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

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Inhalt

1 Hintergrund

1.1 Beschreibung des WCDs

WCD: Therapie zur Prävention des plötzlichen Herzstillstandes

Der tragbare Kardioverter-Defibrillator (engl. wearable cardioverter defibrillator = WCD) ist eine Therapie, die in der primären und sekundären Prävention des plötzlichen Herzstillstands (engl. sudden cardiac arrest = SCA) zum Einsatz kommen soll. Der WCD ist in Form einer tragbaren Weste erhältlich und soll von der/dem PatientIn den Großteil des Tages getragen werden (Ausnahmen: Duschen/Baden und dergleichen) [1].

seit 2011 CE-Kennzeichnung

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].

Indikation: Überbrückungstherapie zu einer angemessenen Therapie

Der WCD soll als „Überbrückungstherapie" einen vorübergehenden Schutz vor SCA in den Hochrisiko-Perioden zwischen der Diagnose oder dem Auftreten von ventrikulärer Tachykardie (VT) oder ventrikulärer Fibrillation **(VF) und einer angemessenen Behandlung (oder deren Optimierung) er**möglichen.

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 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, damit der Schock durch Drücken von 2 Antworttasten, die sich am tragbaren Monitor befinden, verhindert bzw. zurückgehalten werden kann. Der WCD kann auf verschiedene VT- oder VF-Zonen programmiert und auf unterschiedliche Zeiten 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

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.

1.2 Gesundheitsbedrohung: plötzlicher Herztod

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 postakutem Herzinfarkt (MI).

Risikofaktoren in jüngeren und älteren Menschen unterschiedlich

Screening bei Angehörigen von SCA Betroffenen

Österreich: 15.000 Menschen plötzlicher Herztod p.a.

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 für ältere 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].

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
Pharmakologische Therapien
RFA
AEDs

- 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].
- (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 zur Verringerung der Häufigkeit koronarer thrombotischer Verschlüsse beitragen [5].
- (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].

Bisherige Evidenzprüfung des WCDs

EUnetHTA Assessment in 2016:

Im Jahr 2016 wurde der WCD vom LBI-HTA im Rahmen von EUnetHTA („European Network for Health Technology Assessment) evaluiert [11].

Ergebnis:

keine Aussagen zu komparativer Wirkung und Sicherheit möglich

Zur Beurteilung der klinischen Wirksamkeit wurden in diesem Assessment die Gesamtmortalität (all-cause mortality) und die 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 (UE) wie Hautausschlag und Juckreiz, Fehlalarme, Herzklopfen, Benommenheit, Ohnmacht und Abbruch wegen Komfort- und Lifestyle-bezogener Beeinträchtigungen ausgewählt. Als schwerwiegende unerwünschte Ereignisse (SUE) wurden unangemessene und erfolglose Schocks definiert. Die folgenden Komparatoren wurden im EUnetHTA Assessment gewählt: ICD, Guideline-basierte pharmakologische Therapie, Radiofrequenz (Katheter) Ablation und an öffentlichen Orten angebrachte externe Defibrillatoren (AED).

Basis: 5 prospektive Beobachtungsstudien ohne Kontrollgruppe

Die Resultate des Berichts 2016 besagen, dass es zu diesem Zeitpunkt keine Evidenz zur Beurteilung der komparativen Wirksamkeit und Sicherheit gab. Der Bericht basierte auf 5 prospektiven Studien ohne Kontrollgruppe, die Aussagen zur vergleichenden Wirksamkeit und Sicherheit des WCDs nicht zuließen.

Avalia-t Update 2017 keine wesentliche Veränderung der Studienlage

Im Jahr 2017 folgte ein Update-Assessment – durchgeführt von der spanischen HTA-Institution Avalia-t [12]. Es wurden 6 weitere prospektive Studien ohne Kontrollgruppe identifiziert. In Ermangelung einer Kontrollstudie änderte sich damit an der Evidenzlage der vergleichenden Wirksamkeit und Sicherheit nichts.

Schlussfolgerung 2016 & 2017: Mangel an solider Evidenz

Beide der bisherigen HTA-Berichte schlussfolgerten, dass es einen Mangel an solider wissenschaftlicher Evidenz zum WCD gibt: Resultate von randomisierten Kontrollstudien sind erforderlich, um die (vergleichende) Wirksamkeit und Sicherheit überprüfen zu können.

2 Methodisches Vorgehen Update 2018

Update 2018 Zusammenarbeit: AGENAS & LBI-HTA

In dem vorliegenden Assessment – eine Zusammenarbeit zwischen der italienischen HTA-Institution AGENAS und dem LBI-HTA – wurde erneut eine systematische Übersichtsarbeit der publizierten klinischen Studien zu Wirksamkeit und Sicherheit der WCD durchgeführt.

AGENAS führte eine systematische Literatursuche in folgenden 3 Datenbanken durch: Cochrane (CENTRAL), Embase, Medline. Eine Handsuche, Internetsuche und Kontaktaufnahme mit dem Hersteller (ZOLL) ergänzte die Literatursuche.

systematische Literatursuche in 3 Datenbanken, Handsuche

Zur Berichterstattung kam das EUnetHTA Core Model© zur Anwendung. Die Hintergrundinformationen wurden vom vorherigen EUnetHTA-Bericht 2016 übernommen und um weitere Informationen ergänzt. Die Studienselektion – also das Abstract-Screening und die Durchsicht der Voll-Texte – wurde von 2 Wissenschaftern (MO, GG) unabhängig voneinander durchgeführt. Im Falle eines Konflikts wurde ein dritter Wissenschafter (TJ) konsultiert.

Anwendung des EUnetHTA Core Models

Die relevanten Daten der eingeschlossenen Studien wurden von einem Wissenschafter (MO) extrahiert und von einem zweiten Wisssenschafter (GG) kontrolliert. Die methodische Qualität der Studien wurde mittels der IHE-20 Checklist für Fallserien und dem Cochrane Risk of Bias Tool bei randomisierten Kontrollstudien von GG bewertet und von MO überprüft. Darüber hinaus wurde die Stärke der Evidenz mit der Grading of Reccommendations, Assessment, Development and Evaluation (GRADE)- Methode durchgeführt – ebenfalls durch 2 Wissenschafter (MO, GG).

alle Arbeitsschritte von 2 Wissenschaftern durchgeführt

3 Ergebnisse

Verfügbare Evidenz, Komparatoren, Endpunkte

Insgesamt wurden 11 Studien identifiziert: eine multi-institutionelle randomisierte Kontrollstudie sowie 10 weitere Beobachtungsstudien.

verfügbare Evidenz

Für die Evidenzprüfung der Wirksamkeit wurden nur (randomisierte) Kontrollstudien berücksichtigt. 1 Studie erfüllte die Einschlusskriterien zur Evaluierung der klinischen Wirksamkeit des WCDs. Die eingeschlossene Studie war eine multi-institutionelle randomisierte Kontrollstudie mit 2.348 StudienteilnehmerInnen (PatientInnen).

Wirksamkeit: 1 RCT

Zur Evidenzprüfung der Sicherheit wurden auch prospektive Beobachtungsstudien herangezogen: Es wurden zusätzlich zum RCT 10 weitere unkontrollierte Beobachtungsstudien im Zuge der systematischen Literatursuche identifiziert, die den Einschlusskriterien entsprachen.

Sicherheit: 11 Studien
1 RCT
10 Beobachtungsstudien

Die gewählten Komparatoren des WCDs waren Ergebnis eines Konsensfindungsprozesses: alle Interventionen, die in klinischen Leitlinien zum Management des Risikos von SCA genannt werden (vgl. [11]) vs. nur „realistische" Komparatoren (Beobachtung im Krankenhaus inkl. pharmakologische Therapien). Die Entscheidung fiel auf letzteres.

Komparatoren:
Beobachtung im KH & pharmakologische Therapien

Die krankheitsspezifische Mortalität (arrhythmische Mortalität) und die Gesamtmortalität wurden als primäre Endpunkte gewählt. Sekundäre Endpunkte umfassten die gesundheitsbezogene Lebensqualität, Hospitalisierungsrate, PatientInnen-Zufriedenheit und Compliance.

Endpunkte Wirksamkeit:
krankheitsspezifische & Gesamtmortalität, QoL, Compliance etc.
(un-) angemessene Schocks, etc.

Zur Beurteilung der Sicherheit wurden unerwünschte Ereignisse (UE) wie Hautauschlag, Fehlalarme, Schwindel, Ohnmacht, Herzklopfen und Komfort- und Lifestyle-bezogene Beeinträchtigungen ausgewählt. Als schwerwiegende unerwünschte Ereignisse (SUE) wurden unangemessene und nicht erfolgreiche Schocks definiert.

Sicherheit:

SUE & UE

Wirksamkeit:

Zur Evaluierung der Wirksamkeit wurde eine randomisierte Kontrollstudie [13] identifiziert: Die Studie verglich den WCD in Kombination mit pharmakologischer Therapie (Guideline-Directed Therapy/GDT) mit Guideline-basierter pharmakologischer Therapie alleine. 2.348 PatientInnen mit Post-Myokardinfarkt und Ejektionsfraktion ≤35% wurden in einer 2:1 Ratio randomisiert. Davon wurden 46 StudienteilnehmerInnen ausgeschlossen und 2.302 PatientInnen analysiert: 1.524 PatientInnen befanden sich in der Interventionsgruppe (WCD+GDT) und 778 PatientInnen in der Kontrollgruppe (GDT alleine). Durchschnittlich lag die Länge des Follow-Ups bei 84.3 Tagen (SD:15,6).

Wirksamkeit 1 RCT:
WCD + pharmakologische Therapie (1.524 pts) vs. pharmakologische Therapie (778 pts)

Der RCT [13] fand **keinen statistisch signifikanten Unterschied beim primären Endpunkt, arrhythmische Mortalität,** zwischen Interventionsgruppe (WCD+GDT) und Kontrollgruppe (GDT alleine); arrhythmische Mortalität: 25 von 1.524 (1,6%) in der Interventionsgruppe vs. 19 von 778 (2,4%) in der Kontrollgruppe (p=0,18). In der Gesamtmortalität konnte **ein statistisch signifikanter Unterschied zwischen** der Interventionsgruppe (WCD+GDT) und der Kontrollgruppe (GDT alleine) gefunden werden: 3,1% vs. 4,9% (p=0,04). Es besteht jedoch erhöhtes Risiko, dass dieses Ergebnis ein Zufallsbefund ist, weil keine Korrektur für multiples Testen vorgenommen wurde.

arrhythmische Mortalität:
kein stat. signifikanter Unterschied

Gesamtmortalität:
stat. signifikanter Unterschied
3,1% vs. 4,9%
aber: Zufallsbefund ?

Es wurden Daten zu zwei der gewählten vier sekundären Endpunkte in der eingeschlossenen Studie berichtet.

- **Gesundheitsbezogene Lebensqualität:** Die gesundheitsbezogene Lebensqualität wurde in dem eingeschlossenen RCT zwar gemessen, jedoch wurden diese Daten in der verfügbaren Publikation nicht berichtet.
- **Hospitalisierungsrate:** Es wurde kein statistisch signifikanter Unterschied zwischen Interventions- und Kontrollgruppe gefunden (31,2% vs. 32,5%; p=0,51).
- **PatientInnen-Zufriedenheit:** Es wurde keine Evidenz zur PatientInnen-Zufriedenheit gefunden. Die eingeschlossene Studie berichtete nicht von diesem Endpunkt.
- **Compliance**: In Summe haben 97,2% der Interventionsgruppe den WCD getragen. Durchschnittlich trugen sie das Medizinprodukt 14 Stunden pro Tag (SD: 9,3). Die mediane tägliche Tragezeit des WCDs betrug 18 Stunden (IQR: 3,8-22,7).

keine stat. signifikante Unterschiede bei Hospitalisierungsrate

Compliance niedrig

Keine Evidenz zu PatientInnen-Zufriedenheit und Lebensqualität

Das GRADE Assessment zur Qualität der Evidenz zur Wirksamkeit besagt, dass in den einzelnen Endpunkten niedrige (Gesamtmortalität, arrhythmische Mortalität), moderate (Hospitalisierungsrate) und hohe (Compliance) Sicherheit besteht.

Sicherheit:

Insgesamt wurden 11 Studien identifiziert, die den Einschlusskriterien zur Evaluation der Sicherheit entsprachen. Für die Beurteilung der komparativen Sicherheit konnte jedoch nur eine randomisierte Kontrollstudie herangezogen werden.

Sicherheit: 11 Studien
1 RCT
10 Beobachtungsstudien

Schwerwiegende unerwünschte Ereignisse (SUE):

Die Ergebnisse des RCT [13] zu schwerwiegenden unerwünschten Ereignissen berichten, dass 3 PatientInnen wegen des WCDs ins Krankenhaus eingeliefert wurden (2 PatientInnen wegen abgebrochener Schocks und 1 PatientIn wegen unangemessenem Schock). 9 PatientInnen/1.524 in der Interventionsgruppe (0.6%) erhielten **unangemessene Schocks.** Es wurde im RCT nicht explizit erwähnt, ob es zu **erfolglosen Schocks** kam. Der RCT berichtete nicht von der Häufigkeit der SUEs, welche zum Tod führten. 1 PatientIn (0,1%) starb jedoch während des Tragens des WCDs.

SUE
1 RCT:
unangemessene Schocks: 9/1.524 (0.6%)
erfolglose Schocks: NR

Aus den Resultaten der 10 Beobachtungsstudien [14-23] hinsichtlich SUEs ist Folgendes zu berichten: 6 der 10 Studien gaben an, dass kein **unangemessener Schock** aufgetreten ist. 4 Studien gaben an, dass die Rate der unangemessenen Schocks zwischen 0,5% und 2% lag. Die Berichterstattung der **erfolglosen Schocks** war auf 2 von 10 Studien beschränkt. Diese gaben an, dass keine erfolglosen Schocks zu verzeichnen waren. Die anderen 8 Studien gaben nicht explizit an, ob Schocks erfolglos blieben. 5 der 10 Studien berichteten von der Häufigkeit der SUEs, welche zum Tod führten (0%).

10 Beobachtungsstudien:
unangemessene Schocks: 0%-2%
Rate der erfolglosen Schocks in 2 Studien berichtet: 0%
Tod aufgrund von SUE: 5 Studien: 0%

Unerwünschte Ereignisse (UE):

Die Ergebnisse des RCT [13] zu unerwünschten Ereignissen berichten, dass PatientInnen in der Interventionsgruppe statistisch signifikant häufiger **Hautausschlag (**13% vs. 3,8%; p<0,001) und **Jucken** (14,5% vs. 3,1%; p<0,001) hatten. Keine statistisch signifikanten Unterschiede waren bei **Schwindel, Ohnmacht, Herzklopfen** festzustellen. Hinsichtlich **Fehlalarm** fehlte eine Berichterstattung. Es wurde im RCT nicht von der Rate der Abbrüche wegen Komfort- und Lifestyle-bezogener Beeinträchtigungen berichtet.

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

Die 10 Beobachtungsstudien [14-23] zeigten ähnliche UEs, jedoch war die Berichterstattung bei vielen Studien unvollständig. Nur eine der 10 Studien berichtete über die Anzahl der Personen, die **Hautauschlag** bekamen (2/102 pts; 2%). Die **Fehlalarm-Rate** wurde von 2 der 10 Studien beschrieben: Eine Studie gab an, dass kein Fehlalarm bei 24 PatientInnen auftrat und eine weitere Studie berichtete von 58 von 102 der in dieser Studie eingeschlossenen PatientInnen (57%), bei denen ein Fehlalarm auftrat. **Schwindel, Ohnmacht, Herzklopfen** wurde in 2 der 10 Studien festgestellt (2-9% in 2 Studien). Ein Abbruch wegen Komfort- und Lifestyle-bezogener Beeinträchtigungen wurde von 3 Studien berichtet (4% bis 18%).

10 Beobachtungsstudien:
Hautausschlag: 2%
Fehlalarm-Rate: 0-57%
Schwindel, Ohnmacht, Herzklopfen: 2-9%

Abbruch wegen mangelndem Komfort: 4-18%

Das GRADE Assessment zur Qualität der Evidenz zu SUE und UE besagt, dass in den einzelnen Endpunkten nur **sehr niedrige** (erfolglose Schocks, Häufigkeit der SUEs, welche zum Tod führten, Fehlalarm, Abbruch wegen Komfort- und Lifestyle-bezogener Beeinträchtigungen) bis **moderate** (unangemessene Schocks, Hautausschlag, Jucken, Schwindel, Ohnmacht, Herzklopfen) **Sicherheit** besteht.

Laufende Studien

Es wurden keine weiteren laufenden (randomisierten) Kontrollstudien gefunden. Ein RCT, das die LifeVest bei PatientInnen im Endstadium einer Nierenkrankheit untersuchen sollte, wurde frühzeitig abgebrochen.

4 Diskussion

Auf Basis der eingeschlossenen Studien sind Aussagen zur Wirksamkeit des WCDs (LifeVest®) gegenüber einer Standardtherapie hinsichtlich der Endpunkte arrhythmischer Mortalität und Gesamtmortalität möglich: Das eingeschlossene RCT hat ein solides Studiendesign und ein ausreichend großes Sample (2.348 PatientInnen, wovon 2.302 zur Analyse herangezogen wurden; 1.524 davon waren in der Interventionsgruppe mit WCD). Die Studie fand keine statistisch signifikanten Unterschiede bei arrhythmischer Mortalität und es liegt nahe, dass der Unterschied in der Gesamtmortalität ein Zufallsbefund sein könnte (aufgrund der fehlenden Korrektur für multiples Testen).

Wirksamkeit: 1 RCT
keine s. s. Unterschiede der arrhythmischen Mortalität zwischen WCD+GDT und GDT alleine

Es ist jedoch darauf zu verweisen, dass selektive Berichterstattung der Endpunkte in der randomisierten Kontrollstudie wahrscheinlich war. Die Lebensqualität wurde im RCT als Endpunkt definiert, jedoch in der Veröffentlichung nicht erwähnt. Nach Kontaktaufnahme mit dem Hauptverantwortlichen der Studie wurde uns mitgeteilt, dass die Daten zur Lebensqualität vorhanden, jedoch noch nicht analysiert sind. Es ist unabdingbar – sowohl für PatientInnen als auch für Entscheidungsträger – auch über diese Daten informiert zu werden.

Daten zur Lebensqualität von RCT erhoben, jedoch nicht publiziert

In Hinblick auf Sicherheitsendpunkte sind eingeschränkt vergleichende Aussagen möglich: Im eingeschlossenen RCT wurden 9 von 1.524 PatientInnen mit WCD (0,6%) einem unangemessenen Schock ausgesetzt. Die Rate der erfolglosen Schocks wurde in der Publikation der Studie nicht berichtet. Hautausschläge und Jucken waren in der Interventionsgruppe (WCD+GDT) signifikant höher als in der Kontrollgruppe (GDT). Keine statistisch signifikanten Unterschiede konnten bei Schwindel, Ohnmacht und Herzklopfen festgestellt werden. Der RCT berichtete nicht von der Fehlalarm-Rate. Die weiteren 10 Beobachtungsstudien berichteten ebenfalls von UEs und SUEs, jedoch ohne Vergleich. In den Beobachtungsstudien wurden die UE nur mangelhaft berichtet.

Sicherheit
SUEs: Unangemessene Schocks, erfolglose Schocks

UEs: z.B. Hautauscchlag, Jucken

Darüber hinaus wurde im Rahmen der Wirksamkeitsevaluierung des WCDs deutlich, dass die Compliance mit dem WCD niedrig ist. Nicht-Compliance mit Therapien ist ein Zeichen dafür, dass die Erforschung der Gründe der niedrigen Compliance (bspw. aufgrund von Nebenwirkungen, die Lebensqualität schmälern) wesentlich ist, um eine mögliche Wirkung des WCDs in einer kleineren Zielgruppe überprüfen zu können. Neben der weiterführend zu evaluierenden vergleichenden Wirksamkeit und Sicherheit des WCDs ist – bei eventueller Wirksamkeit in Subgruppen – die Kosteneffektivität zu berücksichtigen.

niedrige Compliance mit WCD:

Lebensqualität mit WCD?

5 Schlussfolgerungen

Die Evidenz weist darauf hin, dass der WCD in Kombination mit Guideline-basierter pharmakologischer Therapie bei PatientInnen mit Post-MI und Ejektionsfraktion von ≤35% nicht nachgewiesen wirksamer ist als pharmakologische Therapie alleine. Diese Schlussfolgerung basiert auf dem Endpunkt arrhythmische Mortalität, der in einem großen RCT gemessen wurde. Die niedrige Compliance könnte dieses Ergebnis verzerrt haben.

WCD+GDT
NICHT nachgewiesen wirksamer
als GDT alleine
Compliance im RCT niedrig

Neue Studien (RCTs und CTs) könnten die Effektschätzer verändern.

Die Evidenz zur Sicherheit weist darauf hin, dass der WCD eine relativ sichere Intervention ist. Eine bessere Berichterstattung, insb. der UEs und SUEs, ist

WCD relativ sicher

jedoch angebracht, um robustere Aussagen zur Sicherheit des WCDs treffen zu können.

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Ministero della Salute

Agenzia Nazionale per i Servizi Sanitari Regionali

Wearable Cardioverter-Defibrillator (WCD) therapy in primary and secondary prevention of sudden cardiac death in patient at risk

– Rapid HTA report –

March 2019

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List of Abbreviations

ACE	Angiotensin-Converting Enzyme
AE	Adverse Event
AED	Automated External Defibrillator
AGENAS	Agenzia nazionale per i servizi sanitari regionali
AHA	American Heart Association
ARB	Angiotensin II Receptor Blocker
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CE	Conformité Européene
CT	Controlled Trial
CUR	Health Problem and Current Use of the Technology domain
DCM	Dilated Cardiomyopathy
ECG	Electrocardiogram
EF	Ejection Fraction
EFF	Clinical Effectiveness domain
ESC	European Society of Cardiology
EUnetHTA	European network for Health Technology Assessment
FDA	Food and Drug Administration
FV	Fibrillazione Ventricolare
GDMT	Guideline-Directed Medical Therapy
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HF	Heart Failure
HRQoL	Health-related quality of life (HRQOL)
HTA	Health Technology Assessment
ICD	Implantable Cardioverter Defibrillator
ICM	Ischemic Cardiomyopathy
ID	Identification
IFU	Instructions For Use
IHE	Institute of Health Economics
LBI HTA	Ludwig Boltzmann Institute for Health Technology Assessment
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction

MRI	Magnetic Resonance Imaging
NICM	Non-Ischaemic Cardiomyopathy
NIH / NHLBI	National Institutes of Health / National Heart Lung and Blood Institute
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PICOS framework	Population, Intervention, Control, Outcomes, Study design framework
PPCM	Peripartum Cardiomyopathy
pt(s)	patient(s)
QoL	Quality of Life
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SAF	Safety domain
SCA	Sudden cardiac arrest
SCD	Sudden Cardiac Death
SD	Standard Deviation
SVT	Supraventricular tachycardia
TdP	Torsades de Point
TEC	Description and Technical Characteristics of Technology domain
TV	Tachicardia Ventricolare
U.S.	United States
VA	Ventricular Arrhythmias
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
WCD	Wearable Cardioverter-Defibrillator
Yr(s)	Year(s)

Introduction

The present rapid HTA report was carried out following the Agenas' Manual of Procedures [Agenas, 2014] and the procedures outlined in the Agency's Corruption Prevention and Transparency Plan (2017-2019) [http://www.agenas.it/images/agenas/hta/Manuale_procedure_HTA.pdf]. This document was developed following the EUnetHTA Core Model® version 3.0. The Core Model is divided into domains representing each a specific area of technology impact to be assessed. Each domain contains a series of research questions or Assessment Elements identified by a capital letter and number (e.g., A0001). To test the Core Model applicability, an adapted model was elaborated by Agenas (see APPENDIX 1 for a full description). The use of the Core Model is mirrored in the structure of this report, where each chapter corresponds to a domain and reports the Assessment Elements considered for the assessment.

This Rapid Assessment relies on the procedures and methods presented in the Agenas HTA Manual and the EUnetHTA Core Model. The evaluation was carried out by Domains and for each of them a set of Assessment Elements from the Agenas version of the Core Model was selected. In each chapter's methods paragraph a list of the selected Assessment Elements is provided together with the methodology to answer them. We focused on a reduced set of domains: technology, regulation, current use, effectiveness and safety, economic and patient and social aspects.

