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Health Technology Assessment on the use of the Wearable Cardioverter Defibrillator in Patients with Myocardial Infarction and with ICD Explant

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SUPPLEMENT

Health Technology Assessment on the use of the Wearable Cardioverter Defibrillator in Patients with Myocardial Infarction and with ICD Explant

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ABSTRACT

The objective of the present work is to conduct a Health Technology Assessment (HTA) on the use of the Wearable Cardioverter Defibrillator (WCD) in patients at risk of Sudden Cardiac Arrest (SCA) following Myocardial Infarction (MI) or with an explanted Implantable Cardioverter Defibrillator (ICD).

Keywords

Health Technology Assessment; Cardioverter Defibrillator; Myocardial Infarction

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Abbreviations

Abbreviation	Meaning
ACC/AHA/HRS	American College of Cardiology/American Heart Association/Heart Rhythm Society
AE	Adverse Event
AED	Automated External Defibrillator
AMI	Acute Miocardial Infarction
CA	Cardiac Arrest
CDI	Cardiac Device related Infections
CIEDI	Cardiovascular Implantable Electronic Device
CPR	Cardio-pulmonary resuscitation
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CEA	Cost Effectiveness Analysis
COSCA	Core Outcome Set for Cardiac Arrest
CUSAS	Centro Universitario di Studi in Amministrazione Sanitaria
CV	Cardiovascular
DRG	Disease Related Group
EF	Ejection Fraction
ECG	Electrocardiogram
EHRA	European Heart Rhythm Association
HRS	Heart Rhythm Society
APHRS	Asia Pacific Heart Rhythm Society
HF	Heart Failure
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
IADL	Instrumental Activities in Daily Living
ICER	Incremental Cost Effectiveness Ratio
CRT-D	Cardiac Resynchronization Therapy-Defibrillator
ICD	Implantable Cardioverter Defibrillator
ICM	Ischemic cardiomyopathy
ICU	Intensive Care Unit
ILCOR	International Liaison Committee on Resuscitation
ISTAT	Italian National Institute of Statistics
LY	Life Year
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MeSH	Medical Subject Heading
MI	Myocardial Infarction
NHS	National Health Service
NYHA	New York Heart Association
NICM	Non-ischemic cardiomyopathy

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Abbreviation	Meaning
NR	Not Reported
PCI	Percutaneous Coronary Intervention
PTSD	Post-Traumatic Stress Disorder
QALY	Quality Adjusted Life Year
RCT	Randomized Clinical Trial
SAE	Serious Adverse Event
SCA	Sudden Cardiac Arrest
SCD	Sudden Cardiac Death
SNF	Skilled Nursing Facility
VA	Ventricular Arrhythmia
VACAR	Victorian Ambulance Cardiac Arrest Registry
VALIANT	Valsartan in Acute Myocardial Infarction Trial
VAS	Visual Analogic Scale
VEST	Vest Prevention of Early Sudden Death Trial
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
WCD	Wearable Cardioverter Defibrillator

Summary

SCD is a non-traumatic, unexpected fatal event occurring in a person without any prior condition that would appear fatal. By definition, a patient with SCD does not survive. When the patient survives, the event is termed aborted SCD or SCA. SCA is a life-threatening condition, recognized for being a leading cause of death worldwide. Annually, there are more than 900,000 cases of SCA worldwide. In Italy, SCA affects over approximately 60,000 patients per year. The majority of these SCA events happen at home or outside of the hospital. The immediate cause of SCD in most instances are ventricular arrhythmias, specifically electrical abnormalities of the heart i.e., ventricular fibrillation (VF) or ventricular tachycardia (VT). However, the mechanisms are multifactorial. SCA and aborted SCD lead to serious health consequences for individuals and imposes a significant economic burden on the health care system, the patient's family and caregivers. Furthermore, the impact on quality of life and activities of daily living is substantial. Costs for SCA and aborted SCD have risen over time, and they are expected to rise continuously due to an aging population, longer life expectancies and an increased prevalence of the underlying conditions. SCD can be prevented by a timely defibrillation, which is the golden standard of treatment for successfully terminating VF or VT. Effective treatment of SCA not only reduces mortality, but also efficiently saves resources otherwise used to manage the consequences of late resuscitation and intensive care for brain damaged patients. Accordingly, proactive and targeted investment is clearly justified to optimize the health status and treatment pathway in subjects at risk of SCA. An HTA on the use of WCD in two categories of subjects with an increased risk of SCD was performed: adult patients with a recent MI and adult patients with an ICD explant.

In regards to the existing published literature, the most recent reviews and meta-analysis on studies involving subjects with previous MI or with previous ICD explant concluded: the WCD effectively bridges a limited time period, in patients with a high risk for SCA and can be a helpful tool for risk stratification to better select patients for primary prevention ICD placement. The WCD can be considered when a transient contraindication to ICD is present, such as endocarditis or device related infection. The WCD is recommended in several cases, including patients with an ICD and a history of SCA or sustained VA in whom removal of the ICD is required, as well as for patients at an increased risk of SCD but who are not eligible for an ICD, with an LVEF $\leq 35\%$ and within 40 days post MI. The WCD is a feasible bridge to ICD therapy and/or safe observation for patients at high risk for SCD, especially in the acute recovery phase of cardiac diseases.

The LifeVest is the only WCD currently available and is worn outside of the body. It was designed to continuously monitor a patient's heart, detects life-threatening rapid heart rhythms and automatically delivers a treatment shock to restore normal heart rhythm. The WCD is intended for the outpatient setting, and allows patients to go home from the hospital with protection from SCD. The LifeVest service package includes: training and 24/7 technical assistance and support by ZOLL Medical Corporation trained representatives; component replacement within 24 hours; cleaning and testing procedures of the device with reconditioning or repair completed when required; inclusion in the LifeVest Network. This is an online patient management system, that allows clinicians to monitor patient data downloaded from the device and it gives health care professionals access to the most current information about their patient during their recovery after a cardiac event.

The experience on the use of WCD shows promising results. In the most recent randomized trial, the WCD was highly effective at restoration of sinus rhythm in patients with a VT/VF and significantly decreased overall mortality, although no statistically significant SCD mortality benefit was reported, most likely due to insufficient power of the study. However, as experience with this technology increases, it is expected that clinical benefits for WCD use will be better recognized.

