlich wurde der Hersteller (ZOLL Medical Corporation) kontaktiert und gebeten, ein Dossier einzureichen. Klinische Studienregister (ClinicalTrials.gov und die International Clinical Trials Registry Platform (ICTRP)) wurden durchsucht, um laufende klinische Studien oder Beobachtungsstudien zu identifizieren. Zusätzlich wurde eine Guideline-Suche (G-I-N, National Guidelines Clearinghouse, TRIP-Datenbank und Handsuche) durchgeführt.

Qualitätsbeurteilung

Zur Beurteilung der Qualität der Fallserien wurde ein dafür entwickeltes Qualitätsbeurteilungsinstrument für prospektive Studien ohne Kontrollgruppe verwendet [12]; die Bewertung der Evidenz erfolgte mittels „Grading of Recommendations, Assessment, Development and Evaluation” (GRADE) [13].

unabhängige Begutachtung der Abstracts und Volltexte von 2 AutorInnen

Alle Arbeitsschritte wurden von zwei AutorInnen (des LBI-HTA) unabhängig voneinander durchgeführt und von den Ko-Autorinnen überprüft: Durchsicht der Abstracts gemäß des Scopes dieses Berichts und den vordefinierten Ein- und Ausschlusskriterien; Durchsicht der ausgewählten Volltexte für die Bereiche Wirksamkeit und Sicherheit; Kontrolle der Extraktionstabellen; Bewertung der Qualität der eingeschlossenen Studien sowie die Bewertung der Evidenz nach GRADE [13]. Eventuelle Meinungsverschiedenheiten wurden durch Diskussion gelöst.

Ethik, organisatorische, soziale und legistische Aspekte

Handsuche

Für die Bereiche Beschreibung der Technologie und des Gesundheitsproblems wurde relevante Literatur aus der systematischen Literatursuche und des Dossiers verwendet, gefolgt von einer Handsuche. Für die Bereiche Ethik, organisatorische, soziale und legistische Aspekte wurde einschlägige Literatur aus der systematischen Literatursuche herangezogen, gefolgt von einer Handsuche. Für diese Informationen wurde kein Qualitätssicherungsinstrument verwendet; es wurden jedoch mehrere Quellen herangezogen, um einzelne, möglicherweise voreingenommene, Quellen zu validieren.

Patientenbeteiligung: Fokusgruppe und qualitative Auswertung

Transkription, Framework-Analyse, Clustering von Endpunkten

Zusätzlich wurde eine semi-strukturierte Fokusgruppendiskussion mit Patienten – potentiellen Kandidaten für den WCD – geführt: Ziel der Fokusgruppe war, PatientInnen im Scoping zu beteiligen, um mögliche, vernachlässigte Endpunkte zu identifizieren und um die Möglichkeit der Verwendung des WCD zu evaluieren. Weiters zielte die Patientenbeteiligung auf die Beantwortung von Fragen zu ethischen, organisatorischen, sozialen und legistischen Aspekten ab. Die Fokusgruppe (in deutscher Sprache) wurde von einer Expertin für Patientenbeteiligung moderiert. Die Aufzeichnungen wurden (nach Zustimmung der Teilnehmer) transkribiert, anonymisiert und mittels einer Framework- Analyse analysiert [14]. Die Extraktion patientenrelevanter Endpunkte (Clustering/Charting) erfolgte durch eine Autorin und wurde von einer zweiten Autorin überprüft. Laut dem österreichischen Ethik-Komitee war kein Ethikantrag erforderlich.

4 Ergebnisse

Verfügbare Evidenz, Komparatoren, Endpunkte

Wirksamkeit: keine RCTs und nicht-randomisierte CTs identifiziert

Sicherheit: 1 einarmige Studie 2 Fallserien 2 Registerstudien

Keine Studie erfüllte die Studieneinschlusskriterien für die Beurteilung der klinischen Wirksamkeit des WCD: nur kontrollierte Vergleichsstudien (RCTs und nicht-randomisierte CTs) wurden für den Einschluss in Betracht gezogen. In der systematischen Literatursuche konnten keine kontrollierten Vergleichsstudien identifiziert werden. Die Studieneinschlusskriterien für die Bewertung der Sicherheit erlaubten neben kontrollierten Vergleichsstudien auch das Heranziehen prospektiver Studien ohne Kontrollgruppe (interventionelle einarmige Studien, Fallreihen und Registerstudien). Die systematische Literatursuche identifizierte eine prospektive interventionelle einarmige Studie [15], zwei prospektive Fallreihen [16, 17] und zwei prospektive Registerstudien [18, 19], die den Studieneinschlusskriterien entsprachen.

qualitative Studien für organisatorische, ethische, soziale und legistische Aspekte

Es wurde keine Mindestanzahl an PatientInnen innerhalb einer Studie als Einschlusskriterium für die Beurteilung der klinischen Wirksamkeit oder Sicherheit verwendet. Einzelfallberichte wurden jedoch ausgeschlossen. Zusätzlich wurden – laut dem EUnetHTA Core Model® 3.0 [20] – qualitative Studien für ethische, organisatorische, soziale und legistische Bereiche eingeschlossen.

Auswahl der Komparatoren: aus klinischen Leitlinien zum Management von RisikopatientInnen

Die Komparatoren wurden auf Basis von Informationen aus relevanten veröffentlichten klinischen Leitlinien zum Management des Risikos von SCA [5] und gemäß der EUnetHTA Leitlinien [21] ausgewählt. Sie umfassen ICD, Guideline-basierte pharmakologische Therapie, Radiofrequenz (Katheter) Ablation und an öffentlichen Orten angebrachte externe Defibrillatoren (AED).

Wirksamkeit: primärer Endpunkt: Mortalität sekundäre Endpunkte: (un-)angemessene Schocks etc.

Zur Beurteilung der klinischen Wirksamkeit wurden Mortalität (all-cause) und krankheits-spezifische Mortalität als primäre Endpunkte gewählt. Als sekundäre Endpunkte wurden Inzidenz von VT oder VF, angemessene Schocks, zurückgehaltene Schocks, die Vermeidung von ICD-Implantation, gesundheitsbezogene Lebensqualität (HRQoL), Hospitalisierungsrate, Zufriedenheit mit der Technologie und Compliance verwendet.

Zur Beurteilung der Sicherheit wurden unerwünschte Ereignisse (AE) wie Hautausschlag und Juckreiz, Fehlalarme, Herzklopfen, Benommenheit, Ohnmacht, und Abbruch wegen Komfort- und Lifestyle-bezogener Beeinträchtigungen ausgewählt. Als schwerwiegende unerwünschte Ereignisse (SAE) wurden unangemessene und nicht erfolgreiche Schocks definiert.

Sicherheit: unerwünschte und schwerwiegende unerwünschte Ereignisse

Klinische Wirksamkeit

Keine Studie erfüllte die Studieneinschlusskriterien für die Beurteilung der klinischen Wirksamkeit des WCD.

keine Evidenz aus vergleichenden Studien

Sicherheit

Es wurde keine Evidenz gefunden, um die Forschungsfrage hinsichtlich des Vergleichs des WCD mit Komparatoren zu beantworten. Die folgenden AEs wurden in den einarmigen Studien angegeben: Hautausschlag und Juckreiz (6 % der PatientInnen) [15], falsche Alarme (14 % der Patientinnen) [16], Herzklopfen, Benommenheit und Ohnmacht (9 % der PatientInnen) [18] und Abbruch wegen Komfort- und Lifestyle-bezogener Beeinträchtigungen (16-22 % der PatientInnen) [15, 18]. Zwei Studien gaben an, dass 2 % [15] bzw. 0,5 % [19] der PatientInnen unangemessene Schocks (definiert als „nicht-VT/VF" – klassifizierte Episoden, die dennoch durch einen WCD-Schock behandelt wurden [19]) erfahren hatten, während die verbleibenden drei Studien keine unangemessenen Schocks berichteten. Eine Studie zeigte, dass 0,7 % der PatientInnen [15] erfolglose Schocks aufgrund fehlerhafter Platzierung der Therapie-Elektroden erlebt hatten. Drei Studien berichteten über keine erfolglosen Schocks [16, 17, 19] und eine Studie machte keine Angaben zu diesem Endpunkt. Alle fünf Studien berichteten über die Häufigkeit der SAEs, welche zum Tod führten, wobei diese in einer Studie auftraten (0,3 %) [15] (siehe Tabelle 1).

5 prospektive Studien ohne Kontrollgruppe

SAE:
in 2 Studien: 0,5-2 % unangemessene Schocks
1 Studie: erfolglose Schocks

Tod aufgrund von SAE:
1 Studie: 0,3 %

Laufende Studien

Derzeit laufen zwei RCTs, von denen erwartet wird, dass sie robuste klinische Daten liefern. Beide RCTs verwenden eine Standardbehandlung als Komparator. Eine Studie soll im Dezember 2017 (2.300 PatientInnen mit ventrikulärer Dysfunktion unmittelbar nach MI) und die andere im Oktober 2019 (2.600 PatientInnen im Endstadium einer Nierenkrankheit, die mit Hämodialyse beginnen) abgeschlossen werden.

2 laufende RCTs
Abschluss:
Dez 2017
Okt 2019

Tabelle 1: Summary table of benefits and harms of WCD therapy for prevention of SCA

	Health benefit**							Harm	
	Mortality	Incidence of VT/VF	Avoidance of ICD implantation	(Health-Related) QoL	Hospitalisation rate	Satisfaction	Compliance	SAEs	AEs
WCD	*No evidence available*	*No evidence available*	*No evidence available*	*No evidence available*	*No evidence available*	*No evidence available*	*No evidence available*	***Inappropriate shocks:*** 2 % of patients [15] and 0.5 % of patients [19], 0 % of patients [16-18] ***Unsuccessful shocks:*** 0.7 % of patients [15], 0 % of patients [16, 17, 19] ***Frequency of SAEs leading to death:*** 0.3 % of patients [15], 0 % of patients [16-19]	***Skin rash and itching***: 6 % of patients [15] ***False alarms***: 14 % of patients [16] ***Palpitations, lightheadedness and fainting***: 9 % of patients [18] ***Discontinuation of WCD use due to comfort and lifestyle issues***: 22 % of patients [15] and in 16 % of patients [18]
Quality of body of evidence+								*Very low*	*Very low*

Abbreviations: *AE-adverse event; ICD-implantable Cardioverter Defibrillator; QoL-quality of life; SEA-serious adverse event; VT-Ventricular Tachycardia; VF-Ventricular Fibrillation.*

+ Quality of body of evidence according to GRADE-methodology was classified as follows: high (i.e. „Further research is very unlikely to change our confidence in the estimate of effect"); moderate (i.e. „Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate"); low (i.e. „Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate"); very low (i.e. „Any estimate of effect is very uncertain").

*** Further information can be found in the discussion of clinical effectiveness domain*

5 Diskussion

Wirksamkeit bez. Mortalität: keine Aussage möglich

in Beobachtungsstudien: Verbesserung der LVEF

Da derzeit keine vergleichenden Studien vorliegen, kann keine Aussage zur Wirksamkeit gegenüber einer Standardtherapie hinsichtlich der Endpunkte Gesamtmortalität und/oder krankheitsbezogene Mortalität getroffen werden. Aber auch die Ergebnisse der prospektiven Beobachtungsstudien lassen aufgrund der niedrigen Fallzahl in drei der fünf Studien [16-18], aufgrund des Fehlens jeglicher Komparatoren und aufgrund der Vielfalt der Indikationen der eingeschlossenen Patientengruppen in allen fünf Studien keine Aussagen zu. In Abwesenheit von Informationen über die Langzeitmortalität (>1 Jahr) der in den Studien eingeschlossenen PatientInnen ist die beobachtete Verbesserung der linksventrikulären Ejektionsfraktion (LVEF) (d. h. Verbesserung um 5-22,5 % Mittelwert/Median) [16-18] in Frage zu stellen, da sich diese im Laufe der Zeit ändern kann.

keine Information über historische Kontrollen zu SCA in verschiedenen Indikationsgruppen

in Beobachtungstudien fehlen viele relevante Informationen

Darüber hinaus gab es in keiner der fünf Studien Informationen über historische Kontrollen von SCA in den verschiedenen Patientengruppen, womit ein Vergleich zur potentiellen Vermeidung von SCA angestellt werden hätte können. Der WCD zeigte einen geringen Einfluss auf die Behandlung von SCA, weniger als 2 % der PatientInnen hatten angemessene Schocks [22]. Nur eine von fünf Studien zeigte die Vermeidung von ICD-Implantation bei PatientInnen, welche eine Indikation für einen ICD vor der WCD-Anwendung hatten [19]. Bei den vorliegenden Registerstudien fehlten einige wichtige Informationen, wie das verwendete Gerätemodell, die Einstellungen des Monitors, wie oft die Antworttaste gedrückt wurde, die Anzahl der falschen Alarme, mögliche Geräte-Interaktionen, Informationen darüber, ob ein ICD zu Beginn der WCD-Anwendung indiziert war und möglicherweise vermieden wurde, sowie Informationen über die Schwere der Erkrankung bei Studieneinschluss (wie weit fortgeschritten die Krankheit war). Daten über HRQoL und Zufriedenheit mit der Technologie wurden großteils nicht mit standardisierten Methoden erhoben.

Sicherheit: Mangel an Berichterstattung über AEs und SAEs

Ergebnisse: erfolglose, unangemessene Schocks

heterogene Ergebnisse zu angemessenen Schocks

Im Hinblick auf die Sicherheit der LifeVest® ist der Mangel an Berichterstattung zu AEs und SAEs in den eingeschlossenen Studien zu diskutieren. Die berichteten AEs und SAEs waren möglicherweise nicht vollständig. Die Vermeidung von ICDs könnte für die Zahler relevanter sein als für PatientInnen – dies zeigten die Ergebnisse der Fokusgruppe, wo Patienten ICDs bevorzugt hätten. Die Ergebnisse in Bezug auf erfolglose Schocks (bei 0-0,7 % der PatientInnen), unangemessene Schocks (bei 0-2 % der PatientInnen) sowie die Häufigkeit von SAEs als Todesursache (bei 0-0,3 % der PatientInnen) waren homogen. Im Gegensatz dazu waren die Ergebnisse bezüglich angemessener Schocks (1,1 %-43 % der PatientInnen) heterogen. Dies zeigt, dass eine Risikostratifizierung von PatientInnen von hoher Relevanz ist. Weitere Sicherheitsaspekte, die berücksichtigt werden müssen, waren das (unerwünschte) Einschreiten von BeobachterInnen und das Entstehen von Signalstörungen durch fallende und sich verdrehende Körper, welche dann zu nichterfolgreiche Schocks führen [23].

2 laufende RCTs werden Aussagen zur Wirksamkeit möglich machen

Prospektive Studien mit hoher Fallzahl und mit gut definierten Indikationsgruppen sind notwendig, um jene Patientengruppe zu bestimmen, welche von der Intervention profitieren würde. Zwei laufende Studien, die Ende 2017 resp. 2019 Ergebnisse vorlegen, werden neue Erkenntnisse bringen und gegebenenfalls Aussagen zur Wirksamkeit machen können.

mögliche Probleme: Passform des WCD, keine Schrittmacherfunktion des WCD

In den vorliegenden Studien wird weiters über die Passform der LifeVest® diskutiert, da bei einigen PatientInnen aufgrund des Körperbaus Probleme auftreten könnten [22]. Der maximale Brustumfang für PatientInnen, die den WCD tragen können, beträgt 144 cm, das Mindestgewicht 18,6 kg und der Mindest-Brustumfang 66 cm [1]. Darüber hinaus hat der WCD keine Schrittmacherfunktion für eine Backup-Bradykardie-Stimulation oder für eine Anti-Tachykardie-Overdrive-Stimulation [4, 23]. Der WCD zeigte auch eine mögliche Unverträglichkeit mit unipolaren Stimulationstechniken [24], und hinsichtlich des Wirkungsunterschiedes zwischen mono- und biphasischer Wellenform scheint es keinen Unterschied in der Effektivität zu geben [25].

Unklarheiten: SCA-Prävalenz, Arten von Arrhythmien, die zu SCA führen

Risikostratifizierung notwendig!

Die breite CE-Kennzeichnung, die keine konkreten Indikationen vorgibt, ist problematisch, da die Indikationsstellung unklar bleibt. Unklarheiten bei Risikogruppen, SCA-Prävalenz und bei Arten von Arrhythmien, die zu SCA führen, erschweren eine Risikostratifizierung. Diese wäre aber erforderlich, um festzustellen, welche PatientInnen am meisten vom WCD profitieren und wann dieser demnach verwendet werden sollte. Dies lässt dem WCD Raum, als eine „greifbare Versicherung" zu dienen, die Sicherheit vermittelt, obwohl nur begrenzte Evidenz vorliegt.

LifeVest® vermittelt Sicherheit

Die Rolle des WCD in der Behandlung, Prävention sowie im Management bestimmter PatientInnen, bei denen die Erstlinientherapie nicht erfolgreich ist oder die auf eine Therapie warten, muss noch geklärt werden.

Übertragbarkeit der Evidenz

Sicherheit: Evidenz niedrig bis sehr niedrig

methodische Einschränkungen

Insgesamt ist die Evidenz bezüglich der Beurteilung der Sicherheit niedrig bis sehr niedrig. Vier Studien unterlagen einem hohen und die fünfte Studie einem sehr hohen Bias-Risiko [17]. Zu den methodischen Einschränkungen gehörten: keine aufeinanderfolgende Rekrutierung von StudienteilnehmerInnen [15, 18, 19]; Unklarheit, ob die StudienteilnehmerInnen zu einem ähnlichen Zeitpunkt ihrer Krankheit in die Studie eingetreten sind [15, 19] oder dies nicht der Fall war [18]; keine Offenlegung von Interessenskonflikten oder Herkunft der finanziellen Unterstützung für die Studie [15, 17] und hoher Verlust an Follow-up [15]. Vier Studien wurden vom Hersteller ZOLL Medical Corporation finanziell gefördert, für die fünfte Studie war das Sponsoring unklar [17].

Selektionsbias sehr wahrscheinlich

Fehlen von Komparatoren

Das Auftreten eines Selektionsbias ist wahrscheinlich, da Personen, die an einer Studie teilnehmen, eher daran interessiert und bereit sind, Anweisungen zu befolgen und sich an diese zu halten, als reguläre PatientInnen. Die Fallserien waren anfällig für Selektionsbias, da PatientInnen aus einer bestimmten Population – d. h. im Krankenhaus – rekrutiert wurden, und daher möglicherweise nicht die durchschnittliche Bevölkerung (z. B. bzgl. Multimorbidität) repräsentieren. Aufgrund des Fehlens eines Komparators kann nicht ausgeschlossen werden, dass die Effekte durch andere Gründe hervorgerufen wurden (z. B. im Fall von Hautausschlag).

Zielpopulation des WCD und Risikofaktoren für SCA sind nicht klar definiert

Zusätzliche Unsicherheiten hinsichtlich der Übertragbarkeit der Evidenz sind: Drei Studien machten keine Angaben zur Altersgruppe [16, 17, 19]; Personen, die nicht von einem/einer BegleiterIn oder BetreuerIn täglich versorgt wurden, waren von der Teilnahme an der Studie ausgeschlossen [15]. Einige Betroffene leben jedoch ohne täglichen Kontakt zu anderen Menschen und müssen daher in der Lage sein, den WCD alleine zu bedienen und zu benützen. Die Zielpopulation des WCD ist nicht klar definiert, was sich in der Vielfalt der Krankheitsgruppen in den eingeschlossenen Studien bemerkbar

machte. Das Risiko von SCA hat sich in den klinischen Untergruppen und auch innerhalb der Untergruppen unterschieden. Risikofaktoren für SCA sind nicht klar definiert, was die Auswahl der Indikationen für den WCD weiter erschwert. Um das Risiko für SCA zu ermitteln, können elektrophysiologische Tests nach einem MI und genetische Analysen durchgeführt werden [26]. Eine individuelle Patientendatenanalyse wäre eine Option, dieser Herausforderung zu begegnen.

6 Schlussfolgerung

keine Aussage über Wirksamkeit

Sicherheit: Qualität der Evidenz sehr gering

Ergebnisse von 2 RCTs abwarten

Risikostratifizierung notwendig!

Da derzeit keine vergleichenden Studien vorliegen, kann keine Aussage zur Wirksamkeit gemacht werden. Im Hinblick auf die Sicherheit ist die Qualität der Evidenz sehr gering. Studien deuten darauf hin, dass der WCD in der kurz- bis mittelfristigen Anwendung eine relativ sichere Intervention ist. Jedoch sind mehr Daten und eine angemessenere Berichterstattung von AEs und SAEs erforderlich, um robuste Aussagen zur Produktsicherheit machen zu können. Um die Wirksamkeit und Sicherheit des WCDs evaluieren zu können, werden RCTs benötigt – Ergebnisse von zwei laufenden RCTs werden erwartet.

Aufgrund der breiten Palette von Indikationen bedarf es einer weitergehenden Risikostratifizierung, um eine effektive und kosten-effektive Nutzung des WCD zu gewährleisten.

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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA Joint Action 3 WP4

**Rapid assessment of other technologies using the HTA Core Model®
for Rapid Relative Effectiveness Assessment**

WEARABLE CARDIOVERTER-DEFIBRILLATOR (WCD) THERAPY IN PRIMARY AND SECONDARY PREVENTION OF SUDDEN CARDIAC ARREST IN PATIENTS AT RISK

Project ID: OTCA01

Version 1.4, 30 November 2016

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V1.2	**12/10/2016**	Input from dedicated reviewers has been processed.
V1.3	**30/10/2016**	Input from external reviewers/experts has been processed.
V1.4	**30/11/2016**	Input from the medical editor has been processed.

Disclaimer

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Conflict of interest

All authors and reviewers involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA declaration of interest and confidentiality undertaking of interest statement form.