Summary

Background

The Wearable Cardioverter-Defibrillator (WCD) represents a therapy in primary and secondary prevention of sudden cardiac death (SCD). It is a defibrillation technology that is worn by the patient for most of the day, except when taking a bath/shower when a caregiver or a family member might be present. The WCD monitors the patient's heart continuously and if it detects a life-threatening heart rhythm that it can restore, such as VT or VF, it delivers an automatic treatment shock. As a result, the WCD may reduce the risk of SCD by reverting the life-threatening ventricular tachycardia (VT)/ventricular fibrillation (VF) that are responsible for the majority of sudden cardiac arrests (SCA)s. It is primarily indicated as a temporary measure, inter alia, before the insertion of an implantable cardioverter defibrillator (ICD).

The evidence regarding the WCD was assessed in 2016 by the LBI-HTA within a EUnetHTA "collaborative assessment" and by the Spanish Avalia-t in 2018 as an update assessment. Both reports highlighted the lack of sound scientific evidence and concluded that results from randomised controlled trials (RCTs) are necessary to prove the (comparative) effectiveness and safety of the device in a solid manner.

Due to ongoing research and new results from a previously conducted RCT, there is a need for another assessment of the most recent evidence on the use of the WCD. This report is a rapid systematic review on the effectiveness and safety of the WCD conducted collaboratively by the Italian National Agency for Regional Health Services (AGENAS) and the Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA). LBI manifested the intention of updating its previous EUnetHTA report "WEARABLE CARDIOVERTER-DEFIBRILLATOR (WCD) THERAPY IN PRIMARY AND SECONDARY PREVENTION OF SUDDEN CARDIAC ARREST IN PATIENTS AT RISK" (Project ID: WP4-ACB-CA-1). As Agenas was independently commissioned an assessment on the same topic, the two agencies decided to collaborate in the production of this report.

Methods

The current use of the technology in Italy

The current use of the technology LifeVest® 4000 in Italy was described by using information gathered by a structured questionnaire sent to manufacturers. We also searched information within the Flusso Consumi (the Italian databank for monitoring the use of medical devices) of the NSIS (New Health Information System).

Systematic search

Relevant studies were identified through a systematic literature search in the following databases: Cochrane (CENTRAL), Embase, Pubmed. PsycINFO was also consulted for the evaluation of patients perspective. In addition, a hand-search was conduct and manufacturers were contacted for further information.

Selection criteria and selected outcomes

Studies that enrolled patients using a WCD 4000 as a temporary measure (i.e., before implantation of an ICD, prior to or protection during pharmacological therapy, during prognostic stratification in post-MI patients with an increased risk of arrhythmic death, prior to heart transplantation in patients without ICD) were eligible to be included in this systematic review. For the evaluation of the effectiveness, only RCTs and observational studies with concomitant controls were considered for inclusion. The study inclusion criteria for assessing safety differed from the ones for assessing clinical effectiveness. In addition to RCTs and observational studies with concomitant controls, prospective studies without a control group were judged to be eligible to assess the safety of the WCD.

The chosen indications and comparators of the intervention under investigation (WCD) were a result of a long consensus finding process between AGENAS and LBI-HTA. Finally, we decided to compare the use of WCD with whatever alternative was available in any setting (i.e. hospital or community on guideline-directed medical therapy - GDMT).

For the evaluation of the effectiveness of the WCD, all-cause mortality and disease-specific mortality were selected as the primary outcomes of this systematic review. Secondary outcomes were health-related quality of life (HRQoL), hospitalisation rate, satisfaction, and compliance. For the evaluation of the safety of the WCD, adverse events (AEs) and serious adverse events (SAEs) were selected as outcomes to assess the safety of the WCD.

Study selection, data extraction and quality appraisal

The EUnetHTA Core Model® was used as the methodological framework. Two review authors (MO, GG) screened the abstracts independently and evaluated their eligibility to be included in the assessment. In case of disagreement, a third researcher was consulted (TJ). Risk of bias assessment was conducted by two researchers (GG, MO). For RCTs, the Cochrane risk of bias tool was applied, while the Institute of Health Economics (IHE) checklist was utilised to assess the risk of bias for observational studies. Data of the included studies was then extracted systematically by one researcher (MO) and verified by another researcher (GG). The strength of evidence was

assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Economic evaluation

We carried out the economic evaluation of WCD researching the available evidence and analysing the Italian context. For the analysis of evidence we carried out the literature research, using the same search strategies used to evaluate efficacy and safety, consulting the following databases: Pubmed, The Cochrane Library (CENTRAL) and Embase; for the context economic analysis we consulted the Ministerial database (NSIS) - *Flusso contratti* to collect data on consumption and relative prices (purchase' contracts of local trust) and we contacted the manufacturer to collect data on price/cost of the device through an ad hoc questionnaire.

Patient and Social Aspects domain

A systematic literature search on Pubmed, The Cochrane Library (CENTRAL), Embase and Psycinfo was made to answer the research question on patients perceptions. We aimed at including literature involving adults who were real users of WCD. We read the full text of 15 titles and eventually included one of them, Lackermair et al. 2018, which is a preliminary study on QoL among patients using the WCD.

Analysis

For the evidence synthesis, a qualitative approach was selected. Because only 1 RCT was retrieved, it was not feasible to perform an inferential statistical analysis.

Results

The current use of the technology in Italy

As reported by the manufacturer, since the full launch in Italy in April 2015, 570 patients have been fitted with the device exceeding 1000 months of rental (with an estimated average of 2 months of rental per patient). In Italy, 121 public hospitals are using the device, and only a few private hospitals. In the same period only eight Regions and Autonomous Provinces-PA (out of 21), reported data on WCD use in the Flusso Consumi database (Campania, Emilia Romagna, Lazio, Lombardia, Marche, Trento PA, Toscana and Veneto). There was only one center per Region reporting data of WCD use.

Available evidence

Overall, one study fulfilled the study inclusion criteria for assessing clinical effectiveness of the WCD. The study was a RCT, comparing the WCD in combination with GDMT to GDMT alone in patients with a recent myocardial infarction (MI) and an ejection fraction of 35% or less.

For the evaluation of the safety of the WCD, the systematic literature search identified 1 RCT and further 10 prospective observational studies that met the less strict inclusion criteria to evaluate the safety of the WCD.

Clinical Effectiveness

One RCT was included for the evaluation of the clinical effectiveness of the WCD. The study compared the WCD in combination with GDMT with GDMT alone in patients with a recent MI and an ejection fraction of 35% or less.

In total, 2,348 patients who had been hospitalised with an acute MI (and EF≤35%) were enrolled and randomised in a 2:1 ratio in the included study. Of those, 46 patients were excluded from the analysis, resulting in 2,302 patients included in the analysis (1,524 and 778 patients in the device and control group respectively). Patients in the device group received a WCD and GDMT, while the control group received GDMT alone. The mean follow-up time of the randomly assigned patients was 84.3 days (SD: 15.6).

No statistically significant difference was found in the included study when comparing the primary outcome of the study, that is, **arrhythmic death**, between device and control group, with 25 out of 1,524 (1.6%) and 19 out of 778 (2.4%) arrhythmic deaths in those groups respectively (p = 0.18) (GRADE evidence: low). The included study did find a statistically significantly lower rate of the secondary outcome **deaths from any cause** in the device group when compared to the control group, with 48 out of 1,524 (3.1%) and 38 out of 778 (4.9%) deaths from any cause in those groups respectively (p = 0.04)[1] (GRADE evidence: low).

With respect to **rehospitalisation rate**, the RCT did not find a statistically significant difference when comparing the rehospitalisation rate between device group and control group, with 31.2% and 32.5% rehospitalised patients (any cause) in those groups respectively (p-value = 0.51) (GRADE evidence: moderate).

The **compliance** with the WCD was measured by the included RCT. In the device group, 1,481 out of 1,524 patients (97.2%) wore the WCD[2]. Those patients wore the device on average 14

[1] The p-value was not corrected for multiple testing, increasing the risk that this statistically significant difference was a chance finding (see section 4.7 Discussion for more information).

[2] Also, 20 patients in the control group (n=778) wore the WCD (2.6%) as well. Cross-overs were considered to be a protocol deviation in the included study.

hours per day (SD: 9.3). The median wear-time was 18 hours (IQR: 3.8-22.7) (GRADE evidence: high).

No evidence was found for the secondary effectiveness endpoints **quality of life** and **patient satisfaction** of the WCD. However, the included RCT did gather data on quality of life of the patients without reporting on it in the main publication.

Safety

The evidence base for the evaluation of safety of the WCD is 1 RCT and 10 observational studies.

The RCT reported the following safety results: Three patients (0.2%) were hospitalized (two due to aborted shocks and one due to an inappropriate shock), and one patient (0.1%) died while wearing the device (deemed likely to not be an arrhythmic death). There were also 9/1524 (0.6%) **inappropriate shocks** in patients in the device group (GRADE evidence: moderate). AEs as rash and itching in the torso area were more common, and statistically significant differences between the device group and the control group were observed (GRADE evidence: moderate). The **unsuccessful shock rate** was not reported by the RCT.

The 10 observational studies reported the following safety results (GRADE evidence: very low). Six studies state that no inappropriate shock occurred, while 4 studies reported a ratio of inappropriate shocks between 0.5% and 2%. Only 2/10 studies mentioned unsuccessful shocks describing that all the shocks delivered were successful. Five out of 10 studies reported the outcome of SAEs leading to death, reporting that no patients died wearing the WCD. One study reported allergic skin reactions in 2% of the patients. Two studies reported false alarms: one study reported that no patient received false WCD alarms, while another study reported that 57% of the patients experienced "false alarms" due to incorrect detection of electrocardiogram (ECG) episodes, defined as artifacts upon review. Three studies reported discontinuation due to comfort and lifestyle issues that ranged from 4% to 18% of the patients.

Upcoming evidence

The search for ongoing studies in clinicaltrials.gov revealed that there may not be any RCTs or observational studies currently evaluating the effectiveness of the WCD for the patients in the scope of this assessment. Only uncontrolled ongoing studies (n=8) were identified that may not change the conclusions. The reader is referred to the APPENDIX 7 for the full list of identified ongoing studies.

Economic evaluation

We found 12 articles in our search in literature. After screening titles and abstracts, only one study (Healy 2015) potentially eligible was included. We also included another study (Sanders et al., 2015) pointed out in the questionnaire by the manufacturer. After the reading of full texts we confirmed these two studies included. In the first study (Healy 2015), the authors carried out a cost-effectiveness evaluation of the WCD compared with other alternatives of management for the prevention of SCD in patients with infected ICD removed. The authors concluded that the WCD is likely a cost-effective treatment for the prevention of SCD in a significant number of at-risk patients. The analysis resulted that discharge home with a WCD was a cost-effective treatment strategy with an incremental cost-effectiveness of $20,300/LY and $26,436/QALY when compared to discharge home with no device.

In the second study (Sanders et al., 2015) the authors developed a Markov model to assess the costeffectiveness of the WCD compared with the current standard of care for early post-MI patients. The aim was to identify an alternative approach to reduce the risk of SCD, considered elevated in the early post-MI period coupled with the lack of success of the ICD in this setting. The model assessed the survival of patient, quality-of-life, and costs. The study included direct costs of medical care associated with WCD use, EMS (emergency medical services), ICD implantation and follow-up,

treatment of patients with standard care.

The study results showed that the WCD strategy was more expensive than the standard-of-care strategy with estimated life-time discounted cost higher by $11,503. The WCD strategy had better clinical outcomes, with an improvement in life expectancy of 0.261 life years or 0.190 QALYs. The authors concluded that the analysis suggest that WCD use could reduce the rate of SCD during the recovery period of patients who have had a recent MI and have reduced left ventricular function at a cost that appears to be economically attractive when compared with other generally accepted treatments in the United States.

Regarding the economic analysis Zoll Medical Italia srl stated that the rental list price per month is €6,000 (plus 4% VAT), and the real average price in Italy is €3,600 per rental month. Morover, the manufacturer also reported in the questionnaire several services included and all items use for a single procedure.

From the consultation of the database *Flusso contratti* of the Italian Ministry of Health, from 2015 to 2017, and the fist semester of the 2018, we relieved a total of 32 WCD (units). Data were referred respectively to 6 Regions and 9 local health trusts. According to the manufacturer statement all prices are referred to "rental" price. The value of €3,400 is the price rental more common (> 60%) and the value of €3,500 is reported in 16% of cases.

Patient and Social Aspects domain

We assessed the quality of Lackermair et al. study which has a retrospective design, no control group and the cohort is very heterogeneous. We described it anyways as its results give some hints on how the WCD was perceived in terms of QoL and its different aspects. Aspects related to QoL and patients perception, besides compliance, need to be further analyzed via proper study designs and results presented in international journals (e.g. many congress abstracts were found in databases about QoL, but no articles related in international database).

Conclusion

Currently, the evidence from one RCT indicates that the use of the WCD in combination with guideline-directed medical therapy (GDMT) in patients with a recent MI and an ejection fraction of 35% or less is not proven to be more effective when compared to GDMT alone based on the outcome arrhythmic mortality. In addition, the compliance with the WCD in the included RCT was low.

For the evaluation of safety of the device, the evidence indicates that the WCD could be a relatively safe intervention. However, more data and more adequate reporting on AEs and SAEs are needed to confirm the safety of the device.

More RCTs are needed to consolidate or question those evidence-based conclusions.

Sintesi in italiano

Introduzione

Il defibrillatore indossabile (Wearable Cardioverter-Defibrillator - WCD) rappresenta una nuova terapia per la prevenzione primaria e secondaria della morte cardiaca improvvisa (Sudden Cardiac Death - SCD). Il WCD è un dispositivo che viene indossato dal paziente per gran parte della giornata, tranne quando ha necessità di fare un bagno o una doccia: in questi casi è richiesta la sorveglianza da parte di un caregiver o di un membro della famiglia. Il WCD permette il monitoraggio cardiaco continuo del paziente e interviene quando rileva un ritmo potenzialmente letale causato da una tachicardia ventricolare (TV) o da una fibrillazione ventricolare (FV) responsabili della maggior parte degli eventi di arresto cardiaco improvviso (Sudden Cardiac Arrest – SCA). È indicato principalmente come misura temporanea prima dell'inserimento di un defibrillatore cardiaco impiantabile (ICD).

Lo studio delle evidenze relative al WCD è stato condotto, nel 2016, dal Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA), nell'ambito di una "valutazione collaborativa" EUnetHTA e, nel 2018, dalla Galician Agency for Health Technology Assessment (AVALIA-T), come valutazione di aggiornamento. Entrambe le valutazioni hanno evidenziato la mancanza di solide prove scientifiche e hanno portato alla conclusione che, per dimostrare l'efficacia (comparativa) e la sicurezza del dispositivo, sono necessari studi randomizzati controllati (RCTs).

Le ricerche in corso e i nuovi risultati di un precedente RCT hanno indotto il Ministero della Salute a commissionare all'Agenzia Nazionale per i Servizi Sanitari Regionali (AGENAS) un'altra valutazione delle prove più recenti sull'uso del WCD.
La revisione sistematica sull'efficacia e la sicurezza del WCD è stata condotta in collaborazione con il LBI-HTA che ha manifestato l'intenzione di aggiornare il suo precedente rapporto EUnetHTA "WEARABLE CARDIOVERTER-DEFIBRILLATOR (WCD) THERAPY IN PRIMARY AND SECONDARY PREVENTION OF SUDDEN CARDIAC ARREST IN PATIENTS AT RISK" (ID progetto: WP4-ACB-CA-1).

Obiettivi

Questo report ha l'obiettivo di valutare l'uso del WCD per la prevenzione primaria e secondaria della morte cardiaca improvvisa in pazienti a rischio, descrivendo lo stato regolatorio del dispositivo, le caratteristiche tecniche della tecnologia e dei suoi comparatori, la sua diffusione

all'interno del contesto nazionale ed effettuando una valutazione della sua efficacia, sicurezza e dei costi associati al suo utilizzo.

Metodi

Uso corrente della tecnologia in Italia

Per la descrizione dell'uso corrente del LifeVest® 4000 in Italia sono state utilizzate le informazioni raccolte attraverso un questionario compilato direttamente dal produttore. Inoltre, è stata consultata la banca dati del Flusso Consumi del Nuovo Sistema Informativo Sanitario (NSIS) del Ministero della Salute.

Descrizione della tecnologia e stato regolatorio

Per la descrizione della tecnologia e delle caratteristiche tecniche sono state consultate diverse fonti, principalmente le informazioni contenute nel 'collaborative report' di EUnetHTA (Ettinger 2016) e quelle fornite dal produttore Zoll Medical Italia srl. Per la descrizione delle informazioni di carattere regolatorio (marcatura CE e approvazione FDA) ci si è basati principalmente su quelle fornite da Zoll Medical Italia srl; le stesse sono state poi integrate da ricerche internet ad hoc e da ricerche condotte nei database degli enti regolatori nazionali e internazionali.

Criteri di inclusione e outcome

Gli studi rilevanti sono stati identificati attraverso una ricerca sistematica della letteratura nei principali database elettronici: la ricerca di efficacia e sicurezza è stata effettuata su Pubmed, Embase e Cochrane Controlled Register of Trials (CENTRAL), mentre per la ricerca sulle prospettive dei pazienti, in aggiunta a questi tre database, è stato consultato anche PsycINFO. Inoltre, è stata condotta una ricerca manuale ed è stato contattato il produttore per ottenere ulteriori informazioni.

Nella revisione sistematica sono stati inclusi gli studi che hanno arruolato pazienti in cui il WCD 4000 è stato utilizzato come misura temporanea, ad esempio: prima dell'impianto di un defibrillatore impiantabile – ICD, come protezione prima o durante la terapia farmacologica, nella stratificazione prognostica dei pazienti con pregresso infarto miocardico e aumentato rischio di morte aritmica, o prima del trapianto cardiaco nei pazienti senza ICD. Per la valutazione dell'efficacia sono stati inclusi solo studi randomizzati e studi osservazionali prospettici con gruppo di controllo. I criteri di inclusione degli studi per la valutazione della sicurezza erano diversi da quelli per la valutazione dell'efficacia clinica. Per la valutazione della sicurezza del WCD, oltre agli

RCT e agli studi osservazionali comparativi, sono stati inclusi anche gli studi osservazionali prospettici senza gruppo controllo.
Le indicazioni e i comparatori scelti per il WCD sono il risultato di un lungo confronto tra AGENAS e LBI-HTA. Gli autori delle due Agenzie hanno, infine, deciso di selezionare un gruppo di indicazioni ristretto e più aderente alla pratica clinica. Di conseguenza si è deciso di confrontare l'uso del WCD con le alternative disponibili in qualsiasi contesto: ad esempio in ospedalizzazione o in terapia farmacologica al di fuori del contesto ospedaliero secondo linee guida (guideline-directed medical therapy – GDMT).
L'efficacia del WCD è stata valutata utilizzando come outcome primari la mortalità per tutte le cause e la mortalità correlata alla patologia. Gli outcome secondari sono stati la qualità della vita correlata alla salute (HRQoL), il tasso di ospedalizzazione, la soddisfazione e la compliance. Per la valutazione della sicurezza del WCD sono stati selezionati, come outcome, gli eventi avversi (AE) e gli eventi avversi gravi (SAE).

Selezione degli studi, estrazione delle informazioni e valutazione della qualità

Il modello EUnetHTA® è stato utilizzato come quadro metodologico di riferimento. Due revisori (MO, GG) hanno esaminato gli abstract in modo indipendente e hanno valutato la loro idoneità a essere inclusi nella valutazione. In caso di disaccordo, è stato consultato un terzo ricercatore (TJ). La valutazione del rischio di *bias* è stata condotta da due ricercatori (GG, MO). Per la valutazione del rischio di *bias* degli RCT è stato utilizzato il Risk of Bias (RoB) tool della Cochrane, mentre per valutare il rischio di *bias* degli studi osservazionali è stata applicata la checklist dell'Institute of Health Economics (IHE). I dati degli studi inclusi sono stati quindi estratti sistematicamente da un ricercatore (MO) e verificati dall'altro (GG). La qualità delle evidenze e la certezza nelle stime di effetto sono state valutate utilizzando il metodo Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Analisi

Per la sintesi delle evidenze è stato adottato un approccio di tipo qualitativo. Poiché è stato recuperato solo un RCT non è stato possibile eseguire un'analisi statistica inferenziale.

Valutazione economica

La valutazione economica del dispositivo WCD è stata condotta attraverso la ricerca dell'evidenza disponibile e l'analisi del contesto italiano. L'analisi della letteratura è stata effettuata usando la stessa strategia di ricerca utilizzata per la valutazione dell'efficacia e della sicurezza e, quindi, sono stati consultati i database Pubmed, The Cochrane Library ed Embase. Invece, per l'analisi

economica di contesto è stato consultato il database del Ministero della Salute (NSIS) – Flusso contratti e Flusso consumi, con la finalità di raccogliere dati relativi ai prezzi (contratti di acquisto relativi alle singole Aziende Sanitarie). I dati economici sono stati raccolti anche dal produttore che li ha forniti tramite la compilazione di un questionario**.**

Aspetti sociali e legati al paziente

Abbiamo condotto una ricerca sistematica di letteratura su Cochrane, Embase, Pubmed e Psycinfo, con l'obiettivo di includere solo la letteratura riguardante gli adulti che abbiano utilizzato il WCD. Abbiamo letto il testo completo di 15 titoli ed incluso un solo studio, Lackermair K. et al. (2018).

Risultati

Uso corrente del WCD in Italia

Come dichiarato dal produttore, in Italia da aprile 2015 (periodo in cui è stato commercializzato LifeVest® 4000) ad oggi, 570 pazienti hanno utilizzato il dispositivo per circa 1000 mesi di noleggio (con una media stimata di 2 mesi di noleggio per paziente). LifeVest® 4000 è utilizzato in 121 strutture ospedaliere prevalentemente pubbliche. Nello stesso periodo solo otto Regioni e Province Autonome (su 21), hanno riportato dati sull'utilizzo del WCD nella banca dati Flusso Consumi (Campania, Emilia Romagna, Lazio, Lombardia, Marche, Trento, Toscana e Veneto) coincidenti con un solo centro per Regione/PA.

Evidenze disponibili

Per la valutazione dell'efficacia clinica del WCD è stato incluso un solo RCT in cui si confrontava il WCD in combinazione con terapia farmacologica (guideline-directed medical therapy – GDMT) alla sola terapia farmacologica in pazienti con infarto miocardico recente (IM) e con una frazione di eiezione del 35% o inferiore.

Per la valutazione della sicurezza del WCD, la ricerca sistematica della letteratura ha identificato un RCT e ulteriori 10 studi prospettici osservazionali.

Efficacia clinica

Un solo RCT è stato incluso per la valutazione dell'efficacia clinica del WCD. Lo studio confronta il WCD in combinazione alla terapia medica ottimizzata (GDMT) e la terapia medica da sola nei pazienti con recente infarto del miocardio e con una frazione di eiezione uguale o minore del 35%.

Nello studio incluso, 2.348 pazienti ospedalizzati per un infarto miocardico acuto (e EF ≤35%) sono stati arruolati e randomizzati in un rapporto di 2:1. Di questi pazienti, 46 sono stati esclusi dall'analisi: dei rimanenti 2.302 pazienti, 1.524 sono stati inseriti nel gruppo che ha utilizzato il dispositivo e 778 pazienti nel gruppo di controllo. I pazienti del gruppo di intervento erano anche in GDMT, mentre il gruppo di controllo ha ricevuto solo GDMT. Il tempo medio di follow-up dei pazienti assegnati in modo casuale è stato di 84,3 giorni (SD: 15,6).

Nello studio incluso, confrontando l'*endpoint* primario, ovvero i casi di morte per aritmia, non è stata trovata alcuna differenza statisticamente significativa tra il gruppo trattato con il dispositivo e il gruppo di controllo, con 25 su 1.524 (1,6%) e 19 su 778 (2,4%) eventi rispettivamente, (p=0,18) (livello di evidenza GRADE: basso). Lo studio incluso ha rilevato un tasso statisticamente significativo più basso per l'endpoint secondario relativo ai decessi per qualsiasi causa nel gruppo trattato con dispositivo rispetto al gruppo di controllo, con 48 su 1.524 (3,1%) e 38 su 778 (4,9%) eventi rispettivamente, (p = 0,04)[3] (livello di evidenza GRADE: basso).

Per quanto riguarda il tasso di ri-ospedalizzazione, l'RCT non ha riscontrato una differenza statisticamente significativa tra il gruppo con il dispositivo e il gruppo di controllo, con il 31,2% e il 32,5% di pazienti riospedalizzati (per qualsiasi causa) (p=0,51) (livello di evidenza GRADE: moderato).

La *compliance* dell'uso del WCD è stata misurata dall'RCT incluso. Il gruppo che ha indossato il WCD è stato di 1.481 su 1.524 pazienti (97,2%). Questi pazienti hanno indossato il dispositivo in media 14 ore al giorno (SD: 9,3). Il tempo medio di utilizzo è stato di 18 ore (IQR: 3,8-22,7) (livello di evidenza GRADE: alto).