In post-MI patients, the base-case analysis conducted from the Italian NHS point of view, reported an ICER of € 47,709 per QALY gained comparing WCD vs medical therapy, which

is significantly lower than the referenced cost-effectiveness threshold of € 60,000 per QALY gained used in Italy. This analysis was based on the overall mortality at 90 days data estimated in the VEST trial by the Intention to Treat Analysis (ITT) which reflects the low WCD adherence of the patients involved in the trial: 3.1% overall mortality at 90 days in the WCD group and 4.9% in the medical therapy group. Using ITT mortality data is a conservative approach, considering the better efficacy reported by the VEST Trial in the "As Treated" analysis (0.50 per 100 person-months of patients wearing the WCD and 1.91 per 100 person-months of patients not wearing the WCD). It seems that the adherence seen in published observational studies reflects the assumptions in the "As Treated" analysis. Although an economic model calculating the cost-effectiveness of WCD was not conducted on the "As Treated" cohorts, it is clear that cost calculations conducted with this data would be lower than those reported for the ITT economic model. Further, a cost-minimization analysis was conducted in patients requiring ICD explant due to an associated infection, since this option was assumed to be equivalent compared with the standard therapy (3 weeks hospitalization in a low intensity hospital). In this analysis, made from the Italian NHS point of view, the WCD provides a cost saving of € 1,782 per patient. The results of the two models were confirmed with univariate and probabilistic sensitivity analyses.

In conclusion, the use of WCD according to guidelines can therefore contribute not only to an improvement in patient care in clinical practice, but also to a more effective utilization of resources in the Italian NHS. In addition, further research on risk factors for SCA and SCD should be conducted to continue to improve the identification of the target population. All evidence provided in this HTA was considered reliable by Italian clinical and HTA experts. Accordingly, the results can be considered applicable within the Italian NHS.

Objective and Methods

OBJECTIVE

The objective of the present work is to conduct a Health Technology Assessment (HTA) on the use of the Wearable Cardioverter Defibrillator (WCD) in patients at risk of Sudden Cardiac Arrest (SCA) following Myocardial Infarction (MI) or with an explanted Implantable Cardioverter Defibrillator (ICD).

METHODS

The present work was conducted using previous HTA reports as a guide [1-4]. In particular, we described the target health condition from a clinical and epidemiological perspective, its economic burden and consequences on patients' health and on their families' wellbeing. We also described the WCD technology, and its implications in terms of effectiveness, safety, compliance, and in the health economic implications from a national payer perspective.

The present work was conducted using mainly an extensive literature research, but also using the advises of clinical experts and the application of a decision analytical model to conduct economic evaluations.

Research of data from literature

We performed an extensive literature search, adopting the following approach. First, electronic databases (Medline using PubMed and Web of Science) were consulted on 1st March 2018. We conducted the research using index/MeSH (Medical Subject Heading) and strings of keyword terms, according to the field of research: clinical description of the target conditions; epidemiological description of the target conditions; treatment with focus on WCD use; treatment with focus on other options (e.g., ICD); economic implications (i.e., burden of disease, economic evaluations); patients reported outcomes and Health Related Quality of Life (HRQoL). The research strings included the following terms:

1. ("Sudden Cardiac Death" OR "Sudden Cardiac Attack" OR "Sudden Cardiac Arrest") AND ("prevalence" OR "incidence" OR "mortality" OR "survival" OR "life expectancy" OR "risk" OR "death") for the epidemiological domain;
2. ("Sudden Cardiac Death" OR "Sudden Cardiac Attack" OR "Sudden Cardiac Arrest") AND ("symptoms" OR "cause" OR "diagnosis" OR "prognosis" OR "severity" OR "risk" OR "treatment" OR "therapy" OR "death") for clinical domain;
3. ("Sudden Cardiac Death" OR "Sudden Cardiac Attack" OR "Sudden Cardiac Arrest") AND ("treatment" OR "therapy" OR "implantable cardioverter defibrillator "OR "ICD" AND "efficacy" OR "effectiveness" OR "benefit" OR "outcome" OR "resuscitation" OR "risk" OR "safety" OR "adverse event" OR "side effect" OR "LifeVest" OR "wearable cardioverter defibrillator" OR "WCD") for treatment domain (including LifeVest);
4. ("Sudden Cardiac Death" OR "Sudden Cardiac Attack" OR "Sudden Cardiac Arrest") AND ("quality of life" OR "health related quality of life" OR "patient perspective" OR "patient reported outcomes" OR "utility" OR "wellbeing") for quality of life and psychosocial domain;
5. ("Sudden Cardiac Death" OR "Sudden Cardiac Attack" OR "Sudden Cardiac Arrest") AND ("cost" OR "economic" OR "burden" OR "cost of illness" OR "cost of treatment" OR "cost consequences" OR "cost-effectiveness" OR "cost benefit" OR "cost utility") for economic domains.

Eligibility criteria included the target disease area, the age of the subjects (adults), the language (English or Italian), years of publication (2008 and later) and type of publications: original research from clinical trials, observational retrospective or prospective studies, literature reviews, guidelines and practice guidelines published on clinical and epidemiological evidence. In order to find the most updated documents, further literature research focusing on

specific topics (e.g., new papers on WCD and on HRQoL in patients experiencing SCA (Sudden Cardiac Arrest) were found published in late March and in July 2018) was conducted in April and in July 2018. Furthermore, the Vest Prevention of Early Sudden Death Trial (VEST) [5], published in September 2018, was included as well. All identified titles found were analyzed and duplicates were removed.

After a first screening process based on the title and abstract of article retrieved, a full-text screening was conducted. From the included publications, we searched the full-texts and then screened their references lists to identify other possible relevant ones, following the same process above of publication selections from the titles and abstracts. Finally, we read the full texts for a final selection of the eligible publications. Two of the authors (L.S.D. and L.S.) independently evaluated eligibility of all the studies retrieved from the electronic literature search. Two other reviewers (P.A.C. and L.G.M.) were also involved to reach consensus in case of disagreement. Exclusion criteria included all documents not reporting any information on our target populations (i.e., on post-MI patients and on ICD explanted). Regarding the publications reporting results on safety, effectiveness and compliance of WCD in the target populations, we also checked if overlapping of participants were present in two or more studies. Studies characteristics and data reported were systematically extracted by two authors (L.S.D. and L.S.) according with and reported in pre-defined structured table. A third author (P.A.C.) subsequently validated data extraction independently. Any disagreement on data extraction was resolved by discussion. The evidence extracted by the literature were used to draft this HTA.