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACE	Angiotensin-Converting Enzyme
ACEi	Angiotensin-Converting Enzyme inhibitors
AE	Adverse Events
AED	Automated External Defibrillator
AF	Atrial Fibrillation
AHA	American Heart Association
APHRS	Asia Pacific Heart Rhythm Society
ARB	Angiotensin II Receptor Blocker
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
AV	Atrio-Ventricular
CA	Collaborative Assessment
CAD	Coronary Artery Disease
CABG	Coronary Artery Bypass Grafting
CE	Conformité Européene
CFDA	China Food and Drug Administration
CMR	Cardiac Magnetic Resonance
CPVT	Cathecholaminergic Polymorphic Ventricular Tachycardia
CT	Controlled Trials
CT	Computed Tomography
CRT-D	Cardiac Resynchronisation Therapy
CUR	Health Problem and Current Use of the Technology domain
d(s)	day(s)
ECG	Electrocardiogram
EFF	Clinical Effectiveness domain
EHRA	European Heart Rhythm Association
EPS	Electrophysiological Study
epub	e-publication
ESC	European Society of Cardiology
ETH	Ethical analysis domain
EU	European
FDA	Food and Drug Administration
GKV	Interessenvertretung der gesetzlichen Kranken- und Pflegekassen
GL	Guideline
GMDN	Global Medical Device Nomenclature
HAS	Haute Autorité des Santé
HRQoL	Health Related Quality of Life
HRS	Heart Rhythm Society

hr(s)	hour(s)
HSA	Health Sciences Authority
HTA	Health Technology Assessment
ICD	Implantable Cardioverter Defibrillator
ICD	International Classification of Diseases
ID	Identification
J	Joules
LEG	Legal aspects domain
LVEF	Left Ventricular Ejection Fraction
LBBB	Left Bundle Branch Block
LQTS	Long QT Syndrome
LQTS3	Long QT Syndrome Type 3
MeSH	Medical Subject Headings
MI	Myocardial Infarction
min(s)	minute(s)
mo(s)	month(s)
MOH	Ministry of Health
NICM	Non-Ischaemic Cardiomyopathy
NSTEMI	on-ST-segment Elevation Myocardial Infarction
NYHA	New York Heart Association
ORG	Organisational aspects domain
PM	Pacemaker
PMDA	Pharmaceuticals and Medical Devices Agency
PPCM	Peripartum Cardiomyopathy
pre-op	pre-operation
pt(s)	patient(s)
PVC	Premature Ventricular Complex
QoL	Quality of Life
REA	Relative Effectiveness Assessment
RCT	Randomised Controlled Trials
RVOT	Right Ventricular Outflow Tract
SA-ECG	Signal-Averaged ECG
SAE	Serious Adverse Events
SAF	Safety domain
SCA	Sudden Cardiac Arrest
SCD	Sudden Cardiac Death
SD	Standard Deviation
SPECT	Single-Photon Emission Computed Tomography
SOC	Patient and Social aspects domain

SQTS	Short QT syndrome
STEMI	ST-segment Elevation Myocardial Infarction
TdP	Torsade de Pointes
TEC	Description and Technical Characteristics of Technology domain
TEC	Technology Evaluation Centre
TGA	Therapeutic Goods Administration
TOE	Transoesophageal Echocardiography
V	Ventricular
VA	Ventricular Arrhythmias
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
WCD	Wearable Cardioverter Defibrillator
WPW	Wolff-Parkinson-White
yr(s)	year(s)

SUMMARY

Scope

The aim of this collaborative assessment (CA) is to summarise the information on clinical effectiveness and safety of the wearable cardioverter defibrillator (WCD) therapy in primary and secondary prevention of sudden cardiac arrest (SCA) in adults over 18 years of age (according to CE mark) and paediatric patients (outside of CE mark) at risk. Specific indications are listed in the Scope.

The comparators that have been chosen based on the information from relevant published clinical guidelines (GLs) [1] and according to the European Network for Health Technology Assessment (EUnetHTA) GLs [2], include implantable cardioverter defibrillator (ICD), GL directed pharmacological therapy, GL directed radiofrequency (catheter) ablation, and automated external defibrillators (AEDs) that are to be used in three settings: homes, public places, and/or used by medical emergency staff during resuscitation.

For the clinical effectiveness domain (EFF), the primary outcomes were all-cause mortality and disease specific mortality. Secondary outcomes were incidence of ventricular tachycardia (VT) or ventricular fibrillation (VF) – appropriate shocks and withheld shocks, avoidance of ICD implantation, health-related quality of life (HRQoL), hospitalisation rate, satisfaction, and compliance. Study designs were randomised controlled trials (RCT) and prospective non-randomised controlled trials (CT).

For the safety domain (SAF), adverse events (AE) of skin rash and itching, false alarms, palpitations, light-headedness, fainting, and discontinuation due to comfort and lifestyle issues were chosen and for serious adverse events (SAE), inappropriate shocks and unsuccessful shocks were chosen. Study designs were RCTs, prospective non-randomised CTs, and prospective studies without a control group e.g. observational studies, case series, and registry studies.

No minimum number of patients within a study was used as inclusion criteria for the assessment of clinical effectiveness or safety. However, individual case reports were excluded. Additionally, for Organisational, Ethical, Patient and Social, and Legal aspects (ETH, ORG, SOC, LEG), qualitative studies were included according to the EUnetHTA Core Model® 3.0 [3].

Introduction

Description of technology and comparators

The WCD represents a novel therapy in primary and secondary prevention of SCA. It is a defibrillation technology that is 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 [4]. Currently, there is only one WCD on the market, the LifeVest® WCD manufactured by ZOLL Medical Corporation, which has five generations. In the studies included in this assessment, the following device generations were used: WCD 2000, 3000, 3100, 4000. Hence, these device generations were analysed in this assessment. The latest model, WCD 4000 – CE marked in Europe in 2011, is the device described in the Technical Characteristics of Technology domain (TEC) as it is the only model currently offered in Europe. The WCD consists of two main components: (1) an electrode belt and garment that surrounds the patient's chest, and (2) a monitor that the patient wears around the waist or from a shoulder strap. The electrode belt connects to the monitor and provides digitised ECG data available to be viewed on LifeVest® Network [5] (**B0001**).

The WCD monitors the patient's heart continuously and in case it detects a life-threatening heart rhythm that it can restore, such as VT or VF, it delivers an automatic treatment shock [5]. In case of an alarm triggered by a life-threatening heart rhythm, the conscious patient can prevent the shock by pressing two response buttons found on the monitor unit anytime during the treatment sequence. The WCD can be programmed to different VT or VF zones and can be adjusted to different times and shock energy (between 75 and 150 Joules (J), biphasic) [6]. A single shock event typically takes less than one minute (**B0001**).

There are four categories of standard treatments, depending on the indication, that are being replaced, postponed, bridged, or optimised by the introduction of a WCD for the management of ventricular arrhythmia (VA) and for the prevention of SCA [1, 7]:

- ICDs, which have the capacity to correct most arrhythmias and provide backup bradycardia pacing and anti-tachycardia overdrive pacing have their battery life from six to ten years, and can be implanted transvenously or subcutaneously [8].
- GL directed pharmacological therapy, which offers management of VAs via discontinuation of offending pro-arrhythmic drugs and appropriate anti-arrhythmic therapy that includes a) anti-arrhythmic drugs, b) electrolytes, or c) other drugs that improve reverse remodelling and drugs that are helpful for reducing the frequency of coronary thrombotic occlusions [1].
- GL directed catheter (radiofrequency) ablation, a procedure that involves a series of thin and flexible catheters (wires) that are inserted in a blood vessel via the patient's neck, groin, or arm and guided to the heart. The catheters carry heat energy that destroys those areas of the heart where abnormal heartbeats cause arrhythmias [1].
- AEDs available at homes, public places, and/or used by medical emergency staff during resuscitation [1] (**B0001**).

The LifeVest® system is indicated for patients 18 years of age and older who are at risk for SCA and are not candidates for or refuse an ICD [5]. The device first received an FDA approval in 2001 and in 2015, it received the FDA approval also for children who are at risk for SCA, but are not candidates for an ICD due to certain medical conditions or lack of parental consent [9]. The WCD claims to offer temporary protection from SCA in high risk periods during diagnosis, or an experience of VT/VF, and the appropriate treatment (or optimisation of it) (**A0020**, **B0002**).

Health problem

The LifeVest® claims to reduce the risk of SCA by restoring the life-threatening VT/VF that are responsible for the majority of SCAs. 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 that naturally leads to death. Survival with good neurological function occurs in a small minority of patients [5]. SCAs occur without warning and because patients tend to lose consciousness within seconds, they cannot call for help. Further causes of SCA are slow heart rate (bradycardia), no cardiac electrical activity (asystole), or electromechanical dissociation post-acute MI, which the WCD cannot treat [1, 10] (**A0002**).

The risk factors associated with SCA differ in young and old individuals, where there is a predominance of myocarditis and substance abuse, channelopathies and cardiomyopathies in the young, and chronic degenerative diseases in the old (coronary artery disease (CAD), valvular heart diseases and heart failure) [1]. Dysfunction of the left ventricle is a significant determinant of the risk of SCA, but family history, lifestyle (no smoking, sports, healthy diet), diabetes mellitus, obesity, and heart rate profile during exercise make the determinants diverse and multifactorial [11]. Particular risk factors for VT/VF caused SCA are determined by respective indications. Nationwide screening for the risk of SCA is rare, but the screening of families of SCA victims is of importance (**A0003**, **A0024**).

In Europe, there are about 350 000 out of hospital SCAs per year [12] and in Austria, approximately 15 000 people are affected by sudden cardiac death (SCD) per year [13]. The expected annual prescription of WCD is 160 prescriptions per year in Austria, when assuming the same prescribing practice as in the US (**A0007**, **A0023**).

Methods

The selection of assessment elements for this CA was based on the EUnetHTA Core Model® Application for Rapid Relative Effectiveness (REA) Assessments (4.2) [14]. The checklist for potential ETH, ORG, SOC, LEG aspects of the HTA Core Model® for rapid REA was filled in as well. A systematic literature search was performed on 14/07/2016 in Medline via Ovid, Embase, The Cochrane Library, and CRD (DARE, NHS-EED, HTA) databases and, at the time of the systematic literature search, no limitations to study design were applied. In addition, handsearch of literature (web-search) was performed. Furthermore, the systematic literature search was complemented by a "Scopus search".

The manufacturer (ZOLL Medical Corporation) was contacted by LBI-HTA to send a submission file and clinical trial registries were assessed for registered ongoing clinical trials or observational studies: ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP). A separate GL search (G-I-N, National Guidelines Clearinghouse, TRIP-Database, and handsearch) was performed as well.

Two authors (from LBI-HTA) reviewed and included/excluded abstracts independently from each other according to the scope. These two authors also included and excluded studies (full texts) for EFF and SAF independently from each other. Any disagreements were resolved through discussion. For TEC and Health Problem and Current Use of the Technology domain (CUR), relevant literature from the systematic literature search and the EUnetHTA submission file were used and followed by a handsearch. For ETH, ORG, SOC, LEG, relevant literature from the systematic literature search was used and followed by a handsearch for relevant qualitative studies in order to answer respective assessment element questions – furthermore results from the Focus group were incorporated here as well (see below). All steps were checked and verified by co-authors.

"Quality appraisal tool for case series" document was used for prospective studies without a control group [15] and the assessment of strength of evidence was done using "Grading of Recommendations, Assessment, Development and Evaluation" – GRADE approach [16]. These steps were performed by two authors independently from each other (from LBI-HTA). Any disagreements were resolved by consensus. Co-Authors checked this step. For TEC and CUR, as well as for the ETH, ORG, SOC, LEG, no quality assessment tool was used, but multiple sources were used in order to validate individual, possibly biased, sources.

Additional semi-structured Focus group interviews with patients were developed and questions were discussed among two researchers and a third one was consulted for an independent opinion. The aim was to involve patients in scoping to identify possible neglected outcomes and to evaluate the possibility of the WCD use. Furthermore, the patient involvement primarily aimed to help answering questions regarding ETH, ORG, SOC, LEG, but results were considered for use in other domains as well. The four-hour face to face meeting was moderated by a patient support expert who also helped with gathering patients for the Focus group. The meeting that was held in German was recorded and transcribed upon participants' consent. The anonymised transcript was analysed using framework analysis [17]. Extraction of patient-relevant endpoints (clustering/charting) was done by one author (from LBI-HTA) and checked by the second (from LBI-HTA). According to the Austrian Ethics Committee, no ethical approval was needed.

Results

Available evidence

No study fulfilled the study inclusion criteria for assessing clinical effectiveness of the WCD. RCTs and non-randomised CTs were considered for inclusion, but could not be identified through the systematic literature search (see Figure 1: Flow chart).

The study inclusion criteria for assessing safety differed from the ones for assessing clinical effectiveness. In addition to RCTs and non-randomised CTs, prospective studies without a control group (interventional single arm studies, case series, and registry studies) were considered for the assessment of safety. The systematic literature search (see Figure 1: Flow chart) identified one

prospective interventional single arm study [18], two prospective case series [19, 20], and two prospective registry studies [21, 22], which matched the study inclusion criteria.

Clinical effectiveness

No study fulfilled the study inclusion criteria for assessing clinical effectiveness of the WCD (**D0001**, **D0005**, **D0006**, **D0011**, **D0016**, **D0012**, **D0013**, **D0017**, **D0010**, **D0023**).

Safety

No evidence was found to answer the research question comparing the WCD with comparators, since none of the included studies had a control group. The following AEs were reported: skin rash and itching, false alarms, palpitations, light-headedness and fainting and discontinuation due to comfort and lifestyle issues. In terms of SAEs, inappropriate WCD therapy was defined as non-VT/VF episodes detected and treated by a WCD shock [22]. Two studies indicated that 2% [18] and 0.5% [22] of patients respectively experienced inappropriate shocks, whereas the remaining three studies reported no inappropriate shocks. Unsuccessful shocks were reported in four out of five studies. One study indicated that 0.7% of patients [18] experienced unsuccessful shocks due to incorrect placement of the therapy electrodes. Three studies reported no unsuccessful shocks [19, 20, 22] and one study did not report on this outcome. All five studies reported on the outcome frequency of SAEs leading to death, where death occurred in one study (0.3%) [18] (**C0008**). See Table 1: Summary table of benefits and harms of WCD therapy for prevention of SCA.

Upcoming evidence

Two RCTs are already ongoing and are expected to yield robust clinical data. Both RCTs use conventional treatment as a comparator. One study aims to be completed in December 2017 (2300 patients with ventricular dysfunction immediately following MI) and the other one in October 2019 (2600 patients with end stage renal disease beginning haemodialysis). Prospective studies with long-term mortality measures including well defined disease groups are necessary in order to determine the patient group that would benefit most from the intervention. For the full list of ongoing trials, see Table 8: List of ongoing studies with WCD in Appendix 1.

Reimbursement

The WCD is currently approved for use in Europe, United States, Australia, Israel, Japan, and Singapore. It has regulatory approval, but is not yet launched in Canada and China. The WCD is fully reimbursed for particular indications in France, Luxemburg, and Switzerland; see Table 13: Summary of reimbursement recommendations in European countries for the technology in Appendix 2 (**A0021**).

Table 1: Summary table of benefits and harms of WCD therapy for prevention of SCA

	Health benefit**							Harm	
	Mortality	**Incidence of VT/VF**	**Avoidance of ICD implantation**	**HRQoL**	**Hospitalisation rate**	**Satisfaction**	**Compliance**	**SAEs**	**AEs**
WCD	***No evidence available***	***No evidence available***	***No evidence available***	***No evidence available***	***No evidence available***	***No evidence available***	***No evidence available***	***Inappropriate shocks:*** 2% of patients [18] and 0.5% of patients [22], 0% of patients [19-21] ***Unsuccessful shocks:*** 0.7% of patients [18], 0% of patients [19, 20, 22] ***Frequency of SAEs leading to death:*** 0.3% of patients [18], 0% of patients [19-22]	***Skin rash and itching*:** 6% of patients [18] **False alarms:** 14% of patients [19] **Palpitations, light-headedness and fainting:** 9% of patients [21] **Discontinuation of the WCD use due to comfort and lifestyle issues:** 22% of patients [18] and in 16% of patients [21]
Assessment elements	***(D0001)***	***(D0005), (D0006)***	***(D0023)***	***(D0012), (D0013)***	***(D0010)***	***(D0017)***	***(H0203)***	***(C0008)***	***(C0008)***
Comparator								***Lacking***	***Lacking***
Quality of body of evidence+								***Very low***	***Very low***

Abbreviations: AE-adverse event; ICD-implantable Cardioverter Defibrillator; QoL-quality of life; SEA-serious adverse event; VT-Ventricular Tachycardia; VF-Ventricular Fibrillation.

+ Quality of body of evidence according to GRADE-methodology was classified as follows: high (i.e. “Further research is very unlikely to change our confidence in the estimate of effect”); moderate (i.e. “Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate”); low (i.e. “Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate”); very low (i.e. “Any estimate of effect is very uncertain”).

** Further information can be found in the Discussion of the EFF.

Discussion

Concerning the technical characteristic of the technology, the issues discussed include problems with the device fitting, as some patients may not have a good fit due to body habitus [23]. The maximum chest circumference for patients wearing the WCD is 144cm, the minimum weight is 18.6kg, and the minimum chest circumference is 66cm [4]. To date, the WCD has no pacing capabilities for backup bradycardia pacing or for anti-tachycardia overdrive pacing [6, 24]. The WCD has also shown a possible incompatibility with unipolar pacing technologies [25] and concerning the difference in effectiveness between mono and biphasic waveform, there does not seem to be any difference in effectiveness [26].

With regard to health problem and current use, the issues discussed include problems with a broad CE mark definition that does not specify concrete indications and hence leaves room for broad use of the WCD. There is unclarity in terms of SCA prevalence, types of arrhythmias that lead to SCA, and the risk stratification needed in order to establish which patients would benefit most and therefore when the WCD should be used. This leaves room for the WCD to serve as a tangible insurance that provides security with limited evidence for it. The role of the WCD in treatment/ prevention as well as in the management of specific patients, in whom the first line therapy is not successful, needs to be clarified.

Concerning the clinical effectiveness, issues discussed include problems with the impossibility of making valid statements whether mortality increased or decreased, due to small sample sizes in three studies [19-21], the lack of any comparators, and the variety of enrolled patient groups in all five included studies (for the assessment of safety). In the absence of information on long-term mortality (> 1 year) from prospective studies, the improvement in left ventricular ejection fraction (LVEF) outcome is questioned as the improvement may change over time. Furthermore, no information on historic controls of SCA in different patient groups was provided in any of the five studies in order to compare how many SCAs could have been avoided. The WCD was shown to have very little impact in the treatment of SCA, maximum of 2% of patients, who wore the LifeVest® received appropriate shocks in almost any cohort [23]. Only one study out of five clearly stated the avoidance of ICD implantation in patients who have been indicated for an ICD before WCD use [22]. The existing registry studies are lacking some important information such as device model used, settings of the monitor, how often the response button was used, number of false alarms, possible device-device interactions, information whether an ICD was indicated at the beginning of the WCD use and possibly be avoided after the WCD use, and information on disease status (how far advanced the disease is) at baseline. Data on HRQoL and satisfaction should be collected using standardised methods, and RCTs and non-randomised CTs should be pursued in order to provide a strong evidence base.

With regards to safety the issues discussed include problems with the lack of reporting on AEs in the included studies. The named AEs and SAEs were relevant for patients, but some might have been missed. Avoidance of ICDs might be more relevant for payers than for patients according to the results of the Focus group, where patients favoured ICDs. There is homogeneity in results with regard to unsuccessful shocks (in 0-0.7% of patients), inappropriate shocks (in 0-2% of patients), and frequency of SAEs leading to death (in 0-0.3% of patients). In contrast, there is heterogeneity in appropriate shocks (1.1% to 43% of patients), which might show that risk stratification of patients is of utmost importance. Other safety issues are bystander interference and unsuccessful shocks caused by signal disruption due to falling and wedging bodies [24].

Applicability of evidence

Overall, the strength of evidence is low to very low for safety outcomes. Four of five studies were subject to high risk of bias, the fifth study to very high risk of bias [20]. The methodological limitations include: non-consecutive recruitment of study participants [18, 21, 22], unclear if entering the study at a similar point in the disease [18, 22], or clearly not fulfilling this criteria [21], non-reporting about competing interests or sources of support for the study [18, 20], and high loss to follow up [18]. Four studies were sponsored by the manufacturer ZOLL Medical Corporation and for the fifth study, sponsoring was unclear [20]. See Table 9: Risk of Bias – on study level.

Selection bias might have occurred since people who participate in a trial might be more eager to follow instructions and adhere to requirements than regular patients. Case series were vulnerable to selection bias since patients were drawn from a particular population i.e. the hospital, which may not appropriately represent the average population (e.g. multimorbidity, non-compliant personality traits). Due to the lack of a comparator exposed to the same array of intervening variables, effects seen may be due to intervening effects (e.g. in case of skin rash).

Uncertainties about the applicability of evidence derive from the fact that three studies did not indicate an age range [19, 20, 22]. Not seen at least daily by a companion or caregiver was an exclusion criteria in one study [18]. In real life, some people might live alone without having contact with people on a daily basis, so they need to be able to use and handle the WCD on their own. The target population of the WCD is not clearly defined, which can be seen in the diversity of disease groups in the included studies. The risk of SCA differs across clinical subgroups and also within the reported subgroups – See Table 11: Summary table characterising the applicability of a body of studies. Risk factors for SCA are not yet well defined, which further complicates the selection of appropriate indications for the WCD. The assessment of different baseline risks of patients is important. In order to identify the risk for SCA, electrophysiological testing after myocardial infarction (MI) and genetic analysis could be applied [27]. An individual patient data analysis would be one option to counter this challenge. Risk stratification would be necessary.

Conclusion

According to the published data, no statement can be made about the device effectiveness. With regard to safety, the quality of the body of evidence is very low (see Table 10: GRADE assessment – on outcome level). Studies suggest that the WCD could be a relatively safe intervention in the short to medium term. However, more data and more adequate reporting of AEs and SAEs are needed in order to establish the device safety. For the sake of both effectiveness and safety, RCTs are needed – results of the two ongoing RCTs are awaited (see Table 8: List of ongoing studies with WCD in Appendix 1).

Due to the wide range of indications, more research into risk stratification is needed in order to secure an effective and cost-effective usage of the WCD.

The Focus group approach proved useful in Scoping as well as in identifying answers to questions raised in the HTA on the WCD therapy. Gathered results informed the inclusion of outcome measures relevant to the target group and revealed patients' views on HRQoL. Lessons learned from this pilot project guide future HTAs in further improving patient involvement processes for European assessments within the EUnetHTA project.