Nessuna evidenza è stata trovata per gli *endpoint* secondari di efficacia relativi alla qualità della vita e alla soddisfazione del paziente. Tuttavia, l'RCT incluso ha raccolto dati sulla qualità della vita dei pazienti senza riportarli nella pubblicazione principale.

Sicurezza

Le evidenze scientifiche per la valutazione della sicurezza del WCD sono relative a un RCT e a 10 studi osservazionali.

Per i dati relativi alla sicurezza, l'RCT ha evidenziato che: 3 pazienti (0,2%) sono stati ricoverati in ospedale (due a causa di shock interrotti utilizzando i tasti di risposta del WCD e uno a causa di uno shock inappropriato) e un paziente (0,1%) è deceduto mentre indossava il dispositivo (gli autori ritengono che la causa di morte non sia per aritmia). Lo studio ha rilevato 9/1524 (0,6%) shock inappropriati nei pazienti del gruppo che indossava il dispositivo (livello di evidenza GRADE:

[3] Il p-value non è stato corretto per test multipli, aumentando il rischio che questa differenza statisticamente significativa sia un valore casuale (per ulteriori informazioni vedere la sezione 4.7 Discussione).

moderato). Sono state rilevate differenze statisticamente significative tra il gruppo che ha indossato il WCD e il gruppo di controllo per gli eventi avversi più comuni come l'eruzione cutanea e il prurito nella regione toracica (livello di evidenza GRADE: moderato). Il tasso di shock inefficaci non è stato riportato nello studio.

Per la valutazione della sicurezza, i 10 studi osservazionali hanno riportato i seguenti risultati (livello di evidenza GRADE: molto basso). Sei studi affermano che non si sono verificati shock inappropriati, mentre 4 studi hanno riportato una percentuale di shock inappropriati compresa tra lo 0,5% e il 2%. Solo 2/10 studi hanno considerato gli shock inefficaci, descrivendo che tutti gli shock erogati hanno avuto successo. Cinque studi su 10 hanno riportato l'esito fatale per eventi avversi gravi, segnalando che nessun paziente è morto indossando il WCD. Uno studio ha riportato reazioni allergiche cutanee nel 2% dei pazienti. Due studi hanno riportato falsi allarmi: uno studio ha riportato che nessun paziente ha ricevuto falsi allarmi, mentre un altro studio ha riferito che il 57% dei pazienti ha riscontrato falsi allarmi a causa di un errato rilevamento del tracciato ECG e definiti dagli autori dello studio come artefatti. Tre studi hanno riportato la sospensione del trattamento a causa di problemi legati al comfort e allo stile di vita che ha coinvolto dal 4% al 18% dei pazienti.

Studi in corso

La ricerca degli studi in corso, condotta su *clinicaltrials.gov*, ha fatto emergere che non ci saranno ulteriori studi randomizzati o studi osservazionali in cui sarà valutata l'efficacia del WCD nei pazienti individuati dal presente rapporto. Sono stati identificati solo studi non controllati (n=8) che potrebbero non modificare le conclusioni. Si rimanda all'APPENDICE 7 per l'elenco completo degli studi in corso individuati.

Valutazione economica

La ricerca in letteratura ha selezionato 12 studi. Dopo la lettura dei titoli e degli abstract è risultato potenzialmente eleggibile un solo studio; inoltre, è stato incluso un altro studio segnalato dal produttore attraverso il questionario. Successivamete gli studi sono stati inclusi dopo lettura dell'intero articolo.

Nel primo studio (Healy 2015) gli autori hanno effettuato una valutazione di costo-efficacia confrontando il WCD con alternative di trattamento per la prevenzione della morte improvvisa nei pazienti sottoposti alla rimozione di ICD per infezione. Il modello era finalizzato a raccogliere sia i dati di costo che di utilità e ha valutato la sopravvivenza, la qualità della vita e i costi per il sistema sanitario. Gli studi hanno concluso che il WCD è probabilmente un trattamento costo-efficace per la prevenzione della morte improvvisa in un numero significativo di pazienti ad alto rischio.

Dall'analisi è risultato che la dimissione a casa con il WCD rispetto alla dimissione senza dispositivo è un trattamento costo-efficace con un costo incrementale di $20,300/LY e $26,436/QALY.
Nel secondo studio incluso (Sanders et al., 2015) gli autori hanno sviluppato un modello di Markov per valutare la costo-efficacia del WCD confrontandolo con i trattamenti standard nei pazienti con recente infarto miocardico. Scopo dello studio era quello di identificare un approccio alternativo al fine di ridurre il rischio di morte improvvisa, poiché elevato nei pazienti con recente infarto miocardico e trattamento con ICD inefficace. Il modello ha valutato la sopravvivenza, la qualità della vita e i costi. Lo studio ha analizzato i costi diretti associati all'utilizzo del dispositivo WCD, i costi dei servizi di emergenza, i costi dell'impianto di ICD e il relativo follow-up e i costi relativi al trattamento standard. I risultati dello studio hanno mostrato che il trattamento con WCD era più costoso rispetto alla terapia standard, con un costo in termini di anni di vita guadagnati più alto di $11,503. Il trattamento con WCD ha migliori outcome clinici, con un miglioramento dell'aspettativa di vita di 0,261 anni o 0,190 QALYs. Gli autori hanno concluso che l'uso del WCD potrebbe ridurre il tasso di morte improvvisa durante il periodo di degenza nei pazienti che hanno avuto recentemente un infarto del miocardio e la cui funzione ventricolare sinistra risulta ridotta, con un costo che appare economicamente vantaggioso se confrontato con altri trattamenti utilizzati negli Stati Uniti.
Con riferimento all'analisi di contesto il produttore ha dichiarato che il prezzo di listino per il noleggio del dispositivo è di €6.000 (IVA esclusa), mentre il prezzo medio reale in Italia è pari a €3.600/mese ed include una serie di servizi e tutte le componenti necessarie all'utilizzo del dispositivo.
Per l'analisi di contesto è stata consultata la banca dati del Ministero della Salute – Flusso contratti (NSIS), dal 2015 al 2017 e il primo semestre del 2018. Dall'analisi sono stati rilevati 32 WCD (unità). In particolare, gli eventi di acquisto si riferiscono rispettivamente a 6 Regioni e 9 aziende sanitarie locali. Secondo quanto dichiarato dal produttore del WCD tutti i prezzi rilevati dal Flusso NSIS sono riferiti alla modalità di noleggio e non all'acquisto del dispositivo. In più del 60% dei casi, il prezzo riscontrato è pari a €3.400,00 e nel 16% dei casi a €3.500,00.

Aspetti sociali e legati al paziente

L'unico studio incluso, Lackermair K. et al. (2018), è di tipo retrospettivo, senza gruppo di controllo e si basa su una coorte molto eterogenea. Tuttavia i principali risultati sono stati descritti perché forniscono alcune informazioni utili per studi futuri, ad esempio su come il WCD sia stato percepito in termini di QoL dai suoi effettivi utilizzatori. Gli aspetti relativi alla QoL e alla percezione dei pazienti andrebbero approfonditi utilizzando i risultati pubblicati su riviste internazionali (esistono

molti abstract presentati in occasione di congressi sull'argomento ma nessuna pubblicazione/articolo in extenso nei database consultati).

Conclusioni

Ad oggi, dall'unico studio RCT emerge che, nella valutazione della riduzione della mortalità per aritmie nei pazienti con IM recente ed una frazione di eiezione del 35% o inferiore, l'uso del WCD in combinazione con la terapia farmacologica secondo le linee guida (GDMT), non si è dimostrato più efficace rispetto alla sola terapia GDMT. Inoltre, la *compliance* nell'utilizzo del WCD riscontrata nell'RCT incluso è risultata bassa. Per la valutazione della sicurezza del dispositivo, le evidenze indicano che il WCD potrebbe essere un intervento relativamente sicuro. Tuttavia, per confermare la sicurezza del dispositivo sono necessarie più informazioni e un maggior numero di studi che riportano informazioni su AE e SAE.
Sono necessari ulteriori RCT per consolidare o mettere in discussione le attuali conclusioni.

1. OBJECTIVES: POLICY AND RESEARCH QUESTIONS

The present report focuses on the assessment of the WCD for therapy in primary and secondary prevention of sudden cardiac death in patient at risk. We provided an assessment on the WCD presenting regulatory status of the device, technical characteristics of the technology and its comparators, an analysis of its spread within national context, and an assessment of its effectiveness, safety, and costs.

1.1 Policy question

What is the advantage of introducing the WCD in subjects at risk of sudden cardiac death in terms of clinical outcomes and patient perspectives for the health service?

1.2 Research questions

The systematic literature review was conducted using the EUnetHTA Core Model® for rapid relative effectiveness assessment. For each domain we report the Assessment Element (research question) with its Identification (ID).

1.3 Inclusion criteria according to the PICOS framework

Evidence inclusion has been performed according to the PICOS framework. The inclusion criteria are summarized in Table 1.

Table 1: Inclusion criteria according to the PICOS framework

Population	Adults over 18 years of age (according to CE mark) with the following indications: 1. As a temporary intervention prior to the insertion of an ICD for: a. patients immediately after explantation of an ICD, if an immediate reimplantation of an ICD is not possible; b. patients in whom an immediate implantation of an ICD is indicated, but not possible due to temporary contraindications. 2. As a temporary measure prior to optimal pharmacological therapy, or as a protection during pharmacological therapy optimisation when a heightened risk of SCD is present, but possibly resolvable over time or with treatment of left ventricular dysfunction; for patients with: a. ischaemic heart disease with envisaged or recent revascularization (90-day waiting period post revascularization with either CABG or PCI); b. secondary cardiomyopathy (tachycardia mediated, thyroid mediated, etc.) or induced arrhythmias (secondary to hypothermia, electrolyte imbalance, iatrogenic prolongation of the QT interval, etc.) in which the underlying cause is potentially treatable; c. with certain forms of structural heart disease associated with risk of malignant arrhythmias or primary electric diseases, prior to diagnostic tests such as MRI. 3. Post Myocardial Infarction (MI) and LVEF of ≤ 35%, as a temporary measure during prognostic stratification in situations associated with increased risk of arrhythmic death within 40 d of MI. 4. As a temporary measure prior to heart transplantation in patients without ICD.
Intervention	WCD/LifeVest® (WCD 4000), from ZOLL (Lifecor) Medical Corporation, Pittsburgh, PA, USA.
Comparator	Hospital observation; Guideline-Directed Medical Therapy (GDMT)
Outcomes	**Effectiveness** Primary endpoints: • Mortality: - All-cause mortality, - Disease-specific mortality. Secondary endpoints: • HRQoL, • Hospitalisation, • 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).
Study design	**Effectiveness**: Randomised and observational studies with concomitant controls. **Safety**: Randomised and observational studies with concomitant controls; observational prospective studies and register studies. **Patients aspects**: qualitative studies (according to the EUnetHTA Core Model® 3.0).
Publication Period	2009-2018
Language	English

2. HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

The information provided in this chapter, excluding information on Italian context, are based on the previous EUnetHTA report [1] published in 2016. Since no changes in information regarding the health problem and current use of the WCD has occurred meanwhile, it was possible to include the information with minor adaptations only.

2.1 Methods

The Assessment Elements of this domain were:

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 SCD?
A0004	What is the natural course of VT/VF and SCD?
A0005	What are the symptoms and the burden of SCD?
A0006	What are the consequences of SCD for the society?
A0024	How is the risk of SCD currently diagnosed according to published guidelines and in practice?
A0025	How is SCD 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?

The current use of the technology LifeVest® 4000 in Italy was described by using information gathered by a structured questionnaire sent to manufacturers (APPENDIX 2 – Questions for the manufacturer)

We also searched information within the *Flusso Consumi* (the Italian databank for monitoring the use of medical devices) of the NSIS (New Health Information System). The database is fed by the Regions that gather data from public health care providers on their territory. At present, the database reaches a suitable coverage rate at national level but with differences among Italian Regions [2]. We extracted data related to the volume of WCDs using the National Classification of Medical Devices (CND) code associated to this kind of devices: "Z12030503 - DEFIBRILLATORI

AUTOMATICI". The searches were carried out in November 2018. We identified the current use of WCD using the RDM/BD codes reported in the Italian National Medical Devices Inventory and Database (for more details see Chapter 3).

2.2 Results

Overview of the disease or health condition

The LifeVest® is supposed to reduce the risk of sudden cardiac death (SCD), 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 (extreme bradycardia, A-V III degree block), no cardiac electrical activity (asystole), or electromechanical dissociation pulseless electrical activity (PEA) post-acute MI or cardiac tamponade [3-6]. (A0002)

Overall, the risk factors associated with SCD differ in young and older individuals. There is a predominance of myocarditis and substance abuse, channelopathies and cardiomyopathies in young patients, and chronic degenerative diseases in older patients (CAD, valvular heart diseases, and heart failure) [6]. In the older individuals, multiple chronic cardiovascular conditions contribute to the risk of SCD 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 SCD elusive [6]. Dysfunction of the left ventricle (LV) is a significant determinant of the risk of SCD, but family history, diabetes mellitus, obesity, and heart rate profile during exercise make the determinants diverse and multifactorial [7]. Lifestyle is very important in prevention of SCD (e.g., no smoking, sports, healthy diet) [8].

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 American Heart Association (AHA) and the European Society of Cardiology (ESC) [6, 9]:

- Those 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.
- Those who are indicated for an ICD, but refuse it due to personal or other reasons.
- Those 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 coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)]; newly diagnosed non-ischaemic cardiomyopathy (NICM) patients starting GDMT; secondary cardiomyopathy patients (tachycardia mediated, thyroid mediated, etc.) with induced arrhythmias (secondary to hypothermia, 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.

- Those who are at risk of SCD and in the process of diagnosis.
- Those who are post MI and have their Left Ventricular Ejection Fraction (LVEF) ≤ 35% and are awaiting therapy.
- Those who are awaiting a heart transplant. (A0003)

The natural course of a SCA is death. Survival with good neurological function occurs in a small minority of patients [1]. 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 chance of survival drops by 10% [1]. 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 [1]. Symptoms that indicate further evaluation for the risk of SCA are palpitations (or sensation of sudden rapid heartbeats), pre-syncope, and syncope [6]. The burden of disease for the patient is death or the consequences that follow a delayed intervention, mainly a permanent neurological deficit. (A0003, A0004, A0005)

Effects of the disease or health condition

Approximately 25% of all 17 million deaths worldwide related to cardiovascular disease are caused by SCD each year [1, 6]. In Europe, there are about 350,000 out of hospital SCDs per year [1] and in the US, it is estimated that 326,000 people experience out-of-hospital SCD each year, while the majority of these SCDs occur at home with half of the cases unwitnessed [1].

Worldwide, there are 4.25 million deaths caused by SCA each year [1], however, the exact target population of this intervention is difficult to estimate. (A0023)

One approach would be to estimate based on the ICD usage. 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 [10].

In Italy, the exact target population of this intervention is difficult to estimate as well. Approximately 50,000 Italian people are affected by SCD every year in the age band 20-75 years [11]. In Austria, approximately 15,000 people are affected by SCD per year. One-third of SCDs happen unexpectedly outside of the hospital. Of these SCDs, two thirds occur at home, and the remainder of SCDs occur in the office or in public [12]. (A0006, A0007)

Current clinical management of the disease or health condition

Because of the limited ability to prevent SCDs above all in general population, risk predictors remain the only reliable indicators. However, as low LVEF is one of the key indicators, it does not include 50% of SCD victims whose LV function is preserved [13].

Further information on non-invasive/invasive evaluation methods and the diagnostic work-up for patients at risk of SCD can be found in a previously conducted EUnetHTA report [1]. (A0024)

Nationwide screening for the risk of SCD is rare as only Italy and Japan have implemented ECG screening systems that may identify asymptomatic patients with inherited arrhythmogenic disorders [6]. There is a consensus among Europe and the US that there is a need for SCD 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 SCD in competitive athletes following implementation of screening programs [6].

The screening of families of SCD 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, especially cardiomyopathies [14] and channelopathies, where currently only 40% of family members are screened [6].

For most patients at risk of SCD, implantation of an ICD is the solution of choice. Alternative solutions are the use of pharmacological therapy, catheter (radiofrequency) ablation, and the use of automated external defibrillators (AEDs). 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 (ICD implantation for the primary prevention of SCD is generally not indicated 40 days after myocardial infarction-IIIA; ICD implantation or temporary use of a WCD may be considered <40 days after myocardial infarction in selected patients -incomplete revascularization, pre-existing LVEF dysfunction,occurrence of arrhythmias >48h after the onset of ACS, polymorphic VT or VF-IIb C), or patients requiring timely defibrillation by AEDs – for bystander use of the AED is not an effective method of protection for

high risk patients [15] and relying on emergency medical service response also results in poor outcomes [16].

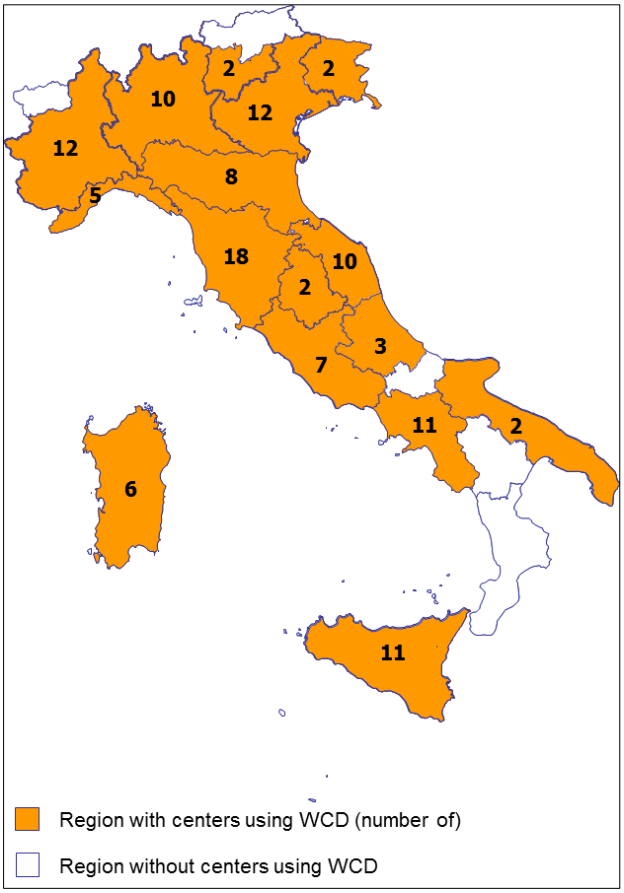
The WCD is recommended on the basis of a low level of evidence by the ESC for adult patients with poor LV systolic function who are at risk of sudden arrhythmic death for a limited period, but are not candidates for an ICD (e.g., as a stop gap measure to transplant and to transvenous implant, peripartum cardiomyopathy (PPCM), active myocarditis, and arrhythmias in the early post-MI phase) [6, 17]. The AHA also states 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 [9].

The reader is referred to the original EUnetHTA report [1] for further description of prevention and management of SCD according to published guidelines and in practice. (A0025)

The current use of the technology in Italy

(A0011) As reported by the manufacturer, the LifeVest® 4000 is supplied in service with monthly fee payment. Since the full launch in Italy in April 2015, 570 patients have been fitted with the device exceeding 1000 months of rental (with an estimated average of 2 months of rental per patient). In Italy 121 public hospitals are using the device, and only a few private hospital (APPENDIX 3 – List of Italian Centers using WCD). Figure 1 shows the geographical distribution of the Italian regions in which the WCD is used and the relative number of user centers.

Figure 1: Italian Regions using UCD



Source: Information provided the manufacturer

With the aim of verifying the current use of WCD (in terms of number of months of rental) in Italian public health structures from 2015 to first half of 2018 (last data available), we searched information within the *Flusso Consumi* database of the NSIS.

From January 2015 to the first half of 2018, the analysis showed that 51 events[4] matched the BD/RDM registration codes. Table 2 showed the trend of months of WCD rental, reported in Flusso Consumi database, from 2015 to first half of 2018.

Table 2: Months of WCD rental per year

Time	2015	2016	2017	2018(*)	Total
Number of months	10	21	14	6	51

(*) First half of 2018

[4] The full launch of LifeVest® 4000 was in April 2015. For this reason, both the LifeVest® 3100 and LifeVest® 4000 models could be used during a portion of the period under review.

Source: Agenas analysis based on *Flusso Consumi* 2015 – 2018

In the same period only eight Regions and Autonomous Provinces-PA (out of 21), reported data on WCD use in the *Flusso Consumi* database (Campania, Emilia Romagna, Lazio, Lombardia, Marche, Trento PA, Toscana and Veneto). In the period under review there was only one center per Region reporting data of WCD use; the months of WCD rental per center ranged from 2 to 29 and almost all centers (n=7) used less than 5 months of WCD rental.

2.3 Discussion

As the WCD is CE marked very broadly, for patients 18 years of age and older who are at risk of SCD 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 [1]. As a consequence the list of indications considered in this report is the result of a long consensus finding process: after having consulted external experts from both AGENAS and LBI-HTA, the views regarding the indications for the use of the WCD that need to be included in this assessment were diverging. These varied from a broad indication list that was originally used in the previous EUnetHTA report [1] to use in a more realistic indication group (that is not identical to the broad CE-mark) as the expert consulted by AGENAS highlighted. After a meeting of both institutes, we finally chose the narrow, more realistic indication group that can be found in Table 1 in chapter 2.

The previous EUnetHTA report highlighted further critical aspects of the use of the WCD that relate to off-label use, risk stratification, the WCD's role as a prevention or treatment, and the lack of clarity in care pathways. The reader is referred to the EUnetHTA report [1] for further critical information on aspects of WCD use.

3. DESCRIPTION OF TECHNOLOGY (TEC) AND REGULATORY ASPECTS

3.1 Methods

The Assessment Elements of this domain were:

Element ID	Research question
B0001	What is the WCD technology and comparator(s)?
B0002	What is the claimed benefit of the WCD in relation to the comparator(s)?
B0003	What is the phase of development of the technology and implementation of the WCD and the comparator(s)?
B0004	Who administers the WCD and the comparators and in what context and level of care are they provided?
A0020	For which indications has the WCD received marketing authorization or CE marking?

The technology and its technical characteristics were presented by using information from different sources: the "collaborative assessment" report within the EU-project EUnetHTA [1], by a structured questionnaire [18] sent to the manufacturers Zoll Medical Italia srl in June 2018 (APPENDIX 2- Questions for the manufacturer) supplemented by *ad hoc* internet searches, manufacturers' websites, product brochures, instructions for use (IFU) documents [18, 19], and regulatory bodies' databases. The regulatory status of the identified devices (CE marking and FDA approvals) was described by using information provided by Zoll Medical Italia srl [18] and supplemented by ad hoc internet searches on regulatory bodies' websites and databases, and manufacturers' press releases.

3.2 Results

Description of the technology

The WCD is a device temporarily used in primary and secondary prevention of SCD. It is a defibrillator (B0001) worn by the patient for the most of the day, except when taking a bath/shower when the presence of a caregiver or a family member is recommendable [20] (B0004). The indications for WCD use are as a temporary measure before ICD implantation in

patients at risk of sudden cardiac death in the subacute phase of acute myocardial damage, those with accepted indicators for ICD implantation but also other contraindications (e.g., infection), or those waiting for a final decision regarding ICD implantation [21] (B0003). Patients who cannot undergo immediate device re-implantation have 4 alternative options until reimplantation is possible: 1) discharge home with a WCD; 2) discharge home without a WCD; 3) discharge to a skilled nursing facility (SNF); 4) remaining in hospital without a WCD [22] (B0002).

The WCD monitors the patient's heart function and automatically delivers electrical therapy. If it detects a life threatening rhythm, (the WCD is tested for ventricular tachicardia or ventricular fibrillation thanks to a specific tracking algorithm), the device delivers treatment to restore normal rhythm. If patients are conscious, they can prevent the treatment by using the response buttons when the device alerts them that treatment is coming [18, 19].

Currently, the LifeVest® – WCD 4000 (Zoll Medical Corporation, Pittsburg, USA) is the only commercially available WCD in Europe, The WCD is a Class IIb device. The first WCD version (the WCD 1) was commercialised in 1999, followed by WCD 2000 (in 2000), 3000 (in 2001) and 3100 (in 2006) all manufactured by Zoll Medical Corporation (B0003). Figure 2 shows, the principal characteristics of WCDs including the previous generations [18].