Results

The information found in the selected literature proved useful to describe the several aspects of the phenomenon under study, is reported below and quoted. The list of publications retrieved by the literature review on WCD in patients with MI and/or with ICD explant is reported in Table I.

n.	Reference	Subjects	Type of study	Study design
1	Agarwal et al. 2018 [6]	**Mixed indication**	Review	Not Applicable
2	Ellenbogen et al. 2018 [7]	**Mixed indication**	Original Research	Retrospective
3	Leyton-Mange et al. 2018 [8]	**Mixed indication**	Original Research	Retrospective
4	Nguyen et al. 2018 [9]	**Mixed indication**	Meta-Analysis	Not Applicable
5	Niwano et al. 2018 [10]	**Mixed indication**	Review	Not Applicable
6	Olgin et al. 2018 [5]	**POST AMI**	Original Research Clinical trial (VEST)	Randomized
7	Röger et al. 2018 [11]	**Mixed indication**	Original Research	Prospective
8	Viani et al. 2018 [12]	**Mixed indication**	Review	Not Applicable
9	Weinstock et al. 2018 [13]	**Mixed indication**	Review	Not Applicable
10	Al Khatib et al. 2017 [14]	**Mixed indication**	Guidelines	Not Applicable
11	Barraud et al. 2017 [15]	**POST AMI**	Original Research	Prospective
12	Barraud et al. 2017 [16]	**Mixed indication**	Review	Not Applicable
13	Barsheshet et al. 2017 [17]	**Mixed indication**	Original Research Clinical trial (SWIFT)	Prospective
14	Beiert et al. 2017 [18]	**Mixed indication**	Original Research	Retrospective
15	Cappato et al. 2017 [19]	**Mixed indication**	Review	Not Applicable
16	Castro et al. 2017 [20]	**EXPLANTED**	Original Research	Retrospective
17	Ellenbogen et al. 2017 [21]	**EXPLANTED**	Original Research	Retrospective
18	Erath et al. 2017 [22]	**Mixed indication**	Original Research	Prospective
19	Ettinger et al. 2017 [23]	**Mixed indication**	HTA	Not Applicable
20	Francis 2017 [24]	**Mixed indication**	Editorial	Not Applicable
21	Naniwadekar et al. 2017 [25]	**Mixed indication**	Original Research	Retrospective
22	Nichol et al. 2017 [26]	**Mixed indication**	Review	Not Applicable
23	Quast et al. 2017 [27]	**Mixed indication**	Original Research	Retrospective
24	Reek et al. 2017 [28]	**Mixed indication**	Review	Not Applicable
25	Reek et al. 2017 [29]	**Mixed indication**	Review	Not Applicable
26	Sasaki et al. 2017 [30]	**Mixed indication**	Original Research	Prospective
27	Tofield 2017 [31]	**Mixed indication**	Letter	Not Applicable
28	Bhaskaran et al. 2016 [32]	**Mixed indication**	Original Research	Retrospective
29	Duncker et al. 2016 [33]	**Mixed indication**	Review	Not Applicable
30	Piccini et al. 2016 [34]	**Mixed indication**	Recommendation	Not Applicable
31	Ponikowski et al. 2016 [35]	**Mixed indication**	Guideline	Not Applicable
32	Wäßnig et al. 2016 [36]	**Mixed indication**	Original Research	Retrospective
33	Healy et al. 2015 [37]	**EXPLANTED**	Original Research (Economic evaluation)	CEA based on decision model
34	Kondo et al. 2015 [38]	**POST AMI**	Original Research	Retrospective

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n.	Reference	Subjects	Type of study	Study design
35	Kutyifa et al. 2015 [39]	**Mixed population**	Original Research WEARIT-II Registry	Prospective
36	Priori et al. 2015 [40]	**Mixed indication**	Guideline	Not Applicable
37	Sanders et al. 2015 [41]	**POST AMI**	Original Research (Economic evaluation)	CEA based on decision model
38	Sasaki et al. 2014 [42]	**Mixed indication**	Original Research	Prospective
39	Chung 2014 [43]	**Mixed indication**	Review	Retrospective
40	Francis et al. 2014 [44]	**Mixed indication**	Review	Not Applicable
41	Kusumoto et al. 2014 [45]	**Mixed indication**	Expert Consensus	Not Applicable
42	Pedersen et al. 2014 [46]	**Mixed indication**	Expert Consensus	Not Applicable
43	Tanawuttiwat et al. 2014 [47]	**EXPLANTED**	Original Research	Retrospective
44	Adler et al. 2013 [48]	**Mixed indication**	Review	Not Applicable
45	Epstein et al. 2013 [49]	**POST AMI**	Original Research	Retrospective
46	Klein et al. 2013 [50]	**Mixed indication**	Review + reporting results from a previous original research	Retrospective as regard as the original research
47	Zishiri et al. 2013 [51]	**Mixed indication**	Original Research	Retrospective
48	Kao et al. 2012 [52]	**Mixed indication**	Original Research	Retrospective
49	Chung et al. 2010 [53]	**Mixed indication**	Original Research	Retrospective
50	Dillon et al. 2010 [54]	**Mixed indication**	Original research	Retrospective
51	Verdino et al. 2010 [55]	**Mixed indication**	Review	Not Applicable
52	Wilkoff et al. 2009 [56]	**EXPLANTED**	Expert consensus	Not Applicable
53	Feldman et al. 2004 [57]	**Mixed indication**	Original Research Results of WEARIT/ BIROAD study	Prospective

Table I. *List of publications on WCD where patients with MI and/or with ICD explant were involved*

EPIDEMIOLOGICAL DESCRIPTION OF TARGET CONDITION AND CLINICAL IMPACT

Sudden Cardiac Death (SCD) can be defined as a non-traumatic, unexpected fatal event occurring within 1 hour of the onset of symptoms in a person without any prior condition that would appear fatal [40,58,59]. SCD may be preceded by symptoms such as chest pain, dyspnea, palpitations, pre-syncope and syncope, although many individuals have no symptoms before the event. By definition, a patient with SCD does not survive. When the patient survives, the event is termed aborted SCD or SCA.

Sudden Cardiac Arrest

SCA is a life-threatening condition, recognized for being a leading cause of death worldwide. Annually, there are approximately 375,000-700,000 SCA cases in Europe [60], and around 360,000-380,000 cases in the US [61,62]. Mozaffarian et al. [63] stated that according to estimations, in the US, 326,000 persons are affected by SCAs outside of the hospital annually, and a large part of these SCAs happen at home.

Ellenbogen et al. [7] stated that according to the American Heart Association 2013 Heart Disease and Stroke Statistics, 209,000 in-hospital and 359,400 out-of-hospital cardiac arrests occur annually.