1 SCOPE

Description	Project scope
Population	Patients: adults over 18 years of age (according to CE mark) and paediatric patients (outside of CE mark) with the following indications: 1. As a bridge to an ICD [28]; e.g. for: a) patients immediately after explantation of an ICD, if an immediate reimplantation of an ICD is not possible [29, 30], b) patients in whom an immediate implantation of an ICD is indicated, but not possible [29], 1. due to temporary contraindications to an ICD, 2. due to being post VT/VF on the waiting list for an ICD. 2. Patients indicated for an ICD, who refuse implantation for personal or other reasons. 3. As a bridge 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; [29, 30] e.g. for patients with: a) ischaemic heart disease with envisaged or recent revascularization (90-day waiting period post revascularization with either CABG or PCI), b) newly diagnosed non-ischaemic dilated cardiomyopathy (NICM) in patients starting GL directed medical therapy, c) secondary cardiomyopathy (tachycardia mediated, thyroid mediated, etc.) induced arrhythmias (secondary to hypothermia, electrolyte imbalance, iatrogenic prolongation of the QT interval, etc.) in which the underlying cause is potentially treatable, d) with certain forms of structural heart disease associated with risk of malignant arrhythmias or primary electric disease and in those with significantly impaired left ventricular systolic function. 4. “Watch and wait” strategy for patients at risk for SCA during diagnosis. 5. Post MI and LVEF of ≤ 35%, as a bridge therapy “in situations associated with increased risk of death in which ICDs have been shown to reduce SCA, but not the overall survival such as within 40 d of MI” [1, 29]. 6. As a bridge to a heart transplant [1, 29]. Rationale: According to GLs (e.g. from the American Heart Association (AHA)) [31], there is a recommended waiting time in some situations before an ICD is indicated. A recovery of structural abnormality and an improvement of ventricular dysfunction could occur so that an ICD therapy may not be indicated anymore. Furthermore, a patient could have some contraindications (e.g. an infection) and therefore should not receive an ICD for some time, or an ICD needs to be (temporarily) explanted due to specific reasons. Thus a WCD could be used as a bridge to an ICD or to a heart transplant (in order to cover the waiting period) [7, 23, 32, 33]. ICD-10 codes: VT (I47.2), VF and flutter (I49.0), Cardiomyopathy (I42), Acute MI (I21) MeSH-terms: sudden cardiac arrest, ventricular tachycardia, ventricular fibrillation, myocardial infarction, myocardial revascularization, heart transplantation Intended use of technology: treatment (prevention)

Description	Project scope
Intervention	WCD/LifeVest® (WCD 2000, 3000, 3100, 4000 which have CE mark), from ZOLL (Lifecor) Medical Corporation, Pittsburgh, PA, USA. The WCD device consists of 2 components: • an electrode belt that fits within a lightweight garment worn on the patient's chest • a monitor that the patient wears around the waist or from a shoulder strap MeSH-terms: (cardioverter-) defibrillator (external), electric countershock
Comparison	In primary and secondary prevention: • ICD, • GL directed pharmacological therapy, • GL directed catheter (radiofrequency) ablation, • External defibrillators to be used in three settings: homes, public places, and/or used by medical emergency staff during resuscitation. Rationale: Comparators have been chosen based on the information from relevant published clinical GLs [1] and according to the EUnetHTA GLs [2].
Outcomes	**Effectiveness:** Primary endpoint: • Mortality (long term mortality), o All-cause mortality, o Disease-specific mortality. Secondary endpoints: • Incidence of VT/VF, • Avoidance of ICD implantation, • HRQoL, • Hospitalisation rate, • Satisfaction, • Compliance. **Safety:** • AEs, device related and patient related (frequency of AEs, what are these, frequency of discontinuation due to AEs, frequency of unexpected AEs), • SAEs, device related and patient related (frequency of SAEs, what are these, frequency of SAEs leading to death). Rationale: Outcomes have been selected based on the recommendations from relevant clinical GLs [1, 2, 32] and according to EUnetHTA GLs on Clinical and Surrogate Endpoints and Safety [34].
Study design	**Effectiveness**: RCTs, prospective non-randomised CTs **Safety**: RCTs, prospective non-randomised CTs, prospective studies without a control group e.g. observational studies, case series, registry studies (manufacturer database). No minimum number of patients within a study was used for inclusion criteria for the assessment of clinical effectiveness or safety because there would have been the possibility of identifying smaller RCTs or CTs through the systematic literature search, which the authors did not want to exclude based on its small sample size. However, individual case reports were excluded. **Organisational, ethical, patient and social, legal aspects**: Qualitative studies (according to the EUnetHTA Core Model® 3.0) [3]

2 METHODS AND EVIDENCE INCLUDED

2.1 Assessment Team

Description of the distribution of responsibilities and the workload between authors and co-authors:

LBI-HTA (1st authors):

- Develop first draft of EUnetHTA project plan.
- Perform the literature search.
- Carry out the assessment: answer assessment elements, fill in checklist regarding potential ETH, ORG, SOC, LEG aspects of the HTA Core Model® for rapid REA.
- Send "draft versions" to reviewers, compile feedback from reviewers and perform changes according to reviewers' comments.
- Prepare the final assessment and write the final summary of the assessment.

AAZ (co-authors):

- Review the draft EUnetHTA project plan.
- Check and approve all steps (e.g. literature selection, data extraction, assessment of risk of bias).
- Agree with 1st authors on the conclusions made.
- Review the draft assessment, propose amendments where necessary (perform additional handsearch of literature if needed) and provide written feedback.

2.2 Source of assessment elements

The selection of assessment elements was based on the EUnetHTA Core Model® Application for rapid REA (4.2) [14]. The checklist for potential ETH, ORG, SOC, LEG aspects of the HTA Core Model® for rapid REA was filled in as well. Additionally, further assessment elements from the EUnetHTA Core Model® (3.0) [3] domains: ETH, ORG, SOC, LEG aspects – relevant for medical and surgical interventions – were included if deemed relevant. The selected issues (generic questions) were translated into actual research questions (answerable questions). Some assessment element questions were answered together i.e. questions were listed below each other and a summarised answer is provided.

2.3 Search

A systematic literature search was performed on 14/07/2016 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA).

At the time of the systematic literature search, no limitations to the study design were applied. In addition, handsearch of literature (web-search) was performed. Furthermore, the systematic literature search was complemented by a "Scopus search" (i.e. citation tracking); See Figure 1: Flow chart.

The manufacturer (ZOLL Medical Corporation) was contacted by LBI-HTA on 10/05/2016, received the EUnetHTA submission file for medical devices on 06/06/2016, and sent the completed submission file back on 19/07/2016 (including some corrections sent on 26/07/2016).

Clinical trial registries were assessed for registered ongoing clinical trials or observational studies: ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP).

A separate GL search (G-I-N, National Guidelines Clearinghouse, TRIP-Database, and handsearch) was performed as well.

Detailed tables can be found in the Documentation of the Search Strategies in Appendix 1.

2.4 Literature selection and data extraction

Literature selection: Two authors (from LBI-HTA) reviewed and included/excluded abstracts independently from each other according to the scope. These two authors also included and excluded studies (full texts) for assessment of clinical effectiveness and safety independently from each other (see Table 2. Main characteristics of studies included) – as defined in the scope. Any disagreements were resolved through discussion. For TEC and CUR, relevant literature from the systematic literature search and the EUnetHTA submission file were used and followed by a handsearch. For ETH, ORG, SOC, LEG, relevant literature from the systematic literature search was used and followed by a handsearch for relevant qualitative studies in order to answer respective assessment element questions. All steps were checked and verified by co-authors.

Data extraction for EFF and SAF: One author extracted the data and a second controlled the extracted data (from LBI-HTA). Co-Authors checked and verified this step as well.

2.5 Flow chart of study selection

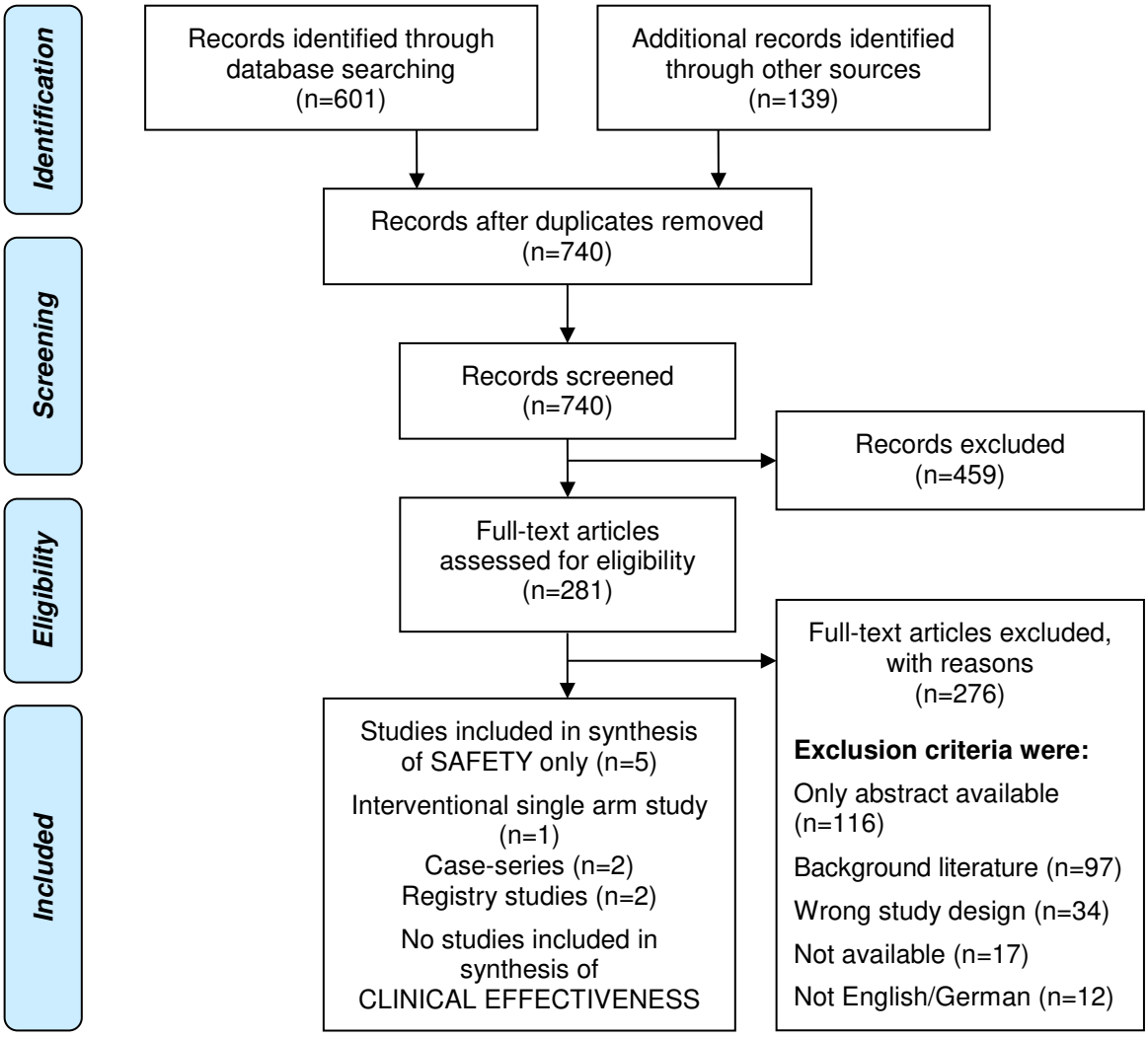

Figure 1: Flow chart

After deduplication of systematic literature search, 601 bibliographic citations remained. By means of handsearch (including Scopus search), 139 citations were identified, which enhanced the total number of citations to 740 citations. The Scopus search added one citation for acquisition of full texts.

2.6 Quality rating of studies

All reporting of clinical effectiveness and safety data was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement 2012) [35].

The "Quality appraisal tool for case series" document was used for prospective studies without a control group [15]. Assessment of the strength of evidence was done using the "Grading of Recommendations, Assessment, Development and Evaluation" – GRADE approach [16]. These steps were performed by two authors independently from each other (from LBI-HTA). Any disagreements were resolved by consensus. Co-Authors checked and verified this step.

For TEC and CUR, no quality assessment tool was used, but multiple sources were used in order to validate individual, possibly biased, sources. Descriptive analysis of different information sources was performed. The completed EUnetHTA submission file from the manufacturer was used as the starting point.

For other domains (ETH, ORG, SOC, LEG), no quality assessment tool was used, but multiple sources were used in order to validate individual, possibly biased, sources. Descriptive analysis of different information sources was performed.

Outcomes were selected based on the recommendations from relevant clinical GLs [1, 2, 32] and according to EUnetHTA GLs on Endpoints used in REA: Surrogate Endpoints [34]. Furthermore, outcomes were discussed among authors, co-authors, dedicated reviewers, and external experts.

2.7 Description of the evidence used

Table 2. Main characteristics of studies included

Author and year or study name	Study type	Number of patients	Intervention	Main endpoints	Included in clinical effectiveness and/ or safety domain
Feldman 2004 [18] (WEARIT/ BIROAD)	Prospective interventional single arm study	289 (177 in WEARIT, 112 in BIROAD)	WCD	Mortality (all-cause, disease specific), appropriate WCD shocks, unnecessary WCD shocks, AEs and SAEs	Safety domain
Duncker 2014 [19]	Prospective case-series	12 (7 treated with WCD)	WCD	Mortality (all-cause, disease specific), improvement in LVEF, incidence of VT/VF, incidence of syncope	Safety domain
Kondo 2015 [20]	Prospective case-series	24	WCD	Mortality (all-cause, disease specific), appropriate WCD shocks, SAEs, improvement in LVEF*, ICD implantation after WCD use	Safety domain
Kao 2012 [21] (WIF)	Prospective registry study	89 (82 completed the study)	WCD	Mortality (all-cause, disease specific), improvement in LVEF, WCD daily use in hrs (compliance with the WCD), AEs	Safety domain
Kutyifa 2015 [22] (WEARIT-II)	Prospective registry study	2000	WCD	Mortality (all-cause, disease specific), VT/VF events, improvement in LVEF, ICD implantation	Safety domain

*** They reported on these endpoints, which were not clearly stated in the introduction or methods section**

Abbreviations: AE-Adverse Events; ICD-Implantable Cardioverter Defibrillator; LVEF-Left Ventricular Ejection Fraction; SAE-Serious Adverse Events; VF-Ventricular Fibrillation; VT-Ventricular Tachycardia; WCD-Wearable Cardioverter Defibrillator.

For further information please see Table 7: Characteristics of included studies in Appendix 1.

2.8 Patient involvement

Patients were involved in scoping in order to understand the patient's perspective, to identify possible neglected outcomes and to evaluate the possibility of WCD use. Furthermore, relevant results were incorporated in the assessment element domains as appropriate. A standardised e-mail was sent to members of the nine regional associations of the Austrian organisation for heart and lung transplant patients (www.hlutx.at) to identify eligible participants for a Focus group.

Guiding questions for semi-structured interviews were developed according to relevant literature [17], based upon a handsearch of relevant initiatives' websites (such as the Scottish Medicine Consortium and its PACE process and relevant literature), and discussed among two researchers; a third one was consulted for an independent opinion. The four-hour face to face meeting was moderated by a patient support expert who also helped with gathering patients for the Focus group. The meeting that was held in German was recorded and transcribed upon approval of the participants. The anonymised transcript was analysed using framework analysis [17]. Extraction of patient-relevant endpoints (clustering/charting) was done by one author (from LBI-HTA) and checked by a second author (from LBI-HTA).

According to the Austrian Ethics Committee, no ethical approval was needed. Patients were asked to sign an informed consent form. The Focus group was a pilot qualitative research done in the context of EUnetHTA in order to further inform appraisal of the WCD therapy. The Focus group questions can be found in Appendix 1.

2.9 Deviations from project plan

- Some deadlines within the timelines were postponed due to time constraints mainly caused by delay in finalisation of the project plan (i.e. extended scoping phase).
- Two additional assessment elements were identified for the EFF (**D0010**, **D0023**).
- One patient and social assessment element was deleted as there was not enough data found to answer the question (G0010).
- One legal assessment element was deleted as there was not enough data found to answer the question (F0014).
- Patient involvement: Analysis of the transcript was not done by two authors independently (one did the analysis, the other one checked it). Furthermore no patients blog, informal patient website or discussion forum were consulted.
- The scope of the intervention was extended to WCD 2000, 3000, and 3100, since the included studies did not explicitly state which models they used.
- Extraction table: With regard to patient characteristics, ejection fraction in % (range)±SD was added, duration of therapy was deleted. With regard to efficacy outcomes, first shock success n (%) and % of improvement in ejection fraction in mean±SD (range) were added.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

3.1 Research questions

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

3.2 Results

Features of the technology and comparators

B0001 – What is the WCD and what are the comparators?

The WCD represents a novel therapy in primary and secondary prevention of SCA. It is a defibrillation technology that is 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 [4].

The following description of the device is based upon the latest version WCD 4000. The WCD consists of two main components: (1) an electrode belt and garment that surrounds the patient's chest, and (2) a monitor that the patient wears around the waist or from a shoulder strap. The electrode belt connects to the monitor and provides digitised ECG data [5]. The electrode belt further contains a vibration box that vibrates when a treatable arrhythmia is detected [5]. The garment comes in various sizes and is worn under the patient's clothing to hold four dry, non-adhesive sensing electrodes and three therapy pads on the electrode belt against the patient's skin [5, 6]. After taking out the set of electrodes, the garment should be washed every one or two days [5]. The monitor weighs a total of 600 g and it contains response buttons, alarm system, defibrillator, and batteries that last for 24 hours and can take up to 16 hours to charge [6]. The patient is provided with a total of two battery packs [5]. The monitor connects to the electrode belt, it analyses ECG data, and communicates with the charger to provide encrypted data for viewing availability on LifeVest® Network [5]. For depiction, see Figure 2: The garment and the electrode belt [5]

The WCD monitors the patient's heart continuously and in case it detects a life-threatening heart rhythm that it can restore, such as VT or VF, it delivers an automatic treatment shock [5]. Once it detects such treatable arrhythmia, an alarm sequence, which is to alert the patient, begins. The patient is instructed to sit or lie down to avoid injury in the event of loss of consciousness [6]. In case of alarm, the conscious patient can prevent the shock by pressing two response buttons found on the monitor unit anytime during the treatment sequence. If, however, the patient does not respond or release the response buttons, the WCD continues to give alarms, vibration and two alarms g to bystanders that a treatment shock is imminent [5]. Then, the electrode pads release a blue gel prior to delivering the treatment shock and in case a treatable arrhythmia persists after the first shock, up to 5 shocks may be given in a treatment sequence [5]. After receiving a WCD shock therapy, patients are instructed to call their doctor or seek medical attention, where evaluation of arrhythmias that triggered the shock and replacement of the old electrodes should be provided [6].

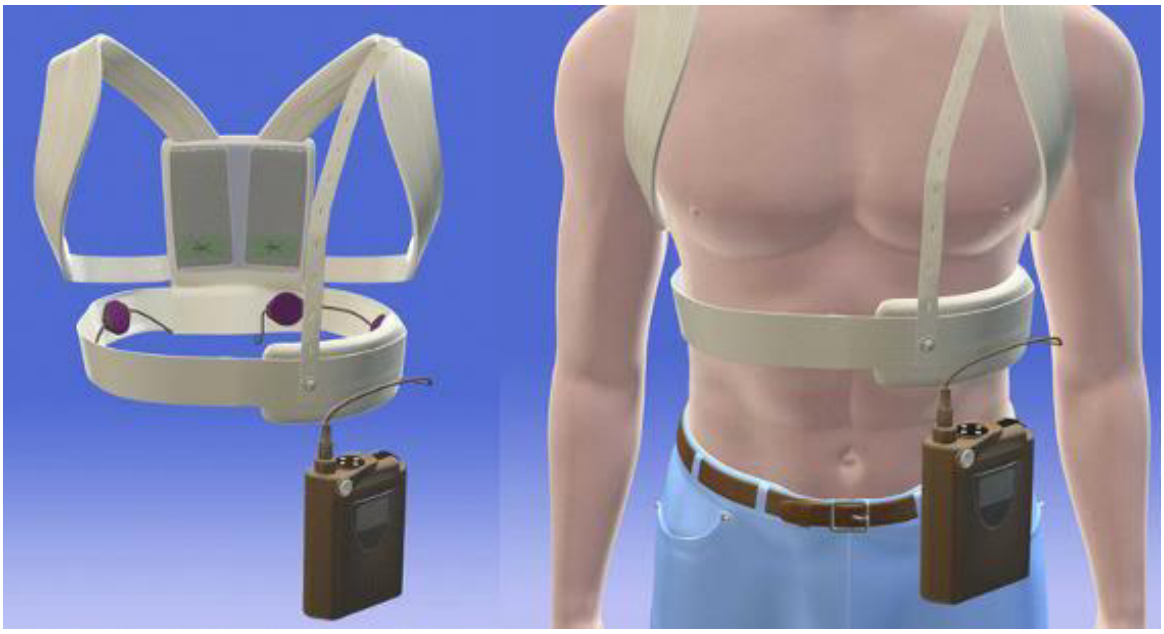

Figure 2: The garment and the electrode belt [5]

The WCD can be programmed to different VT or VF zones and can be adjusted to different times (time from detection to defibrillation sequence activation) and shock energy (between 75 and 150J, biphasic) [6]. A single shock event typically takes less than one minute. Apart from defibrillation as such, the device continuously monitors for VTs and VFs and can transmit event recordings to an internet website that allows a patient's health care professional to view the ECG and other data related to the patient's use of the device.

Marketed products

Currently, there is only one WCD on the market, the LifeVest® WCD manufactured by ZOLL Medical Corporation (see Table 3: Features of the intervention). The LifeVest® WCD has five generations. The 1st generation, WCD 1, received the CE mark in 1999 and together with the 2nd generation, WCD 2000, it delivered shocks in the form of monophasic waveforms with a maximum of 300J. The 3rd generation, WCD 3000, the 4th generation, WCD 3100, and the latest 5th generation, WCD 4000 – CE marked in 2011, all deliver biphasic shocks with a maximum of 150J [5]. Only the WCD 4000 is currently offered in Europe.

Standard treatments

There are four categories of standard treatments, depending on the indication, that are being replaced, postponed, bridged, or optimised by the introduction of the WCD for the management of VA and for the prevention of SCA [7, 36]: ICD, GL directed pharmacological therapy, GL directed catheter (radiofrequency) ablation, and AEDs available at public places and/or used by medical emergency staff during resuscitation.

- The ICD has been in use for more than three decades since its first implantation in the 1980 and it is now an established first line treatment and prophylactic therapy for patients at risk of SCA due to its ability to perform defibrillation, cardioversion, and pacing [6, 37]. It has the capacity to correct most arrhythmias and its battery life is six to ten years. It can be implanted transvenously or subcutaneously [8].
    - Transvenous ICD is implanted under the skin in the left upper chest and it comprises of 1) a generator that includes a computer chip with a RAM memory, software, capacitor, and batteries, and 2) electrode wire/s connected to the generator that pass through a vein to the right chambers of the heart and can consist of one to two leads [8]. Furthermore, when choosing the right ICD, what needs to be considered is whether to choose a single or dual chamber ICD, and whether to combine it with cardiac

resynchronisation therapy (CRT-D). A dual chamber ICD is to be considered in patients with significant sinus bradycardia due to sinus node disease, or the presence of an atrial lead that would allow an increase in beta-blocker dose [8]. Combining the ICD with CRT should be considered in patients with LVEF <35% and with broad QRS duration—particularly those with left bundle branch block (LBBB) [8].