Figure 2: Different generations of WCD

WCD 1	WCD 2000	WCD 3000	WCD 3100	WCD 4000
-Original IDE device -Monophasic waveform -2 monitors with integrated batteries -2 detachable belts with tethered display -Complex display -Patient Base Station to re-charge monitor battery -Separate Modem -Physician's console for programming, data download and retrieval, and testing device -CE Mark March 1999	-Original PMA approved device -Pivotal clinical trial device -Monophasic waveform (300J Max) -1 monitor with 2 detachable battery packs -1 detachable belt -Alarm module tethered to monitor and display inside monitor -Reconfigured display -Standalone battery charger -Expansion port for modem communications -PC for programming and data retrieval -CE Mark April 2000	-Clinical sub-study -Biphasic waveform (150J Max) -Smaller, lighter -Inline modem -Continued monitoring during download -Replaceable Li-ion battery pack -Incorporates design change to prevent inadvertent therapy electrode placement -CE Mark September 2001	-Integrated alarm module into Monitor (response button front and back) -4 way toggle switch for screen navigation -Screw locking belt connector -CE Mark June 2006	-Touch sensitive color LCD screen -Relocated ECG acquisition circuitry from monitor to belt -Bluetooth module -Charger incorporates cellular and landline modem -Belt cables thinner, more flexible -Plug-in belt connector -Improved battery latching mechanism -Smaller, lighter -CE Mark June 2011

Source: information provided by the manufacturer

The following description of the device is based upon the latest version LifeVest® – WCD 4000. In this report will interchangeably use the terms WCD LifeVest® 4000, LifeVest® or WCD.

WCD consists of four main components:

(1) The monitor is the main unit of the LifeVest system. It connects to the electrode belt for heart monitoring and to the plates through which energy is released for shock. It monitors the heart rhythm and delivers defibrillating treatment;

(2) The garment and electrode belt, vest-type garment containing the electrode belt weighing approximately 0.5 kilograms that has an inner layer with the sensing and energy delivering electrodes against the patient's skin in the chest area;

(3) The charger which rechargers the battery and communicates wirelessly with the monitor (when the monitor is near the charger) and transmits clinical data for physician review (using the online patient management system -LifeVest network). The LifeVest network can be used mainly for evaluating the compliance, notification of patient events and ECG review. ECG information captured by LifeVest can help physicians to diagnose sustained VT/VF, non-sustained VT, atrial arrhythmias/supraventricular tachycardia (SVT) as well as severe bradycardia/asystole. At the same time technical data are sent to Zoll servers for the troubleshooting and monitoring device right working [18, 19]. These functionalities can be guaranteed only if the WCD is supplied in service.

(4) The holster, designed to support the monitor, battery packs and other components that are not in direct contact with the patient's skin, and these weigh approximately 0.6 kilograms [18].

The electrode belt connects to the monitor and provides digitised ECG data [18, 19]. The electrode belt further contains a vibration box that vibrates when a fatal arrhythmia, as VT/VF, is detected [18, 19]. The garment comes in various sizes and is worn under the patient' s clothing to hold four dry, nonadhesive sensing electrodes and three therapy pads on the electrode belt against the patient's skin [18, 23]. After taking out the set of electrodes, the garment should be washed every one or two days [18]. The monitor contains response buttons, alarm system, defibrillator, and batteries that last for 24 hours and can take up to 16 hours to charge [18]. The patient is provided with two battery packs [18]. The monitor connects to the electrode belt and analyses ECG data and communicates with the charger to provide encrypted data for viewing availability on LifeVest® Network [18] (see Figure 3).

Figure 3: WCD LifeVest® 4000

Source: https://lifevest.zoll.com/patients/what-is-lifevest/

The WCD monitors the patient's heart continuously, and if it detects a life-threatening heart rhythm that it can restore, such as VT or VF, it delivers an automatic treatment shock [18]. Once it detects such treatable arrhythmia, an alarm rings to alert the patient. The patient is instructed to sit or lie down to avoid injury in the event of loss of consciousness [1, 23]. 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 two alarms: a vibration and a siren alarm to bystanders that a treatment shock is imminent [18]. Then, the device releases a Blue™ gel over the therapy electrodes 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 [18]. Healthcare professionals also monitor the patient by using the LifeVest Network. After receiving WCD shock therapy, patients are instructed to call their doctor or seek medical attention, when evaluation of arrhythmias that triggered the shock and replacement of the old electrodes should be provided [1, 23]. The WCD delivers biphasic shocks with a maximum of 150J and 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) [1, 23].

4. CLINICAL EFFECTIVENESS (EFF)

4.1 Methods

The Assessment Elements of this domain were:

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?

The evidence synthesis of the comparative effectiveness of the WCD was conducted qualitatively. Only RCTs and observational studies with concomitant controls were eligible for inclusion in the evidence synthesis. In addition, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to assess the quality of the evidence. The data was based on the data-extraction-table (see APPENDIX 4). The research questions (assessment elements) were then answered systematically in plain text format. The final conclusion of the evidence on the comparative effectiveness of the WCD was based on the GRADE evidence profile (see APPENDIX 5).

4.2 Systematic literature search

The systematic search was conducted on the 27th of August 2018 in the following databases:

- Pubmed
- Cochrane
- Embase

The search was limited to articles published in English. Overall 714 hits were identified. The specific search strategy employed can be found in APPENDIX 6. A hand-search on the internet and contact with the manufacturers supplemented the search.

By hand-search, 2 additional studies were found, resulting in 570 hits after the deduplication.

Furthermore, to identify ongoing and unpublished studies, a search in one clinical trials register (ClinicalTrials.gov) was conducted on the 19.09.2018 resulting in 8 potentially relevant hits for ongoing studies. The reader is referred to APPENDIX 7 for the full list of identified ongoing studies.

4.3 Flow chart of study selection

Overall, after duplicates removal, 570 hits were identified. The references were screened by two independent researchers (MO, GG) and in case of disagreement a third researcher (TJ) was involved to solve the differences. The selection process is displayed in Figure 4.

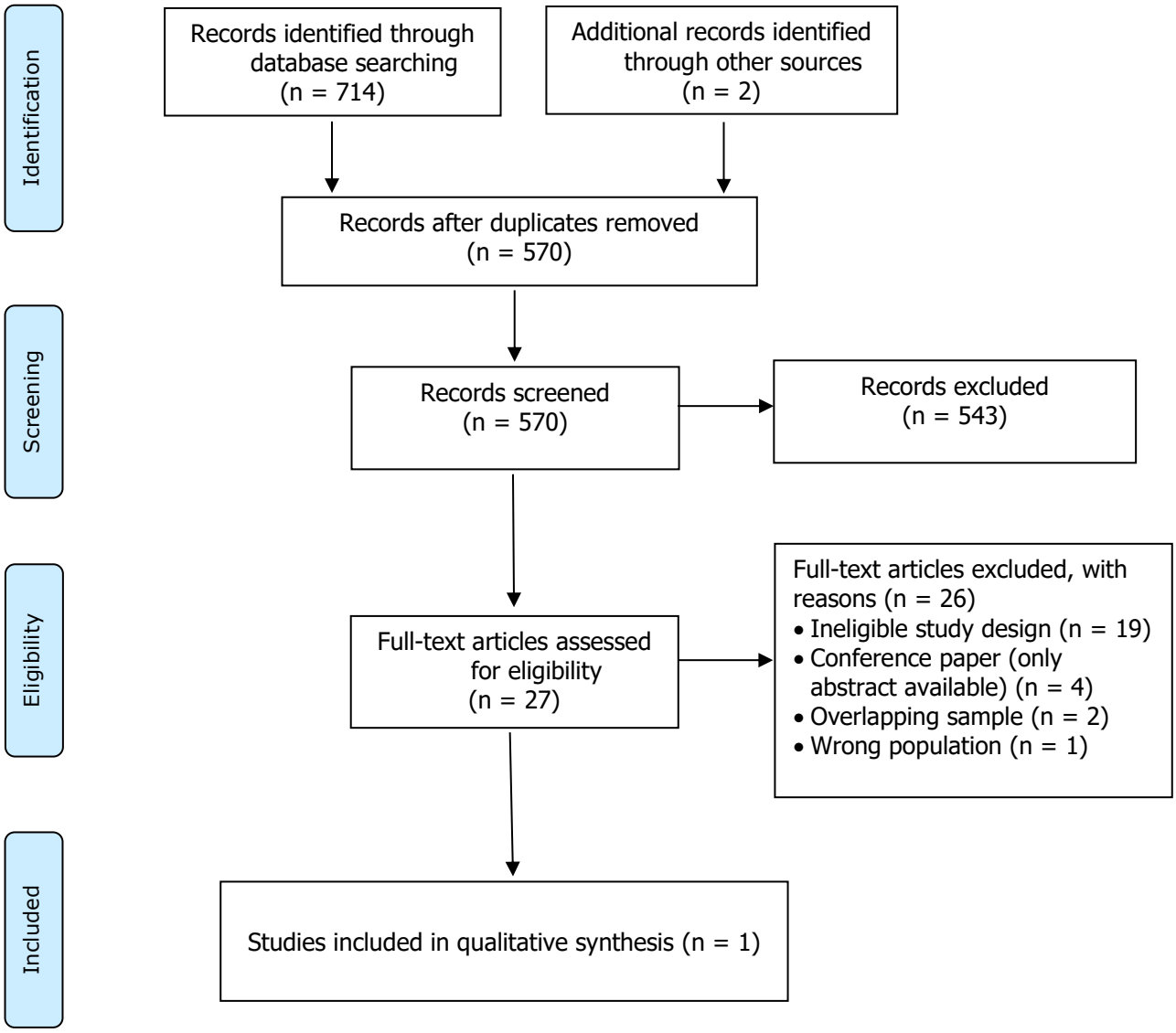


Figure 4: Flow chart of study selection for Effectiveness analysis (PRISMA Flow Diagram)

4.4 Analysis

Relevant data from the selected study were extracted into data-extraction-table (see APPENDIX 4). The single-data extraction method with verification of another researcher was used: one reviewer (MO) extracted the data and another reviewer (GG) controlled the extracted data.
Two independent researchers (MO, GG) assessed the quality of evidence. The risk of bias assessment of the included study was conducted by one reviewer (GG) and checked by another reviewer (MO) using the Cochrane Risk of Bias (RoB) Tool [24] (see APPENDIX 8).

4.5 Synthesis

Due to the presence of a single RCT, no inferential statistical analyses were feasible. Therefore, a qualitative evidence synthesis was conducted. Based on the data-extraction-table (see APPENDIX 4), data on each selected outcome category were synthesised across studies according to GRADE (see APPENDIX 5). The research questions were answered in plain text format.

4.6 Results

Included studies

For the assessment of the clinical effectiveness of the WCD, one RCT (the VEST study by Olgin et al.) met the inclusion criteria [25]. The RCT assessed the efficacy of the Wearable Cardioverter-Defibrillator (WCD) during the period before implantable cardioverter-defibrillators (ICDs) are indicated: the study compared the use of the WCD and guideline-directed medical therapy (GDMT) to GDMT alone in patients who have had a MI and an ejection fraction of 35% or less.
The reader can consult the data extraction table in APPENDIX 4 for all retrieved information on the included study, e.g., study characteristics, information on patient population, intervention, control, and study design.

Study characteristics

The multicentre RCT [25] included sites in the United States (n=76), Poland (n=24), Germany (n=6), and Hungary (n=2). Zoll Medical Corporation and the National Institutes of Health (NIH) / National Heart Lung and Blood Institute (NHLBI) funded the study. In 2011, however, NIH / NHLBI decided to end funding the study – 1 year prior to the end of the planned 5-year funding period (see also Section 4.7).
In total, 2,348 patients who had been hospitalised with an acute MI (and EF≤35%) were enrolled and randomised in a 2:1 ratio in the included study [25]. 46 participants were excluded from the analysis due to irregularities found by the institutional review board at one of the sites. Thus, 2,302

participants were included in the analysis, resulting in 1,524 and 778 patients in the device and control group respectively. Regarding cross-overs, 20 participants (2.6%) in the control group received the WCD by prescription outside of protocol by treating medical doctors, while 43 participants (2.8%) in the device group, never wore the device after randomization. Patients in the device group received a WCD and GDMT, while the control group received GDMT solely. The mean follow-up time of the randomly assigned patients was 84.3 days (SD: 15.6), and further 22 patients were lost to follow-up, with 10 out of 1,524 patients (0.7%) and 12 out of 778 patients (1.5%) in device and control group respectively.

Patient characteristics

The inclusion criteria from the VEST trial are [25]: patients who were hospitalised with an acute MI and who had an ejection fraction of 35% or less were enrolled within 7 days after hospital discharge. Patients who had/were undergoing one of the following were excluded [25]: ICD or unipolar pacemaker, clinically significant valve disease, long-term haemodialysis, chest circumference being too little or too large to accommodate the Wearable Cardioverter-Defibrillator, pregnancy or discharge to a nursing facility with an anticipated stay of more than 7 days.
Previous interventions of the patients included CABG (8.7% and 9% of pts in device and control group respectively) and PCI (24.6% and 26% of pts in the device and control group respectively).
The reader is referred to APPENDIX 4 for more information of the included study.
The mean age of the patients in the device group and control group was 60.9 years (SD: 12.6) and 61.4 years (SD: 12.3) respectively. The mean ejection fraction (EF) was 28.2% (SD: 6.1) for patients in the device group and 28.2% (SD: 5.8) for patients in the control group.

Mortality

Disease-specific mortality

(D0001) The VEST study [25] found no statistically significant difference between device and control groups when comparing the primary outcome (arrhythmic death) between device and control group, with 25 out of 1,524 (1.6%) and 19 out of 778 (2.4%) arrhythmic deaths in those groups respectively ($p = 0.18$).

All-cause mortality

(D0001) The VEST trial by Olgin et al. [25] found a statistically significantly lower rate of the secondary outcome deaths from any cause in the device group when compared to the control

group, with 48 out of 1,524 (3.1%) and 38 out of 778 (4.9%) deaths from any cause in those groups respectively (p = 0.04)[5].

Morbidity

Appropriate shocks

In the included study [25], 20 out of 1,524 patients (1.3%) in the device group received an appropriate shock. Of those, 13 patients received 1 shock, and 7 patients received 2 or more appropriate shocks. In the control group, 1 out of 778 patients (0.1%) received 2 or more appropriate shocks[6].

Withheld shocks

In the included study [25], withheld shocks were present in both the intervention and control group. As such, 69 patients in the device group (4.5%) and 1 patient in the control group (0.1%) withheld a shock by using the response button to delay therapy[6].

First shock success

The included study [25] did not report on the first shock success rate.

No evidence was found to answer the research question D0006, D0011, D0016.

Health-related quality of life

(D0012) No evidence was found to answer the research question. However, the authors of the included trial [25] gathered data on quality of life of the patients without reporting it in the main publication of the VEST study (see section 5.3 Discussion for more information).

(D0013) No evidence was found to answer the research question.

Satisfaction

(D0017) No evidence was found to answer the research question.

Change-in-management

Rehospitalisation rate

(D0010) In the included study [25], the rehospitalisation rate was measured. The authors did not find a statistically significant difference when comparing the rehospitalisation rate between device

[5] The p-value was not corrected for multiple testing, increasing the risk that this statistically significant difference was a chance finding (see section 4.7 Discussion for more information).

[6] 20 patients in the control group received the WCD by prescription outside of protocol by treating medical doctors. The use of a WCD by a control participant was considered to be a protocol deviation.

group and control group, with 31.2% and 32.5% rehospitalised patients (any cause) in those groups respectively (p-value = 0.51).

Resource utilisation

(D0023) No evidence was found to answer the research question.

Other

Compliance

The included study [25] measured the compliance/patient adherence. In the device group, 1,481 out of 1,524 patients (97.2%) wore the WCD[7]. Those patients wore the device averagely 14 hours per day (SD: 9.3). The median wear-time was 18 hours (IQR: 3.8-22.7).

Data on the overall WCD wear-time in days was not reported in the included study [25].

Improvement in ejection fraction (EF)

The included study [25] did not report on improvement in EF.

Assessment of the methodological quality of the included study and quality of the evidence

The methodological quality assessment of the RCT [25] was conducted using the Cochrane Risk of Bias (RoB) tool. The quality of the RCT was affected by selective outcome reporting and by poor compliance that could have distorted the effect estimates. Further information on the risk of bias assessment of the included study can be found in APPENDIX 8.

According to the GRADE assessment, there is moderate certainty to believe in the results of the following endpoints: appropriate shocks, withheld shocks, and rehospitalisation by any cause. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. We downgraded the certainty to moderate for the aforementioned outcomes primarily because of the low compliance in the study that could have potentially distorted the effect estimates equally in this study. For the endpoints arrhythmic death and all-cause mortality we found low certainty to believe in the effect estimate. We downgraded the endpoint arrhythmic death due to serious risk of bias (see APPENDIX 4) and serious imprecision. We downgraded the endpoint all-cause mortality due to the fact that no correction was made for multiple testing. Therefore, we judged the significant result in all-cause mortality likely to be a chance finding. Also, we did not downgrade the endpoint compliance, leading to high certainty to believe in this

endpoint. The reader is referred to the GRADE evidence profile to be found in APPENDIX 5 for more information.

4.7 Discussion

Although the evidence was derived from a RCT with a sufficient sample size, further aspects concerning the results, the funding of the study, the reported outcomes, and the compliance with the device need to be discussed.

First, the RCT [25] found a statistically significant difference when comparing the secondary outcome death from any cause between participants of the device group and the control group, with 48 out of 1,524 (3.1%) and 38 out of 778 (4.9%) deaths from any cause in those groups respectively (p=0.04). Over the past year, this result has been positively marketed (e.g., in conferences and press releases[8]). The presentation of the results of what is a secondary outcome was debated by experts and researchers internationally because a trial with negative results from the primary outcome assessment appeared to market the secondary outcome in a way that led to the (false) perception that there is evidence proving the (comparative) effectiveness of the WCD[9]. In the study published recently in the New England Journal of Medicine (NEJM), however, the conclusion was clear (i.e., no statistically significant difference when comparing the primary outcome between intervention and control group) and the limitations regarding the statistically significant result of the secondary endpoint were also sufficiently described. The statistically significant difference of the secondary outcome (death from any cause) in favor of the WCD was only mentioned in the discussion section, reporting that the p-value (0.04) was not corrected for multiple testing, leading to a high likelihood that this result was a chance finding.

Second, the study [25] mentioned that the National Institutes of Health (NIH) / National Heart Lung and Blood Institute (NHLBI) ended funding the VEST trial 1 year earlier than anticipated. As a result, Zoll Medical Corporation was the only funder that continued funding the VEST trial. Also, Zoll Medical Corporation added funding for a VEST Register [25]. Our project team was unclear on the reasons for the NIH decision to end funding earlier than anticipated but in a meeting with ZOLL

[7] Also, some 20 patients in the control group (n=778) wore the WCD (2.6%) as well.

[8] See, for instance, 26. American College of Cardiology (ACC). *Wearable Defibrillator Cuts Overall Mortality, But Not Sudden Deaths After Heart Attack. Press release.* 2018 15.09.2018]; Available from: https://www.acc.org/about-acc/press-releases/2018/03/09/16/08/sat-9am-et-wearable-defibrillator-cuts-overall-mortality-but-not-sudden-deaths-after-heart-attack, 27. ZOLL Medical Corporation. *LifeVest Wearable Defibrillator Reduces Total Mortality By 36 Percent At 90 Days. The Landmark VEST Trial Shows 90-Day Use of LifeVest WCD Reduces Total Mortality After Heart Attack*. 2018 15.09.2018]; Available from: https://www.prnewswire.com/news-releases/lifevest-wearable-defibrillator-reduces-total-mortality-by-36-percent-at-90-days-300611957.html..

[9] See, for instance, 28. Mandrola, J.M. *The VEST Trial Failed, and So Did the Press Release*. 2018; Available from: https://www.medscape.com/viewarticle/893756#vp_1 [Accessed: 15/09/2018]..

Medical Corporation, we were told that this was because of slow recruitment in the United States and the NIH was apparently not prepared for a permanent commitment.

Third, selective outcome reporting may have been present in the included study [25]. In the protocol of the VEST study[10], quality of life (QoL) is mentioned as a secondary outcome – measured using the SF-36 tool. This tool also measures anxiety – an outcome that is of great importance considering the risk of SAEs (e.g., inappropriate shocks) when using the WCD. We contacted the primary investigator of the VEST study to clarify the questionable way of selectively reporting on some, but not all, of the outcomes that have been selected as outcomes in their study protocol. He clarified that QoL data was assessed in the VEST study without including it in the NEJM publication. He pointed out that the QoL data analysis is not finished yet. A further publication is planned that includes a QoL and cost analysis of the data gathered within the VEST study. However, it was unclear to the authors why the report of the VEST study that was published in the NEJM neither reported on, nor indicated of having measured QoL data.

Fourth, patients wore the WCD less often than anticipated: The patients wore the device on average 14 hours per day (SD: 9.3) and the median wear-time in the included study [25] was 18 hours (IQR: 3.8-22.7). The distribution of the data on the wear time of the WCD in the device group leads to the impression that patients seemed to have an "all or nothing"-approach towards wearing the WCD. Half of the patients wore the device less than 18 hours a day, while the more compliant other half of the sample wore the device longer than 18 hours a day. More strikingly, the least compliant quartile of patients wore the WCD less than 3.8 hours per day, while the most compliant quartile of patients within the sample wore the WCD more than 22.7 hours a day. The low-compliance is also evident when looking at how many patients actually wore the WCD at time of death or event leading to death: only 12 out of the 48 patients who died in the device group actually wore the device at the time of death (any cause). Hence, the "all or nothing"-approach towards wearing the WCD may have been a factor that distorted the results.

It appears that the compliance of the WCD of the patients enrolled in the RCT [25] may be worse than in the included 10 observational studies [29-38]. As such, the mean daily use of the WCD in the observational studies ranged from 19.5 to 23.4 hours/day; the median wearing time ranged from 18.0 to 23.5 hours/day. In those observational studies, the overall population included in all studies was 2,616 patients (mean: 262, range: 8-2000). The reader is referred to the data-extraction table of observational studies for more information on those studies (see APPENDIX 9).

The reasons for the poor compliance in the RCT [25] are unknown and at this moment in time, one can only speculate about factors having influenced the compliance. After a consultation with ZOLL,

we were told that older models of the WCD were used in the RCT as well. There may be a difference in compliance between models. As all ECG tracks were recorded it is possible to identify who was wearing the WCD and then ask why they had not worn it. For instance, it is possible that there was a difference in compliance between models of the WCD or that the consent form indicating the proper use may have been unclear.

For the sake of answers to explain factors contributing to the low compliance, further data analysis is mandatory. The data on quality of life are available and can be analysed to identify factors for the low compliance in the RCT and consequently improve the scientific evidence regarding the effectiveness of the WCD.

In addition, the search for ongoing studies in clinicaltrials.gov revealed that there may not be any RCTs or other comparative designed studies underway. Eight uncontrolled ongoing studies were identified. The reader is referred to APPENDIX 7 for the full list of identified ongoing studies.

4.8 Conclusion

For the assessment of the clinical effectiveness of the WCD, one study [25] was eligible to be included in this assessment: the RCT compared the use of the WCD and GDMT with GDMT alone. Based on the selected effectiveness outcomes, no statistically significant differences were found for disease-specific mortality and rehospitalisation rate. A statistically significant difference was found for all-cause mortality – though the conservative interpretation is that this difference was a chance finding. Quality of life and patient satisfaction with the WCD were not reported. The researchers involved in this assessment judged the compliance to be low in the included study.

Currently, the evidence indicates that the use of the WCD in combination with GDMT in patients with a recent MI and an ejection fraction of 35% or less is not proven to be more effective when compared to GDMT alone in affecting arrhythmic mortality. The evidence base for this conclusion is one RCT. Evidence from new RCTs and cohort studies with concurrent controls may influence the effect estimate considerably.

[10] The protocol can be found in the supplementary appendix of 25. Olgin, J.E., et al., *Wearable Cardioverter–Defibrillator after Myocardial Infarction.* New England Journal of Medicine, 2018. **379**(13): p. 1205-1215..

5. SAFETY (SAF)

5.1 Methods

The Assessment Elements of this domain were:

Assessment Element ID	Research question
C0008	How safe is the WCD in relation to the comparator(s): - What is the frequency and what are serious adverse events (SAEs) of the WCD in relation to the comparator(s)? - What are the most frequent AEs of the WCD in relation to the comparator(s)? - What is the frequency of discontinuation of the WCD due to AEs of the technology in relation to the comparator(s)? - What is the frequency of unexpected AEs in WCD and comparison groups?
C0002	Are the harms related to dosage or frequency of applying the 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)?