In their literature review, Haydon and colleagues state that internationally the survival rate for Cardiac Arrest (CA) is less than 14% [64]. In particular, Ellenbogen and colleagues [7] specified that despite advances in care management, the outcome of patients experiencing in-hospital SCA remains poor, with survival to hospital discharge rates varying from 6% to 18%. In addition, many SCAs occur when the patient is out-of-hospital, asleep or alone. According to the results by Perkins and colleagues [65], among patients with out-of-hospital CA, only 2.4% survived at 30 days. Furthermore, survivors of out-of-hospital CA may sustain brain damage due to inadequate cerebral perfusion during cardiac arrest. After out-of-hospital CA, constant care or assistance with activities of daily living and nursing home care may be needed [66]. In Italy, within the "Piacenza Progetto Vita" [67], the first European system of out-of-hospital early defibrillation by lay volunteers, established in the

Area of Piacenza (a city in the Emilia Romagna region) to prevent SCD, 39 semi-automatic external defibrillators were deployed in the city and in the surrounding. During the first 22 months from the beginning of the project, 354 SCA occurred: 86% in the home, 11% in public streets, less than 1% in an athletic center, 1% at work and 1% in other places. The mean age of the victims was 72 (± 12 years); 61% were male. The volunteers, answering to the emergency call number within an average of 4.8 minutes from the call, treated more than 40% of CAs and the survival percentage increased from 4.3% to 15.5% [67]. Although the current evidence supports the association between bystander automatic external defibrillator (AED) use and improved clinical outcomes [68], the use of AEDs has been identified for not being optimal to manage out-of-hospital CA, since most patients at risk do not spend a sufficient portion of each day in public locations [69]. The wearable cardioverter defibrillator aims to overcome these issues.

Sudden Cardiac Death

The immediate cause of SCD in most instances is Ventricular Arrhythmia (VA) secondary to structural heart disease or primary electrical abnormalities of the heart i.e., either Ventricular Fibrillation (VF) or Ventricular Tachycardia (VT). However, the mechanisms are multifactorial and include scar formation, fibrosis, ventricular dilatation, re-entry, abnormal automaticity [70-74].

Table II, adapted from Kuriachan and colleagues [71], shows the major causes of SCD. SCD has a multitude of potential etiologies but is most commonly associated with ischemic heart disease, while Non-Ischemic Cardiomyopathy (NICM) and other structural abnormalities may also be causative. Patients without structural disease have a primary electrical abnormality like long-QT syndrome or Brugada syndrome. Severe left ventricular systolic dysfunction is the main marker for sudden death in patients with ischemic or NICM [71]. Genetic factors can play a role in SCD in the pathophysiological pathway. Mutations and polymorphisms can influence the risk of SCD in both Coronary Artery Disease (CAD) and non-CAD etiologies, while other risk factors include smoking, hypertension, dyslipidemia, obesity, diabetes and lifestyle [75].

SCD occurs in 184,000-462,000 individuals in the US annually, with an incidence of 60 per 100,000 individuals per year, accounting for 5.6% of all deaths in the US [70,71,76]. Kuriachan and colleagues [71], using death certificate data, report that SCD accounts for up to 15% of all deaths in Western nations. According to Capucci et al. [67] about 45,000 SCDs occur every year in Italy, and incidence of SCD in Italy was estimated to be from 55,000-60,000 persons per year [77].

Subjects with the highest risk of SCA and SCD are those with known heart disease, although the majority of SCDs occur in low-risk populations [78]. The incidence of SCD increases 2- to 4-fold, in the presence of coronary disease and 6- to 10-fold in the presence of structural heart disease [74]. The estimated incidence of SCD is about 15-20% per year in patients with heart failure and/or with arrhythmia markers, compared with about 1-2% per year occurring in the general population, who generally have an unknown pre-existing heart disease [79]. In individuals with known CAD or a prior MI, this population accounts for 38-50% of all cardiovascular deaths [79]. However, a significant proportion of SCD happens also in patients with NICM [72,80].

SCD incidence increases with age and is generally more frequent in men. The incidence of SCD in younger populations (<30 years) is 100-fold lower than that in older individuals [71]. Data from MONICA study [81], conducted in Italy between 80s and early 90s referred a wide range of incidence of SCD, according to age. The incidence of SCD was 0.1/1,000 in men at 35-44 years of age, 0.37/1,000 in men at 45-64 years of age, 0.88/1,000 in men at 55-64 years of age and 2.86/1,000 in men at 65-74 years of age. Women are relatively protected from SCD until the menopausal years when the incidence increases to approach that of men. The lifetime risk of SCD for women is at least half that of men. Results from a work recently published [82], conducted using individual participant data from the Framingham Heart Study, reported a lifetime risk estimate for SCD of 10.1-11.2% in men aged 45, 55, and 65 years, and of 2.4-3.4% in women at the same age.

Stecker and colleagues [76] found that in men, SCD incidence exceeds other causes of death including cancers (lung, prostate, and colorectal), accidents, chronic respiratory diseases, diabetes, and cerebrovascular disease. In women, SCD incidence is similar or higher to that of different types of cancer, cerebrovascular disease, Alzheimer disease, and accidents.

Wellens et al. [83] classified 4 different groups of individuals at risk of SCD: patients with a history of heart disease and severe cardiac dysfunction (Left Ventricular Ejection Fraction –

Major causes	Causes description
Ischemic heart disease	• CAD with MI • CAE • Non-atherogenic CAD (arteritis, dissection and congenital coronary anomalies) • CAS
Non-ischemic heart disease	• Hypertrophic cardiomyopathy • Dilated cardiomyopathy • VHD • CHD • Arrhythmogenic right ventricular cardiomyopathy • Myocarditis • Cardiac tamponade • Acute myocardial rupture • Aortic dissection
No structural heart disease	• Idiopathic ventricular fibrillation or J-wave syndrome • Brugada syndrome • Long-QT syndrome with torsades de pointes • Pre-excitation syndrome • High grade atrioventricular block with torsades de pointes • Familial SCD • Commotio cordis
Non-cardiac disease	• Pulmonary embolism • Intracranial hemorrhage • Drowning • Pickwickian syndrome • Drug overdose or toxicity • Central airway obstruction • Sudden infant death syndrome

Table II. *Major causes of SCD. Adapted from [71]*
CAD = Coronary Artery Disease; MI = Myocardial Infarction; CAE = Coronary Artery Embolism; CAS = Coronary Artery Spasm; VHD = Valvular Heart Disease; CHD = Congenital Heart Disease; SCD = Sudden Cardiac Death

LVEF <40%), accounting for 13% of SCD, and patients with a history of heart disease with no or mild cardiac dysfunction (LVEF >40%), accounting for 40% of SCD. There are also patients who are diagnosed with a genetically based cause for a life-threatening cardiac arrhythmia, accounting for 2% of SCD. Finally, there is a large subset without a prior diagnosis of heart disease, accounting for 45% of all SCD: in these populations, risk stratification is particularly challenging.