- Subcutaneous ICD (S-ICD) is comprised of a subcutaneous lead that runs parallel to the left sternal edge and along the inferior border of the heart to a generator in the axilla [8]. S-ICD's target population are younger patients with no indications for bradycardia or anti-tachycardia pacing [8].

- GL directed pharmacological therapy is based on the associated arrhythmia, the associated medical conditions that may contribute to and/or exacerbate arrhythmia, the risk posed by arrhythmia, and the risk – benefit aspects of the potential therapy [36]. The management of VAs includes discontinuation of offending pro-arrhythmic drugs and appropriate anti-arrhythmic therapy that includes a) anti-arrhythmic drugs, such as amiodarone, or beta-blockers (for the full list, please see Table 15: Antiarrhythmic drugs for treatment of VT/VF [1] in the Appendix 4), b) electrolytes, such as potassium or magnesium, or c) other drugs that improve reverse remodelling, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) [36], or drugs that are helpful for reducing the frequency of coronary thrombotic occlusions in high-risk patients, such as anticoagulants and antiplatelet drugs [36].
- GL directed catheter (radiofrequency) ablation is a treatment option for patients with scar-related heart disease presenting with VT or VF. Catheter (radiofrequency) ablation in ischaemic heart disease patients decreases the likelihood of subsequent ICD shocks and prevents recurrent episodes of VT [36]. It targets the isthmus of slow conduction (critical isthmus) within the VT re-entry circuit [36]. The procedure involves a series of thin and flexible catheters (wires) that are inserted in a blood vessel via the patient's neck, groin, or arm. Guided to the heart, the catheters carry heat energy (created also by radio frequency medium alternating current in the range of 350–500 kHz) that destroys those areas of the heart where abnormal heartbeats cause arrhythmias [36].
- AEDs, available at public places and/or used by medical emergency staff during resuscitation, are another treatment option for patients at risk of SCA. Most SCAs occur outside of the hospital setting and public access defibrillation combined with cardiopulmonary resuscitation has been shown to be effective particularly at places where trained volunteers can be readily available (e.g. casinos, airports, sports stadiums) [36]. Even though most SCAs occur at home, as they are infrequently witnessed, home-based defibrillators are scarcely helpful [36].

Table 3: Features of the intervention

	Technology
Name	Wearable cardioverter defibrillator
Proprietary name	LifeVest® wearable cardioverter defibrillator
Manufacturer	ZOLL Medical Corporation
Names in other countries	NA
Reference codes	FDA Product code: MVK CE Mark certificate unique ID: DRKS00005653
Class/GMDN code	35972 – Defibrillator, Automatic

Abbreviations: CE-Conformité Européene; FDA-Food and Drug Administration; GMDN-Global medical device nomenclature; ID-identification; NA-not available.

Sources: [5]

A0020 – For which indications has the WCD received marketing authorisation or CE marking?

LifeVest® WCD received the CE mark for its 1st generation model, WCD 1, in 1999 and for the latest, 5th generation WCD 4000, in 2011. The LifeVest® system is indicated for patients 18 years of age and older who are at risk for SCA and are not candidates for or refuse an ICD [5]. The device first received an FDA approval in 2001 and in 2015, it received the FDA approval also for children who are at risk for SCA, but are not candidates for an ICD due to certain medical conditions or lack of parental consent [9]. Information on the regulatory status is found in Table 12: Regulatory status of the technology.

B0002 – What is the claimed benefit of the WCD in relation to the comparators?

LifeVest® WCD claims to offer temporary protection from SCA in high risk periods during diagnosis, or an experience of VT/VF, and the appropriate treatment (or optimisation of it). In these so called "bridging" periods, a WCD claims to a) allow for implantation of ICDs only in the cases where it is required (in order to prevent possible morbidity issues linked with complication post ICD implantation such as infections [38] and the high cost of an ICD implantation as such [1]), b) provide protection during drug optimisation, c) allow for recovery of the heart function and the improvement of the LVEF, and d) provide protection to at risk heart transplant patients.

B0003 – What is the phase of development and implementation of the WCD and the comparators?

The WCD received its CE mark in 1999 based upon a 1998 study of induced arrhythmias in ten patients [39]. Currently, it is the 5th generation of the device that is in use and this novel technology is trying to find its place in clinical practice. As the device can be used for multiple indications, risk stratification for each indication is the subject matter that needs to be determined. Current clinical trials are investigating the use of the device in further subgroups of patients at risk of SCA and an altered form of the device, hospital WCD, that is not part of this assessment, is being researched. Data on implementation of the device based upon retrospective registry studies in the US and Germany are outlined in the Table 4: Registry experience with WCD indications in the US and Germany below.

Table 4: Registry experience with WCD indications in the US and Germany

Indications	US [24] in %	Germany [40] in %
ICD explants	23.4	10
VT/VF prior to ICD implants	16.1	NA
Genetic predisposition to SCD	0.4	18 (part of it)*
Recent MI Recent MI	12.5 (and LVEF ≤ 35%) 3.8 (and LVEF >35%)	39
Post-CABG	8.9 (and LVEF ≤ 35%)	25
Cardiomyopathy	20 (Nonischaemic cardiomyopathy and LVEF ≤ 35%) 8.1 (Unspecified cardiomyopathy and LVEF ≤ 35%)	18 (part of it)*
Heart transplantation or left ventricular-assist devices	NA	6
Unknown	6.8	NA

* The category of "risk stratification" that makes up 18% of patients includes assumed myocarditis/dilated cardiomyopathy, aborted SCA, and inherited channelopathies (LQTS, Brugada syndrome).

Abbreviations: ICD-Implantable Cardioverter Defibrillator; LVEF-Left Ventricular Ejection Fraction; MI-Myocardial Infarction; CABG-Coronary artery bypass grafting; NA-not available; US-United States.

Sources: [24] [40]

ICDs are part of the established clinical practice and current developments are concerned with a) the use of CRT-D alongside ICD implantation, b) the implantation of single, or dual chamber ICDs, and c) the implantation of transvenous or subcutaneous ICDs [8]. The compatibility between ICDs and Magnetic Resonance Imagining is currently being researched as well [41].

Pharmacological therapy has shown limited success in preventing SCAs [37]. Anti-arrhythmic drug therapy has shown little success with sodium channel blockers, calcium antagonists, blockers of potassium channels, or amiodarone [37]. For patients post MI and patients with heart failure, anticoagulants, ACE inhibitors, statins, and aldosterone antagonists have been shown to reduce the incidence of SCD [37]. Currently, studies are under way that compare anti-arrhythmic drug therapy with catheter (radiofrequency) ablation and the question whether the primary ablation of well-tolerated sustained monomorphic VT in patients with an LVEF > 40% without a backup ICD is beneficial needs further study [36].

The phase of development of AEDs revolves around the simplicity of AED utilisation by lay persons, around comparisons between biphasic or monophasic waveforms, and around mechanisms of operation when used alongside with cardiopulmonary resuscitation [42].

B0004 – Who administers the WCD and the comparators and in what context and level of care are they provided?

B0008 – What kind of special premises are needed to use the WCD and the comparators?

B0009 – What equipment and supplies are needed to use the WCD and the comparators?

Strictly speaking, the WCD system does not require any bystander or healthcare provider interaction to deliver the required treatment. However, a cardiologist needs to decide on the time from detection to defibrillation sequence activation and the required shock energy (between 75 and 150J, biphasic) [6]. Also, for the device to fulfil its “bridging” purpose, the data gathered by the device need to be analysed by the cardiologist, so that the appropriate treatment method is selected. The WCD’s primary target is out-of-hospital patients who, however, should call their doctor or seek other immediate medical evaluation after receiving a shock [6]. No additional equipment, premises, or personnel of the health care provider or system are necessary for the use of the WCD [5].

Maintenance costs and investments necessary to support the use of the WCD are, for the time being, defrayed by the manufacture ZOLL Medical Corporation. The LifeVest® WCD system is a service that includes training and 24/7 technical assistance and support by ZOLL Medical Corporation trained representatives. If component replacement is needed, it is typically done within 24 hours and once a patient completes use, the registered LifeVest® is returned for cleaning and testing of the device with reconditioning or repair completed when required. Devices must pass an inspection and testing process in order to be sent to another patient. Devices that do not pass this inspection process are fully serviced or removed from patient’s use if they cannot be repaired [5].

Implantation of the ICD, as well as catheter (radiofrequency) ablation, are administered in the hospital setting. Catheter (radiofrequency) ablation is performed under local anaesthesia and the ICD implantation can be performed both under general anaesthesia as well as local anaesthesia with sedation [43, 44]. The premises, the operation team, and the supplies are similar; the difference between catheter (radiofrequency) ablation and implantation of the ICD is in the intervention, where ablation is a one-off treatment while the ICD is an implanted device. If successful, catheter (radiofrequency) ablation requires less follow-up visits compared to post-ICD monitoring by the cardiologist [43].

Pharmacological therapy is prescribed by cardiologists and taken in the out-of-hospital setting. AEDs are administered in emergency units by the emergency unit personnel, by trained volunteers at public places, caregiver staff in nursing homes, or family members in the home settings.

A0021 – What is the reimbursement status of the WCD?

The WCD is currently approved for use in Europe, United States, Australia, Israel, Japan and Singapore, and has regulatory approval, but is not yet launched in Canada and China. The WCD is fully reimbursed for particular indications in France, Luxemburg, and Switzerland (see Table 13: Summary of reimbursement recommendations in European countries for the technology in Appendix 2). In Germany, Sickness Funds make individual decisions regarding reimbursement because the LifeVest® is included on the Hilfsmittel list for medical supplies [45] – see Table 14: Summary of recommendations in European countries for the technology in the indication under assessment. In the UK, hospitals will rent the LifeVest® directly from the manufacturer if they choose to use it [5]. No monthly reimbursement estimate from the manufacturer ZOLL Medical Corporation was provided.

3.3 Discussion

Some device characteristics such as the garment size, limited device functions, noise disruptions, and differences between shock waveforms need to be reflected upon and further discussed.

Especially in the context of making comparisons between a WCD and an ICD, it is important to highlight the issues related to the garment size. The device must be fitted to each patient and some patients may not have a good fit due to body habitus [23]. The maximum chest circumference for patients wearing the WCD is 144cm, which means that morbidly obese patients are left unprotected [23]. In this report, the use of the WCD in children under 18 years of age is analysed even though it is not approved in Europe, but only in the USA. In the absence of clinical trials that would meet the selection criteria, no data on effectiveness and safety is reported, yet the garment size remains to be an issue. The minimum weight for use of the WCD is 18.6kg and minimum chest circumference 66cm [4]. Not only size limitations, but also issues with fitting of the garment seem to be responsible for providing low protection to children under 18 years [4].

To date, the WCD has no pacing capabilities for backup bradycardia pacing or for anti-tachycardia overdrive pacing [4, 6], which leaves those groups of patients for whom ICD is a comparator particularly unprotected, as these functions are offered in the new generations of ICDs [43]. In these circumstances then, the WCD finds itself in an ambiguous situation where on the one hand, it claims to offer protection to patients at risk of SCA, yet on the other hand, it offers protection only against SCAs induced by VT or VF [4], compared to an ICD that can provide both bradycardia pacing as well as anti-tachycardia overdrive pacing. Also, an inappropriate WCD shock can potentially induce VF as it may not be synchronised correctly [25].

Not only that the WCD does not provide protection in the form of pacing, it has also shown a possible incompatibility with unipolar pacing technologies [25]. A case occurred where a patient using a WCD developed a polymorphic VT, which was correctly detected by the WCD and the treatment protocol was initiated. However, inconsistencies in the analysed arrhythmia waveform due to the presence of the unipolar ventricular pacemaker artefacts led to termination of the treatment algorithm, which lead to patient's death [46].

The 1st and 2nd generation of WCDs delivered shocks in the form of monophasic waveforms with a maximum of 300J, while typically programmed to begin a treatment sequence with an energy level of 200J [47]. The 3rd, 4th, and the latest 5th generation deliver biphasic shocks with a maximum of 150J based upon a prospective, randomised study done in an electrophysiological laboratory setting with 30 patients that concluded that first shock defibrillation efficacy rate was 97% regardless of the waveform used [26]. Using lower-energy waveforms provides technical advantages (i.e. smaller and lighter devices as well as longer battery longevity). Data on the suitability of the different waveforms for either VT or VF was not found. In the latest generation, there are several settings that can be changed in the monitor of the WCD e.g. the pulse energy (75-150J), whereas the default setting is 150J for 5 shocks [48]. An observational study suggested programming the WCD to deliver maximum shock energy (150J), beginning with the first shock in ambulatory patients, but no dose-dependent differences were evaluated [47].

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

4.1 Research questions

Element ID	Research question
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for SCA?
A0004	What is the natural course of VT/VF and SCA?
A0005	What are the symptoms and the burden of SCA?
A0006	What are the consequences of SCA for the society?
A0024	How is the risk of SCA currently diagnosed according to published guidelines and in practice?
A0025	How is SCA currently prevented and managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the WCDs utilised?

4.2 Results

Overview of the disease or health condition

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

The LifeVest® claims to reduce the risk of SCA, the health condition in the scope of this assessment. VF and VT, with a subset of Torsades de Pointes (TdP), are responsible for the majority of SCAs. 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 (bradycardia), no cardiac electrical activity (asystole), or electromechanical dissociation post-acute MI [10, 36].

A0003 – What are the known risk factors for SCA?

Overall, the risk factors associated with SCA 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 (CAD, valvular heart diseases, and heart failure) [36]. In the older individuals, multiple chronic cardiovascular conditions contribute to the risk of SCA and hence it is difficult to determine which contributed most, while in the younger individuals, inherited channelopathies or drug-induced arrhythmias that are devoid of structural abnormalities may make the diagnosis of SCA elusive [36]. Dysfunction of the left ventricle is a significant determinant of the risk of SCA, but family history, diabetes mellitus, obesity, and heart rate profile during exercise make the determinants diverse and multifactorial [49]. Lifestyle is very important in prevention of SCA (e.g. no smoking, sports, healthy diet) [37].

Particular risk factors for VT/VF caused SCA are determined by respective indications. Patients with the following indications are at most risk according to the AHA and the European Society of Cardiology (ESC) [7, 36]:

- Who are awaiting ICD implantation after an explantation and in whom immediate reimplantation is not possible due to temporary contraindications or waiting time for the ICD implantation.

- Who are indicated for an ICD, but refuse it due to personal or other reasons.
- Who need optimisation of pharmacological therapy to resolve the left ventricular dysfunction such as ischaemic heart disease patients with envisaged or recent revascularization (90-day waiting period post revascularization with either CABG or PCI); newly diagnosed NICM patients starting (GL directed) medical therapy; secondary cardiomyopathy patients (tachy-cardia mediated, thyroid mediated, etc.) with induced arrhythmias (secondary to hypother-mia, electrolyte imbalance, iatrogenic prolongation of the QT interval, etc.) in which the underlying cause is potentially treatable; or patients with certain forms of structural heart disease associated with the risk of malignant arrhythmias, and in those with significantly impaired left ventricular systolic function.
- Who are at risk of SCA and in the process of diagnosis.
- Who are post MI and have their LVEF ≤ 35% and are awaiting therapy.
- Who are awaiting a heart transplant.

A0004 – What is the natural course of VT/VF and SCA?

A0005 – What are the symptoms and the burden of SCA?

The natural course of an SCA is death and survival with good neurological function that occurs in a small minority of patients [5]. SCAs occur without warning, and because patients tend to lose consciousness within seconds they cannot call for help. In the absence of timely defibrillation delivered within minutes, the SCA is typically life-threatening and with each passing minute, a patient's chances of survival drop by 10% [5]. Around one third of patients with significant left ventricular dysfunction recover and move to a lower SCA risk category, while those that do not, are for the most part indicated for a permanent ICD implantation. Those patients in whom risk is not related to left ventricular dysfunction generally have a temporary contraindication for ICD placement that resolves over time [5]. Symptoms that indicate further evaluation for the risk of SCA are palpitations (or sensation of sudden rapid heartbeats), pre-syncope, and syncope [36]. The burden of disease for the patient is death, or the consequences that follow a delayed intervention, mainly a permanent neurological deficit.

Effects of the disease or health condition

A0006 – What are the consequences of SCA for the society?

Approximately 25% of all 17 million deaths worldwide related to cardiovascular disease are caused by SCA each year [1, 5]. In Europe, there are about 350 000 out of hospital SCAs per year [12] and in the US, it is estimated that 326 000 people experience out-of-hospital SCA each year, while majority of these SCAs occur at home with half of the cases unwitnessed (39). In Austria, approximately 15 000 people are affected by SCD per year. One third of SCDs happen unexpectedly outside of hospital (i.e. 5 000). Of these 5 000 SCDs, two thirds occur at home and the remainder of SCDs occur in the office or in public [13].

Current clinical management of the disease or health condition

A0024 – How is the risk of SCA currently diagnosed according to published guidelines and in practice?

For non-invasive as well as invasive methods for the evaluation of patients with suspected or known VAs – see Table 16: Non-invasive and invasive evaluation methods [1] in the Appendix 4. Because of the limited ability to prevent SCAs, risk predictors remain the only reliable indicators. However, as low LVEF is one of the key indicators, it fails to grasp 50% of SCA victims whose LV function is preserved [50]. The diagnostic work-up for patients at risk of SCA is reported in Figure 3: Diagnostic work-up [1] in Appendix 4.

A0025 – How is SCA currently prevented and managed according to published guidelines and in practice?

Nationwide screening for the risk of SCA is rare as only Italy and Japan have implemented ECG screening systems that may identify asymptomatic patients with inherited arrhythmogenic disorders [36]. There is a consensus among Europe and the US that there is a need for SCA screening in competitive athletes (as endorsed by the International Olympic Committee), even though a recent study in Israel reported no change in incidence rates of SCA in competitive athletes following implementation of screening programs [36].

The screening of families of SCA victims is of importance. The diagnosis of an inherited arrhythmogenic disorder is established in up to 50% of the families with the sudden arrhythmic death syndrome victim, especially channelopathies, where currently only 40% of family members are screened [36].

For most patients at risk of SCA, implantation of an ICD is the solution of choice. Alternative solution is the use of pharmacological therapy, catheter (radiofrequency) ablation, and the use of AEDs, as outlined above. However, there remain to be specific high risk patient groups whose protection is an unmet need, such as post-MI patients, who are recommended not to be implanted with the ICD <40 days post-MI with no revascularization, or patients requiring timely defibrillation by AEDs – for bystander use of the AED is not an effective method of protection for high risk patients [51] and relying on emergency medical service response also results in poor outcomes [52].

The WCD is recommended based upon a low level of evidence by the ESC for adult patients with poor LV systolic function who are at risk of sudden arrhythmic death for a limited period, but are not candidates for an ICD (e.g. bridge to transplant, bridge to transvenous implant, peripartum cardiomyopathy (PPCM), active myocarditis, and arrhythmias in the early post-MI phase) [1, 29]. The AHA states along the same lines that WCDs can serve as a temporary means of aborting arrhythmic death in patients with transient risk of SCD or those with indications for ICD implantation who have a transient barrier to permanent device implantation [7]. For more data on GL directed WCD use, see Table 5: Overview of guidelines in Appendix 1.

Target population

A0007 – What is the target population of this assessment?

A0023 – How many people belong to the target population?

A0011 – How much are the technologies utilised?

As CE marked, the target population of this assessment are patients 18 years of age and older who are at risk for SCA and are not candidates for or refuse an ICD.

Worldwide, there are 4.25 million deaths caused by SCA each year [5], however, the exact target population of this intervention is difficult to estimate. One approach would be to estimate it based on the ICD usage. In 2014 in Austria, 1045 patients received an ICD (men: 842, women: 203) [53]. However, this approach is inaccurate because some patients who are indicated for an ICD may not receive one, while some patients who receive an ICD may have a condition that would have improved without one [54]. Contributing to the estimate are 57 patients that had their hearts transplanted in Austria in 2007 [55], whereas this number in Germany in 2015 was 286 patients [56].

The expected annual prescription of WCD is 160 prescriptions per year in Austria, when assuming the same prescribing practice as in the US.

4.3 Discussion

Some aspects of the current and future use of the WCD such as the indication, off-label use, risk stratification, WCD's role as a prevention or treatment, and the unclarity in care pathways need to be further discussed.

Due to the fact that WCD is CE marked very broadly, for patients 18 years of age and older who are at risk for SCA and are not candidates for or refuse an ICD, the device indications and the patients that benefit most from the device are not clearly defined [5]. The list of indications considered in this report is the result of consulting international GLs, clinical/external experts, and project partners. This broad CE mark definition that does not specify concrete indications leaves room for broad use of the WCD.

Connected to the issue of CE mark is the issue of risk stratification. As the WCD claims to provide protection in the "bridging periods" only against specific arrhythmias (VTs/VFs) and the prevalence of these types of arrhythmias is not reported in the studies, it is unclear which patients can benefit the most from the WCD. In this way, the WCD serves as a tangible insurance that, as indicated in the two studies with larger cohorts of patients included in this assessment [18, 22], delivered appropriate shocks to less than 2% of the patients (described in further detail in the EFF discussion) [23]. Hence, due to the potential for the device overuse driven by the inevitable fear behind the risk of SCA, there is a particular need for setting a threshold of risk for particular patient groups. This is also suggested by Singh for NICM patients, where none of the 254 patients in the retrospective study independent from manufacturer sponsorship actually received an appropriate WCD shock, which casts doubts on the actual risk of SCAs in NICM patients [57]. Therefore, there is a need for more data in order to analyse the WCD's place in clinical practice so that it is not prescribed for patients that do not need it out of fear [58]. In particular, more data is needed for specific risk stratification of high risk patients whose data is available, yet reported as part of larger subgroups. That skews the results and presents the WCD as the treatment of choice for the whole subgroup, even though it is most needed for the high risk patient groups as it is the case in [22], where e.g. previous SCA and syncope patients at highest risk fall under the general subgroup of NICM. In order to establish risk factors for SCA, it is necessary to use the manufacturer ZOLL Medical Corporation data from the company's database.