Evidence analysis for safety domain has been performed according to the PICOs framework defined in Table 1. RCTs, observational studies with concomitant controls, observational uncontrolled prospective studies and register studies were deemed eligible for inclusion in the evidence synthesis. The characteristics of included studies were extracted and described in APPENDIX 4 (RCT) and APPENDIX 9 (Observational Studies). The methodological quality assessment of the RCT [25] was conducted using the Cochrane Risk of Bias (RoB) tool [24] (see APPENDIX 8), while the observational studies were assessed through the 20-items checklist developed by the IHE [39] (see APPENDIX 10). In addition, the GRADE framework was used to assess the quality of the evidence and the certainty in the effect estimates. The data was based on the data-extraction-tables (see APPENDIX 4 and 9). The research questions (assessment elements) were then answered systematically in plain text format. The final conclusion of the evidence on the safety of the WCD was based on the GRADE evidence profile (see APPENDIX 5).

5.2 Systematic literature search

The systematic search of the literature has been already described in the EFF domain.

5.3 Flow chart of study selection

Overall, after duplicates removal, 570 hits were identified. The references were screened by two independent researchers (MO, GG) and in case of disagreement a third researcher (TJ) was involved to solve the differences. The selection process is displayed in Figure 5.

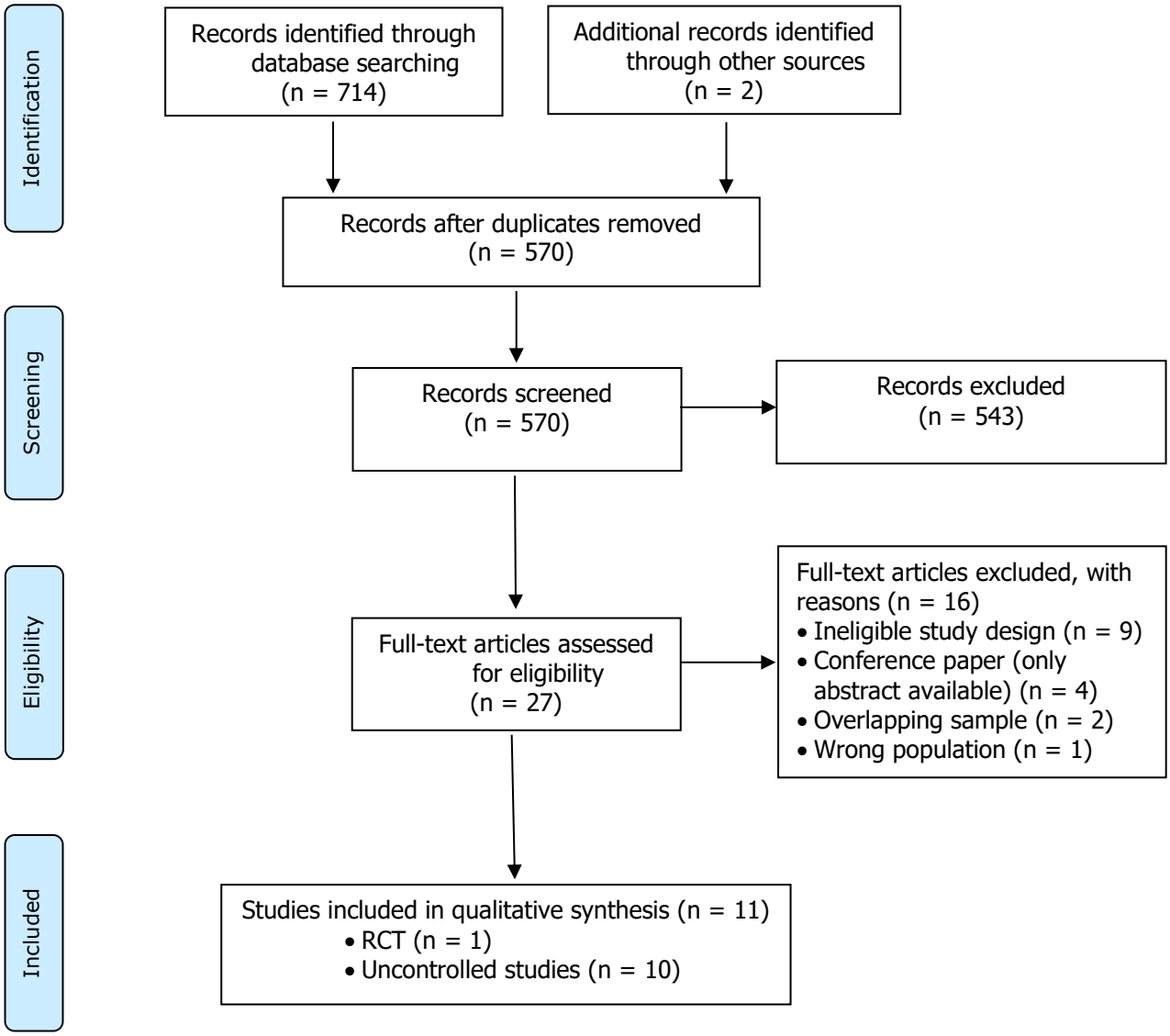


Figure 5: Flow chart of study selection for Safety analysis (PRISMA Flow Diagram)

5.4 Results

Included studies

For the safety analysis, 11 studies [25, 29-38] were included; one study [25] was the RCT already included for the clinical effectiveness analysis, while the remaining 10 studies [29-38] were observational prospective studies or prospective register studies. The characteristics of the included studies for safety are described in the APPENDIX 4 and APPENDIX 9.

Randomised study: The characteristics of the included RCT are described in the clinical effectiveness analysis.

Observational studies

Ten observational studies [29-38] were included in the safety analysis: eight were prospective case series [29-33, 35, 37, 38], and two were register studies [34, 36]. Seven studies were single-center [29, 31-33, 35, 37, 38] (4 from Germany [32, 33, 35, 37], 1 from Australia [31], 1 from France [29], and 1 from Japan [38]); three studies were multi-center [30, 34, 36] (2 from USA [34, 36] and 1 from USA/Israel [30]), all funded by ZOLL Medical Corporation. The overall population included in all studies was 2,616 patients (mean 262, range 8-2,000). The patient's mean or median age ranged from 51 to 69 years; the percentage of male participants in the included studies ranged from 69% to 92%. The LVEF ranged from 22% to 52%. The mean/median follow-up time range was 3-19 months. Patients lost to follow-up were 7/89 (8%) in Kao et al. [34], 9/114 (8%) in Röger et al. [37], none in five studies [29, 31-33, 38], and not reported in three studies [30, 35, 36].

All studies clearly reported inclusion criteria that widely differed between the studies, while only 4 studies [29, 30, 34, 38] reported exclusion criteria that mainly referred to having a previous ICD placement or having cognitive impairment.

Serious Adverse Events (SAEs)

(C0008) **RCT**: The only comparative study included [25] reported the safety outcomes described below: four SAEs related or potentially related to the WCD occurred. Three of them were patient hospitalizations (two due to aborted shocks and one due to an inappropriate shock), and one was a patient that died while he was wearing the device. The authors state that it was deemed likely not to be an arrhythmic death (no tachyarrhythmia was recorded by the device and emergency medical technicians noted pulseless electrical activity on arrival).

Other SAEs were inappropriate shocks (one was the hospitalized patient already described above) that occurred in 9/1524 (0.6%) patients in the device group vs none in the control group.

Observational studies: The observational studies without a control group (comparator), reported the AEs occurring to patients wearing the WCD described below. In the studies AEs were reported for the overall population and not reported separately for patients with ischemic cardiomyopathy (ICM), non-ischemic cardiomyopathy (NICM), or other subgroups.

The SAEs reported were inappropriate shocks, unsuccessful shocks, and frequency of SAEs leading to death.

All the studies reported on inappropriate shocks. Six studies [29-31, 34, 35, 38] state that no inappropriate shock occurred. One study [37] reported that one inappropriate shock occurred in 1/105 patient (1%). This patient was a 74-year-old female with mild cognitive defects and newly diagnosed ICM. She received an inappropriate WCD shock that was triggered by artifactual voltage fluctuations misinterpreted by the WCD as ventricular arrhythmia. She ignored both tactile and audible alarms and failed to press the response button of her WCD.

One study [33] reported 2/102 (2%) inappropriate WCD shocks due to atrial fibrillation/flutter with rapid ventricular conduction. Although hemodynamically stable, both patients did not abort WCD therapy pushing the button. One study [32] reported two inappropriate WCD shocks that occurred in 2/130 (2%) patients, both due to rapidly conducted supraventricular tachycardia. The multi-center, prospective, registry study by Kutyifa et al. [36] involving 2000 patients reported 10 (0.5%) inappropriate shocks because of ECG artifacts. Inappropriate shocks did not induce VT or VF. Only two studies [35, 36] out of 10 reported the outcome of unsuccessful shocks, reporting that all the shocks delivered were successful. Five studies [31, 34-36, 38] out of 10 reported the outcome of SAEs leading to death, describing that no patients died wearing the WCD.

Adverse events (AEs)

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

Observational studies: The AEs reported in the 10 observational studies were: skin rash and itching; false alarms; discontinuation due to comfort and lifestyle issues.

Erath et al. 2017 [33] reported that 2/102 (2%) patients developed allergic skin reactions due to nickel hypersensitivity that could not be controlled with local or systemic steroid therapy, leading to stop wearing WCD.

Two studies [29, 33] reported on false alarms. Barraud et al. [29] reported that no patient received false WCD alarms; Erath et al. 2017 [33] reported that 58/102 (57%) patients experienced "false

alarms" (vibration, siren or bystander warning) due to incorrect detection of ECG episodes, defined as artifacts upon review.
Three studies [29, 34, 37] reported on discontinuation due to comfort and lifestyle issues. Röger et al. [37] described that 8/114 (7%) patients returned their WCD during the first hours after initiation because of unwillingness or inability to handle it. Barraud et al. [29] reported that 1/24 (4%) patient, after having had an alarm due to a sustained VT, pressed the response buttons to withhold the shock and then decided to remove his WCD. Kao et al. [34] reported 16/89 (18%) discontinuations: 3/89 (3%) patients dropped out after wearing the WCD for a couple of hours; 6/89 (7%) patients refused to wear the WCD due to discomfort and other reasons, and 7/89 (8%) other patients due to unknown/other reasons. No studies reported adverse events by WCD model.

(C0002) Although it could be reasonable to associate some AEs as skin rash and itching with the WCD wearing time, none of the included studies specifically addressed this issue.

(C0004) The available evidence on the WCD did not address specifically whether the frequency or severity of harms changed over time or in different settings of use.

(C0005) Patients with cognitive impairment could be at higher risk of inappropriate shocks, due to their possible inability to press the response buttons [37].

(C0007) The most important potential user-dependent harm is related to compliance in wearing the WCD. Compliance is crucial for patients to be protected from SCD caused by VT/VF. Patients must wear the WCD as many hours/day as possible, taking it off just to have bath or shower. Poor compliance could result in a raised risk of sudden death. In the RCT by Olgin et al. [25], the compliance was poor, with a mean wearing time of 14.0 (SD 9.3) hours/day [median 18 (IQR 3.8–22.7) hours/day]. In the observational studies included, the mean wearing time ranged from 19.5 to 23.4 hours/day; the median wearing time ranged from 18.0 to 23.5 hours/day.
Another issue related to user-dependent harms is the appropriate use of the response buttons. There are two main possible sources of harms. Firstly, patients might push the buttons when it is not clinically appropriate and avert a possible life-saving treatment; also, bystanders could wrongly push the buttons averting a possible life-saving shock. Secondly, for various reasons, conscious patients could fail to push the response buttons, receiving an inappropriate shock [37].
Lastly, also professionals might cause harm because of their responsibility of setting up the monitor and choosing the settings for each patient. However, the default setting can also be used [19].

(B0010) Register studies are set in an everyday context of use, in patients wearing the WCD with different diagnoses (ICM, NICM, dilated cardiomyopathy, etc.) and collecting data on their medical history, comorbidities, and other baseline clinical characteristics, as well as clinical effectiveness and safety outcomes associated with the use of WCD. However, according to our PICOS, no conclusions can be drawn on the effectiveness from register studies.

In this report, we included two prospective register studies [34, 36] on the device WCD. The study by Kutyifa et al. [36] included 2,000 patients having ICM (40%), NICM (46%), and with congenital or inherited heart disease (14%). This study collected data on the patient's compliance, clinical and arrhythmic events during WCD use. At 3 months follow-up after the WCD use, it was further assessed whether the patients were implanted with an ICD or they had an improved ejection fraction. However, clinical effectiveness data as patient's satisfaction with technology, HRQoL, hospitalisation rate, and safety data as skin rash and itching, and false alarms were missing.

The other register study by Kao et al. [34] reported the experience of 89 patients wearing the WCD (7 patients were excluded from final analysis due to loss to follow-up and early discontinuations). This study included heart failure (HF) patients listed for heart transplantation, patients with dilated cardiomyopathy (DCM), and patients using inotropes. Data collected were compliance, defibrillation events, arrhythmia detection, and ECG recordings. Other data results were missing: patient's satisfaction with technology, HRQoL, hospitalisation rate, safety data as skin rash and itching, and false alarms.

In conclusion, regarding safety issues, these two register studies and in particular the larger study [36], did not report adequately all the important safety outcomes related to the WCD use.

Assessment of the methodological quality of the included studies and quality of the evidence

RCT: The methodological quality assessment of the RCT by Olgin [25] was described in the effectiveness analysis.

According to the GRADE assessment (APPENDIX 5), there is moderate certainty to believe in the results of the following safety endpoints: rash and itch in the torso area, and inappropriate shocks. We downgraded the certainty from high to moderate for these safety outcomes because of serious risk of bias due to low compliance in the study that could have potentially distorted most of the effectiveness and safety effect estimates. The other items of the certainty assessment (inconsistency, indirectness, imprecision, and other considerations) were considered not to present serious risk of bias.

Observational studies: The methodological quality assessment of the observational studies was made through the 20-items checklist developed by the IHE [39] (APPENDIX 10). Applying the IHE checklist, 8 studies [29, 30, 32-37] were at high risk of bias, while 2 studies [31, 38] were at very high risk of bias. The main concerns for risk of bias were: 7/10 studies were single-centre with a limited sample size; patients entered the study at a similar point in the disease only in 1/10 study; in all studies outcome assessors were not blinded to the intervention that patients received; losses to follow-up were reported only in 3/10 studies; AEs were fully reported only by one study, while 7 studies reported them partly, and 2 studies did not reported them at all.

The GRADE assessment (APPENDIX 5) for safety outcomes showed a very low certainty in the estimated proportions of AEs due to serious or very serious risk of bias for all the safety outcomes, and serious imprecision (due to small sample size, the estimated proportions of AEs have wide confidence intervals) for some of the safety outcomes (allergic skin reactions and false alarms).

5.5 Discussion

The available evidence on the safety of WCD derives from one RCT and ten observational studies. In most of the included studies, there was a lack of reporting on AEs.

The RCT showed relatively few SAEs occurring in the device group, as hospitalizations or inappropriate shocks, while AEs as rash and itching in the torso area were more common. However, the quality of the RCT was affected by selective outcome reporting and compliance issues. The certainty in the outcome estimates was judged low for the outcome death from any cause, and moderate to high for the other outcomes by the GRADE assessment.

The observational studies showed a low rate of SAEs as well, with a ratio of inappropriate shocks between 0.5% and 2%. This ratio is in line with that reported by the RCT (0.6%).

Regarding AEs, only one study reported allergic skin reactions in 2% of the patients. This ratio is much lower than the occurrence of skin rash reported by Olgin et al. (13%).

Two studies reported on false alarms: one study reported that no patient received false WCD alarms, while another study reported that 57% of the patients experienced "false alarms" due to incorrect detection of ECG episodes, defined as artifacts upon review. This discrepancy is quite surprising and could be interpreted as selective reporting of this outcome in the included studies leading to potentially biased results.

Three studies reported discontinuation due to comfort and lifestyle issues that ranged from 4% to 18% of the patients. These discontinuations could have derived from a lack of the perceived quality of life of patients wearing the WCD, even if we did not find specific data about QoL in the included studies.

The overall quality of the observational studies was judged to be at high or very high risk of bias, and the GRADE assessment for safety outcomes showed a very low certainty in the estimated proportions of AEs in the WCD patients.

Studies that could have reported on an overlapping sample are those by Erath 2017 [33] and by Erath 2018 [32]. In fact, these studies were performed in the same institution (J. W. Goethe University Hospital, Frankfurt), had a very similar sample size (124 vs 130 patients), and in Erath 2018 [32], the start and the completion dates were not reported. Another two studies could have considered an overlapping sample [30, 36]. Barsheshet et al. [30] reported on 50 patients from the University of Rochester Medical Center (NY, U.S.A.) and they did not report the start and the completion dates, while Kutyifa et al. [36] reported on a multicenter registry (WEARIT-II) of patients from USA sites (patients were enrolled from August 2011 to February 2014) and the coordination and data center was the University of Rochester. The other included studies were performed in different countries or time frames.

5.6 Conclusions

The available evidence indicates that the WCD could be a relatively safe intervention for patients at risk of SCD. However, the quality of evidence was at high or very high risk of bias and the certainty in the safety endpoints according to GRADE was very low. There was a lack of reporting of AEs and SAEs in most of the studies. More data from high quality studies with a more complete reporting on AEs and SAEs are needed to confirm the safety of the device.

6. ECONOMIC EVALUATION (ECO)

The following information are based on the literature research and context analysis. In particular, we carried out the literature research, using the same search strategies used to evaluate efficacy and safety reported in APPENDIX 6, to collect the information useful to answer to the research questions reported in the following methods.

6.1 Methods

For the context economic analysis we consulted the Ministerial database (NSIS) on consumption and relative prices and we contacted the manufacturer to collect further information through an ad hoc questionnaire (APPENDIX 2) (E0001).

Element ID	Research question
E0001	What types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?
E0002	What amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?
E0009	What were the measured and/or estimated costs of the assessed technology and its comparator(s) (resource-use valuation)?
D0023	How does the technology modify the need for other technologies and use of resources?
G0007	What are the likely budget impacts of implementing the technologies being compared?
E0005	What is (are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s) (outcome identification, measurement and valuation) and in practice?
E0006	What are the estimated differences in costs and outcomes between the technology and its comparator(s)?
E0010	What are the uncertainties surrounding the costs and economic evaluation(s) of the technology and its comparator(s)?
E0013	What methodological assumptions were made in relation to the technology and its comparator(s)?

6.2 Results

(E0001) From research literature, consulting the databases Pubmed, The Cochrane Library and Embase, resulted 12 articles and after screening of titles and abstracts we included only one study potentially eligible [22]. We also included another study pointed out by manufacturer [40] in the questionnaire. After the read of full text we confirmed these two studies included.

(E0009, D0023, E0005) Healy et al. [22] carried out a cost-effectiveness evaluation of the WCD compared with other alternatives of management for the prevention of SCD in patients with infected ICD removed.

The analysis is focused on the patients cannot undergo immediate device re-implantation. For these patients are available 4 options: 1) discharge home with a WCD until re-implantation; 2) discharge home without a WCD until re-implantation; 3) discharge to a skilled nursing facility (SNF) without a WCD until re-implantation; 4) remaining in the hospital without a WCD until re-implantation.

Exist the uncertainty related to the window after device removal and re-implantation, due to different reasons, and WCD could be considered to an alternative approach to inpatient monitoring for the prevention of SCD.

The authors developed a decision model, a Markov process, to compare the cost-effectiveness on use of the WCD to several different strategies for patients who undergo to ICD removal. The model aimed to capture both cost and utility and assessed event as: survival, quality of life, costs to the healthcare system; its considered the societal perspective for costs and benefits, discounted at 3% annually. The model compared WCD with: Strategy 1) No WCD and discharge home; Strategy 2) no WCD and discharge to a skilled nursing facility; Strategy 3) No WCD and patients in hospital stay. To compare the effectiveness among strategies the authors considered both life-years (Lys) and quality-adjusted life-years (QALY).

The costs were adjusted to 2014 dollars using an inflation rate of 3% to reflect inflation in the consumer price index. The monthly cost for the WCD was $2,754 and was applied on weeks 1 and 5 (the analysis considered a range of 1 to 8 weeks before ICD re-implantation).

Other costs considered were: cost of ambulance service and postarrest care, telemetry unit stay, cost of medical care for inappropriate shocks from the WCD (by 2014 Medicare Payment Schedule and professional Feeds or published data). Besides loss of income and productivity for pre-mature death was also considered by adding the age-specific average annual wages from the Bureau of Labor Statistics.

It is important to notice that the sensitivity analysis showed that SCA event rate had a profound impact on the cost-effectiveness of the WCD strategy; at high SCA event rates the WCD strategy had both lower cost and better clinical outcome than all alternative therapies, but WCD cost-effectiveness decreased as SCA event rates decreased. The WCD remained cost-effectiveness as long as the 2-month SCA risk was at least 4.2% less than the 4.55% per patient-month observed previously (by ZOLL Registry).

Other variable that impacts on cost-effectiveness is WCD treatment efficacy. The base-case scenario estimated efficacy of 84.5% resulted in an ICER of $26,436/QALY. The ICER was as low

as $15,392/QALY if the WCD successfully terminated 95% of SCA events and exceeded the $50,000/QALY WTP if the efficacy was <69%.

The authors concluded that the WCD is likely a cost-effective treatment for the prevention of SCD in a significant number of these at-risk patients. The analysis resulted that discharge home with a WCD was a cost-effective treatment strategy with an incremental cost-effectiveness of $20,300/LY and $26,436/QALY when compared to discharge home with no device. One of authors declared to be a consultant of manufacturer.

The study of Sanders et al. [40] developed a Markov model to assess the cost-effectiveness of the WCD compared with the current standard of care for early post-MI patients. The model assessed the survival of patient, quality-of-life, and costs.

The population was patients who have had a recent myocardial infarction (MI) with a reduced left ventricular ejection fraction (LVEF) and that cannot undergo to implant within 40 days post MI or 3 months of revascularization.

The ratio of this study is to identify an alternative approach to reduce the risk of SCD, considered elevated in the early post-MI period coupled with the lack of success of the ICD in this setting.

The study based on data of population from VALIANT study [41] and it included direct costs of medical care associated with WCD use, EMS (emergency medical services), ICD implantation and follow-up, treatment of patients with standard care.

Per WCD strategy the costs included were: WCD use, equal to $2,754/month, and additional physician visit for patients who received an inappropriate shock. Per standard care strategy the costs included were: EMS cost, equal to $18,500 for EMS service, and subsequent hospitalization. The patients survivor of SCA, for both strategies, received additional costs related to ICD implantation. In particular, for ICD implantation the costs included were: initial ICD implantation; generator replacement; lead replacement. The costs included were based on 2014 fiscal year and updated to 2014 US dollars using the gross domestic product deflator. The sensitivity analyses is performed and costs were varied by 25%.

The study' results showed that the WCD strategy was more expensive than the standard-of-care strategy with estimated life-time discounted cost higher by $11,503. The WCD strategy had better clinical outcomes, with an improvement in life expectancy of 0.261 life years or 0.190 QALYs. The ICER of the WCD compared with usual care was $44,100/LY or $60,600/QALY.

The authors concluded that the analysis suggest that use of a WCD could reduce the rate of SCD during the recovery period of patients who have had a recent MI and have reduced left ventricular function at a cost that appears to be economically attractive when compared with other generally accepted treatments in the United States. The study was supported by manufacturer and the authors have been paid as consultant.

(E0001, E0002) For the context economic analysis we sent a questionnaire to the manufacturer to collect data on price/cost of the device and also we performed an context analysis consulting database of Italian Ministry of Healthcare NSIS - *Flusso contratti,* containing the purchase' contracts of local health trust. Regarding to the information from manufacturer in the questionnaire he stated that the rental list price per month is €6,000 plus VAT equal to 4%, and the real average price in Italy is €3,600 per rental month.

He reported the service includes, as below reported:

- patient training on how to wear and handle the device;
- activation and addition of the patient in the LifeVest network system, which enables the treating physician to analyse the patients ECG;
- possible replacement of all the pieces constituting the device in case of malfunctioning;
- online telephone service 24 hours per day and 7 days a week for assistance;
- withdrawal of the device after use termination with the obligation from the client to inform ZOLL;

and also all items use for a single procedure, as below reported:

- 1 monitor;
- 2 rechargeable batteries;
- 1 electrode belt;
- 1 holster;
- 1 charger/transmitter;
- 2 disposable garments;
- 2 gel packs (electrodes);
- Patient Instruction Manual.

Regarding to the context analysis we consulted the database *Flusso contratti* for the period from 2015 to 2017; we also collected data of 2018, if data consolidated (year ongoing).