An inverse relationship between the incidence of SCD and absolute numbers of events in the various epidemiologic or clinical categories was reported [59]. When SCD is analyzed in terms of the absolute number of annual events within subpopulations, as shown in Figure 1, it is possible to see that the highest risk clinical subgroups, i.e., patients with reduced LVEF, a history of heart failure, and survivors of out-of-hospital cardiac arrests, do not generate most SCD events. Instead, subgroups with the highest case fatality rates have the lowest population attributable risk. In contrast, the larger population subgroups, with much lower relative fatality rates, generate the largest absolute numbers of SCD events. Myerburg et al. [84] affirmed that the importance of recognizing this principle relates to the magnitude of population that can benefit from preventative interventions. For example, the very high-risk patient categories studied in the clinical trials of implantable defibrillators represent only a very small part of the universe of SCD risk, and the reported benefits apply only to those small subgroups. This highlights the importance of finding specific risk markers for more general segments of the population from which the potential for greater public health impact can emerge.

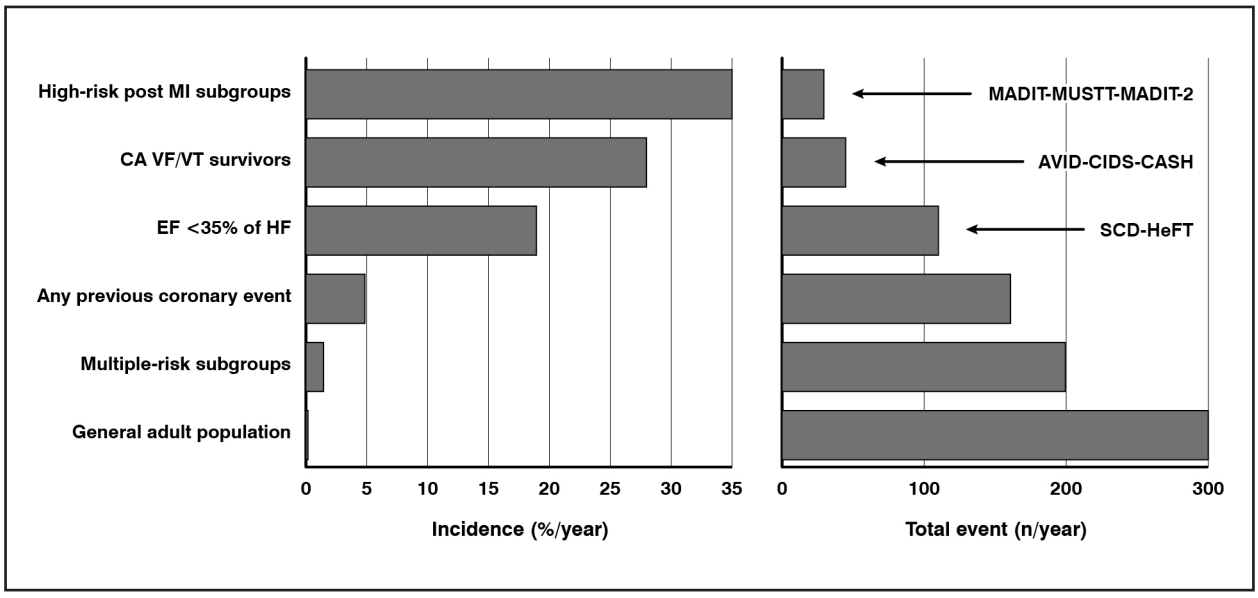

Figure 1. *Incidence of SCD and total population burden: relationship between population subsets. Modified from [84]*
AVID = Antiarrhythmics vs Implantable Defibrillator study, CASH = Cardiac Arrest Study Hamburg; CIDS = Canadian Implantable Defibrillator Study; EF = Ejection Fraction; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MI = Myocardial Infarction; MUSTT = Multicenter UnSustained Tachycardia Trial; SCD-HeFT = The Sudden Cardiac Death in Heart Failure Trial, VT/VF = Ventricular Tachycardia–Ventricular Fibrillation

Patients with MI (at risk of SCA)

Subjects experiencing an Acute Myocardial Infarction (AMI) remain at high risk of SCD. Several studies have quantified the risk of SCD after MI, estimating an overall incidence ranging between 2% and 4% per year [85-88].

The Valsartan in Acute Myocardial Infarction Trial (VALIANT) [86,87], a Randomized Controlled Trial (RCT) involving 14,609 patients with a first or subsequent AMI complicated by Heart Failure (HF) and LVEF ≤40% assessed the risk and time course of sudden death in high-risk patients, after MI. In the trial, 7% of the participants had an event a median of 180 days after MI: 903 died suddenly and 164 were resuscitated after SCA. Of these events, 19% occurred within the first 30 days post-MI with 74% of the patients that were resuscitated still alive one year later. The risk of an event was 10-fold higher in the first 30 days at a rate of 1.4% per month, decreasing exponentially over the first 6 months to reach a steady rate of 0.14% per month, at 2 years. Patients with an LVEF ≤30% demonstrated the highest risk in this early period. This significant higher risk of SCD within the first month after MI was confirmed in several other studies [89-93]. However, the risk of SCD in patients after MI estimated in clinical trials can be different from the one present in the community. Furthermore, since advances in therapies for MI have increased the numbers of survivors living with chronic CAD and impaired left ventricular function [94-98], more patients nowadays live at increased risk of fatal and non-fatal events [86,87,99]. A large, population-based study was conducted in the Olmsted County in Minnesota to evaluate the risk of SCD post-MI and the impact of recurrent ischemia and HF on SCD [89]. In this study observing 2,997 subjects for a median follow-up of 4.7 between the years 1979 and 2005, 1,160 deaths occurred, 24% of these being SCD. The 30-day cumulative incidence of SCD was 1.2%. The risk of SCD declined over time after the first 30 days. Recurrent ischemia was not associated with SCD, since the incremental risk, expressed as hazard ratio, corresponded to 1.26, with a 95% CI= 0.96-1.65, while HF markedly increased the risk of SCD, corresponding to a hazard ratio of 4.20, with a 95% CI=2.9-5.8. The authors underline the importance of continued surveillance of patients who experienced an MI and the dynamic nature of risk stratification.

Patients with ICD explant

Prevention of SCA after ICD removal is a challenging issue. The most common indications for lead replacement are infection, venous occlusion, advisory or recall for possible lead malfunction, or mechanical lead failure. Lead management involves the assessment of risks and benefits of whether or not to remove the lead based on the individual clinical condition of the patient as well as lead characteristics [100-102].