Following the AHA, the WCD is analysed as a treatment option for VT and VF [7]. However, because VT and VF lead to SCA, the risk of which is the health condition in the scope of this assessment, the WCD is also understood as a primary as well as secondary preventative measure; primary in patients post-MI or post-explantation of an ICD when immediate reimplantation is not possible, and secondary in patients with a history of SCA or sustained VT and VF, in whom ICD is ineffective. The well-defined role of the WCD in treatment and prevention needs to be clarified.

There is a lack of published data on the management of specific patients in whom the first line therapy is not successful. It is unclear what the care pathway is for patients who, for instance, have an ICD removed due to an infection or other comorbidities that contraindicate reimplantation. The ESC suggests that the subcutaneous ICD may be considered as a useful alternative to the transvenous ICD system in such circumstances [1], yet the AHA outlines that the subcutaneous ICD shares many of the same hazards as transvenous ICDs, including lead dislodgement, skin erosion, and infection, along with the incidence of inappropriate shocks [7]. Same unclarity applies to the care pathways for patients who are awaiting optimisation of pharmacological therapy, or in whom catheter (radiofrequency) ablation was not successful. In such situations, patients seem to be dependent on the emergency services and the use of AEDs. In these circumstances as well as when the "watch and wait" strategy can be applied, the WCD might be potentially useful, but more comparative data for risk stratified subgroups is needed to establish the WCD's effectiveness.

5 CLINICAL EFFECTIVENESS (EFF)

5.1 Research questions

Element ID	Research question
D0001	What is the expected beneficial effect of the WCD on mortality (disease-specific and all-cause)?
D0005	How does the WCD affect symptoms and findings (severity, frequency) of VT/VF?
D0006	How does the WCD affect progression (or recurrence) of VT/VF?
D0011	What is the effect of the WCD on patients' body functions?
D0016	How does the use of WCD affect activities of daily living?
D0012	What is the effect of the WCD on generic health-related quality of life?
D0013	What is the effect of the WCD on disease-specific quality of life?
D0017	Were patients satisfied with the WCD?
D0010	How does WCD modify the need for hospitalisation?
D0023	How does WCD modify the need for other technologies and use of resources?

5.2 Results

Included studies

No study fulfilled the study inclusion criteria for assessing clinical effectiveness of the WCD. RCTs and non-randomised CTs were considered for inclusion, but could not be identified through the systematic literature search (see Figure 1: Flow chart).

Non-randomised CTs were listed in the inclusion criteria in the attempt of providing the 'best guess', rather than no answer at all, for the relatively new technology of WCD regardless of its not-very-large effect, even though an RCT would be possible and ideal for assessing clinical effectiveness [3].

Study characteristics (see results in SAF)

Patient characteristics (see results in SAF)

Mortality

D0001 – What is the expected beneficial effect of the WCD on mortality (disease-specific and all-cause)?

No evidence was found to answer the research question.

Morbidity

D0005 – How does the WCD affect symptoms and findings (severity, frequency) of VT/VF?

No evidence was found to answer the research question.

D0006 – How does the WCD affect progression (or recurrence) of VT/VF?

No evidence was found to answer the research question.

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

No evidence was found to answer the research question.

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

No evidence was found to answer the research question.

Health-related quality of life

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

No evidence was found to answer the research question.

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

No evidence was found to answer the research question.

Satisfaction

D0017 – Were patients satisfied with the technology?

No evidence was found to answer the research question.

Change-in-management

D0010 – How does WCD modify the need for hospitalisation?

No evidence was found to answer the research question.

Resource utilisation

D0023 – How does WCD modify the need for other technologies and use of resources?

No evidence was found to answer the research question.

5.3 Discussion

Although the WCD was first approved in 1999 in Europe and in 2001 in the US, valid data on clinical effectiveness and safety of the device are scarce. The WEARIT/BIROAD study (including 289 patients), completed in 2001, in which pre-specified safety and effectiveness GLs had been met[1] [18], was crucial in getting the FDA approval for the WCD. The current assessment of effectiveness was restricted to prospective CTs, of which none was identified. Due to the lack of RCTs comparing the WCD with the ICD, GL directed pharmacological therapy, GL directed catheter (radiofrequency) ablation, and AEDs (comparator might vary depending on indication), strong evidence on patient benefit is missing. However, there exist many retrospective registry studies (> 15), majority of which are based upon ZOLL Medical Corporation datasets.

[1] The study was designed to test the hypothesis that successful resuscitations would occur in at least 25% of events. The power had to be at least 50% if the true successful resuscitation rate was 43%.

Though no evidence from comparative trials is available, the data gathered in non-comparative studies [18-22] – also extracted for information on safety – are presented here. The following effectiveness outcomes were compiled: mortality during the course of the study (all-cause and disease specific i.e. prevention of SCA), incidence of VT/VF, appropriate shocks, withheld shocks (due to patients using the response button to delay therapy), first shock success, patient compliance (WCD wear-time, WCD daily use), avoidance of ICD implantation, and improvement in LVEF.

All-cause mortality ranged from 0 to 4.2% across the five studies. Due to the small sample size in three studies [19-21], the lack of comparator, and the variety of enrolled patient groups (with regard to co-morbidities, disease progression, diagnosis) in all five included studies (for the assessment of safety), no valid statement can be made whether mortality increased or decreased. Same applies for disease specific mortality which ranged from 0 to 2.1% in the five studies. Furthermore, only one study reported on resuscitated cardiac arrest: two patients experienced unsuccessful shocks due to incorrect placement of therapy electrodes, but one of the events was nonfatal since the patient received a successful external defibrillation [18]. Incidence of VT/VF ranged from 2.1% [22], to 8% [20], to 43% [19], however, each patient could have had more than one VT/VF event. Appropriate shocks ranged from 1.1 to 8% [18, 20, 22] up to 43% [19], whereas one registry study did not report on this outcome [21]. One registry study reported on withheld shocks (1.1%) [22], whereas it was not reported if the use of the response button was indicated i.e. used correctly. The first shock success rate was 100% in three studies [19, 20, 22], whereas it was not mentioned in the remaining two studies [18, 21]. Compliance was measured as the WCD wear-time and WCD daily use, no subjective patient data was collected. The WCD wear-time was indicated as mean or median days ranging from 33 to 94. Four of five studies reported the WCD daily use of 21.8 to 23.1 hours (mean/median) [19-22]. Avoidance of ICD implantation was shown in one study (40%) [22], unclear in three studies [19-21], and not reported on in one study [18]. Improvement in the LVEF was indicated in three studies as mean or median (5-22.5%) [19-21] and left unreported in two studies [18, 22]. For the outcome satisfaction with the technology, no standardised measure (like a standardised questionnaire etc.) was applied in any of the five studies and could therefore not be compiled. No information on hospitalisation or HRQoL was reported.

It would be important to have the information on long-term mortality (> 1 year) from prospective studies. One study stated that the patients who died had an LVEF improvement at the time of the WCD end of use [21], further patients died after WCD use due to unknown causes. This could suggest that even though patients´ LVEF improved, it does not imply that the patients no longer need an ICD. So the measure of improvement of LVEF could be questioned, since first of all, the improvement might not last life-long and second of all, other indications might emerge that could make the ICD an option. Patients' follow-up and the identification of cause of death would be important. The value of the LVEF represented inclusion criteria for the ICD trials in the past, which might be one of the reasons why it is used in the WCD trials as well. LVEF was measured before and after the WCD use in all four studies – except in one where it was only measured at the beginning [18]. The discussions regarding the use of LVEF as a criterion for the ICD implantation and as a predictive value for arrhythmic events are ongoing [59]. This issue also questions the "watch and wait strategy" in which patients are monitored whether their disease status improves.

Patients suffering from a heart disease often have comorbid diseases like diabetes, hypertension etc., which were not reported in two out of five studies [19, 20], whereas these studies mentioned that patients entered the study at a similar point in the disease. Only one out of five included studies grouped patients according to disease aetiology: ischaemic CM, NICM, congenital/inherited heart disease [22]. The remaining studies did not distinguish between subgroups.

Furthermore, no information on historic controls on SCA in different patient groups was provided in any of the five studies in order to compare how many SCAs could be avoided. The WCD was shown to have very little impact in the treatment of SCA, maximum of 2% of patients, who wore the LifeVest® received appropriate shocks in almost any cohort (see discussion of CUR). There are ongoing efforts to find a calculation method in order to transfer "time to event rates" into a useful standard (e.g. risk per month).

Only one study out of five clearly stated the avoidance of ICD implantation (due to improved cardiac function) in patients who have been indicated for an ICD before the WCD use [22]. The

others stated ICD avoidance, but it is not clear whether the patients have been indicated for an ICD at the start of the WCD use. Furthermore in one study, refusal of an ICD was added to the ICD avoidance group [20], which should only include patients whose health condition improved and therefore did not need the ICD anymore. Two studies showed that there is no benefit of an ICD implantation within 40 days after MI [60, 61]. In 2016, an RCT demonstrated that prophylactic ICD implantation in patients with symptomatic systolic heart failure not caused by CAD was not associated with a significant reduction in long-term mortality [62]. The challenge is to target ICDs to the patients who will most likely benefit from them [63].

The existing registry studies are lacking some important information such as device model used, settings of the monitor, how often the response button was used, number of false alarms, possible device-device interactions, information whether an ICD was indicated at the beginning of the WCD use and possibly could be avoided after WCD use, and information on disease status (how far advanced the disease is) at baseline. Information on patient indication and outcome is crucial in order to narrow down and further specify the indications for the WCD use. Data on HRQoL and satisfaction should be collected by using standardised methods.

These studies did not provide valid data on clinical effectiveness; therefore no evaluation could be performed. RCTs and non-randomised CTs should be pursued in order to provide a strong evidence base. Two RCTs, which are expected to yield robust clinical data, are already ongoing (see Table 8: List of ongoing studies with WCD in Appendix 1). Both RCTs use conventional treatment as the comparator. One study aims to be completed in December 2017 (2300 patients with ventricular dysfunction immediately following MI) and the other one in October 2019 (2600 patients with end stage renal disease beginning haemodialysis). Prospective studies with long-term mortality measures including well defined disease groups are necessary in order to determine the patient groups that would benefit most from the intervention.

6 SAFETY (SAF)

6.1 Research questions

Element ID	Research question
C0008	How safe is the WCD in relation to the comparator(s)?
C0002	Are there harms related to dosage or frequency of applying the medical device-WCD?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the WCD?
C0007	Are the WCD and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of the WCD and the comparator(s)?

6.2 Results

Included studies

The study inclusion criteria for assessing safety differed from the one for assessing clinical effectiveness. In addition to RCTs and non-randomised CTs, prospective studies without a control group (interventional single arm studies, case series, and registry studies) were considered for the assessment of safety. The systematic literature search (see Figure 1: Flow chart) identified one prospective interventional single arm study [18], two prospective case series [19, 20] and two prospective registry studies [21, 22], which matched our inclusion criteria. Study characteristics and results of included studies are shown in Table 2. Main characteristics of studies included and in Table 7: Characteristics of included studies in Appendix 1.

Study characteristics

The prospective interventional single arm study included 289 patients (52 women and 237 men). Overall, 36 patients were reported on in the prospective case series, of which 14 were women and 22 were men. The registry studies included 2089 patients, of which 623 were women and 1466 were men. Four of five studies were sponsored by ZOLL Medical Corporation, whereas funding was not stated for the fifth study [20]. Countries of recruitment were United States [21, 22] and Germany [19, 20], or both [18]. Clinical follow up time ranged from 2.9 to 10.4 months (mean/median) [19-22], whereas it was unclear for one study [18]. The 12 month follow up is currently ongoing for one study [22]. Loss to follow up ranged from 0 to 23.5% with no information provided in two of the studies [20, 22]. Model versions of the technology (generations of LifeVest®) were not reported in any of the studies. However, one study reported that they used commercially available market released WCD devices [22]. The three multi-centre studies included 289, 89, 2000 patients respectively [18, 21, 22], and the single-centre studies 12 and 24 patients respectively [19, 20].

Patient characteristics

The age range of patients varied from 18-75 [18] to 37-83 years [21], whereas no age range was reported in the remaining studies. All studies indicated mean or median ages for their patients between 34 and 69 years, whereas the statistical measure was not clear in one study (i.e. whether it was median or mean) [18]. The mean or median LVEF at baseline was stated between 23 and 30%, whereas the statistical measure was again not clear in one study (i.e. whether it was median or mean) [18].

Patient inclusion criteria showed some heterogeneity in terms of the LVEF (< 30% [18], ≤ 40% [21], other studies left unreported) and form/nature of heart disease (newly diagnosed PPCM [19],

early post-MI phase [20], and a combination of several heart disease groups [18, 21, 22]. However, all patients had a high risk of SCA.

Only two studies stated patient exclusion criteria, which mainly referred to having an active ICD or being unable to use the WCD due to impairment [18, 21]. Only three out of five studies [18, 19, 21] indicated previous treatments.

Patient safety

C0008 – How safe is the WCD in relation to the comparator(s)?

No evidence was found to answer the research question with regard to comparison of the WCD with comparators, since the included studies did not have a control group.

The following AEs were reported: Skin rash and itching, false alarms, palpitations, light-headedness, and fainting, and discontinuation due to comfort and lifestyle issues.

One study indicated skin rash and itching in 6% of patients [18], the other studies did not report on this AE. False alarms were reported in one study with 14% of patients having experienced numerous false alarms [19], the remaining four studies did not provide any information on this AE. Only one study reported on palpitations, light-headedness, and fainting in 9% of patients [21], the other four studies did not report on this AE. Two studies indicated discontinuation of the WCD use due to comfort and lifestyle issues, namely in 22% of patients [18] and in 16% of patients [21]. None of the studies reported on unexpected AEs.

SAEs that occurred were inappropriate shocks and unsuccessful shocks. Inappropriate WCD therapy was only defined in one study, in which it was classified as non-VT/VF episodes detected and treated by a WCD shock [22].Two studies indicated that 2% [18] and 0.5% [22] of patients respectively experienced inappropriate shocks, whereas the remaining three studies reported no inappropriate shocks. Unsuccessful shocks were reported in four out of five studies. One study indicated that 0.7% of patients [18] experienced unsuccessful shocks due to incorrect placement of the therapy electrodes. Three studies reported no unsuccessful shocks [19, 20, 22] and one study did not report on this outcome.

All five studies reported on the outcome frequency of SAEs leading to death, where death occurred in one study (0.3%) [18].

C0002 – Are there harms related to dosage or frequency of applying the medical device-WCD?

The study reporting about skin rash and/or itching, which was indicated as the major objective complaint with the use of the WCD, did not mention any time-dependent issues, whether it would get better or worse with increased use [18] – same with occurrence of palpitations, light-headedness, and fainting [21].

C0004 – How does the frequency or severity of harms change over time or in different settings?

There are several differences in the device generations. The main difference is the change from monophasic waveform to bi-phasic waveform (from the 3rd generation). However, the included studies did not state the device generations used and therefore no statement can be made.

There is no evidence that harms increase or decrease in different organizational settings.

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of the WCD?

It was shown that patients with ischaemic and congenital/inherited heart disease had significantly higher probabilities of sustained VT/VF than those with NICM. Furthermore, compliance was independent of disease aetiology (ICM, NICM, inherited/congenital heart disease) [22]. Patients who

have a more advanced disease status (since they might have other indications or comorbidities as well) might be at a higher risk to be harmed from the use of the WCD. Same applies for non-compliant patients who might be at higher risk for unsuccessful shocks (e.g. when incorrectly placing therapy electrodes), or for inappropriate shocks (e.g. when incorrectly using response button), or for skin rash/itching when incorrectly washing the garment. Women could also be more likely to be harmed because of their body shape (e.g. due to fitting problems of the WCD).

C0007 – Are the WCD and comparator(s) associated with user-dependent harms?

Patients themselves might cause harms: One study reported unsuccessful shocks in 0.7% of patients due to incorrect placement of therapy electrodes [18]. Furthermore, the WCD needs to be worn all day and night, except when taking a bath/shower. Therefore, patient compliance is of the utmost importance. The WCD daily use was reported in mean and medians in four out of five studies, whereas it varied between 21.8 and 23.1 hours [19-22]. User information and training is important.

Activation of the response button could lead to user dependent harms, since patients might push the button when not indicated and avert a possible life-saving treatment. Results of the Focus group showed that patients do not want to have the responsibility of making this decision. Only one out of five studies described the number of withheld shocks (1.1%) [22]. Inappropriate bystander intervention could pose an additional risk.

Professionals might cause harms because of their responsibility of setting up the monitor and choosing the settings (default settings can be used as well). Settings that may be modified in the monitor of the WCD are VT response time (60-180 seconds, default: 60 seconds), VF response time (25-55 seconds, default: 25 seconds), VT rate threshold (120-250 beats per minute, default: 150 beats per minute), and VF rate threshold (120-250 beats per minute, default: 200 beats per minute) [48].

B0010 – What kind of data/records and/or registry is needed to monitor the use of the WCD and the comparator(s)?

The existing registry studies are lacking some important information such as device model used, settings of the monitor, how often the response button was used, number of false alarms, possible device-device interactions, information whether an ICD was indicated at the beginning of WCD use and possibly be avoided after WCD use, and information on the disease status (how far advanced the disease is) at baseline. Information on patient indications and outcomes is crucial in order to narrow down and further specify the indications for WCD use. Data on HRQoL and satisfaction should be collected using standardised methods.

6.3 Discussion

For the evaluation of safety data, one prospective interventional single arm study [18], two prospective case series [19, 20] and two prospective registry studies [21, 22] were included as the best available evidence.

There was a lack of reporting on AEs in the included studies. The registry study with most patients (2000 patients) reported only on SAEs [22]. Each one of the three smaller studies reported on different AEs, skin rash/itching, false alarms and palpitations, light-headedness, and fainting, respectively [18, 19, 21]. Another study revealed that allergic contact dermatitis could be caused by metal hypersensitivity in the WCD use [64]. There are also some hints that compliance with the WCD use is connected to temperature i.e. less wear time in summer than in winter [65] that might also have an impact on the skin related AEs. Three out of five included studies reported on previous treatments [18, 19, 21], whereas it was not clearly stated in all studies if or which treatment patients received during the WCD use, which might have affected some of the outcomes (i.e. pharmacological therapy might lead to side effects).

The named AEs and SAEs were relevant for patients, but some might have been missed. Avoidance of an ICD might be more relevant for payers than for patients according to the results of the Focus group, where patients favoured the ICD. However, comparative studies are missing in order to assess the clinical effectiveness and safety with regard to comparators.

Discontinuation due to comfort and lifestyle issues could be due to several reasons: the WCD needs to be worn 24/7 and therefore affects daily life and routine, and there might be some restrictions doing sports or other leisure activities. Results of the Focus group show that patients would have some hesitations in using the WCD in public. User dependent harms could be in part connected to compliance and personal attitude. However, qualitative studies on HRQoL and satisfaction were missing.

There is homogeneity in results with regard to unsuccessful shocks (in 0-0.7% of patients), inappropriate shocks (in 0-2% of patients), and frequency of SAEs leading to death (in 0-0.3% of patients). Other safety issues are bystander interference and unsuccessful shocks caused by signal disruption due to falling and wedging bodies [24]. However, inappropriate shocks might also vary per subgroup. The WCD has a higher risk of motion-related sensory artefacts than an ICD since it is placed outside of the body [6]. External noise detection could also lead to inappropriate shocks [23]. A fatal device-device interaction between an WCD and a unipolar pacemaker was observed in a patient using both technologies simultaneously. The study suggested that identification of these interactions in patients with congenital heart disease and poor cardiac function is important because there is no access for placement of transvenous pacing leads due to the Fontan palliated single ventricle. Furthermore, children frequently have unipolar epicardial leads [46]. Also, a study showed that cellular telephones can interfere with medical equipment. However, only ZOLL Medical Corporation M-Series defibrillators (AED) were analysed, which showed no interference with cellular telephones [66]. Possible interactions with the WCD were not evaluated and therefore cannot be excluded.

Double reporting was considered in the five studies, but seen as unlikely, since those studies whose study duration overlapped [19, 20, 22] were either performed in different countries, or had different inclusion criteria. One further prospective uncontrolled study (84 patients) was identified [67], but not considered due to several reasons: the study declared that one part of patients was included in the WEARIT/BIROAD study [18] and therefore included double reporting. Another reason was German language (which would not have allowed all assessment authors to read and check). Studies dealing with induced VT/VF in a hospital setting were also disregarded [39, 47].

It must be noted that ICDs are also subject to inappropriate shocks, which may arise from an ICD sensitivity to atrial fibrillation (AF), supraventricular tachyarrhythmias, sinus tachycardia, and benign VAs that would otherwise self-terminate in the absence of a shock. This could be overcome by changing the settings in order to reduce the sensitivity of the device's sensing mechanism [68].

Furthermore, it should be kept in mind that comparators do have other specific harms, which the WCD does not have. In case of ICDs, these are device infections (pocket infection, deeper infection) [38] and procedure related complications including deaths and right ventricular perforation. Pharmacological therapy has side effects especially in elderly patients [69]. Possible complications of catheter ablation are stroke, valve damage, cardiac tamponade, atrio-ventricular block (AV) and procedure-related mortality [1].

7 PATIENT INVOLVEMENT

Results and integration into HTA

Ten patients (nine men and one woman) replied to the request from the standardised email (see METHODS AND EVIDENCE INCLUDED). The woman received a heart transplant recently and therefore was not able to make the journey to the premises of LBI-HTA in Vienna (Austria), where the Focus group meeting was held. Finally, five patients were available at the proposed timeslot and agreed to participate. Four patients were from Austria (one from Lower Austria, Styria, Upper Austria, and Vienna, respectively) and one patient from Germany (Bavaria). All patients have received a heart transplant in the past and four patients have had an ICD at some point before. Men were aged between 55 and 73 years (mean 65).

No patient had an experience with using a WCD or was familiar with this technology. Patients were properly prepared to explain their disease history. The majority of patients were exercising competitive sports. Furthermore, since only men participated in the Focus group, no gender-dependent issues could be evaluated.

Views on patient relevant endpoints were identified:

- Avoidance of an ICD implantation: Patients highlighted the sense of security they experienced through the use of an ICD, because patients were facing fear and anxiety due to their heart disease (fear of diagnosis itself, of reduced physical performance, of repeatedly having symptoms, of worsening, of death – when having a family and responsibility, for the future). All concluded that feeling of security was crucial. One patient stated that the ICD was like a “life insurance”.
- HRQoL: Patients who had an ICD were able to do sports and to live a normal life with few/no limitations in everyday life (e.g. independent mobility), which was of the utmost importance to them.
- Inappropriate/unsuccessful shocks: Patients reported on having received shocks by the ICD at several occasions, which differed in strength and impact on the body. Furthermore, several complications with ICD devices were described. Patients disclosed that receiving a defibrillation shock was terrifying.
- All patients felt that the waiting times for heart transplants were far too long although they acknowledged the scarcity of heart transplants. They agreed that since they have had received their transplant, their QoL improved dramatically.