The analysis relieved a total number of WCD equal to 32 units in 6 Regions and 9 local health trust (see Table 3). (E0010, E0013) We observed that in the *Flusso contratti* database not always the contracts reported the data of purchasing modality in right way; for this reason we assumed, according to the manufacturer statement, that all prices are referred to "rental" price. From F*lusso consumi* we relieved the following number of devices used (Tab. 3).

Table 3: Number of WCD rental in the period 2015-2018

	2015	2016	2017	2018	TOTAL
	Q	Q	Q	Q	
Total	4	14	10	4	**32**

Souce: *Flusso consumi NSIS/Italian Ministry of Health and elaborated by Agenas – November 2018*

The rental price, in all years, was constant with a range from €3,400 to €3,500, and consistent with the manufacturer's statement; we relieved only one case, one unit, rented to €4,950.

We relieved two cases with a rental price equal to €10,000, for two units rented; given the average price and the statement of manufacturer we considered this value as outlier. We also relieved an potential data entry error for 4 units in which the price was equal to €350 per month and another for which nothing price is reported. So, at final the value of €3,400 is the price rental more applied (more 60%) and the value of €3,500 is reported in 16% of cases.

7. Patient and Social Aspects domain

7.1 Methods

The Assessment Elements of this domain were:

Element ID	Research question
H0006	How patients act and react to WCD?

A systematic literature search on Cochrane, Embase and Psychinfo was made to answer the research question on patients perceptions[11]. We excluded case studies, expert opinions, conference abstracts and included qualitative literature involving adults real users of WCD and quantitative studies which used quantitative measures of patients quality of life - QoL using the WCD and compliance. We selected for the full text reading all the studies that included these outcomes. Eventually, since in the effectiveness chapter one important outcome was the "compliance" (time of wearing) and their study designs inclusion criteria did not fit ours (i.e. we also considered retrospective studies), we decided not to extract that endpoint (see Chapter 4 - Clinical Effectiveness). We screened and selected records in double and solved disagreements by discussion. The included study's quality was evaluated via Quality Appraisal Checklist for Case Series Studies [39] (see APPENDIX 11).

7.2 Results

A search strategy (see APPENDIX 12) was performed on the above mentioned database at the end of August 2018 and resulted in 108 records. After screening of title and abstract we excluded 94 records (43 as conference abstracts and 51 as not on our technology or as expert opinion/case studies). We read the full text of 15 titles (APPENDIX 13) and eventually included one of them [43] (see Figure 6 Flow chart of study selection).

[11]This report was thought initially to be a simple adaptation of the EUnetHTA Collaborative Report coordinated by LBI. Since they had involved Austrian and German patients organizations, we first thought to follow LBI's steps. Nonetheless we aimed to reach patients who had a direct real experience of using WCD and, due to the time and resources we had, this was done by involving cardiologists and through them, the real users. We asked to cardiologists who had volunteered to collaborate to this assessment after a call on Agenas' web site. Many of them unfortunately responded that they had never prescribed the WCD, so we could have involved very few patients (namely 2) for the interview. Since we could not reach the saturation of information principle [42. Fusch, P.I. and L.R. Ness, *Are We There Yet? Data Saturation in Qualitative Research.* The Qualitative Report, 2015. **20**(9): p. 1408-1416.] systematic literature search was made to answer the research question on patients perception. Since it was not possible to perform interviews with patients as a source of primary context specific evidence, we focused on assessment element H0006.

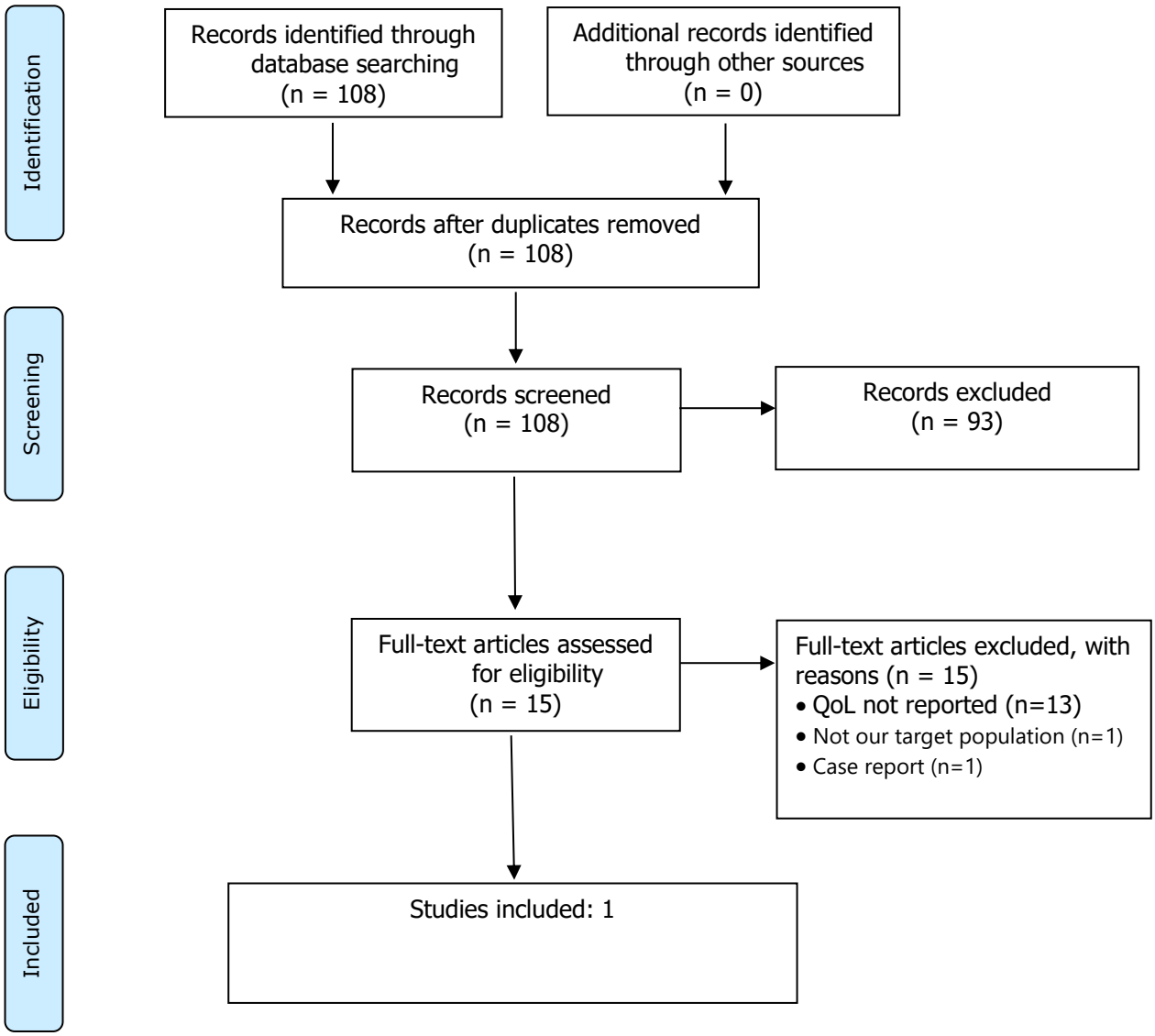


Figure 6: Flow chart of study selection for Patient and Social Aspects domain (PRISMA Flow Diagram)

The Lackermair et al.'s [43] work is a preliminary study on QoL among patients using the WCD. It is a single-centre study which involved 109 consecutive patients who were prescribed with a WCD form 2012 to February 2016 in an unspecified clinics/settings, supposedly in a Munich Hospital (as this is the authors' affiliation). It is a retrospective study, there is no control group and cohort is very heterogeneous so its final results are far to be generalizable. We assessed the quality of this study using the Quality Appraisal Checklist for Case Series Studies [39] (See APPENDIX 11). We describe it anyways as it is the only study that gives some suggestions on how this device affects QoL.

Authors define the study as retrospective as they investigated patients who were prescribed with WCD from 2012 to 2016. Data were collected from routine clinical management of in-hospital patients and also in outpatient settings. Patients prescribed with WCD were at high risk for SCD and not eligible for ICD therapy at the time of diagnosis. Baseline characteristics were raised at the initial presentation before beginning of WCD therapy and at the end of WCD wear time. In this cohort, 78 patients received a WCD without existing prior ICD therapy. At this time patients, within the scope of anamnesis, were administrated with standardized questionnaire for the assessment of QoL, the EQ-5D-3L modified by adding dichotomous questions concerning fear of shock, feeling safe, sleep disturbance, and impairment of usual activities subjectively caused specifically by WCD therapy.

About the five dimension of QoL assessed by the EQ-5D main results are as follows. Mobility resulted to be severely reduced in 2% and mildly in 30%, while for 68% none reduction was declared. The ability of self-care was severely diminished in 1%, mildly 16% and for 83% it was not diminished. For Daily routine activities (e.g., job, housekeeping) 1% of patients reported having severe problems in accomplishing them and 24% had mild problems, while 75% did not perceived any problems. As regard Pain dimension, 5% reported to have severe pain, while mild pain was felt by 31% and none by 64%. For Mental Health (e.g,. depression and anxiety) no patient reported severe mental health issues, while 43% reported mild problems. The overall subjective state of health, on a visual analogue scale from 0 to 100 points, was averagely 70 points. The dichotomous questions specifically addressing the subjective perception during WCD therapy revealed that 29% were afraid of receiving shock therapy. WCD related sleep disturbance or impairment of daily routine activities was reported by 48% and 64% felt protected by the WCD. The influence of the number of warning signals on the dichotomous items was analyzed by authors and, among other results, it was shown that more warning signals was significantly associated with increased fear of shock therapy (18 versus 40%; $p=0.03$). Thirty-five (35) of 78 patients without prior ICD therapy received an ICD after the WCD therapy. Compared to patients with ICD implantation, patients without ICD implantation at the end of WCD therapy reported having felt more safe (77 versus 51%; $p<0.01$) without significant differences of the fear of shock (35 versus 26%; $p=0.39$), WCD related sleep disturbance (51 versus 49%; $p=0.8$), and restriction of daily activities (58 versus 40%; $p=0.11$).

7.3 Conclusion

The selected study has a retrospective design, there is no control group and cohort is very heterogeneous. We described it anyways as its results give some hints on how the WCD was perceived in terms of QoL and its different aspects. Aspects related to QoL and patients

perception, besides compliance, need to be further analyzed via proper study designs and results presented in international journals (e.g. many congress abstracts were found in databases about QoL, but no articles related in international database).

8. CONCLUSIONS

The WCD represents a therapy in primary and secondary prevention of sudden cardiac death (SCD).

The first WCD received CE mark in 1999, while WCD 4000 which received CE mark in 2011, represents the fifth generation and also the most recent model in the market. There was mainly an improvement in the algorithms elaborating heart signals (e.g. a combination of cardiac frequency, morphology, stability, onset) and waveform (from monophasic to biphasic) followed by an improvement in the weight of the controller and plates and garment materials.

Currently, the evidence indicates that the use of the WCD in combination with guideline-directed medical therapy (GDMT) in patients with a recent MI and an ejection fraction of 35% or less is not proven to be more effective when compared to GDMT alone based on the outcome arrhythmic mortality. The evidence base is one RCT. In addition, the compliance with the WCD in the included RCT was low.

For the evaluation of safety of the device, the evidence indicates that the WCD could be a relatively safe intervention. However, more data and more adequate reporting on AEs and SAEs are needed to confirm the safety of the device.

More RCTs and studies with concurrent controls are needed to consolidate or question those evidence-based conclusions.

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APPENDIX 1 - The Agenas adaptation of the EUnetHTA Core Model®

Health Technology Assessment (HTA) is the multidisciplinary evaluation of one or more health interventions in their context of use. Since 2006 Agenas has been involved in the European HTA network EUnetHTA (http://www.eunethta.eu/contactus/all/356/all). EUnetHTA's main aim is to increase collaboration and avoid inefficiencies and duplications by using shared, standardised and agreed methods. These in a continuous development cycle.

One of the methods produced and used is the HTA Core Model® (https://www.eunethta.eu/wp-content/uploads/2018/03/HTACoreModel3.0-1.pdf).

The idea behind the Model is the provision of a standard method for HTA evidence synthesis, structuring and presenting in a standard format to facilitate its use by network agencies and others.

The Core Model is divided into domains which represent the various aspects of the assessment of health technologies' research. Each domain contains a series of research questions or Assessment Elements. Ver 3.0 of the EUnetHTA Core Model is divided into domains:

1. Health problem and current use of technology (CUR)
2. Description and technical characteristics of technology (TEC)
3. Safety (SAF)
4. Clinical effectiveness (EFF)
5. Costs and economic evaluation (ECO)
6. Ethical analysis (ETH)
7. Organisational aspects (ORG)
8. Social aspects (SOC)
9. Legal aspects (LEG)

APPENDIX 2 - Questions for the manufacturer

Agenzia Nazionale per i Servizi Sanitari Regionali

Agenas is carrying on an adaptation report on "Weareable cardioverter-defibrillator (WCD) therapy in primary and secondary prevention of sudden cardiac arrest in patient at risk". You are receiving this request in order to integrate information and data relative to the *LifeVest* to be used in our report for the Italian Ministry of Health (MoH). This will be a public document, so we ask you not to release any confidential information. Please also be aware that the aim of the HTA or HS activities is to conduct a factual assessment of the performance of this class of devices. We are interested in the factual accuracy of the document but the interpretation of those facts is our role. Thank you for your help. Your help will be acknowledged according to your indications in the final report that will be published, after the public consultation phase, on the MoH and Agenas websites.

Manufacturer/Distributor:

Name of technology:

Contact Person:

Questions for the manufacturer/distributor

Health problem and current use of technology

1. Which group(s) of patients represents the target population for *LifeVest*?
2. Which other devices or therapies can be considered as the main comparators[12] of *LifeVest*?
3. Are there specific ICD9-CM (ICD10-CM) codes that identify the use of the *LifeVest* (and comparators) in the hospital discharge database? Are there specific codes in outpatient care?
4. At today, how many *LifeVest* have been used in Italy both in acquisition and/or in rental? How many around the world?
5. At today, how many Italian hospitals use your technology? (Please specify if private or public providers).

Description and technical characteristics of technology

6. What is the current phase of development of the model on the market?
7. How many versions/evolutions of the device have been launched to the last version?
8. [In case of two or more versions] Could you describe the differences between the [n] generations of your device?
9. Which is the risk classification the technology?
10. Could you describe the principle of action and the main characteristics of the technology?
11. What is/are the indication(s) of use of the technology?
12. What are the warnings, precautions, contraindications for the use of the technology?
13. What disposables and supplies are needed to use the *LifeVest*?
14. Does the technology require specific equipment/tools? If yes, please provide descriptions and CND codes for all of them.
15. Are there similar devices/ therapies/procedures that can be considered as "competitors"* of your *LifeVest*? (please specify device names and manufacturers)

Regulatory aspects

16. Has your device obtained the CE mark? If yes, When? (please report month and year for first and last model)
17. Has your device been approved by the FDA?

14.a If yes, when? (Please report month and year)

14.b If not, please report details on the FDA approval status (if any).

18. When was your device launched in Italy? And which is the medical devices' repertory number of the Italian Ministry of Health?
19. What is the reimbursement status of the technology in Italy?
20. Are you aware of any difference in the reimbursement of the technology across the Italian regions? If yes, please provide specific regional reimbursement status.
21. Are you aware of any difference in the reimbursement of the technology across Europe? If yes, please provide specific national reimbursement status.
22. Does the technology require further specific regulations (eg. environmental safety) ?

Clinical Effectiveness and Safety

23. Are there comparative clinical studies (on humans) published/ongoing aimed to compare your device versus other treatments? (if yes, please report full references)
24. Are there non-comparative clinical studies (on humans) published/ongoing aimed to report on effectiveness and safety of your device? (if yes, please report full references)
25. Is there any register for data collection and patient's follow-up? If yes, who runs it? (please specify web-link and/or key-person name and e-mail address)
26. Can you specify the ID number(s) of the ongoing trial(s)?

Costs and economic evaluation

27. What is the list price of your technology? (please, indicate the price, VAT excluded, for all the equipment needed for the implantation procedure)
28. Please fill the table below with all the relevant items for a single procedure:

[12] Comparator is the standard intervention against which the intervention under assessment is compared. The comparator can be no intervention, for example best supportive care.

Item	Number of units	Price per unit (VAT excluded)

29. What is the real cost of your technology (VAT excluded)?
30. Are there economic evaluation studies published/ongoing reporting on *LifeVest*? (if yes, please report full references)

Organisational aspects

31. Which professionals decide on the use of the *LifeVest*?
32. Which professionals (nurses, doctors, and other professionals) use the *LifeVest*? Describe the staff involved in terms of skills and number of units.
33. Is there the need of training for the staff members?

25.a If yes, who provides it?

25.b How much does this training cost and who funds it?

34. Do you have any report about the learning curve of the procedure? (please report full reference).
35. How does the procedure using your device differ from the standard of care in terms of need of additional/special equipment/tool, complexity, dedicated human resources?

Patient/Participant Sphere

Integrations (after first feedback or face-to-face meeting)

APPENDIX 3 – List of Italian Centers using WCD

Information provided by Zoll Medical Italia srl.

Id	Center	City	Italian Region
1	Ospedale SS Annunziata	Chieti	Abruzzo
2	Ospedale Floraspe Renzetti	Lanciano	Abruzzo
3	Ospedale Spirito Santo	Pescara	Abruzzo
4	Ospedale San Giuseppe Moscati	Avellino	Campania
5	Ospedale Sacro Cuore di Gesu	Benevento	Campania
6	Ospedale Maria SS Addolorata	Eboli	Campania
7	Casa di Cura Privata Montevergine S.p.A.	Mercogliano	Campania
8	Azienda Ospedaliera Vincenzo Monaldi	Napoli	Campania
9	Azienda Ospedaliera Vincenzo Monaldi cardio 1	Napoli	Campania
10	Azienda Ospedaliera Vincenzo Monaldi cardio pediatrica	Napoli	Campania
11	Ospedale Umberto I	Nocera inferiore	Campania
12	Presidio Ospedaliero S. Maria Delle Grazie	Pozzuoli	Campania
13	Casa Di Cura Villa Del Sole	Salerno	Campania
14	Azienda Ospedaliera S. Giovanni di Dio e Ruggi d'Aragona	Salerno	Campania
15	Osp. Civile S. Agostino-Estense	Baggiovara	Emilia Romagna
16	Policlinico Sant'Orsola Malpighi	Bologna	Emilia Romagna
17	Ospedale Ramazzini Di Carpi	Carpi	Emilia Romagna
18	Ospedale di Castel San Giovanni	Castel San Giovanni	Emilia Romagna
19	Ospedale Maurizio Bufalini	Cesena	Emilia Romagna
20	Ospedale Guglielmo da Saliceto	Piacenza	Emilia Romagna
21	Arcispedale Santa Maria Nuova	Reggio Emilia	Emilia Romagna
22	Ospedale Infermi di Rimini	Rimini	Emilia Romagna
23	Ospedale Maria Degli Angeli	Pordenone	Friuli Venezia Giulia
24	Ospedale Santa Maria della Misericordia	Udine	Friuli Venezia Giulia
25	Ospedale “Santa Maria Goretti”	Latina	Lazio
26	Policlinico Casilino	Roma	Lazio
27	Policlinico Tor Vergata	Roma	Lazio
28	Ospedale Sandro Pertini	Roma	Lazio
29	Ospedale Santo Spirito in Saxia	Roma	Lazio
30	Az. Ospedaliera San Giovanni Addolorata	Roma	Lazio
31	Ospedale S. Andrea	Roma	Lazio
32	Ospedali Villa Scassi	Genova	Liguria
33	Ospedale Genova Sestri Ponente	Genova	Liguria
34	Ospedale di Imperia	Imperia IM	Liguria
35	ASL 5 - Spezzino	La Spezia, SP	Liguria
36	Ospedale San Paolo	Savona	Liguria
37	Ospedale S. Antonio Abate	Gallarate	Lombardia
38	Ospedale Giuseppe Fornaroli	Legnano	Lombardia
39	Ospedale Giuseppe Fornaroli	Magenta	Lombardia
40	Azienda Ospedaliera Carlo Poma	Mantova	Lombardia
41	Centro Cardiologico Monzino	Milano	Lombardia
42	Fondazione Salvatore Maugeri	Pavia	Lombardia
43	Fondazione IRCCS Policlinico San Matteo	Pavia	Lombardia
44	Multimedica	Sesto San Giovanni	Lombardia
45	Ospedale Civile - Vigevano	Vigevano	Lombardia
46	Ospedale di Vimercate	Vimercate	Lombardia
47	Ospedali Riuniti di Ancona-Torrette Univ	Ancona	Marche
48	Ospedali Riuniti di Ancona-Torrette Cardio	Ancona	Marche
49	Ospedale Mazzoni	Ascoli Piceno	Marche
50	Ospedale Generale Provinciale Macerata	Macerata	Marche
51	Azienda Sanitaria Unica Regionale	Civitanova Marche	Marche
52	Ospedale di Rete Engles Profili""	Fabriano	Marche
53	Ospedale di Fermo	Fermo	Marche
54	Ospedale Carlo Urbani	Jesi	Marche
55	AO Ospedali Riuniti Marche Nord	Pesaro	Marche
56	Ospedale Civile di Urbino	Urbino PU	Marche
57	Ospedale Cardinal Massaia	Asti	Piemonte
58	ASL di Biella	Biella	Piemonte
59	Presidio Ospedaliero S.S. Pietro e Paolo	Borgosesia VC	Piemonte
60	Ospedale S. Biagio	Domodossola (VB)	Piemonte
61	Ospedale Santa Croce di Moncalieri	Moncalieri (Torino)	Piemonte
62	Ospedale Castelli	Pallanza, Verbania	Piemonte
63	Ospedale Maria Vittoria	Torino	Piemonte

Id	Center	City	Italian Region
64	Ospedale Martini	Torino	Piemonte
65	Azienda Ospedaliera Ordine Mauriziano	Torino	Piemonte
66	Ospedale San Giovanni Bosco	Torino	Piemonte
67	Ospedale Molinette	Torino	Piemonte
68	Ospedale S. Andrea	Vercelli	Piemonte
69	Ospedale Policlinico Consorziale	Bari	Puglia
70	Azienda Sanitaria Locale di Taranto	Taranto	Puglia
71	Azienda Ospedaliera G. Brotzu	Cagliari	Sardegna
72	Ospedale Santissima Trinità	Cagliari	Sardegna
73	Ospedale San Francesco	Nuoro	Sardegna
74	Ospedale Giovanni Paolo II	Olbia	Sardegna
75	Ospedale San Martino	Oristano	Sardegna
76	Ospedale Nostra Signora di Bonaria	San Gavino Monreale (VS)	Sardegna
77	Ospedale S. Giovanni di Dio	Agrigento	Sicilia
78	Aziende Sanitaria Provinciale di Siracusa	Augusta	Sicilia
79	Ospedale “Gravina e Santo Pietro” di Caltagirone	Caltagirone CT	Sicilia
80	Azienda Osp. Universitaria POL	Catania	Sicilia
81	Distretto Ospedaliero Enna 1 - U.O.C	Enna	Sicilia
82	Azienda Ospedaliera Universitaria Policlinico G.Martino	Messina	Sicilia
83	Ospedale Civico Arnas	Palermo	Sicilia
84	Azienda Ospedaliera Villa Sofia - Cervello	Palermo	Sicilia
85	Ospedale civile di Ragusa	Ragusa	Sicilia
86	Ospedale Giovanni Paolo II	Sciacca	Sicilia
87	Ospedale Umberto I di Siracusa	Siracusa	Sicilia
88	Ospedale San Donato	Arezzo	Toscana
89	Ospedale Santa Maria Annunziata	Bagno a Ripoli	Toscana
90	Ospedale Castelnuovo Garfagnana	Castelnuovo Garfagnana	Toscana
91	Ospedale San Giuseppe	Empoli	Toscana
92	Ospedale San Giovanni di Dio	Firenze	Toscana
93	Azienda Ospedaliero-Universitaria Careggi	Firenze	Toscana
94	Ospedale Santa Maria Nuova	Firenze	Toscana
95	Ospedale Della Misericordia	Grosseto	Toscana
96	Azienda U.S.L. N 6 Livorno	Livorno	Toscana
97	Ospedale San Luca	Lucca	Toscana
98	Nuovo Ospedale Apuano	Massa	Toscana
99	Ospedale SS. Cosma e Damiano di Pescia	Pescia	Toscana
100	Fondazione Toscana Gabriele Monasterio	Pisa	Toscana
101	Azienda Ospedaliero Universitaria Pisana	Pisa	Toscana
102	Ospedale San Jacopo	Pistoia	Toscana
103	Nuovo Ospedale di Prato - S. Stefano	Prato	Toscana
104	Azienda Ospedaliera Universitaria Senese	Siena	Toscana
105	Ospedale Versilia	Versilia	Toscana
106	Ospedale Di Rovereto	Rovereto	Trentino Alto Adige
107	Ospedale Santa Chiara	Trento	Trentino Alto Adige
108	Ospedale San Giovanni Battista	Foligno	Umbria
109	Azienda Ospedaliera Santa Maria Terni	Terni TR	Umbria
110	Ospedale San Bassiano	Bassano del Grappa	Veneto
111	Ospedale Civile Pietro Cosma	Camposampiero	Veneto
112	Ospedale di Cittadella - ULSS 6 Euganea	Cittadella	Veneto
113	Ospedale Santa Maria dei Battuti	Conegliano	Veneto
114	Ospedale Mater Salutis di Legnago - ULSS 9 Scaligera	Legnago	Veneto
115	Azienda U.L.S.S. N. 3	Mirano	Veneto
116	Ospedale di Monselice - ULSS N.6 Euganea	Monselice	Veneto
117	Azienda Ospedaliera Di Padova	Padova	Veneto
118	Ospedale Fracastoro - San Bonifacio	San Bonifacio	Veneto
119	ULSS 2 Ospedale di Treviso	Treviso	Veneto
120	Ospedaliera Borgo Trento	Verona	Veneto
121	Ospedale San Bortolo	Vicenza	Veneto

APPENDIX 4 - Data extraction table (RCT)

First author, year	Olgin 2018
STUDY CHARACTERISTICS	
Study name	VEST
Study registration number	NCT01446965
Countries of recruitment	U.S.A., Poland, Germany, and Hungary[13]
Sponsor	National Institutes of Health (NIH) / National Heart Lung and Blood Institute (NHLBI)[14] and Zoll Medical
Comparator	Guideline-directed medical therapy
Study design	Multicenter, randomized, controlled trial
Study duration (start and completion date)	07/2008 - 04/2017
Objectives	To determine the efficacy of a Wearable Cardioverter–Defibrillator during the period before ICDs are indicated in patients who have had a myocardial infarction and have a reduced ejection fraction.
PATIENTS CHARACTERISTICS	
Number of pts	2,302[15] (1,524[16] device group and 778[17] control group).
Age in yrs (range) ± SD	Device group, mean ± SD: 60.9 ± 12.6. Control group, mean ± SD: 61.4 ± 12.3.
Sex (female/male)	Device group: 27%/73%. Control group: 25%/75%[18]
EF in % (range) ± SD	Device group, mean ± SD: 28.2 ± 6.1. Control group: 28.2 ± 5.8.
Inclusion criteria	Patients who had been hospitalized with an acute myocardial infarction and who had an ejection fraction of 35% or less were enrolled within 7 days after hospital discharge.
Exclusion criteria	Patients were excluded if they had an ICD or unipolar pacemaker, had clinically significant valve disease, were undergoing long-term hemodialysis, or had a chest circumference that was too small or too large to accommodate the Wearable Cardioverter-Defibrillator. Patients were also excluded if they were pregnant or had been discharged to a nursing facility with an anticipated stay of more than 7 days.