Infection of an ICD or other type of cardiac implantable electronic device (e.g., pacemaker) is associated with significant morbidity, mortality and costs, which increase correspondingly to higher implantation rates [47,101,103-107]. This phenomenon has consequently increased the percentage of infections by 96-210% estimated between 1993 and 2008 [47,101]. Complete system removal together with parenteral antibiotic therapy are recommended for patients who do not tolerate the procedure [102]. Despite device removal with antibiotic therapy, mortality remains high, ranging from 8.0% to 26.9%, while antibiotic therapy alone without device removal carries a higher mortality corresponding to 31.0–66.0% [47].

Sridhar and colleagues [103] examined recent national trends in the incidence of Cardiac Device related Infections (CDI), and lead extractions in hospitalized patients and associated mortality. Using the data of a Nationwide Inpatient Sample database in the US, they identified for the years 2003 and 2011 patients diagnosed with a CDI as determined by discharge ICD-9 diagnostic codes. They found an increase in the number of hospitalizations due to CDI from 5,308 in the year 2003 to 9,948 in 2011. Males (68%), Caucasians (77%) and age group 65–84 years (56.4%) accounted for majority of CDI. The mortality associated with CDI was 4.5%, and was significantly worse in higher age groups: 2.5% in 18-44 years compared to 5.3% in >85 years. Mean hospitalization charges increased from $ 91,348 in 2003 to $ 173,211 in 2011. Among all lead extraction procedures, the percentage of patients undergoing lead extraction secondary to CDI also increased from 2003 (59.1%) to 2011 (76.7%).

The management of patients after ICD removal waiting for re-implantation is challenging for more reasons, since, implanting the device too early may result in re-infection, the patients remain at risk of SCA, and continuous inpatient monitoring is expensive and not beneficial for the patient's health and quality of life [37]. Depending on the patient's risk, the clinician could decide to prolong patient's hospitalization to prevent arrhythmic death, or to consider a device re-implantation before achieving infectious control.

Consequences on health and quality of life of subjects surviving CA

As the brain is highly dependent on a constant blood flow, survivors may suffer from long-term cognitive impairment, which could involve one third or up to 50% of the CA survivors [108-110]. Several publications have been found from our literature research conducted in March and updated in June. We summarize below the results and discussions of those that we found of highest interest on the target topic.

In particular, decrease in social participation and psychiatric condition in survivors to CA have been reported in several publications in the last years. To report the findings of the most recent ones, for instance, Naber and Bullinger [111] listed as cognitive impairment symptoms in their short report: memory impairment, attention impairment, executive function, impairment of visual-spatial abilities and verbal fluency, specifying that there is no consensus on whether cognitive deficits recover over time. Naber and Bullinger underlined that while in the past the interest in the long-term outcomes of patients surviving out-of-hospital CA focused on neurological symptoms, in the last decade, psychiatric symptoms, mental health or more broadly, HRQoL have become areas of scientific interest. Few years ago, patient-reported outcomes and HRQoL were included as supplemental outcomes in the standardized Utstein Resuscitation Registry Templates for out-of-hospital CA [112]. More recently, a consensus article has been published [113] on the Core Outcome Set for Cardiac Arrest (COSCA) initiative, in collaboration with the International Liaison Committee on Resuscitation (ILCOR): after a systematic literature review, a Delphi panel was adopted on 168 participants who were clinicians, patients and their relatives meeting for two days. The consensus reached recommends that a core outcome set for reporting on effectiveness studies of cardiac arrest in adults should include survival, neurological function, and HRQoL. This should be reported as survival status and modified Rankin scale score at hospital discharge, at 30 days, or both, while HRQoL should be measured with ≥1 tools from health utilities index version 3, Short-Form 36-Item Health Survey, and EQ-5D-5L at 90 days and at periodic intervals up to 1 year after CA.

As regards other studies more recently published, Viktorisson and colleagues [114] noticed that although psychological problems following CA have been increasingly highlighted in recent years, there is still paucity of optimal services to provide cognitive, psychological and psychosocial support and rehabilitation. Their cross-sectional study aimed to assess the presence of anxiety, depression and Post Traumatic Stress Disorder (PTSD) and to compare the health state of patients surviving to OHCA and with a good neurological condition with a reference population in Sweden. Survivors were identified through the Swedish Cardiopulmonary Resuscitation Registry, and postal questionnaires were sent out 3 months after the out-of-hospital CA. Main findings were that reduced wellbeing was experienced by half of the patients, above all among older patients and among women and in comparison, with a reference population in Sweden.

Tiainen and colleagues [115] conducted recently a prospective observational study to evaluate the functional status and HRQoL of one-year survivors of a cohort of unconscious patients that after out-of-hospital CA were admitted to Finnish intensive care units during one year. They assessed the proportion of survivors living at home one year after the event, their functional outcome regarding independency in Instrumental Activities in Daily Living (IADL) functions, activities outside home, return to previous work, car driving, and their self-rated HRQoL. Nine out of ten one-year survivors of the participants experienced good neurological and functional outcome, living at home and being independent in basic daily functions. HRQoL was similar as in age- and sex-adjusted Finnish population. Less than 10% of the one-year survivors lived in long-term facilities, and only 3% of the patients who lived at home before the arrest needed long-term facility care one year later. This need was not based solely on the hypoxic-ischemic brain injury.

According to Andrew and colleagues [116], understanding the prognosis of elderly patients with out-of-hospital CA is important to inform decision-making in resuscitation and advanced care planning. However, short-term outcomes such as survival to hospital discharge cannot be considered to understand the post-arrest HRQoL of the patients. They conducted a retrospective analysis of data gathered from the Victorian Ambulance Cardiac Arrest Registry (VICAR) on 20,103 out-of-hospital CA survivors to hospital discharge aged ≥65 years, to describe the 12-month functional recovery and HRQoL of these subjects. During the study period, 44.9% of the participants received a resuscitation attempt, 9.7% of the patients survived to hospital discharge and 777 were alive 12 months post-arrest. Of these, 651 (83.8%) participated in 12-month follow-up. Most (60.6%) resided at home without additional care

and 66.6% reported a good functional recovery, although these percentages decreased with increasing age. Furthermore, the authors of the research found that each 10-year increase in age corresponds with a 40.8% reduction in the odds of good functional recovery, and a 65.8% reduction in the odds of living independently. Physical HRQoL decreased with increasing age, but mental HRQoL increased (not statistically significant) with increasing age and was significantly better than the age- and sex-matched Australian population. Of the 2575 OHCAs in an aged care facility, 2.2% survived to hospital discharge; however, no patient reported a good 12-month functional recovery.