Towards the end of the Focus group, the WCD was explained and presented, and patients were asked to comment on their attitude with regard to the WCD and to pose questions:

- Compliance: Most patients could image using the WCD on a short term basis, but stated that it would be less of an option for long-term use due to the efforts of wearing it (especially in warm weather). Furthermore, its possible weight was mentioned as an issue as well.
- HRQoL: Patients would feel restricted in their working life, when driving a car, or doing sports, and would fear removing the WCD. Patients stated that they do not want to be constantly reminded of their disease – at some point one forgets of having an ICD, which however is not possible when wearing the defibrillator – and that they do not want to exhibit it to others in public. One patient described his inferior QoL with external components of the technology (i.e. with an artificial heart).
- Patients not having any experience with using the WCD reported that they have some reservations towards the WCD. Their trust in the ICD would be higher than in the WCD. The response button, which is integrated in the WCD, was a big topic of discussion. Patients declared that they would be afraid of unintentionally deactivating it and of not wanting to have the responsibility of deciding whether to push the response button or not, because they assumed that they do not have the knowledge and the decision-making competence as clinicians do.
- Furthermore, patients asked whether the WCD has pacing capabilities, which it does not have.

8 POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL, AND LEGAL ASPECTS (ETH, ORG, SOC, LEG)

8.1 Research questions

Element ID	Research question
Ethical assessment elements	
F0010	What are the known and estimated benefits and harms for patients when implementing or not implementing the WCD?
F0011	What are the benefits and harms of the WCD for relatives and care givers?
F0012	How does implementation or withdrawal of the WCD affect the distribution of health care resources?
F0104	Are there any ethical obstacles for evidence generation regarding the benefits and harms of the WCD?
F0017	What are the ethical consequences of the choice of endpoints, and comparators in the assessment?
F0005	Is the WCD used for individuals that are especially vulnerable?
Organizational assessment elements	
G0002	What kind of involvement has to be mobilised for patients/doctors and/or caregivers?
G0003	What kind of process ensures proper education and training of staff?
H0203	What specific issues may need to be communicated to patients to improve adherence?
G0004	What kinds of co-operation and communication of activities have to be mobilised?
H0002	What is the burden on care-givers?
G0101	What are the processes ensuring access to the WCD for patients/participants?
G0009	Who decides which people are eligible for WCD and on what basis?
H0012	Are there factors that could prevent a group or person from gaining access to the WCD?
G0012	In what way is the quality assurance and monitoring system of the WCD organised?
Patient and Social assessment elements	
H0200	What are the experiences of living at risk of SCA?
H0100	What expectations and wishes do patients have with regard to the WCD; what do they expect to gain from the technology?
H0006	How do patients perceive the WCD?
Legal assessment elements	
I0026	What should be known about the legal issues in the case of WCD where the current legislation is not directly applicable?
F0101	Does the WCD invade the sphere of privacy of the patient?

8.2 Results

Ethical assessment elements

F0010 – What are the known and estimated benefits and harms for patients when implementing or not implementing the WCD?

F0011 – What are the benefits and harms of the WCD for relatives and care givers?

F0012 – How does implementation or withdrawal of the WCD affect the distribution of health care resources?

In the analysis of the ethical implications of the WCD, the *principles of beneficence* and *non-maleficence* have to be weighted. The WCD promises to offer manifold benefits for patients at risk of SCA awaiting an ICD, a heart transplant, response to pharmacological therapy, or response to catheter (radiofrequency) ablation. As with many other new technologies – due to the lack of good quality evidence – the uncertainties of the realisation of the promise have to be balanced against the psychological benefit of the feeling of certainty and the possibility for patients to live in their normal environment [5]. These highly subjective benefits must be contrasted with some smaller harms (skin rash, itching, false alarms, palpitations, light-headedness, fainting), but also with serious harms (inappropriate shocks and/or unsuccessful shocks) that may induce further arrhythmias and possibly lead to death – leading to psychological stress and fear or anxiety of technical malfunctions [70].

The eventual *autonomy* and freedom gained in living a normal life through moving in the out-of-hospital setting needs to be balanced against the patient's responsibility of having to decide between appropriate or inappropriate shocks. The feature of using response buttons in order to prevent inappropriate shocks is claimed to be the WCD's benefit, but results from the discussion with patients in the scoping phase point to the contrary. Patients that would have qualified – prior to their heart transplantation and partly had an ICD – for a WCD unanimously stated that they would not want to have the responsibility for pushing the response button in order to prevent an inappropriate shock in the fear of possibly preventing an appropriate therapy. They could imagine using the WCD for short term protection, but implantation of an ICD was undoubtedly the preferable option. This is also supported by research in other areas of disease that shows that 65% of healthy surveyed individuals state that if they had cancer, they would want to choose their treatment, however, only 12% of cancer patients want to choose their mode of treatment [71]. According to Gewande, this discrepancy points to the fact that patients do not value autonomy when their life is in danger, but they rather expect competence on behalf of the medical staff [71]. Furthermore, the *autonomy* is provided at the expense of false security as the patient's understanding of the technology presupposes total protection from lethal arrhythmias and not just protection from VT and VF.

The principle of *beneficence* and *non-maleficence* can be reflected about not only for patients, but also for relatives and care-givers. On the one hand, the WCD allows the relatives to spend more time with the patient, yet on the other hand, the relatives and caregivers are in the position of having to face the possible psychological harm that stems from their need to bear responsibility over the intervention as they are in the position of having to react by pressing the response buttons if needed. Furthermore, the fact that both relatives and caregivers are advised to be present whenever the patient takes the garment off [4] may also contribute to a psychological harm caused by fear or anxiety.

Against the backdrop of the limited knowledge about the right candidates for the technology and a rather big indication group, an issue arises with respect to the principle of *distributional justice* of investing resources in technologies of unknown benefit while not spending the resources elsewhere. Additionally, offering protection (based on promises rather than evidence) to the patients at imminent risk of SCA might be considered unethical. A fair and just implementation of the WCD is dependent on the risk stratification that drives it usage. Even though ZOLL Medical Corporation covers – for the time of market access – the costs for training of cardiologists as well as the maintenance of the device [5], indirect harm is done to the society in case there is too low of a risk for SCA and the resources could have been invested elsewhere. The use of the WCD hence gives rise to ethical issues with respect to principles of *beneficence* and *justice* because of its

wide base of indications that, due to its uncertain or marginal benefit and cost-effective reasons [72], may be difficult to be all covered in practice.

F0104 – Are there any ethical obstacles for evidence generation regarding the benefits and harms of the WCD?

F0017 – What are the ethical consequences of the choice of endpoints, and comparators in the assessment?

The obstacle to conduct a comparative clinical trial in vulnerable patients (of various indication groups) that would be hospitalised due to their physical condition could be overcome by offering the WCD (compared for instance to pharmacological therapy) in a controlled and monitored setting, so that AEs of any intervention could be reacted to fast.

The chosen endpoints – LVEF improvement, reduction of hospitals stays, or avoidance of ICD implantation might not be the endpoints relevant to patients. According to the discussion in the Focus group, QoL, including freedom from anxiety or the ability to perform activities of daily living including sports, is of high importance. The endpoint of avoidance of an ICD implantation ought to be explored more in order to find out if it is a patient relevant endpoint. The reason is that based upon the results from the Focus group, where four patients were once implanted with an ICD, there was no negative reaction associated with an ICD implantation. This suggests that avoidance of an ICD implantation is not necessarily a patient relevant endpoint as the Focus group patients suggested that they see the WCD as a solution for a very short term until the ICD is implanted and not as an alternative (as the WCD claims to be for instance in the period post MI), due to the fact that the protection provided by the ICD is far greater and it bears with itself far less responsibility.

Due to the fact that patients with an LVEF improvement at the end of the WCD use, which lead to the avoidance of an ICD implantation, died of VT or VF post WCD use [21], the endpoint of the LVEF improvement may leave a segment the population unprotected. The fact that a patient's LVEF improves does not mean that the LVEF cannot deteriorate again and hence that the ICD is not needed.

F0005 – Is the WCD used for individuals that are especially vulnerable?

The patients potentially qualifying for the WCD are all at risk of SCA and therefore vulnerable due to their physical, but also their psychological condition (fear, anxiety). Particularly vulnerable are the patient groups of peri- and post-partum women where their unborn, or recently born, child requires mother's care, and older patients with various cardiac comorbidities, who can have reduced decision-making capacity and be cognitively impaired. The WCD is also used in children (since the FDA approval in 2015) that are an especially vulnerable group.

Organizational additional elements

G0002 – What kind of involvement has to be mobilised for patients/doctors and/or caregivers?

G0003 – What kind of process ensures proper education and training of staff?

H0203 – What specific issues may need to be communicated to patients to improve adherence?

G0004 – What kinds of co-operation and communication of activities have to be mobilised?

H0002 – What is the burden on care-givers?

The introduction of the WCD requires involvement of the patient, their family or caregivers, the cardiologist, and the manufacturer (for maintenance) [5]. With the WCD, the tasks that would be otherwise carried out by health care professionals are moved into responsibility of the patient. Therefore, patients and their caregivers need to be trained how to use the WCD and, for the sake

of a successful treatment, comply with the instructions. All are possibly involved in the delivery of the treatment, as the relatives and caregivers are advised to be present when the patient puts the WCD off, and post-treatment, as the patient needs medical treatment post-shock [6].

Patients need to be made aware that complying with the technology requires them to follow a list of instructions from the daily changing and charging of the battery, to washing of the garments, placing of the electrodes, and pressing the response buttons if needed [5].

The WCD does not require new kinds of professionals, but it does require the existing personnel to perform new tasks. It requires the cardiologist to monitor and review the patient's data collected by the device, which may enhance the patient-doctor relationship. It also requires caregivers to help patients with reduced cognitive capacity to comply with the technology. Proper training on the use of the WCD, especially in terms of compliance, might be crucial for good outcomes. As described, implementing of the WCD requires new cooperation between cardiologists and patients, cardiologists and the manufacturer, and patients and the manufacturer.

G0101 – What are the processes ensuring access to the WCD for patients/participants?

G0009 – Who decides which people are eligible for WCD and on what basis?

H0012 – Are there factors that could prevent a group or person from gaining access to the WCD?

Processes insuring access to the WCD are that upon diagnosis, patients receive the device and they are expected to wear it for most of the day (apart from taking a shower/bath or changing the garment) [5]. The studies included in the assessment suggest a high compliance in terms of the device utilisation (see Table 7: Characteristics of included studies in Appendix 1).

The key actors that decide on the use of the technology are, on the macro level, the funding bodies and on the micro level, respective cardiologists. The decision to use a WCD is made upon diagnosis of the patient's risk of SCA, especially if the patient's diagnosis falls under the list of indications outlined above.

Factors that would prevent a group or a person from gaining access to the WCD depend on the price of the device in the respective health care system and the question of patient co-payments, which would make the device accessible only to the financially better-off groups. Also, due to the price of the device, as perceived also by the physicians, the question of cost-effectiveness[2] of the WCD for a Quality Adjusted Life Year and cost-effectiveness thresholds of different countries may make the device hard to access [72, 73].

Furthermore, potential geographical discrimination may be caused by the need to pay a hospital visit post-shock or alternatively, there is a possibility of a gender-related discrimination and stigmatisation due to the fitting of the garment in the chest area of the body.

G0012 – In what way is the quality assurance and monitoring system of the WCD organised?

The main responsibility for quality assurance and maintenance is currently on ZOLL Medical Corporation. The WCD is a rental device and it is returned after patient's use for cleaning and testing of the device, with reconditioning or repair completed when required. Devices must pass an inspection and testing process in order to be sent to another patient. At this point in time during the market introduction phase, the costs of all maintenance and repair are defrayed by ZOLL Medical Corporation [5].

The maintenance needs and costs are not known yet. Such system of centralised monopolistic quality assurance looks effective, but gives reasons for concern to see whether in peripheral geographic regions and in remote areas such quality service is also delivered to patients that are

[2] In the absence of any effectiveness data, assumptions about the device's cost-effectiveness are made based upon the marginal effect of the WCD in the included studies with larger cohorts (less than 2%) (see Table 7: Characteristics of included studies in Appendix 1) and the published cost-effectiveness analyses as referenced above.

not in the ZOLL Medical Corporation distribution countries, as the WCD system and services are provided by trained distributors in Sweden and the UK [5].

Patient and Social assessment elements

H0200 – What are the experiences of living at risk of SCA?

Majority of the endangered population are patients at high risk of CAD who have not had clinical events and hence live with the danger of SCA unaware [10]. Reflections from those patients that survived an SCA event (and so remained to be at risk of further SCAs) include following themes: feelings of insecurity that the heart is not functioning as expected and the need for support. SCA survivors emphasise the need to receive all the health care available [74]. Further themes are: striving to regain former life, being active, fulfilling one's role; gaining a new perspective on life that makes SCA survivors engage in a comprehensive re-evaluation of habits and priorities with the goal of reducing stress and living a healthier life; and going through emotional challenges of fear and anxiety [74]. SCA survivors seem to experience fore-warning symptoms such as heartburn or decreased endurance for hours, days, or even years before the arrest, but pay little attention to them [74].

H0100 – What expectations and wishes do patients have with regard to the WCD; what do they expect to gain from the technology?

H0006 – How do patients perceive the WCD?

Patient expectations include protection from lethal arrhythmias and the ability to remain protected outside of hospital. Compared to alternative interventions, the WCD allows patients to return to home and participate in their social life sooner. Based upon the Focus group results, it is expected that possible issues arising as a consequence of using the technology may be worries about pressing response buttons, anxiety from inappropriate shocks, hope to remain protected during the period of wearing the WCD, and the above mentioned issue of stigmatisation (see **H0012**). The side effects that seem most difficult to manage are skin related side effects, which may lead to allergic dermatitis [64], and comfort and lifestyle related side effects that are most recurrent.

It can be assumed that the patient's understanding of the technology presupposes total protection from lethal arrhythmias and not just a protection from VT and VF. Patients use the only WCD on the market called LifeVest®, name that supports the assumption that the vest will save the patient in a life threatening situation, yet such tangible insurance protects the patient only from the particular lethal arrhythmias.

Legal assessment elements

I0026 – What should be known about the legal issues in the case of WCD where the current legislation is not directly applicable?

F0101 – Does the WCD invade the sphere of privacy of the patient?

In the analysis of legal issues in the case of an WCD, protection of private data and liability need to be highlighted. The WCD does invade the sphere of privacy through gathering of information regarding the individual patient's heart functions and through sending it to the respective cardiologists [5]. However, such handling of personal information may be justified if the benefit of the WCD is proven. Liability for AEs (skin rash, itching, false alarms, palpitations, light-headedness, fainting), SAEs (inappropriate shocks and/or unsuccessful shocks), and issues connected with either of those, such as car accidents caused by inappropriate shocks, require the parties involved to take responsibility. Also, in the absence of comparative data and hence the promise of false security (as outlined in **F0010**), there is a potential issue with liability for harms inflicted on the side of authors, scientists, and the manufacturer.

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

DOCUMENTATION OF THE SEARCH STRATEGIES

Search strategy for Cochrane on 14/07/2016

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

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

#7 #2 or #3 or #4 or #5 or #6 (#1 did not yield any results)

22 Hits

Search strategy for CRD on 14/07/2016

1 (life vest*)

2 (lifevest*)

3 (lifecor*)

4 ((wearable OR portable) NEAR (cardioverter* OR defibrillator*))

5 (wcd)

6 (zoll)

7 #2 OR #3 OR #4 OR #6 (#5 and #7 did not yield any results)

6 Hits

Search strategy for Embase on 14/07/2016

No.	Query	Results
#7.	'life vest*' OR lifevest* OR lifecor OR ((wearable OR portable) NEAR/2 (cardioverter* OR defibrillator*)):ab,ti OR wcd:ab,ti OR zoll:df	501
#6.	zoll:df	175
#5.	wcd:ab,ti	204
#4.	((wearable OR portable) NEAR/2 (cardioverter* OR defibrillator*)):ab,ti	224
#3.	lifecor	20
#2.	lifevest*	75
#1.	'life vest*'	47

Search strategy for Medline on 14/07/2016

1 life vest*.mp. (22)

2 lifevest*.mp. (9)

3 lifecor.mp. (2)

4 ((wearable or portable) adj5 (cardioverter* or defibrillator*)).mp. (121)

5 wcd.ti,ab. (96)

6 zoll.ti,ab. (82)

7 1 or 2 or 3 or 4 or 5 or 6 (276)

8 remove duplicates from 7 (274)

Search strategy for identification of ongoing clinical trials on 31/08/2016

ClinicalTrials.gov

(life vest* OR lifevest* OR lifecor OR wearable cardioverter* OR wearable defibrillator* OR portable cardioverter* OR portable defibrillator* OR wcd) [TREATMENT]

15 Hits

WHO ICTRP (Basic Search Mode)

life vest* OR lifevest* OR lifecor OR wearable cardioverter* OR wearable defibrillator* OR portable cardioverter* OR portable defibrillator* OR wcd

13 Hits

EudraCT

No additional studies identified

Search strategy for Guidelines on 19/09/2016

G-I-N:

Search String: (life vest* OR lifevest* OR lifecor OR wearable cardioverter* OR wearable defibrillator* OR portable cardioverter* OR portable defibrillator* OR wcd)

0 Hits

National Guidelines Clearinghouse:

Search String: ((portable OR wearable) AND (cardioverter* OR defibrillator*)) OR wcd OR lifecor OR lifevest OR “Life Vest“

15 Hits

TRIP-Database

((wearable OR portable) AND cardioverter) OR wcd OR lifevest OR lifecor

67 Hits

Hits in total (15 + 62) = 82

FOCUS GROUP QUESTIONS

Semi-structured interview questions for Focus group participants (please note that the Focus group was held in German i.e. the questions were posed in German)

This is a set of questions for patients who were diagnosed with any indication(s) that may lead to SCA, but who have not been treated with the LifeVest®.

A) Engagement questions

1. Could you tell us about yourselves?
    a. What are the heart problems that you have had?
    b. How did you find out about that?
    c. What did a day in your life with these heath challenges before the heart transplant look like?
    d. What help did you need (relatives, care givers, doctors)?

B) Exploration questions

2. Which treatment options have you and your doctor considered?
    a. Could you rank those treatments from best to worst?
    b. What made them better/worse? (AEs, effectiveness, distress, self-care, capacity to work)
c. If hospitalisation was needed, what did it look like?
    d. How difficult were the treatments to follow in practice?
    e. What could have been improved?

3. What would you think about a wearable defibrillator?
    a. Could you imagine wearing it while awaiting heart transplant? Why?
b. For those who wore an Implantable Defibrillator, what was your experience like?
    c. For those who wore an Implantable Defibrillator, can you imagine wearing a wearable defibrillator instead? Why?

C) Exit question

4. Is there anything else that you would like to say about your experience of living with your health condition?

DESCRIPTION OF THE EVIDENCE USED

Guidelines for diagnosis and management

Table 5: Overview of guidelines

Name of society/organisation issuing guidance	Date of issue	Summary of recommendation	Class of recommendation/Level of evidence*
ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure [28]	20 May, 2016 (epub)	A wearable ICD may be considered for patients with heart failure who are at risk of SCA for a limited period or as a bridge to an implanted device.	II b/C
WCD Therapy for the Prevention of SCD – A Science Advisory From the AHA [7]	28 March, 2016 (epub)	Use of WCDs is reasonable when there is a clear indication for an implanted/permanent device accompanied by a transient contraindication or interruption in ICD care such as infection.	II a/C
		Use of WCDs is reasonable as a bridge to more definitive therapy such as cardiac transplantation.	II a/C
		Use of WCDs may be reasonable when there is concern about a heightened risk of SCD that may resolve over time or with treatment of left ventricular dysfunction; for example, in ischaemic heart disease with recent revascularization, newly diagnosed NICM in patients starting GL directed medical therapy, or secondary cardiomyopathy (tachycardia mediated, thyroid mediated, etc.) in which the underlying cause is potentially treatable.	II b/C
		WCDs may be appropriate as bridging therapy in situations associated with increased risk of death in which ICDs have been shown to reduce SCD but not overall survival such as within 40 d of MI.	II b/C

		WCDs should not be used when non-arrhythmic risk is expected to significantly exceed arrhythmic risk, particularly in patients who are not expected to survive >6 mo.	III/C
2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD [1]	29 August, 2015 (epub)	The WCD may be considered for adult patients with poor LV systolic function who are at risk of sudden arrhythmic death for a limited period, but are not candidates for an ICD (e.g. bridge to transplant, bridge to transvenous implant, peri-partum cardiomyopathy, active myocarditis and arrhythmias in the early post-MI phase).	II b/C
		ICD implantation or temporary use of a WCD may be considered 40 days after MI in selected patients (incomplete revascularization, pre-existing LVEF dysfunction, occurrence of arrhythmias 48 h after the onset of ACS, poly-morphic VT or VF).	II b/C
		WCD should be considered for bridging until full recovery or ICD implantation in patients after inflammatory heart diseases with residual severe LV dysfunction and/or ventricular electrical instability.	II a/C
German Cardiac Society – Statement on the use of the WCD [30]	27 February, 2015 (epub)	In patients immediately after explantation of an ICD, if an immediate reimplantation of an ICD is not possible.	II a/C
		In patients on a waiting list for a heart transplant without an ICD.	II a/C
		If LVEF not yet finally assessed, if heart failure with LVEF ≤ 35% is detected but no permanent risk for SCD yet assessed i.e: • Expected improvement of LVEF in patients with myocarditis or in patients with newly diagnosed dilated cardiomyopathy or with supposed tachymyopathy if dysrhythmia can be removed • In patients with expected improvement in consequence of peri-partum cardiomyopathy • In patients within four weeks after revascularisation by means of percutaneous coronary intervention and within 90 days after revascularisation by means of coronary artery bypass surgery • In patients with secondary prophylactic ICD indication when diagnostics not yet finalised • In patients within 40 days of MI	II b/C
		In patients with terminal non-cardiac disease	III/-

		In patients who refuse an ICD therapy due to personal reasons	III/-
AHA/ACC/HRS – Expert Consensus Statement on the Use of ICD Therapy in Patients Who Are Not Included or Not Well Represented in Clinical Trials [75]	9 May, 2014 (epub)	Two statements are made (no level of evidence indicated): • The WCD may be an option as a "bridge to ICD" for selected patients at high risk of SCD due to VAs, although the data are scant. • The WCD may play a role in patients at risk of SCD in the early period after re-vascularization.	-/-
EHRA/HRS/APHRS – Expert consensus on ventricular arrhythmias [76]	30 August, 2014 (epub)	Two statements are made (no level of evidence indicated): • Patients who have impaired LV systolic function after MI (LVEF <0.35) are at higher risk of sudden death in the first 3 months and may benefit from a WCD. • Patients who are treated with coronary revascularization after MI are also at risk, especially if the LVEF is <0.35. These patients may also benefit from a WCD with reassessment of LV function and the indication for an ICD at 90 days post-revascularization.	-/-
German paediatric cardiac society – guide-line on myocarditis (in children and youth) [77]	13 June, 2012	One statement is made (no level of evidence indicated): In life threatening tachyarrhythmia, a temporary use of a LifeVest® or an AED instead of an ICD could be considered.	-/-
Transvenous Lead Extraction: Heart Rhythm Society Expert Consensus on Facilities, Training, Indications, and Patient Management – endorsed by AHA [78]	22 May, 2009 (epub)	One statement is made (no level of evidence indicated): When there is concern for ongoing infection, alternatives to early re-implantation (after 2–3 days) include WCDs, epicardial lead implantation and surgical debridement of vegetations.	-/-
Heart Rhythm Considerations in Heart Transplant Candidates and Considerations for Ventricular Assist Devices: International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates—2006 [79]	September 2006	An implanted or wearable ICD should be provided for Status 1B patients who are discharged home given that the wait for transplantation remains significant. Furthermore the following statement is made: Use of WCDs can serve as a bridge to transplant. This is particularly true for patients with systemic or device infections or in patients whose anticipated waiting time to transplant is short, such as candidates with blood types A and B.	-/C

*For explanations of terms, see Table 6: Description of level of evidence and classes of recommendations [28]

Abbreviations: ACC – American College of Cardiology; AED-Automated External Defibrillator; AHA-American Heart Association; APHRS-Asia Pacific Heart Rhythm Society; EHRA-European Heart Rhythm Association; ESC-European Society of Cardiology; epub-e-publication; GL-Guideline; HRS – Heart Rhythm Society; ICD-Implantable Cardioverter Defibrillator; LVEF-Left Ventricular Ejection

Fraction; MI – Myocardial Infarction; mo-month; NICM-Non-ischaemic Cardiomyopathy; VF-Ventricular Fibrillation; VT-Ventricular Tachycardia; SCA-Sudden Cardiac Arrest; SCD-Sudden Cardiac Death; WCD-Wearable Cardioverter Defibrillator.