[13] 76 sites in the United States, 24 in Poland, 6 in Germany, and 2 in Hungary

[14] NIH/NHLBI stopped funding the study.

[15] 2,348 patients were initially randomized. 46 participants at one U.S.A. site were excluded after randomization, owing to irregularities found by the institutional review board at that site; therefore, 2,302 participants were included in the analyses.

[16] 43/1524 (2.8%) patients in the device group never wore the WCD after randomization.

[17] 20/778 (2.6%) patients in the control group wore the WCD (2.6%) outside the protocol. Cross-overs were considered to be a protocol deviation.

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

First author, year	Olgin 2018
Follow-up time in months (range), mean ± SD	Mean ± SD: 84.3 ± 15.6 days.
Loss to follow-up, n (%)	68 pts (2.9%)[19]
Diagnosis	Patients with acute myocardial infarction and who had an ejection fraction of 35% or less
Previous treatments	Previous CABG Device group: 133/1521 (8.7), Control group: 70/776 (9.0); Previous PCI Device group: 374/1520 (24.6), Control group: 202/776 (26.0).
OUTCOMES: CLINICAL EFFECTIVENESS	
Mortality, n (%) • **All-cause mortality**[20] • **Disease-specific mortality**[21]	 Device group: 48 (3.1); control group: 38 (4.9). Relative risk (RR): 0.64 (95% CI, 0.43–0.98); p=0.04. Device group: 25 (1.6); Control group: 19 (2.4). RR: 0.67 (95% CI, 0.37–1.21); p=0.18.
• **Appropriate shocks** • **Withheld shocks**[24]	Device group: 20 (1.3%)[22]. Control group: 1 (0.1%)[23]. P=0.008 Device group: 69 (4.5%)[25]. Control group: 1 (0.1%)[26].
First shock success (%)	NA
Health-Related Quality of Life (HRQL)	NA[27]
Hospitalisation rate	Rehospitalisation by any cause, n (%): Device group: 475 (31.2), Control group: 253 (32.5). RR: 0.96 (95% CI, 0.85–1.09). P=0.51.
Satisfaction with technology	NA
Compliance/ patient adherence • **WCD wear-time in days (range), median** • **WCD daily use in hours (range),**	 NA[28] Device group[29], mean ± SD: 14.0 ± 9.3 [Median (IQR): 18.0 (3.8–22.7)]; Control group[30], mean ± SD: 0.4 ± 2.7

[19] 46 (2%) from the U.S.A. site excluded; 10/1524 pts (0.7%) in the device group; 12/778 (1.5%) in the control group.
[20] All-cause mortality was a secondary outcome.
[21] Disease-specific mortality was the primary outcome.
[22] 13 pts had 1 shock; 7 pts had ≥ 2 shocks.
[23] This patient had ≥2 shocks.
[24] Due to patients using the response button to delay therapy.
[25] 1 shock 43 (2.8%), 2-5 shocks 11 (0.7%), ≥5 shocks 15 (1.0%).
[26] 1 shock (0.1%).
[27] Quality of life was a planned secondary outcome in the study protocol, but it was not reported in the final study.
[28] Over the course of the 90 days, the proportion of participants who wore the WCD on a given day fell from 80.8% (CI: 78.8-82.8) just after randomization to 41.3% (CI 37.5, 44.9) at 90 days.

First author, year	Olgin 2018
median	[Median (IQR): 0.0 (0.0–0.0)].
% of improvement in EF in mean ± SD (range)	NA
OUTCOMES: SAFETY	
AEs in n (%) of pts: • **Skin rash and itching** • **False alarms**	 Rash on torso, n (%): Device group: 184 (13.0%), Control group: 27 (3.8%). RR: 3.42 (95% CI, 2.31-5.08), p<0.001[31]. Itch on torso, n (%): Device group: 205 (14.5%), Control group: 22 (3.1%). RR: 4.68 (95% CI, 3.04-7.20), p<0.001[32]. NA[33]
Frequency of discontinuation due to AEs in n (%) of pts: • **Discontinuation due to comfort and lifestyle issues**	 NA
Frequency of unexpected AEs in n (%) of pts	NA
Hospitalisation related to WCD use	3/1524 (0.2%)[34]
Serious Adverse Events (SAEs), n (%) • **Inappropriate shocks** • **Unsuccessful shock**	 9 (0.6%) [7 pts had 1 shock; 2 pts had ≥ 2 shocks] NA[35]
Frequency of SAEs leading to death in n (%) of pts	NA[36]

[29] 1481/1524 (97.2%) worn the device.
[30] 20/778 (2.6%) worn the device.
[31] Rash in any location, n (%): Device group: 216 (15.3%), Control group: 50 (7.1%), p<0.001.
[32] Itch in any location, n (%): Device group: 243 (17.2%), Control group: 45 (6.4%), p<0.001.
[33] Among 41 participants with an alarm indicating asystole, 6 events (all in the device group) were adjudicated as having had a true asystole event.
[34] Two due to aborted shocks and one due to an inappropriate shock.
[35] The shock delivered sometime caused a cardioversion into complex and repeated other cardiac conduction problems which the WCD was not programmed to deal with.
[36] One patient died while he was wearing the device. The authors state that this death could be possibly related to the WCD use. The authors also state that it was deemed likely to not be an arrhythmic death.

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

APPENDIX 5 - GRADE Evidence Profiles Table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WCD + GDMT**	**GDMT**	**Relative (95% CI)**	**Absolute (95% CI)**		
Randomised Control Trial : EFFECTIVENESS OUTCOMES												
Arrhythmic death												
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	25/1524 (1.6%)	19/778 (2.4%)	**RR 0.67** (0.37 to 1.21)	**8 fewer per 1.000** (from 5 more to 15 fewer)	⊕⊕◯◯ LOW	CRITICAL
Death from any cause												
1 [1]	randomised trials	very serious [c]	not serious	not serious	not serious	none	48/1524 (3.1%)	38/778 (4.9%)	**RR 0.64** (0.43 to 0.98)	**18 fewer per 1.000** (from 1 fewer to 28 fewer)	⊕⊕◯◯ LOW	CRITICAL
Appropriate shocks												
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	none	20/1524 (1.3%)	1/778 (0.1%)	not estimable	-	⊕⊕⊕◯ MODERATE	CRITICAL
Withheld shocks												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WCD + GDMT**	**GDMT**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	none	69/1524 (4.5%)	1/778 (0.1%)	not estimable	-	⊕⊕⊕◯ MODERATE	IMPORTANT
Rehospitalization by any cause												
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	none	475/1524 (31.2%)	253/778 (32.5%)	**RR 0.96** (0.85 to 1.09)	**13 fewer per 1.000** (from 29 more to 49 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
WCD daily use in hours												
1 [1]	randomised trials	Not serious	not serious	not serious	not serious	none	1524 Mean hours/ day ± SD: 14.0±9.3	778 Mean hours/ day ± SD: 0.4±2.7	-	-	⊕⊕⊕⊕ High	CRITICAL
Randomised Control Trial: SAFETY OUTCOMES												
Rash on torso												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WCD + GDMT**	**GDMT**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	none	184/1421 (12.9%)	27/714 (3.8%)	**RR 3.42** (2.31 to 5.08)	**92 more per 1.000** (from 50 more to 154 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Itch on torso												
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	none	205/1421 (14.4%)	22/714 (3.1%)	**RR 4.68** (3.04 to 7.20)	**113 more per 1.000** (from 63 more to 191 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Inappropriate shocks												
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	none	9/1524 (0.6%)	0/778 (0.0%)	not estimable	not estimable	⊕⊕⊕◯ MODERATE	CRITICAL
Observational Studies: SAFETY OUTCOMES												
Allergic skin reactions												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WCD + GDMT	GDMT	Relative (95% CI)	Absolute (95% CI)		
1 [2]	observational studies	serious [d]	not serious	not serious	serious [e]	none	2/102 (2.0%)	-	-	-	⨁◯ ◯ ◯ VERY LOW	IMPORTANT
False alarms												
1 [2, 6]	observational studies	serious [f]	not serious	not serious	serious [g]	none	58/126 (46.0%)	-	-	-	⨁◯ ◯ ◯ VERY LOW	CRITICAL
Discontinuation due to comfort and lifestyle issues												
3 [3,5,6]	observational studies	serious [h]	not serious	not serious	not serious	none	25/227 (11.0%)	-	-	-	⨁◯ ◯ ◯ VERY LOW	CRITICAL
Inappropriate shocks												
10 [2,3,4,5,6,7,8,9,10,11]	observational studies	very serious [i]	not serious	not serious	not serious	none	15/2346 (0.6%)	-	-	-	⨁◯ ◯ ◯ VERY LOW	CRITICAL
Unsuccessful shocks												
2 [7,10]	observational studies	serious [j]	not serious	not serious	not serious	none	0/2024 (0.0%)	-	-	-	⨁◯ ◯ ◯ VERY LOW	CRITICAL
SAEs leading to death												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WCD + GDMT**	**GDMT**	**Relative (95% CI)**	**Absolute (95% CI)**		
4 [3,4,7,10, 11]	observational studies	very serious [k]	not serious	not serious	not serious	none	0/2178 (0.0%)	-	-	-	⨁◯ ◯ ◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **WCD**: Wearable Cardioverter-Defibrillator; **GDMT**: guideline-directed medical therapy; **ICD**: implantable cardioverter defibrillator; **SAEs**: serious adverse events.

Explanations

a. This outcome was reported by one RCT judged to be at high risk of bias through the Cochrane Risk of Bias tool due to selective outcome reporting bias and other bias related to the poor compliance that could have influenced the comparative effect estimates for effectiveness outcomes and the estimated proportions of adverse events for safety outcomes.
b. In the study occurred few events leading to a quite wide CI around the estimate of the effect.
c. The endpoint "death from any-cause" was set as a secondary outcome in the included RCT. In addition, the study did not statistically correct the analysis for multiple testing. As a result this significant difference is likely to be a chance finding.
d. This outcome was reported by only one observational study (Erath 2017) having the following possible source of bias: it was a single centre study with limited study population (102 patients); inclusion criteria were only implicitly formulated (exclusion criteria were not mentioned); patients did not enter the study at similar point in the disease; outcome assessors were not blinded to the intervention that patients received; losses to follow-up were not reported.
e. This outcome was reported by two observational studies (Erath 2017 and Barraud 2018) having the following possible source of bias: they were single centre studies with limited study population (126 patients); inclusion criteria were only implicitly formulated (exclusion criteria were not mentioned); patients did not enter the study at similar point in the disease; outcome assessors were not blinded to the intervention that patients received; losses to follow-up were not reported.
f. The study population is limited leading to a quite wide CI: 2.0% (0.2%-6.9%).
g. The study population is small with a wide CI: 46.0% (37.1%-55.1%).
h. The outcome discontinuation due to comfort and lifestyle issues was addressed by three observational studies (Kao 2012, Röger 2018, and Barraud 2018) having the following possible source of bias: patients were not recruited consecutively; the eligibility criteria for entry into the study were not clearly stated; patients did not enter the study at a similar point in the disease; outcome assessors were not blinded to the intervention that patients received; one of the study not provided estimates of random variability in the data analysis of relevant outcomes; adverse events were partly reported.
i. The outcome inappropriate shocks was reported by ten observational studies (Barraud 2018, Barsheshet 2017, Bhaskaran 2016, Erath 2017, Erath 2018, Kao 2012, Kondo 2015, Kutyifa 2015, Röger 2018, and Sasaki 2014) having the following possible source of bias: patients were not recruited consecutively; the eligibility criteria for entry into the study were not clearly stated (or partly stated); patients did not enter the study at a similar point in the disease; outcome assessors were not blinded to the intervention that patients received; losses to follow-up were not reported; adverse events were partly or not reported.

j. The outcome unsuccessful shocks was reported by two studies (Kutyifa 2015 and Kondo 2015) having the following possible source of bias: patients were not recruited consecutively; the eligibility criteria for entry into the study were partly stated; patients did not enter the study at a similar point in the disease; additional interventions were not clearly described; outcome assessors were not blinded to the intervention that patients received; losses to follow-up were not reported; adverse events were partly reported.

k. The outcome SAEs leading to death was reported by five observational studies (Kao 2012, Kondo 2015, Kutyifa 2015 , Sasaki 2014, and Bhaskaran 2016) having the following possible source of bias: patients were not recruited consecutively; patients did not enter the study at a similar point in the disease; outcome assessors were not blinded to the intervention that patients received; additional interventions were not clearly described; was unclear if relevant outcome measures were established a priori and if the relevant outcome measures were made before and after the intervention; it was unclear if follow-up was long enough for important events and outcomes to occur; losses to follow-up were not reported.

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APPENDIX 6 - Search strategy for the effectiveness, safety and economic domains of the WCD

Pubmed

#1. "life vest" OR "life vests" OR lifevest or lifevests OR lifecor

#2. wcd[Title/Abstract] OR wcds[Title/Abstract] OR zoll[Title/Abstract]

#3 wearable AND (cardioverter OR defibrillator OR cardioverters OR defibrillators)

#4 portable AND (cardioverter OR defibrillator OR cardioverters OR defibrillators)

#5 "defibrillator jacket" OR "defibrillator vest" OR "defibrillator jackets" OR "defibrillator vests"

#6 #1 OR #2 OR #3 OR #4 OR #5

#7 #6 AND human AND english

Hits: 291

Cochrane

#1 "life vest" (Title, abstract, keyword)

#2 lifevest OR lifevests (Title, abstract, keyword)

#3 lifecor (Title, abstract, keyword)

#4 (wearable or portable) near (cardioverter* OR defibrillator*)

#5 wcd (Title, abstract, keyword)

#6 zoll (Title, abstract, keyword)

#7 "wearable-cardioverter defibrillator" OR "wearable-cardioverter defibrillators"

#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7) NOT NCT

#9 #8 AND human AND english

Hits: 15 trials

Embase

#1 wcd

#2 lifevest OR lifevests

#3 'wearable cardioverter defibrillators'

#4 'wearable cardioverter-defibrillators'

#5 'wearable cardioverter defibrillator'

#6 'life vest' OR "life vests"

#7 lifecor

#8 'portable defibrillator' OR "portable defibrillators"

#9 "portable cardioverter defibrillator" OR "portable cardioverter defibrillators"

#10 'portable cardioverter-defibrillator' OR "portable cardioverter-defibrillators"

#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

Hits: 408

APPENDIX 7 - List of ongoing studies

Identifier / Trial name	Condition	Study type and design	Intervention / Comparison	Primary Outcome	Actual/estimated enrolment participants	Start date / Estimated completion date	Sponsor
Status: Active, not recruiting							
NCT02700880 / WEARIT-III	Subjects with ischemic cardiomyopathy and heart failure	Observational Cohort, prospective	Device: LifeVest	Number of clinical events in heart failure patients with ischemic cardiomyopathy prescribed Wearable Cardioverter-Defibrillator (WCD)	250	June 2014 / February 2019	Zoll Medical Corporation
Status: Not yet recruiting							
NCT03388905	Patients hospitalized with newly diagnosed severe left ventricular dysfunction (LVEF ≤ 35%)	Interventional Single Group Assignment	Device: Life Vest Wearable Cardioverter-Defibrillator	Left ventricular recovery following WCD use.	30	January 2018 / December 2019	Sheba Medical Center
Recruiting							
NCT03319160	Sudden Cardiac DeathLeft Ventricular DysfunctionCardiac EventCardiac Arrythmias	Observational [Patient Registry] Cohort, prospective	Device: Defibrillation	Appropriate shocks Inappropriate shocks	1,163	February 2017 / December 2018	Zoll Medical Corporation
NCT03016754	Sudden Cardiac DeathSudden Cardiac ArrestHeart FailureHeart Failure Low Output	Observational Cohort, prospective	Device: Wearable Cardioverter-Defibrillator	Do not require ICD implant Continue WCD use Meet GDMT	750	March 2017 / January 2019	Zoll Medical Corporation
NCT02073942	Myocardial InfarctionVentricular DysfunctionMyocarditis	Observational [Patient Registry] Case-Only, prospective	Wearable Cardiac Defibrillator (WCD)	Number of arrhythmic events and arrhythmic risk factors during bridging therapy with wearable defibrillator	100	February 2014 / March 2018	University of Cologne
Completed							
NCT02149290	Heart Failure	Observational Case-Only, prospective	Device: Trends-equipped LifeVest 4000	Precision of Heart Failure (HF) metrics measurements	200	February 2014 / December 2017	Zoll Medical Corporation
NCT01326624	Heart FailureVentricular DysfunctionSudden DeathSudden Cardiac ArrestVentricular TachycardiaVentricular Fibrillation	Observational Cohort, prospective	Device: wearable defibrillator (LifeVest)	Defibrillation for life-threatening ventricular tachyarrhythmias Assess magnitude and complexity of ventricular and atrial arrhythmias during use	25	March 2011 / December 2017	Zoll Medical Corporation
Terminated							
NCT01448005	Sudden Cardiac DeathVentricular FibrillationVentricular TachycardiaVentricular DysfunctionMyocardial Ischemia	Observational Cohort, prospective	Device: wearable defibrillator (LifeVest)	number of patients who experience sudden cardiac death	69	February 2011 / October 2014	Zoll Medical Corporation

APPENDIX 8 - Risk of Bias assessment: Risk of bias – study level (randomised studies)

Trial	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researchers (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Olgin, 2018	Low risk	Low risk	Low risk	Low risk[37]	Low risk	High risk[38]	High risk[39]

[37] Although the study is open label, the primary outcome (arrhythmic death) and many secondary outcomes (death from any cause; non-arrhythmic death; hospitalization for myocardial infarction, atrial fibrillation, congestive heart failure, stroke, or sustained ventricular tachyarrhythmia, etc.) are not deemed likely to be influenced by lack of blinding.

[38] Several secondary outcomes planned in the study protocol were not reported in the final study. Most strikingly, it appears that the study gathered data on quality of life without reporting on it in the published article. This form of reporting bias is a serious problem since it leads to the impression that valuable patient relevant data are available but hidden from the public. The first author was e-mailed for clarification and he said that data on quality of life were collected but not analysed.

[39] Compliance is a potential confounder that may have distorted the effect estimates.

APPENDIX 9 - Data extraction table (observational studies)

First author, year	Röger 2018	Erath 2018	Barraud 2018	Sasaki 2017	Erath 2017	Barsheshet 2017	Bhaskaran 2016	Kutyifa 2015	Kao 2012	Kondo 2015
STUDY CHARACTERISTICS										
Study name	NA	NA	NA	NA	NA	SWIFT	NA	WEARIT-II Registry	WIF	NA
Study registration number	NA	NA	NA	NA	NA	NCT01326624	NA	NA	NA	NA
Country/ies of recruitment	Germany	Germany	France	Japan	Germany	U.S.A. and Israel	Australia	U.S.A.	U.S.A.	Germany
Sponsor	NA	NA	NA	NA	NA	ZOLL Medical Corporation	NA	ZOLL Medical Corporation	ZOLL Medical Corporation	unclear
Comparator	None	none	none	none	none	none	none	none	none	none
Study design	Prospective case series	Prospective case series	Prospective case series	Prospective case series	Prospective case series	Multi-centre, prospective case series	Prospective case series	Multi-centre, prospective register	Multi-centre, prospective register	Prospective case series
Study duration (start and completion date)	4/2012 - 9/2016	NA	09/2015 - 09/2016	04/2014 - 12/2015	2012-2015	NA	11/2013 -	08/2011 – 02/2014	07/2007- 02/2010	08/2010- 11/2014
Objectives	To determine the value of the WCD for therapy optimization of heart failure pts.	To evaluate the clinical development of tachymyopathy pts protected with a WCD in a single-center non-randomized pt cohort.	Evaluate VA occurrence rate and pts compliance with the WCD during the first 90 days following myocardial revascularization with PC) in pts with LVEF <30%.	To report a single center experience of WCD use describing its utilization for in-hospital acute phase care of pts at high risk of VA and its potential roles.	To evaluate the efficacy, safety, and compliance of/to WCD use and subsequent medium-term outcome of pts in a single-center.	To provide clinical data on the safety and efficacy of the WCD among high-risk cardiac pts with advanced HF[40].	Report the single centre Australian experience.	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	To collect SCA events, WCD defibrillation efficacy, and WCD usage data in heart failure pts.	To describe the utility of the WCD therapy in early post-MI phase.

[40] Other objectives: to evaluate comprehensive data regarding VT in the study population; to assess a management strategy in pts that involves initial stabilization during WCD use followed by delayed reassessment for primary ICD implantation.