A sub-study of the VALIANT study [117] involved 2556 patients who completed the EQ-5D at baseline and after 6, 12, 20, and 24 months. Over a 2-year period, 597 patients experienced a nonfatal CV event, with baseline EQ-5D scores on average lower than patients without a subsequent nonfatal CV event (Visual Analogic Scale – VAS = 61.0 ± 19 vs 68.2 ± 18; $p < 0.001$ and US-based utility score = 0.76 ± 0.22 vs 0.83 ± 0.17; $p < 0.001$). Accordingly, patients surviving to MI who experienced a subsequent nonfatal CV event had a significant worsening of their HRQoL in addition to a worse overall baseline HRQoL compared with patients with MI who did not experience another CV event over 2 years.

Van't Wout et al. [118] determined the level of daily functioning and quality of life in caregivers of cardiac arrest survivors two years after the cardiac arrest. Furthermore, they studied the long-term impact of witnessing the event of a CA. A longitudinal cohort study including caregivers of cardiac arrest survivors completed a questionnaire at home on daily activities, emotional functioning, fatigue, caregiver strain, impact of event, and quality of life. In total 57 caregivers participated. Two years after the cardiac arrest, their quality of life was similar to those of the general population, although almost 30% still scored high level of trauma-related stress. However, the study showed that two years after the CA, caregivers that attended the event of CA, experienced significantly more trauma related stress than caregivers who did not experienced the event. The authors of the research recommend future research to focus on screening for stress related to attending a CA of a close relative and the effectiveness of support programs for caregivers that attended a cardiac arrest of a close relative. Another study [119] has shown that in terms of wellbeing, caregivers experience the most problems on the emotional level at one year after the cardiac arrest. Generally, they improve within 12 months from the event, apart from those with emotional problems or perceived cognitive problems at 12 months, who are at risk for developing a higher care burden. However, also less recent studies provide interesting results. For instance, a study conducted in the Netherlands and published in 2009 [120] showed that patients had low participation level in society (74%), severe fatigue (more than 50%), anxiety and/or depression (38%) and decreased HRQoL (24%) and that clinically relevant PTSD symptoms were present in 50% of the family caregivers, compared with 21% of patients themselves. They concluded that after surviving an out-of-hospital CA, both patients and partners could experience important impairments in their lives, similar to those seen in patients with other kinds of brain damage. In a study published in 2014 [121], PTSD was found in 40% of relatives of patients with out-of-hospital CA.

Despite the different aims and methods and healthcare contexts where the several studies have been conducted across the years, bearing to different and generally not comparable results, it is possible to conclude that relevant consequences on health, both clinical and perceived ones, of patients and their families who have experienced CA, can be substantial; accordingly, attention and correct investment is deserved to optimize the health states in involved subjects.

ECONOMIC IMPLICATIONS OF SCA AND SCD

SCA and SCD impose a significant economic burden on patients, on their families and on healthcare systems. Costs for SCA and SCD have risen over time, and are expected to rise due to an aging population and increase of prevalence of these conditions. However, a comprehensive estimate of economic consequences attributable to SCA and SCD does not exist.

The most recent study found on this topic, published in 2018 [122] was conducted in Taiwan. Interestingly, the authors aimed to estimate the 1-year survival rate and related healthcare costs after CA in a population randomly sampled from the National Health Insurance Research Database. They estimated a mean cost per hospital discharge after cardiac arrest less than $ 32,000, which the authors found significantly different from estimates obtained in other studies conducted in different countries ($ 8,000-50,000). The mean costs of medical care for CA until discharge, between those dead in hospital and those survived were $ 522 and $ 18,859, respectively. The mean healthcare cost during the 1-year follow up was $ 12,953,

with the costs for inpatient care accounted for the majority of this amount. In 2017 Geri and colleagues [123] published a systematic review protocol on costs related to cardiac arrest management, underlining that in the developed countries, there is actually a wide variation in the approaches used to manage patients with CA, in both the prehospital care and after the patients are admitted to the hospital. In the hospital, the implementation of multifaceted interventions such as targeted temperature management or immediate coronary angiography with Percutaneous Coronary Intervention (PCI) in successfully resuscitated patients has led to greatly improved survival and health outcomes across countries, although this has come at a significant financial cost, which can limit a widespread adoption of technologies, potentially bearing to suboptimal results. The authors underlined that although there is some literature demonstrating the costs of individual components of care for CA, a comprehensive picture of all the costs associated with treating CA does not exist. This may be in part due to the complex, multidisciplinary care required by these patients. Furthermore, the available studies used different methods, perspectives, were performed in different healthcare systems, hence their results are not directly comparable.

We report below some results from the studies currently available.

In Germany, Graf et al. [124] investigated the costs and health status outcomes of Intensive Care Unit (ICU) admission in patients after SCA with in-hospital or out-of-hospital cardiopulmonary resuscitation. Out of 354 patients involved in the study, 31% were alive 5 years after hospital discharge. Costs per hospital discharge survivor were € 49,952 including the costs of post-hospital discharge. The total costs per Life Year (LY) gained were € 10,107. Considering 5-year survivors only, the costs per LY gained corresponded to € 9,816, and those per QALY gained corresponded to € 14,487. Including 7 patients with severe neurological condition, costs per LY gained in 5-year survivors increased by 18%, to € 11,566. The authors concluded that patients who leave the hospital following CA without severe neurological disabilities might expect a reasonable long-term survival and quality of life compared with age and gender-matched controls, at sustainable costs for the healthcare system.

In a study conducted in the Netherlands and published in 2004 [125], the authors calculated the healthcare costs for the management of out-of-hospital CA related with the time to shock. Incremental CEA and Monte Carlo simulation was applied to compare scenarios of reduction in time to shock of 2, 4, and 6 minutes. Mean prehospital, in-hospital, and post-hospital costs in the first half-year after CA were € 559, € 6,869 and € 666. Mean costs were € 28,636 per survivor and € 2,384 per non-survivor. Among patients shocked early (n = 24), 46% survived, with costs averaging € 20,253. Of the intermediate group (n = 149), 26% survived, with costs averaging € 31,467. Among patients shocked late (n = 135), 13% survived, with costs averaging € 27,781. The point estimates of the ICER of reduction of time to shock of 2, 4, and 6 minutes compared with baseline were € 17,508, € 14,303, and € 12,708 per life saved, respectively. Costs per survivor were lowest with the shortest time to shock because of shorter stay in the ICU.