Table 6: Description of level of evidence and classes of recommendations [28]

Level of evidence	
Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Evidence tables of individual studies included for safety

Table 7: Characteristics of included studies

	Interventional single arm study	Prospective case series		Prospective registry studies	
	Feldman 2004 [18]	**Duncker 2014 [19]**	**Kondo 2015 [20]**	**Kao 2012 [21]**	**Kutyifa 2015 [22]**
Study characteristics					
Study name	WEARIT/BIROAD	NA	NA	WIF	WEARIT-II
Author	Feldman et al.	Duncker et al.	Kondo et al.	Kao et al.	Kutyifa et al.
Year of publication	2004	2014	2015	2012	2015
Study registration number (register identifier)	NA	NA	NA	NA	NA
Country/ies of recruitment	United States, Germany	Germany	Germany	United States	United States
Sponsor	ZOLL Medical Corporation	ZOLL Medical Corporation	unclear[3]	ZOLL Medical Corporation	ZOLL Medical Corporation
Comparator	none	none	none	none	none
Study design	Interventional single arm study	Single-centre prospective case series	Single-centre prospective case series	Multi-centre [4]prospective registry	Multi-centre prospective registry
Study duration (start and completion date)	NA[5]	09/2012-09/2013	08/2010-11/2014	07/2007-02/2010	08/2011 – 02/2014

[3] source of funding not stated

[4] 10 centres

[5] Feb 1998 to July 2001 according to FDA approval document 80. U.S. Food and Drug Administration. Premarket Approval (PMA). 2016 [cited 22/08/2016]; Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P010030.

Objectives	To assess the effectiveness of the WCD in patients at high risk for lethal VAs.	1. To assess the usefulness of the WCD to bridge a potential risk for life-threatening arrhythmic events in patients with early PPCM, severely reduced LVEF, and symptoms of heart failure.	1. To describe the utility of the WCD therapy in early post-MI phase.	1. To collect SCA events, WCD defibrillation efficacy, and WCD usage data in heart failure patients.	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.
Model version of technology	WCD 2000[5]	NA	NA	NA	NA
Patient characteristics					
Number of pts	289[6]	12[7]	24[8]	89[9]	2000
Age in yrs (range)±SD	55[10] (18-75)±12	34 mean±4	69 mean±12	61.0(37-83) mean±11.1	62 median±16
Sex (female/male)	52/237	12/0	2/22	25/64	598/1402
EF in % (range)±SD	23±10	24.3 mean±11.6[11]	30 (20-36) median	23.9 (7.5-65) mean ±9.4	25 median±10

[6] 177 pts in WEARIT and 112 in BIROAD

[7] WCD recommended to 9/12 pts, 2 refused, hence data available on 7 pts

[8] 66 consecutive patients of whom 24 (36%) were in the early post MI phase

[9] out of 89 pts, data on 82 pts collected, 4 pts lost to follow-up, 3 pts dropped out after wearing the WCD for a couple of hours

[10] in an unspecified statistical measure

[11] unclear, as the number 24.0±11.8% also reported in the paper

Inclusion criteria	WEARIT: Pts≥18-75 yrs, high risk of SCA, not eligible for ICD or waiting for ICD, ambulatory pts with NYHA Class III and IV and an LVEF <0.30 BIROAD: Post MI with VT within 48 hrs and LVEF<0.30 at least 3 d post MI or SCA or syncope at least after 48 hrs post MI but not candidates for an ICD. VT within 48 hrs post CABG and LVEF<0.30 at least 3 d after CABG, had SCA or syncope after 48 hrs post CABG, but were unable to receive an ICD, ICD candidates at home waiting 4 mos+, refused ICD	Pts with newly diagnosed PPCM	Pts with high risk of SCA but not eligible for immediate implantation of an ICD Pts in early post-MI phase	Pts listed (or being considered) for heart transplantation, pts with dilated CM (with VT or EF ≤ 40%), pts receiving inotropes	Low EF and high risk of SCA post MI or post coronary revascularization or new onset non-ischaemic DCM or high risk for SCA until stabilisation or inherited or congenial heart disease
Exclusion criteria	Inability to use WCD (i.e., chest circumference <28 or >48''), advanced directive prohibiting resuscitation, participation in another clinical trial, not seen at least daily by a companion or caregiver, inability to provide informed consent, or non-cardiac terminal illness	NA	NA	Pts with an active ICD or unable to use WCD due to impairment	NA
Follow-up time in months (range), mean±SD	unclear[12]	10.4±3.4 (8.4–12.4)[13]	8 median (4-16)	3	2.9[14]

[12] pts followed biweekly and monthly, but no last follow-up stated

[13] 81 days (25-345) in 7 women receiving a WCD

[14] at 1, 3 and 12 months (12 month follow-up ongoing at time of paper)

Loss to follow-up, n (%)	68 (23.5)	0	NA	7 (8)	NA
Diagnosis	Heart failure, awaiting ICD, post MI, post SCA, post syncope, post CABG	Newly diagnosed PPCM	ST elevation, PCI, CABG	Dilated CM with low EF (<40%)	(Non-)ischaemic DCM, congenial/inherited heart disease
Previous treatments	Beta-blockers, AADs, Inotropes	Beta-blockers, ACE inhibitors, Mineralocorticoid receptor antagonists, Bromocriptine	NA	Active pacemaker, Past/ inactive pacemaker, Prior/ inactive ICD Beta Blockers, ACE inhibitors, ARBs, Anti-arrhythmics (Amiodarone), Inotropes	NA
Outcomes					
Efficacy (data were extracted but not used for assessment of effectiveness)					
Mortality n (%) • All-cause mortality • Disease-specific mortality(prevention of SCA)	 12 (4.2) 6[15] (2.1)	 0 0	 0[16] 0	 0[17] 0	 3 (0.2)[18] 0
Incidence of VT/VF n/in n (%) pts • Appropriate shocks • Withheld shocks	NA 6/4 (1.4) NA	4/3 (43) 4/3 (43) NA	3/2 (8) 3/2 (8) NA	NA NA NA	120/41 (2.1) 30/22 (1.1) 90/22 (1.1)
First shock success (%)	NA	100	100	NA	100
HRQL	NA	NA	NA	NA	NA
Hospitalisation rate	NA	NA	NA	NA	NA

[15] 5 pts were not wearing the device – 4 were non-compliant due to size and weight of WCD and 1 pt reversed the device leads that lead to an unsuccessful shock

[16] 2 patients (8.3%) had a fatal non-arrhythmic event within 3 months after MI

[17] after WCD use, 6 pts died of unknown causes

[18] due to an asystole event and none due to VT/VF

Satisfaction with technology	NA	NA	NA	NA	NA
Compliance/patient adherence • WCD wear-time in d (range), median • WCD daily use in hrs (range), median	94 mean NA	81 (25–345) 22 (16.3-23.6) mean±2.4	33 (20-67)[19] 23.1 (21.6-23.6)	79 (1-277)[20] 21.8 (3.7-23.7)[21]	90 22.5
Avoidance of ICD implantation[22] (%)	NA	unclear[23]	unclear[24]	unclear[25]	40
% of improvement in EF in mean±SD(range)	NA	22.5±9.7 (16.8–28.3)	5 median[26]	13.5±15.7[27]	NA

[19] 1 pt was excluded because of irregularities in device use

[20] 2 pts were still wearing the device at the end of the study

[21] calculated based on pts who wore the device for 7 days or greater (n=75)

[22] WCD is not only a bridge to an ICD implantation

[23] 66.6% of pts without implanted ICD however, PPCM is "associated with up to 90% recovery after causative factors are removed", hence avoidance of ICD implantation is not directly associated to the success of the WCD (see reference: 81. Sperzel J. Value of the wearable cardioverter defibrillator (WCD) as a bridging-therapy before implantation of a cardioverter defibrillator (ICD). Journal of Atrial Fibrillation. 2016;8(5):93-8.)

2 pts who experienced VF events and shock delivery underwent secondary prophylactic ICD/CRT-D implantation after these events. The third patient has been wearing the WCD for one year and refuses ICD implantation. Eight patients who did not have arrhythmic events during follow-up and had demonstrated impressive improvement of LVEF with reduction of heart failure symptoms did not receive ICD. One patient underwent CRT-D implantation for primary prevention due to persistently reduced LVEF

[24] 42% of pts without implanted ICD however, ICD implantation during 40 d post MI is not recommended by guidelines, hence avoidance of ICD implantation might not directly be associated to the success of the WCD

[25] at WCD discontinuation: 41.4% of pts were considered much improved due to improved EF (defined as EF≤35%), acute allograft rejection resolved, or feeling better and one unknown reason. 34.1% went on to receive an ICD implant. Not receiving an ICD does not imply a WCD's success as presumably not all pts were indicated for an ICD.

[26] from baseline 30% (20–36%) to 35% (25–40%)

[27] final data from 70/89 pts

Safety					
AEs in n (%) of pts • Skin rash and itching	17 (6)	NA	NA	NA	NA
• False alarms	NA	1 (14)[31]	NA	NA	NA
• Palpitations, ligh-theadedness, and fainting	NA	NA	NA	7 (9)	NA
Frequency of discontinuation due to AEs in n (%) of pts • Discontinuation due to comfort and lifestyle issues	65 (22)[28]	NA	NA	13 (16)[32]	NA
Frequency of unexpected AEs in n (%) of pts	NA	NA	NA	NA	NA
SAEs in n (%) of pts • Inappropriate shocks	6 (2)	0	0	0	10 (0.5)[33]
• Unsuccessful shock	2 (0.7)[29]	0	0	NA	0
Frequency of SAEs leading to death in n (%) of pts	1 (0.3)[30]	0	0	0	0

Abbreviations: AAD-Anti-Arrhythmic Drug; ACE- Angiotensin-converting Enzyme; AE-Adverse Events, CABG-Coronary Artery Bypass Grafting; CM-Cardiomyopathy; d-days; DCM-Dilated Cardiomyopathy; ECG-Electrocardiogram; EF-Ejection Fraction; HRQL-Health-Related Quality of Life; hrs-hours; ICD-Implantable Cardioverter Defibrillator; LVEF-Left Ventricular Ejection Fraction; MI-Myocardial Infarction; min-minute; NA-not available; NYHA-New York Heart Association; PM-Pacemaker; PPCM-Peri-partum Cardiomyopathy; pre-op-pre-operation; pt-patient; SAEs-serious adverse events; SCA-Sudden Cardiac Arrest, SD-Standard Deviation; V-ventricular; VF-Ventricular Fibrillation; VT-Ventricular Tachycardia; WCD-Wearable Cardioverter Defibrillator; yrs-years.

[28] In WEARIT study: 30%; In BIROAD study: 11%; 65 pts discontinuation due to comfort and lifestyle issues + 3pts discontinuation due to AEs

[29] both occurred in patients who had incorrectly placed the therapy electrodes-one of the events was nonfatal as the patient received a successful external defibrillation

[30] Occurred in a patient who removed the leads

[31] pt experienced numerous false alarms “thus revealed reduced compliance to WCD wearing (16.3 h/day)”

[32] 6 pts due to discomfort and other reasons plus 7 pts due to unknown/other reasons

[33] due to ECG artefacts while none due to induced VT/VF

List of ongoing and planned studies

Table 8: List of ongoing studies with WCD

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT01446965	December 2017	RCT (name: VEST study)	2300	LifeVest®	Conventional treatment	Pts with ventricular dysfunction immediately following MI	1) Sudden death mortality 2) Cardiovascular, all-cause, and other cause specific mortality, incidence of VAs, AEs, compliance
NCT02481206	October 2019	RCT (name: WED-HED)	2600	LifeVest®	Conventional Treatment	End Stage Renal Disease pts beginning haemodialysis	1) SCA mortality 2) Total mortality, clinical status of SCA survivors, Incidence of potentially life threatening arrhythmias, risk of inappropriate therapy, compliance, QoL
NCT01326624	March 2016 No study results posted in ClinicalTrials.gov register	Prospective Cohort (name: SWIFT study)	25	LifeVest®	-	Pts with left ventricular dysfunction or advanced heart failure symptoms (NYHA Class III/IV)	1) Defibrillation for life-threatening VT, assess magnitude and complexity of ventricular and atrial arrhythmias during use 2) Total mortality, compliance, QoL, complications (AEs)
NCT02825966	March 2016 No study results posted in ClinicalTrials.gov register	Prospective observational study (name: HS-WCD)	35	LifeVest®	-	Pts (age ≥ 18 years) with at least seven pts > 40 years. At least five pts with a history of heart failure.	1) Heart sounds
NCT02816047	December 2016	Retrospective Cohort (Pt registry)	450	LifeVest®	-	Comprehensive registry including all pts in all Austrian centers who received a WCD in 2010-2016.	Number of participants treated with WCD-treated VAs

NCT02700880	June 2018 (Estimated primary completion date)	Prospective Cohort (name: WEARIT III registry)	1000	LifeVest® 4000	-	Pts with ischaemic cardiomyopathy and heart failure (including NYHA II, III, IV and an ejection fraction ≤ 35%)	1) Number of clinical events 2) All-cause mortality, Number of inappropriate shocks, WCD shock conversion success rate, NYHA functional class
NCT02073942	December 2017	Prospective Case-only (Pt registry) (name: CRWD)	100	WCD	-	Adult pts with an indication for WCD	1) Number of arrhythmic events and arrhythmic risk factors 2) Total mortality, QoL, depression, anxiety
NCT02149290	December 2016	Prospective case-only (name: TRENDS)	200	Trends-equipped LifeVest® 4000	-	Pts with heart failure who are being cared for in an outpatient environment	1) Precision of heart failure metrics measurements 2) Pt interactions with the Trends user interface, Pt interactions with the wearable defibrillator
ISRCTN91372291	February 2018	Prospective registry	550	LifeVest®	-	Pts who have been prescribed LifeVest® treatment in clinical routine	1) Success rate of appropriate shocks 2) Use of LifeVest® in pts at high risk for SCA in clinical practice, amount of inappropriate shocks, pt safety, compliance, factors influencing non-compliance, circumstances associated with withdrawal of LifeVest®, technical malfunctions and misuses
DRKS00005653	NA	Prospective registry (WEARIT II Europe)	700	WCD	-	All pts to whom the WCD will be prescribed during clinical routine	1) incidence of life-threatening VT events, success of cardioversion/defibrillation, short-term outcome and clinical development 2) Evaluate the 1-year outcome of pts after they have started to use the WCD
NCT01448005	October 2014 Study (enrollment) terminated. No study results posted in ClinicalTrials.gov register	Multi-center prospective registry	69	LifeVest®	-	Pts with an ejection fraction (EF) ≤ 35% following CABG surgery	1) number of pts who experience SCD 2) number of pts who experience inappropriate shocks, hours per day of WCD use, number of pts who experience SCA

Abbreviations: AE-Adverse Events; ECG-Electrocardiogram; CABG-Coronary Artery Bypass Grafting; EF-Ejection Fraction; QoL-Quality of Life; MI-Myocardial Infarction; pt-patient; RCT-Randomised Controlled Trial; SAEs-serious adverse events; SCA-Sudden Cardiac Arrest; VT-Ventricular Tachycardia; WCD-Wearable Cardioverter Defibrillator.

Risk of bias tables

Table 9: Risk of Bias – on study level

	Interventional single arm study	Prospective case series		Prospective registry studies	
Study reference/ID	**Feldman, 2004 [18]**	**Duncker, 2014 [19]**	**Kondo, 2015 [20]**	**Kao, 2012 [21]**	**Kutyifa, 2015 [22]**
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes	Yes	Yes	Yes
2. Are the characteristics of the participants included in the study described?	Yes	Yes	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	Yes	No	No	Yes	Yes
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?[34]	Yes	Partially reported	Partially reported	Yes	Partially reported
5. Were participants recruited consecutively?	No	Yes	Yes	No	No
6. Did participants enter the study at similar point in the disease?[35]	Unclear	Yes	Yes	No	Unclear
7. Was the intervention clearly described in the study?	Yes	Yes	Partially reported[36]	Yes	Yes
8. Were additional interventions (co-interventions) clearly reported in the study?[37]	Unclear	Yes	Unclear	Yes	Unclear
9. Are the outcome measures clearly defined in the introduction or methods section?	Yes	Yes	No	Yes	Yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?[38]	Unclear	Unclear	Unclear	Unclear	Unclear
11. Were outcomes measured before and after intervention?	No[39]	Yes	Yes	Yes	Yes
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Yes	Yes
13. Was the length of follow-up reported?	No	Yes	Yes	Yes	Yes
14. Was the loss to follow-up reported?	Yes	Yes	No	Yes	No
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes? [40]	Partially reported	Partially reported	Partially reported	Partially reported	Partially reported

[34] "Partially reported": Only inclusion criteria mentioned

[35] "Unclear": There is no statement about entering the study at a similar point in the disease

[36] "Partially reported": Intervention is only mentioned by name

[37] "Unclear": It is suspected that a co-intervention was administered but the information is not reported

[38] "Unclear": No information is provided on the methods used to measure study´s relevant outcomes

[39] One relevant outcome was only measured before the intervention. Other relevant outcomes could have only been measured after the intervention.

[40] "Partially reported": Estimates of the random variability are not reported for all relevant outcomes.

	Interventional single arm study	Prospective case series		Prospective registry studies	
Study reference/ID	**Feldman, 2004 [18]**	**Duncker, 2014 [19]**	**Kondo, 2015 [20]**	**Kao, 2012 [21]**	**Kutyifa, 2015 [22]**
16. Are adverse events reported?[41]	Yes	Partially reported	Partially reported	Partially reported	Partially reported
17. Are the conclusions of the study supported by results?	Yes	Yes	Partially reported[42]	No[43]	Yes
18. Are both competing interest and source of support for the study reported?[44]	Partially reported	Yes	Partially reported	Yes	Yes
Overall Risk of bias	High	High	Very high	High	High

[41] "Partially reported": It is deducible that only some but not all potential adverse effects are reported.

[42] Vague conclusion that does not sum up results.

[43] No conclusion provided.

[44] "Partially reported": Only one of these elements is reported.

Table 10: GRADE assessment – on outcome level

Outcome Trial	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**	**Importance**
Adverse Events (AE)							
Skin rash and itching							
1(289pts) [18]	Very serious[45]	NA	Serious	Serious[46]	None	Very low	Important
False Alarms							
1 (12pts) [19]	Serious	NA	Serious	Very serious[46],[47]	None	Very low	Critical
Palpitations, light-headedness, and fainting							
1 (89pts) [21]	Very serious[48]	NA	Serious	Serious [46]	None	Very low	Important
Discontinuation due to comfort and lifestyle issues							
2 (378pts) [18, 21]	Serious[49]	Serious	Serious	Serious[46]	None	Very low	Critical
Serious Adverse Events (SAE)							
Inappropriate shocks							
5 (2414pts) [18-22]	Serious	Serious	Serious	Serious[46]	None	Very low	Critical
Unsuccessful shocks							
4 (2325pts) [18-20, 22]	Serious	Serious	Serious	Serious[46]	None	Very low	Critical
Frequency of SAEs leading to death							
5 (2414pts) [18-22]	Serious[50]	Serious	Serious	Serious	None	Very low	Critical

Abbreviations: NA – not applicable

[45] No definition of skin rash/itching (severity, nature, location etc.) provided. No comparison group, patients not consecutively recruited. No data gathered on psychological issues, eating habits etc. Unclear whether additional interventions have been performed (which could have caused side effects).

[46] Few events; no control group.

[47] Very low sample size

[48] Pts not consecutively recruited; no control group. No definition of nature and severity.

[49] Pts in both studies not consecutively recruited. Pts might have been different with regard to confounding factors

[50] Since no control group – cannot make statement on mortality

Applicability tables

Table 11: 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. The target population of the intervention did not differ from the population enrolled in clinical studies, but the trials did not include patients immediately after explantation of an ICD, if an immediate reimplantation of an ICD was not possible, or patients with certain forms of structural heart disease associated with risk of malignant arrhythmias or primary electric disease.
Intervention	WCD/LifeVest® was used autonomously by patients outside of the hospital in all included studies.
Comparators	• ICD (No comparative studies were available.) • GL directed pharmacological therapy (No comparative studies were available.) • GL directed catheter (radiofrequency) ablation (No comparative studies were available.) External defibrillators to be used in 3 settings: home, public places, and/or used by medical emergency staff during resuscitation (No comparative studies were available.)
Outcomes	Safety outcomes that were most frequently reported in the five studies were discontinuation due to comfort and lifestyle issues, inappropriate shocks, unsuccessful shocks, and frequency of SAEs leading to death. Skin rash/itching, false alarms, palpitations, light-headedness, and fainting were only reported in one study each. The outcomes measured reflect the most important SAEs associated with WCD/LifeVest®.
Setting	The studies included were either single-centre or multi-centre studies enrolling patients in Germany and the United States. Clinical settings were not described in any of the 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.