First author, year	Röger 2018	Erath 2018	Barraud 2018	Sasaki 2017	Erath 2017	Barsheshet 2017	Bhaskaran 2016	Kutyifa 2015	Kao 2012	Kondo 2015
								and the need for subsequent ICD implantation.		
PATIENTS CHARACTERISTICS										
Number of pts	114[41]	130[42]	24	50[43]	102[44]	75 pts[45]	8	2000[46]	89[47]	24
Age in yrs [mean (range) ± SD; median (IQR)]	All pts (n. 105): Median (IQR): 60 (26–79). ICM pts (n. 43): 62 (43–78)	All pts, mean ± SD: 58 ± 16 • Cases: 62 ± 9 • Controls: 58 ± 16 (ns)	Mean ± SD: 56 ± 10	Median (IQR): 56 (49-66)	All pts, mean ± SD: 59 ± 11. ICM pts: 66 ± 12.	All pts, mean ± SD: 51.4 ± 13.9. ICM pts, mean ± SD: 60.7 ± 14.4.	NA	All pts, median (IQR): 62 (16). ICM pts, median (IQR): 65 (14).	Mean (range) ± SD: 61.0 (37-83) ± 11.1	Mean ± SD: 69 ± 12
Sex: female / male	All pts: 22% / 78%. ICM pts: 19% / 81%	All pts: 22% / 78% • Cases: 20% / 80% • Controls: 22% / 78%	17% / 83%	8% / 92%	All pts: 28% / 72%. ICM pts: 15% / 85%	All pts: 31% / 69%. ICM pts: 32% / 68%.	NA	All pts: 30% /70%. ICM pts: 23% / 77%.	28% / 72%	8% / 92%
EF in % [mean (range) ± SD; median (IQR)]	All pts (n.105), mean ± SD: 28.3 ± 9.8. ICM pts (n. 43): 28.9 ± 6.0	All pts, mean ± SD: 28 ± 11 • Cases: 26 ± 6 • Controls: 29 ± 12 (ns)	Mean ± SD: 27.3 ± 4.7	Median (IQR): 52.2 (34.7-63.7). Pts primary prevention, median (IQR): 26 (22-29)	All pts, mean ± SD: 30 ± 11. ICM pts: 28 ± 6.	All pts, mean ± SD: 21.5 ± 10.4. ICM pts: 25.5 ± 12.4.	Mean ± SD: 35.9 ± 17.8	All pts, median (IQR): 25 (10). ICM pts, median (IQR): 26 (15).	Mean (range) ± SD: 23.9 (7.5-65) ± 9.4	Median (IQR): 30 (20-36)

[41] 8 patients returned their WCD during the first hours after initiation because of unwillingness or inability to handle it; one more patient was lost to follow up, leaving 105 patients considered for data analysis. 43/105 patients had ICM.
[42] 20 pts in cases group, and 110 pts in control group.
[43] 38 hospital use, and 12 use outside the hospital.
[44] ICM patients: 27/102.
[45] 50 pts from United States and 25 pts from Israel; 25/75 (33%) of these were ICM pts. 65 pts enrolled a hospital setting, 10 (13 %) pts outpatient setting.
[46] ICM pts: 805 (40%). NICM pts: 927 (46%). Congenital/Inherited pts: 268 (14%).
[47] 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.

First author, year	Röger 2018	Erath 2018	Barraud 2018	Sasaki 2017	Erath 2017	Barsheshet 2017	Bhaskaran 2016	Kutyifa 2015	Kao 2012	Kondo 2015
Inclusion criteria	All consecutive pts receiving a WCD at a tertiary care University Center	• Cases: consecutive pts with clinically suspect tachymyopathy and high risk of ventricular arrhythmias • Controls: consecutive pts with high risk of ventricular arrhythmias and another option for use of vests	• Pts with acute myocardial infarction • LVEF < 30 % • myocardial revascularization > 7 days with PCI	Pts at increased risk for SCD for a limited period and not candidates for an implantable defibrillator	Pts at high risk of VT/VF	NYHA functional class III-IV in the last month and one or more of the condition reported in the footnote[48]	Bridging therapy to an ICD	Low EF and high risk of SCA post MI or post coronary revascularization or new onset nonischaemic DCM or high risk for SCA until stabilisation or inherited or congenial heart disease	Pts listed (or being considered) for heart transplantation, pts with DCM (with VT or EF ≤ 40%), pts receiving inotropes	Pts with high risk of SCA but not eligible for immediate implantation of an ICD; Pts in early post-MI phase.
Exclusion criteria	NA	NA	• previous ICD placement • indication of ICD implantation for secondary prevention • cognitive impairment	Elderly pts at high risk of VA	NA	• presence of an ICD prior to enrolment • advanced cerebrovascular disease • non-cardiac terminal illness • No pts with NYHA class <III at baseline	NA	NA	HF pts were excluded from the study if they had an active ICD or if they were impaired such that they could not use the device.	NA

[48] Hospitalisation for cardiac decongestion and stabilization; advanced HF managed in an outpatient setting; acute myocardial infarction; Killip class III/IV; coronary revascularization within 3 calendar months prior to enrolment; pts awaiting cardiac transplantation

First author, year	Röger 2018	Erath 2018	Barraud 2018	Sasaki 2017	Erath 2017	Barsheshet 2017	Bhaskaran 2016	Kutyifa 2015	Kao 2012	Kondo 2015
Follow-up time in months [mean (range) ± SD; median (IQR)]	Mean ± SD: 18.6 ± 12.3	12 months of follow-up (1, 3 and 12 months)	90 days	NA	Mean ± SD: 11 ± 8	3 months after discharge, 3 yrs (on mortality data).	NA	Median (IQR): 3.0 (2.1)[49]	3 months	Median (IQR): 8 (4-16)
Loss to follow-up, n (%)	9 (8)	0	0	0	0	NA	0	NA	7 (8)	NA
Diagnosis	Newly diagnosed ICM, LVEF ≤ 35% (n=43); Newly diagnosed NICM, LVEF ≤ 35% (n=41); ICD explant (n=15); Newly diagnosed CMP (n=6).	Pts with symptomatic congestive HF with impaired LV function	Pts with LVEF <30% who had recent (<7 days) myocardial revascularisation with PCI for an acute MI	Secondary prevention for VA 38 pts (76%), including 28 resuscitated from VF. Primary prevention 12 pts (24%), most common reason was recent MI (N=5)	Newly diagnosed HF	Acute decompensated HF. All pts: NYHA III: 62 (83%), NYHA IV: 13 (17%). ICM pts: NYHA III: 23 (92%), NYHA IV: 2 (8%).	Pts with an explanted infected ICD (3 pts); Idiopathic DCM (2 pts); Postpartum cardiomyopathy (1 pt); Valvular heart disease (1 pt); Myocarditis (1 pt).	(Non-) ischemic DCM, congenital/inherited heart disease	DCM with low EF (<40%)	ST elevation, PCI, CABG
Previous treatments	Medications (betablocker, ACE-I/ARB, MRA, ARNI, procoralan, diuretic, amiodarone)	Medications (betablocker, amiodarone, ACE inhibitors/ARB, aldosterone antagonists, diuretics, statin, NOAC, VKA)	Medications (β-blocker, antiplatelet agents, oral anticoagulant therapy, ACE inhibitor, loop diuretic, aldosterone antagonist, statin)	NA	Medications (β-blocker, amiodarone)	Medications (β-blocker, ACE inhibitor or ARB, aldosterone antagonist, statins)	NA	NA	Active pacemaker, past/inactive pacemaker, prior/inactive ICD Beta Blockers, ACE inhibitors, ARBs, amiodarone, inotropes	NA
OUTCOMES: CLINICAL EFFECTIVENESS										

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

First author, year	Röger 2018	Erath 2018	Barraud 2018	Sasaki 2017	Erath 2017	Barsheshet 2017	Bhaskaran 2016	Kutyifa 2015	Kao 2012	Kondo 2015
Mortality, n (%)										
• **All-cause mortality**	3 (3%)	No deaths during the use of vest[50].	NA	NA	No deaths during the use of vest[51].	1 (1%) NICM pt died at 3 months follow-up (non-cardiac cause)[52].	0	3 (0.2)[53]	0 (after WCD use, 6 pts died of unknown causes)	0 (due to an asystole event and none due to VT/VF).
• **Disease-specific mortality**	0	• Controls: 5 (5%)	NA	NA	4 (4%)	NA	0	0	0	0
• **Appropriate shocks**	All pts (n. 105): 5 (4.8%). ICM pts (n. 43): 3 (7%).	2 pt in the control group (2%)	1 pt (4.2%)	6 (4 sustained VT and 2 VF) (12%)	4 pts (4%)[54]	1 (1%) (ICM pts)	NA	30 events/22 pts (1.1)	NA	3/2 (8)
• **Withheld shocks[55]**	NA	NA	1 pt (4.2%)	1 pt (2%)	NA	1 (1%) (ICM pts)	NA	90 events/22 pts (1.1)	NA	NA
First shock success (%)	100%	NA	100%	5 (83.3 %)	NA	NA	NA	100%	NA	100%
Health-Related Quality of Life	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hospitalisation rate	NA	NA	NA	NA	13 pts hospitalised pts due to cardiac causes	NA	NA	NA	NA	NA
Satisfaction with technology	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

[50] Deaths after the use of the vest: All pts: 5 (4%); Cases: 0; Controls: 5 (5%) (ns).
[51] 6 (6 %) after the end of treatment with vest [of these, 2/27 (7%) were ICM pts]: 5 ICD and 1 not-ICD.
[52] 17 pts died during 3 years of follow-up.
[53] 2 patients (8.3%) had a fatal non-arrhythmic event within 3 months after MI
[54] Patients were adequately shocked for ventricular fibrillation (seven episodes) or for ventricular tachycardia (one episode).
[55] Due to patients using the response button to delay therapy.

First author, year	Röger 2018	Erath 2018	Barraud 2018	Sasaki 2017	Erath 2017	Barsheshet 2017	Bhaskaran 2016	Kutyifa 2015	Kao 2012	Kondo 2015
Compliance/ pt adherence • **WCD wear-time in days [mean (range) ± SD; median (IQR)]**	All pts (n. 105), mean ± SD: 68.8 ± 50.4. ICM pts (n. 43): 57.8 ± 42.6	All pts, median (IQR): 42 (1-166)	Mean ± SD: 3.0 ± 1.3 months	Median (IQR): 16 days (8-33), with a maximum of 171 days[56].	All pts, median: 54 days (1-166). ICM pts, median: 54 days (1–121).	All pts, median (IQR): 59 (17-97) days. ICM pts: 59 (27–105).	Median (range): 77 days (5-180)[57]	Median (IQR): 90 (65)	Mean ± SD: 79.5 ± 57.8 days (median: 79, range: 1–277)[58]	Median (IQR): 33 (20-67)[59]
• **WCD daily use in h/day [mean (range) ± SD; median (IQR)]**	All pts (n. 105), mean ± SD: 21.5 ± 3.5. ICM pts (n. 43): 21.0 ± 3.8	All pts, mean: 23 h/day	• Mean 21.5 h/day • Median 23.5 h/day -18 pts (75%) > 22 h/day -5 pts 10-22 h/day -the other pts > 10 h/day	No significant difference (out-hospital median 23.5 h/day vs in-hospital median 23.6 h/day, p = 0.74)	All pts: median 23.0 h/day (7-24). ICM pts: median 23.0 h/day (12–23.9)	All pts: median (IQR): 18 (13-22) h/day. ICM pts: 18 (14–22).	Mean ± SD: 23.4 ± 0.6	Median (IQR): 22.5 (2.7)[60]	Mean ± SD: 19.5 ± 4.6 h/day (median: 21.8; range: 3.7-23.7)[61]	Median (IQR): 23.1 (21.6-23.6)
% improvement in EF [mean (range) ± SD; median (IQR)]	All pts (n. 105): 28.3 ± 9.8 (baseline) VS 36.1 ± 11.5 (end of WCD use), difference +27.6% (P<0.001). ICM pts (n.	LVEF baseline mean: ALL: 28±11 Cases: 26±6 Controls: 29±12; diff: ns LVEF follow-up mean	12 (50%) pts (27.3±4.7% vs 39.8±4.8%, p=0.0001)	NA	All pts: LVEF follow-up mean: 39 ± 14 (+30% compared to baseline); improvement in 52 (51 %) pts. ICM pts: LVEF follow-	All pts: LVEF improvement in 23 pts (31%). ICM pts: LVEF improvement in 8 pts (32%).	Mean ± SD: 39.1% ± 17.1	End-of-use EF improvement: ICM 41%, NICM 42%, congenital/inherited 31%	Mean ± SD: 13.5 ± 15.7 (final data from 70/89 pts)	5% of improvement in median [from baseline 30% (20–36%) to 35% (25–40%)]

[56] Wearing duration (median): 81 days out-of-hospital vs 12 days in-hospital use, p < 0.0001. Wearing duration (median): pts with ICD (9 days) vs pts without ICD (31 days), p = 0.005.
[57] One pt only used the WCD only in the home environment.
[58] Two pts were still wearing the device at the end of the study.
[59] One pt was excluded because of irregularities in device use.
[60] No significant difference in the daily use among the subgroups of ischemic, nonischemic, or congenital/inherited heart disease.
[61] Calculated based on pts who wore the device for 7 days or greater (n=75).

First author, year	Röger 2018	Erath 2018	Barraud 2018	Sasaki 2017	Erath 2017	Barsheshet 2017	Bhaskaran 2016	Kutyifa 2015	Kao 2012	Kondo 2015
	43): 28.9 ± 6.0 (baseline) VS 36.3 ± 10.3 (end of WCD use), difference +25.6% (P<0.001).	ALL: 41 ± 13 Cases: 50 ± 9 Controls: 39 ± 13 (p=0.04) Improvement (≥ 10%) ALL: 53 (41) Cases: 13 (65) Controls: 40 (36) (p=0.01)			up mean: 39 ± 11 (+39% compared to baseline); Improvement in 19 (70 %) pts.					
OUTCOMES: SAFETY										
AEs in n (%) of pts: • **Skin rash and itching**	NA	NA	NA	NA	2 pts (2%) are allergic to nickel	NA	NA	NA	NA	NA
• **False alarms**	NA	NA	0	NA	58 (57%)	NA	NA	NA	NA	NA
Discontinuation due to comfort and lifestyle issues	Eight pts (7%)[62]	NA	1 pt (4%) leaves the vest after having an alarm	NA	NA	NA[63]	NA	NA	16 (18%)[64]	NA

[62] They returned their WCD during the first hours after initiation because of unwillingness or inability to handle it.
[63] 25/75 (33%) pts ended to use WCD due to noncompliant/uncomfortable/denied by insurance/unspecified reasons.
[64] Three pts dropped out after wearing the WCD for a couple of hours; 6 pts due to discomfort and other reasons plus 7 pts due to unknown/other reasons.

First author, year	Röger 2018	Erath 2018	Barraud 2018	Sasaki 2017	Erath 2017	Barsheshet 2017	Bhaskaran 2016	Kutyifa 2015	Kao 2012	Kondo 2015
Serious Adverse Events (SAEs), n (%)										
• **Inappropriate shocks**	1 (1%) (ICM pt)	2 in the control group (2%)	0	0	2 (2%)	0	0	10 (0.5)[65]	0	0
• **Unsuccessful shock**	NA	NA	NA	NA	NA	NA	NA	0	NA	0
Frequency of SAEs leading to death in n (%) of pts	NA	NA	NA	0	NA	NA	0	0	0	0

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

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

APPENDIX 10 - Risk of bias – study level (case series)

Quality Appraisal Checklist for Case Series Studies by IHE

Study reference/ID	Barraud 2018	Barsheshet 2017	Bhaskaran 2016	Erath 2017	Erath 2018	Kao 2012	Kondo 2015	Kutyifa 2015	Röger 2018	Sasaki 2017
Study objective										
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study design										
2. Was the study conducted prospectively?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	No	Yes	No	No	No	Yes	No	Yes	No	No
4. Were patients recruited consecutively?	Yes	Unclear[66]	No	Yes	Yes	No	Yes	No	Yes	Yes
Study population										
5. Were the characteristics of the patients included in the study described?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Yes	No	Partial[67]	Partial[67]	Yes	Partial[67]	Partial[67]	No	Yes
7. Did patients enter the study at a similar point in the disease?	No	No	No	No	No	No	Yes	No	No	No
Intervention and co-intervention										
8. Was the intervention of interest clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?[68]	Partial	Partial	No	Yes	Yes	Yes	No	Partial	Yes	No
Outcome measures										

[66] It was not clearly stated whether patients were recruited consecutively.
[67] Inclusion criteria were only implicitly formulated. Exclusion criteria were not mentioned.
[68] "Partial": if some sort of heart medication (e.g., beta blockers) were mentioned; "No": if no co-interventions were mentioned.

Study reference/ID	Barraud 2018	Barsheshet 2017	Bhaskaran 2016	Erath 2017	Erath 2018	Kao 2012	Kondo 2015	Kutyifa 2015	Röger 2018	Sasaki 2017
10. Were relevant outcome measures established a priori?	Yes	Yes	Unclear[69]	Yes	Yes	Yes	Unclear[69]	Yes	Yes	Unclear[69]
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No	No	No	No	No	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Statistical Analysis										
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Partial[70]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Results and Conclusions										
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear[71]
16. Were losses to follow-up reported?	Yes	No	Yes	No	No	Yes	No	No	Yes	No
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Partial
18. Were the adverse events reported?	Partial[72]	No	Partial[72]	Yes	No	Partial[72]	Partial[72]	Partial[72]	Partial[72]	Partial[72]
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Competing interests and sources of support										
20. Were both competing interests and sources of support for the study	Yes	Yes	Yes	Yes	Yes	Yes	Partial[73]	Yes	Yes	Yes

[69] There was increased uncertainty whether relevant outcome measures were established a priori.
[70] Statistical analysis was limited to reporting on absolute numbers and relative frequencies.
[71] Length of follow up was not reported in the study.
[72] It is deducible that only some but not all potential adverse effects are reported.

[73] Source of support was not mentioned.

Study reference/ID	Barraud 2018	Barsheshet 2017	Bhaskaran 2016	Erath 2017	Erath 2018	Kao 2012	Kondo 2015	Kutyifa 2015	Röger 2018	Sasaki 2017
reported?										
Overall Risk of bias	**High**	**High**	**Very high**	**High**	**High**	**High**	**High**	**High**	**High**	**Very high**

Overall RoB: low – moderate – high – very high

APPENDIX 11 - Quality Appraisal Checklist for Case Series Studies

Quality Appraisal Checklist for Case Series Studies by IHE

Study reference/ID	**Lackermair K et al., 2018**
Study objective	
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes
Study design	
2. Was the study conducted prospectively?	Unclear
3. Were the cases collected in more than one centre?	No
4. Were patients recruited consecutively?	Yes
Study population	
5. Were the characteristics of the patients included in the study described?	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes
7. Did patients enter the study at a similar point in the disease?	No
Intervention and co-intervention	
8. Was the intervention of interest clearly described?	Yes
9. Were additional interventions (co-interventions) clearly described?	No
Outcome measures	
10. Were relevant outcome measures established a priori?	No
11. Were outcome assessors blinded to the intervention that patients received?	Unclear
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Partial
13. Were the relevant outcome measures made before and after the intervention?	No
Statistical Analysis	
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes
Results and Conclusions	
15. Was follow-up long enough for important events and outcomes to occur?	Unclear
16. Were losses to follow-up reported?	Unclear
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	No
18. Were the adverse events reported?	Yes
19. Were the conclusions of the study supported by results?	Yes
Competing interests and sources of support	
20. Were both competing interests and sources of support for the study reported?	Yes

APPENDIX 12 - Search strategy for patients and social aspects on the WCD

Last update on the 27th August 2018

Pubmed

#1. "life vest" OR "life vests" OR "lifevest" or "lifevests" OR lifecor
#2. wcd[Title/Abstract] OR wcds[Title/Abstract] OR zoll[Title/Abstract]
#3 wearable AND (cardioverter OR defibrillator or cardioverters or defibrillators)
#4 portable AND (cardioverter OR defibrillator or cardioverters or defibrillators)
#5 "defibrillator jacket" OR "defibrillator vest" OR "defibrillator jackets" OR "defibrillator vests"
#6 #1 OR #2 OR #3 OR #4 OR #5 **431 items 291 items con limiti humans e English**
#7 QoL[Title/abstract] OR
#8 "Quality of life" title/abstract OR
#9" "Social activieties" title/abstract OR
#10 wellbeing title/abstract OR
#11 "Patient Compliance" MESH term OR
#12 "Patient Participation" MESH term OR
#13 "Patient Preference" MESH term OR
#14 "Patient Satisfaction" MESH term OR
#15 "Quality of Life" MESH term OR
#16 "Patient Acceptance of Health Care" MESH term OR
#17 "Adaptation,Psychological " MESH term
#18 "Patient compliance" Title/AbstracT
#19 "Patient Participation" Title/Abstract
#20 "Patient Preference" Title/Abstract
#21 "Patient Satisfaction"Title/Abstract
#23 "Patient Acceptance" Title/Abstract
#24 "Patient Acceptance" Title/Abstract
#25 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR OR #20 OR #21 OR #22 OR #23 OR #24 **717.773 Items**
#26 (#6 AND #25) **88 Items; limits: humans e English**

Cochrane

#1 "life vest" (Title, abstract, keyword)
#2 lifevest OR lifevests (Title, abstract, keyword)
#3 lifecor (Title, abstract, keyword)
#4 (wearable or portable) near (cardioverter* or defibrillator*)
#5 wcd (Title, abstract, keyword)
#6 zoll (Title, abstract, keyword)
#7 "wearable-cardioverter defibrillator" OR "wearable-cardioverter defibrillators"
#8 (#1 OR #2 or #3 or #4 or #5 or #6 or #7) **15 items**
#9 "QoL (Title, abstract, keyword) OR
#10 "Quality of life" (Title, abstract, keyword) OR
#11 Patient Compliance" MESH term OR
#12 "Patient Participation" MESH term OR
#13 "Patient Preference" MESH term OR
#14 "Patient Satisfaction" MESH term OR
#15 "Patient Acceptance of Health Care" MESH term OR
#16 "Adaptation,Psychological " MESH term
#17 "Patient compliance" (Title, abstract, keyword)
#18 "Patient Participation" (Title, abstract, keyword)
#19 "Patient Preference" (Title, abstract, keyword)
#20 "Patient Satisfaction" (Title, abstract, keyword)

#21 "Patient Acceptance" (Title, abstract, keyword)
#22 "Patient Acceptance" (Title, abstract, keyword)
#23 (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR OR #20 OR #21 OR #22) **60.711 Items**
#24 (#8 AND #23) **12 Items**

Embase

#1 wcd
#2 lifevest or lifevests
#3 'wearable cardioverter defibrillators'
#4 'wearable cardioverter-defibrillators'
#5 'wearable cardioverter defibrillator'
#6 'life vest' OR "life vests"
#7 lifecor
#8 'portable defibrillator' OR "portable defibrillators"
#9 "portable cardioverter defibrillator" OR "portable cardioverter defibrillators"
#10 'portable cardioverter-defibrillator' OR "portable cardioverter-defibrillators"
#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) Items 501 (All results), Items 408 (limits: human, english)
#12 "Patient Compliance"/exp EMTREE term OR
#13 "Patient Attidude"/exp EMTREE term: OR
#14 "Patient Participation":ab,ti OR
#15 "Patient Preference" :ab,ti OR
#16 "Patient Satisfaction" :ab,ti OR
#17 "Quality of Life"/exp EMTREE term OR
#18 "Patient Acceptance of Health Care"
#19 "Patient Adaptation":ab,ti
#20 (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19) 769.580 Items
#21 (#11 AND #20) Items 68 (limits: human, english)

Psychinfo was consulted with 0 risults

All results 168, 108 with deduplication

APPENDIX 13 - PSA List of studies read in full text included and excluded (with reasons for exclusion)

1. Lackermair K, Schuhmann CG, Kubieniec M, Riesinger LM, Klier I, Stocker TJ, et al. Impairment of Quality of Life among Patients with Wearable Cardioverter Defibrillator Therapy (LifeVest®): A Preliminary Study. BioMed Research International. 2018;

Included

2. Barraud J, Pinon P, Laine M, Cautela J, Orabona M, Koutbi L, et al. Ventricular Arrhythmia Occurrence and Compliance in Patients Treated With the Wearable Cardioverter Defibrillator Following Percutaneous Coronary Intervention. Heart Lung and Circulation. 2018;27(8):984-8.

Reasons for exclusion: not data reported on QoL

3. Wan C, Szymkiewicz SJ, Klein HU. The impact of body mass index on the wearable cardioverter defibrillator shock efficacy and patient wear time. Am Heart J. 2017;186:111-7.

Reasons for exclusion: not data reported on QoL

4. Ettinger S, Stanak M, Szymański P, Wild C, Haček RT, Erčević D, et al. Wearable cardioverter defibrillators for the prevention of sudden cardiac arrest: A health technology assessment and patient focus group study. Medical Devices: Evidence and Research. 2017;10:257-71.

Reasons for exclusion: not our target population

5. Chung MK, Szymkiewicz SJ, Shao M, Zishiri E, Niebauer MJ, Lindsay BD, et al. Aggregate national experience with the wearable cardioverter-defibrillator: event rates, compliance, and survival. J Am Coll Cardiol. 2010;56(3):194-203.

Reasons for exclusion: not data reported on QoL

6. Kaspar G, Sanam K, Gholkar G, Bianco NR, Szymkiewicz S, Shah D. Long-term use of the wearable cardioverter defibrillator in patients with explanted ICD. International Journal of Cardiology. 2018.

Reasons for exclusion: not data reported on QoL

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