Abbreviations: GL-Guideline; ICD-implantable cardioverter defibrillator; SAE-Serious Adverse Event; SCA-Sudden Cardiac Arrest; WCD-wearable cardioverter defibrillator.

APPENDIX 2: REGULATORY AND REIMBURSEMENT STATUS

Table 12: Regulatory status of the technology

Country	Institution issuing approval	Authorisation status yes/no /ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
Counties where CE mark is accepted (Notifying body is in Germany)	DQS Med	Yes	The LifeVest® system is indicated for patients 18 years of age and older who are at risk for sudden cardiac arrest.	Being a candidate for or refusing an implantable defibrillator.	Original Approval 1999 WCD 4000 Approval 2011	Yes	285855
United States	FDA	Yes	The LifeVest® system is indicated for patients 18 years of age and older who are at risk for sudden cardiac arrest. The LifeVest® system is indicated for patients under 18 years of age who are at risk for sudden cardiac arrest. Patients must have a chest circumference of 26 inches (66 centimeters) or greater and a weight of 18.75 kilograms (41.3 pounds) or greater.	Being a candidate for or refusing an implantable defibrillator. Chest circumference of less than 26 inches (66cm) and a weight of 18.75kg (41.3 pounds) or less.	Original Approval 2001 WCD 4000 Approval 2009	Yes	P010030
Australia	TGA	Yes	The LifeVest® system is indicated for patients 18 years of age and older who are at risk for sudden cardiac arrest.	Being a candidate for or refusing an implantable defibrillator.	2006	Yes	130613
Israel	MOH	Yes	The LifeVest® system is indicated for patients 18 years of age and older who are at risk for sudden cardiac arrest.	Being a candidate for or refusing an implantable defibrillator.	2010	Yes	NA
Japan	PMDA	Yes	The LifeVest® system is indicated for patients 18 years of age and older who are at risk for sudden cardiac arrest.	Being a candidate for or refusing an implantable defibrillator.	2013	Yes	22500BZI00 017000
Singapore	HSA	Yes	The LifeVest® system is indicated for patients 18 years of age and older who are at risk for sudden cardiac arrest.	Being a candidate for or refusing an implantable defibrillator.	2014	Yes	DE0014998
Canada	Health Canada	Yes	The LifeVest® system is indicated for patients 18 years of age and older who are at risk for sudden cardiac arrest.	Being a candidate for or refusing an implantable defibrillator.	2015	No, date of launch NA	96006
China	CFDA	Yes	The LifeVest® system is indicated for patients 18 years of age and older who are at risk for sudden cardiac arrest.	Being a candidate for or refusing an implantable defibrillator.	2016	No, date of launch NA	20163212082

Abbreviations: CFDA-China Food and Drug Administration; FDA-Food and Drug Administration; HAS-Health Sciences Authority; MOH-Ministry of Health; NA-not available; PMDA-Pharmaceuticals and Medical Devices Agency; TGA-Therapeutic Goods Administration.

Sources: [5]

Table 13: Summary of reimbursement recommendations in European countries for the technology

Country and issuing organisation e.g. G-BA, NICE	Summary of reimbursement recommendations and restrictions	Summary of reasons for recommendations, rejections and restrictions
France, HAS	ICD explant; awaiting cardiac transplant; post-MI with low EF	Therapeutic reason in the selected indications and public health reason due to severity of the pathology.
Luxemburg, NA	ICD explant; awaiting cardiac transplant; post-MI with low EF	NA
Switzerland, NA	• as a temporary treatment measure, if ICD implantation is not immediately possible or in patients with a planned heart transplant and • at high risk for SCA, particularly when ventricular dysfunction, cardiomyopathy, status after MI, myocarditis, patients after surgical or percutaneous revascularization, a LVEF<36%	NA
For countries with indication specific reimbursement include only the recommendations for the indication under assessment Include a reference to any publically available guidance document		

Abbreviations: EF-ejection fraction; HAS-Haute Autorité des Santé; ICD-implantable cardioverter defibrillator; LVEF-left ventricular ejection fraction; MI-myocardial infarction; NA-Not available.
Sources: [5]

In April 2014, Haute Autorité de santé (HAS) in France performed an HTA on WCD 4000, in which they included one prospective study (as included in the current HTA [21]) but added retrospective studies as well [80, 82-84]. For Luxemburg and Switzerland, data from manufacturer's submission file was used, but the assessments as such were not found in the systematic literature search or handsearch, and so no comparative data were retrieved.

Table 14: Summary of recommendations in European countries for the technology in the indication under assessment

Country	Organisation	Summary of recommendations and restrictions	Summary of reasons for recommendations and restrictions
Germany	GKV Spitzenverband and [45]	• explantation of an ICD, if an immediate reimplantation of an ICD is not possible, • when an immediate implantation of an ICD is indicated but not possible e.g. due to contraindications of an operation, • in patients with right atrial or right ventricular thrombus or tumour in whom an immediate implantation of an ICD is indicated but not possible	NA
United States (non-EU HTA)	TEC – Blue Cross and Blue Shield [33]	Not recommended	The available evidence is insufficient to determine whether WCDs improve the net health outcome, or are as beneficial as any established alternatives, when used as a bridge to permanent ICD implantation. There is no direct evidence in CTs to evaluate the efficacy of the WCD in comparison to usual treatment or alternatives.

Abbreviations: EU-European; GKV-"Interessenvertretung der gesetzlichen Kranken- und Pflegekassen"; HTA-health technology assessment; ICD-implantable cardioverter defibrillator; NA-not available; TEC-Technology Evaluation Center; WCD – wearable cardioverter defibrillator.
Sources: [5]

The technology evaluation centre of the Blue Cross and Blue Shield Association did an assessment on the WCD in November 2010, which took into account only two studies [18, 39], the remainder of included studies were RCTs of early ICD implantation for patients at high risk for VAs [61, 85, 86]. They concluded that the studies only focused on detection and abortion of VT/VF, not on its effect and stated that there is a lack of high-quality evidence [33].

APPENDIX 3: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL, AND LEGAL ASPECTS

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes
The use of WCD gives rise to ethical issues with respect to principles of beneficence and justice. That is because of its wide base of indications that, due to its marginal benefit and cost-effective reasons, cannot be all covered in practice. Also, the WCD can only be used by patients who can (mentally and physically) operate it (i.e. push the "false alarm button" if necessary, who wear it appropriately), and hence it prefers those who are cognitively better-off to begin with.	
1.2. Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	Yes
Ethically relevant differences between the WCD and its comparators depend on particular indications. Possible ethical issues may arise by comparing the standard medical therapy with WCD due to the increased number of serious AEs caused by the medical therapy. Further issues may arise by comparing the ICD to the WCD due to the ICD's intrusion on bodily integrity that brings along more mortality related harms at the expense of the ICD's better protection.	
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	Yes
The introduction of the WCD requires training of doctors (i.e. briefing on how the WCD works, how the data can be monitored and evaluated etc.). Furthermore, the doctors might need to dedicate more time to the patients (e.g. extra time for reviewing the data) and so the patient/ doctor communication is enhanced.	
2.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	Yes
Depending on the comparator, free capacity of hospital beds can be generated, less emergency ambulance calls needed.	
3. **Patient and Social**	
3.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	Yes
As the technology alters the person's outlook, its use may lead to stigmatisation particularly in women, as the technology makes the chest area look unnatural. By comparing the WCD to best medical practices, it may cause a possible harm to bystanders which may be considered as a new social issue.	
3.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	Yes
Compared to alternative interventions, the WCD allows patients to return home and participate in their social life sooner.	

4. **Legal**	
4.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	Yes
Introduction of the new technology gives rise to legal issue concerning person's rights and state's duties that will presumably vary upon particular indications. Further legal issues with respect to responsibility and insurance may arise in situations of false shocks when delivered in inappropriate moments such as when driving a car.	
4.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	Yes
Comparing the WCD to existing alternatives leads to legally relevant differences depending on particular indications. With reference to medical therapy, patients may claim their right to be treated by the WCD when faced with the option of medical therapy and its side effects. Patients may claim their right to be treated by the WCD when faced with the alternative of a surgical intervention that intrudes on their bodily integrity. Also, in particular settings with an elevated cultural perception of the notion of liability, patients may be themselves required to be legally responsible for wearing the WCD.	

APPENDIX 4: ADDITIONAL TABLES AND FIGURES

Table 15: Antiarrhythmic drugs for treatment of VT/VF [1]

Anti-arrhythmic drugs (Vaughan Williams class)	Oral dose# (mg/day)[a]	Common or important adverse effects	Indications	Cardiac contra-indications and warnings
Amiodarone (III)	200–400	Pulmonary **fibrosis**, hypothyroidism and hyperthyroidism, neuropathies, corneal deposits, photosensitivity, skin discolouration, hepatotoxicity, sinus bradycardia, QT prolongation, and occasional TdP.	VT,VF	Conditions and concomitant treatments associated with QT interval prolongation; inherited LQTS; sinus bradycardia (except in cardiac arrest); sinus node disease (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); decompensated HF or cardiomyopathy.
Beta-blocker (II)	Various	Bronchospasm, hypotension, sinus bradycardia, AV block, fatigue, depression, sexual disturbances.	PVC,VT, LQTS, CPVT	Severe sinus bradycardia and sinus node disease (unless a pacemaker is present); AV conduction disturbances (unless a pacemaker is present); acute phase of myocardial infarction (avoid if bradycardia, hypotension, LV failure); decompensated HF; Prinzmetal's angina.
Disopyramide (IA)	250–750	Negative inotrope, QRS prolongation, AV block, pro-arrhythmia (atrial **flutter**, monomorphic VT, occasional TdP), anticholinergic effects.	VT, PVC	Severe sinus node disease (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances; previous myocardial infarction; CAD; HF; reduced LVEF; hypotension.
Flecainide (IC)	200–400	Negative inotrope, QRS widening, AV block, sinus bradycardia, pro-arrhythmia (atrial **flutter**, monomorphic VT, occasional TdP), increased incidence of death after myocardial infarction.	PVC,VT	Sinus node dysfunction (unless a pacemaker is present); **AF/flutter** (without the concomitant use of AV-blocking agents); severe AV conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances; previous myocardial infarction; CAD; HF; reduced LVEF; haemodynamically **significant** valvular heart disease; Brugada syndrome; inherited LQTS (other than LQTS3); concomitant treatments associated with QT-interval prolongation.
Mexiletine (IB)	450–900	Tremor, dysarthria, dizziness, gastrointestinal disturbance, hypotension, sinus bradycardia.	VT, LQT3	Sinus node dysfunction (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); severe HF; reduced LVEF; inherited LQTS (other than LQTS3); concomitant treatments associated with QT-interval prolongation.
Procainamide (IA)	1000–4000	Rash, myalgia, vasculitis, hypotension, lupus, agranulocytosis, bradycardia, QT prolongation, TdP.	VT	Severe sinus node disease (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances; previous myocardial infarction; CAD; HF; reduced LVEF; hypotension; reduced LVEF, Brugada syndrome.
Propafenone (IC)	450–900	Negative inotrope, gastrointestinal disturbance, QRS prolongation, AV block, sinus bradycardia, pro-arrhythmia (atrial **flutter**, monomorphic VT, occasional TdP).	PVC,VT	Severe sinus bradycardia and sinus node dysfunction (unless a pacemaker is present); **AF/flutter** (without the concomitant use of AV-blocking agents); severe AV-conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances; previous myocardial infarction; CAD; HF; reduced LVEF; haemodynamically **significant** valvular heart disease; Brugada syndrome; inherited LQTS (other than LQTS3); concomitant treatments associated with QT interval prolongation.
Quinidine	600–1600	Nausea, diarrhoea, auditory and visual disturbance, confusion, hypotension, thrombocytopenia, haemolytic anaemia, anaphylaxis, QRS and QT prolongation, TdP.	VT,VF, SQTS, Brugada syndrome	Severe sinus node disease (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances; previous myocardial infarction; CAD; HF; reduced LVEF; hypotension; inherited Long QT Syndrome; concomitant treatments associated with QT interval prolongation.
Ranolazine (IB)	750 –2000	Dizziness, nausea, constipation, hypotension, gastrointestinal disturbance, headache, rash, sinus bradycardia, QT prolongation.	LQTS3[b]	Severe sinus bradycardia and sinus node disease; severe HF; inherited Long QT Syndrome (other than LQTS3); concomitant treatments associated with QT interval prolongation.
Sotalol (III)	160–320	As for other beta-blockers and TdP.	VT, (ARVC)[c]	Severe sinus bradycardia and sinus node disease (unless a pacemaker is present); AV conduction disturbances (unless a pacemaker is present); severe HF; Prinzmetal's angina; inherited LQTS; concomitant treatments associated with QT interval prolongation.
Verapamil (IV)	120–480	Negative inotrope (especially in patients with reduced LVEF), rash, gastrointestinal disturbance, hypotension, sinus bradycardia, AV block, VT.	LV fascicular tachycardia	Severe sinus bradycardia and sinus node disease (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); acute phase of myocardial infarction (avoid if bradycardia, hypotension, left ventricular failure); HF; **significantly** reduced LVEF; atrial **flutter** or **fibrillation** associated with accessory conducting pathways (e.g. WPW syndrome).

AF = atrial fibrillation; ARVC = arrhythmogenic right ventricular cardiomyopathy; AV = atrio-ventricular; CAD = coronary artery disease; CPVT = cathecholaminergic polymorphic ventricular tachycardia; HF = heart failure; LQTS3 = long QT syndrome type 3; LQTS = long QT syndrome; LV = left ventricle/ventricular; LVEF = left ventricular ejection fraction; PVC = premature ventricular complex; SQTS = short QT syndrome; TdP = Torsade de Pointes; VF = ventricular fibrillation; VT = ventricular tachycardia; WPW = Wolff–Parkinson–White.

[a]Adult drug doses are quoted in this table.

[b]Ranolazine is only approved for the treatment of chronic stable angina. Note that other doses may apply in special conditions.

[c]Sotalol has been indicated for ARVC but its use has been questioned.

Table 16: Non-invasive and invasive evaluation methods [1]

Non-invasive evaluation of patients with suspected or known ventricular arrhythmias

Recommendations	Class[a]	Level[b]	Ref.[c]
Resting 12-lead ECG			
Resting 12-lead ECG is recommended in all patients who are evaluated for VA.	I	A	1
ECG monitoring			
Ambulatory ECG is recommended to detect and diagnose arrhythmias. Twelve-lead ambulatory ECG is recommended to evaluate QT-interval changes or ST changes.	I	A	93
Cardiac event recorders are recommended when symptoms are sporadic to establish whether they are caused by transient arrhythmias.	I	B	94
Implantable loop recorders are recommended when symptoms, e.g. syncope, are sporadic and suspected to be related to arrhythmias and when a symptom–rhythm correlation cannot be established by conventional diagnostic techniques.	I	B	95
SA-ECG is recommended to improve the diagnosis of ARVC in patients with VAs or in those who are at risk of developing life-threatening VAs.	I	B	96,97
Exercise stress testing			
Exercise stress testing is recommended in adult patients with VA who have an intermediate or greater probability of having CAD by age and symptoms to provoke ischaemic changes or VA.	I	B	98
Exercise stress testing is recommended in patients with known or suspected exercise-induced VA, including CPVT, to achieve a diagnosis and define prognosis.	I	B	99
Exercise stress testing should be considered in evaluating response to medical or ablation therapy in patients with known exercise-induced VA.	IIa	C	1
Imaging			
Echocardiography for assessment of LV function and detection of structural heart disease is recommended in all patients with suspected or known VA.	I	B	100, 101
Echocardiography for assessment of LV and RV function and detection of structural heart disease is recommended for patients at high risk of developing serious VAs or SCD, such as those with dilated, hypertrophic or RV cardiomyopathies, survivors of acute myocardial infarction or relatives of patients with inherited disorders associated with SCD.	I	B	100
Exercise testing plus imaging (exercise stress echocardiography test or nuclear perfusion, SPECT) is recommended to detect silent ischaemia in patients with VAs who have an intermediate probability of having CAD by age or symptoms and in whom an ECG is less reliable (digoxin use, LV hypertrophy, >1-mm ST-segment depression at rest, WPW syndrome, or LBBB).	I	B	102
Pharmacological stress testing plus imaging modality is recommended to detect silent ischaemia in patients with VAs who have an intermediate probability of having CAD by age or symptoms and are physically unable to perform a symptom-limited exercise test.	I	B	103
CMR or CT should be considered in patients with VAs when echocardiography does not provide accurate assessment of LV and RV function and/or evaluation of structural changes.	IIa	B	1

ARVC = arrhythmogenic right ventricular cardiomyopathy; CAD = coronary artery disease; CMR = cardiac magnetic resonance; CPVT = catecholaminergic polymorphic ventricular tachycardia; CT = computed tomography; ECG = electrocardiogram; LBBB = left bundle branch block; LV = left ventricular; RV = right ventricular; SA-ECG = signal-averaged ECG; SCD = sudden cardiac death; SPECT = single-photon emission computed tomography; VA = ventricular arrhythmia; WPW = Wolff–Parkinson–White.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Invasive evaluation of patients with suspected or known ventricular arrhythmias

Recommendations	Class[a]	Level[b]	Ref.[c]
Coronary angiography			
Coronary angiography should be considered to establish or exclude significant obstructive CAD in patients with life-threatening VAs or in survivors of SCD, who have an intermediate or greater probability of having CAD by age and symptoms.	IIa	C	104
Electrophysiological study			
Electrophysiological study in patients with CAD is recommended for diagnostic evaluation of patients with remote myocardial infarction with symptoms suggestive of ventricular tachyarrhythmias, including palpitations, presyncope and syncope.	I	B	105
Electrophysiological study in patients with syncope is recommended when bradyarrhythmias or tachyarrhythmias are suspected, based on symptoms (e.g. palpitations) or the results of non-invasive assessment, especially in patients with structural heart disease.	I	C	106
Electrophysiological study may be considered for the differential diagnosis of ARVC and benign RVOT tachycardia or sarcoidosis.	IIb	B	107

ARVC = arrhythmogenic right ventricular cardiomyopathy; CAD = coronary artery disease; RVOT = right ventricular outflow tract; SCD = sudden cardiac death; VA = ventricular arrhythmia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

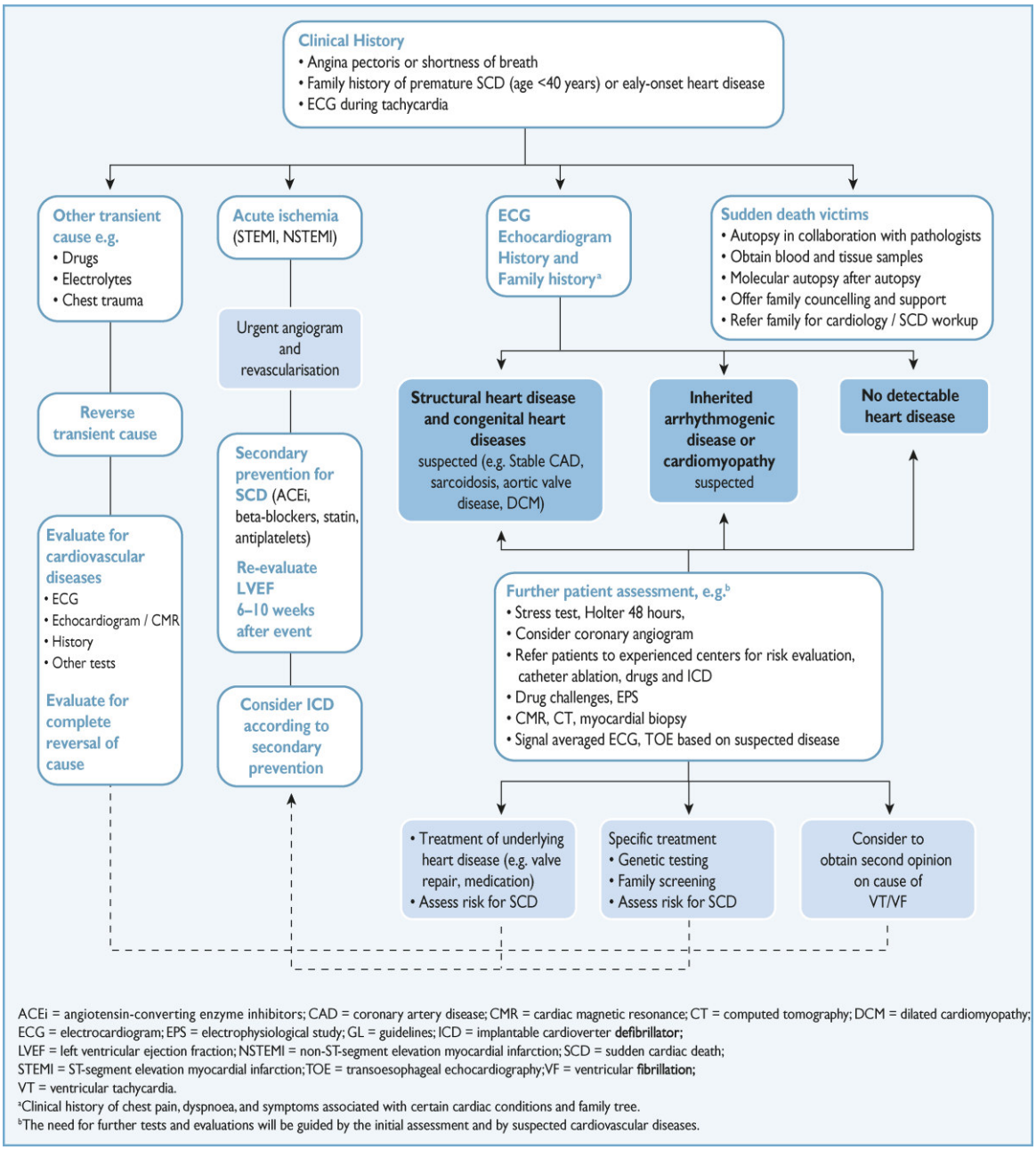

Figure 3: Diagnostic work-up [1]