The paper by Gage and colleagues [126] reports an estimate of health system resources used in the treatment of in-hospital CA in a British district general hospital, considering both the resources used during the resuscitation attempts and during the post-resuscitation phase in survivors observed during a prospective phase. The average variable cost per resuscitation attempt was £ 195.66; 76.5% was for staff, and 13.1% for drugs and fluids. The average fixed cost per resuscitation attempt was £ 928.81; 12% for capital equipment and 73% for staff training. The average post-resuscitation costs attributable to the CA of the 29 people surviving more than 24 hours after Cardio-Pulmonary Resuscitation (CPR) were estimated to be £ 1589.72. Eighty percent or more of the costs associated with resuscitation were attributable to the provision and maintenance of staff and physical capital. Length of stay was a crucial factor in post-resuscitation expenditure.

As regards Italy, during 2006, a research project was initiated on SCD by the Centro Universitario di Studi in Amministrazione Sanitaria (CUSAS) and the Institute for internal medicine and cardiology of the University of Florence [77]. Among the study objectives, the authors estimated the socio-economic impact due to LYs lost each year to SCD, using net individual median work salary for the basis of the calculation, ranging between € 6,482 million and € 12,216 million, each year. The Authors considered that half of the events occur in patients in whom, due to their high-risk factor, SCD can be accurately predicted and avoided. Accordingly, they estimated the financial investment necessary to prevent SCD in at least these individuals, using the Disease Related Group (DRG) tariff as a proxy for the economic calculation of the procedure costs: an additional investment of € 310 million would have been necessary, representing the 0.33% of the national health budget in the year considered.

DESCRIPTION OF THE TECHNOLOGY

The WCD can be considered an innovative addition to the spectrum of strategies for the prevention of SCD. The WCD is designed for patients at risk of SCD who are not immediate candidates for ICD therapy, and was granted FDA approval in the United States in 2001. In Europe, the LifeVest® was granted a CE mark for its first-generation model, WCD 1, in 2000, and for the latest fifth generation, WCD 4000, in 2011. The indication for the LifeVest® refers primarily to patients aged 18 years or older, at risk of SCA, and who are not candidates for, or refuse an ICD. In the US, the FDA approved the WCD in 2015 for pediatric use in subjects aged 13 years or older who weigh at least 18.75 Kg and have a chest circumference of at least 66 cm.

The WCD device consists of two main components: A) an electrode belt and garment that surrounds the patient's chest, and B) a monitor that the patient wears around the waist or from a shoulder strap (Figure 2).

Washable garments are available in different sizes to suit most patients. The garment is worn around the chest of the patient. The monitor is attached around the waist or carried using the shoulder strap. The device's electrodes are dry and non-adhesive to provide patient comfort. The monitor weighs about 1.4 pounds, making it lightweight and easy to wear. The heart of the patient is permanently monitored. The device contains pushbuttons and indicators for the user, as well as a speaker for sounding alarms and voice prompts. When the device detects a treatable arrhythmia, an alarm sequence begins, giving a conscious patient time to stop the treatment. If the patient holds the two "response" buttons at any time during the treatment sequence, the alarms will stop, and no shocks will be delivered. If the patient does not respond or releases the response buttons, the device continues to give alarms and verbal warnings to bystanders that a treatment shock is about to be delivered. Blue™ Gel within the electrodes is released just prior to delivering the treatment shock in order to avoid burns and to deliver the shock most efficiently. The entire event, from arrhythmia detection to delivery of the shock treatment, typically takes less than one minute. If a treatable arrhythmia persists after the first shock, up to 5 shocks may be given in a treatment sequence.

By providing automatic therapy, the WCD does not depend on a second person to defibrillate, as required with a manual or AED. Unlike the ICD (including both transvenous and subcutaneous devices), the WCD requires no surgical operation, can be provided for a short period of time, is temporary, and is easily removed [34]. The patients need to wear the WCD all day and night long, except while taking a bath or shower.

The use of the WCD requires involvement of the patients, the cardiologist and the hospital and the manufacturer for service and maintenance. Patients need to be trained on how to use the WCD, and it can be helpful if a family member attends the training. Among the things to know, patients need to be made aware that a correct use of the technology requires them to follow a list of instructions on the daily changing and charging of the battery, on the washing of the garments, placing of the electrodes, and pressing the response buttons if prompted. Proper training on the use of the WCD, especially in terms of compliance, is crucial for good outcomes.

The WCD is a rental device and is returned after patient use for cleaning and testing of the device, with reconditioning or repair completed when required. Devices must pass an inspection and testing process in order to be sent to another patient. ZOLL Medical Corporation has territory managers or agents in all the territories so that they guarantee a full service and delivery within 48 hours. ZOLL gathers the data that is absolutely needed in order to provide service to the patient, more specifically, to provide 24/7 technical support to the patient. Every patient is informed on what data is collected and the patient provides his/her written consent.

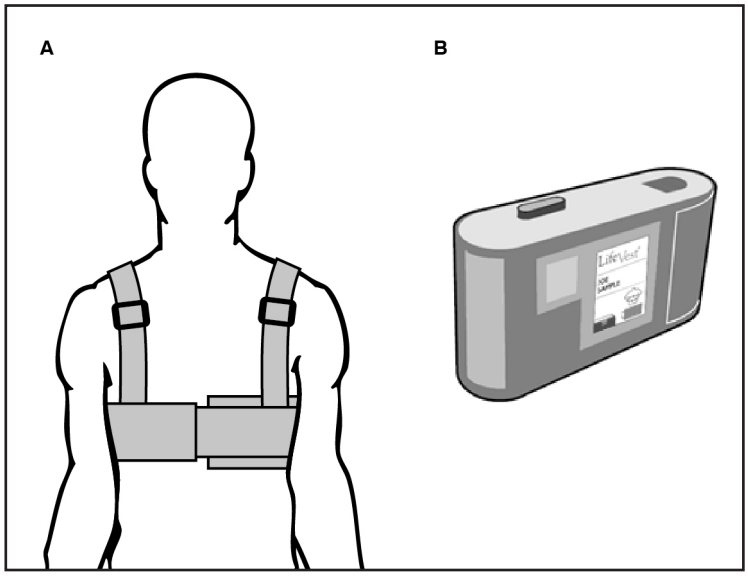

Figure 2. *LifeVest® Device: A) electrode belt and garment that surrounds the patient's chest, and B) monitor that the patient wears around the waist or from a shoulder strap*

Possible and potential indications for WCD use

We report below the list of possible and potential indications for the use of WCD according to Reek et al. [29].

Proposed indications:

- Acute MI with LVEF ≤ 35%;
- Before/after revascularization procedures (Coronary Artery Bypass Graft – CABG/PCI) with LVEF ≤ 35%;
- Recent onset cardiomyopathy NICM or presumed myocarditis with acute heart failure and/or LVEF ≤ 35%;
- Intermittent bridging after ICD removal (e.g., infection);
- Delayed but indicated ICD implantation;
- Bridge to heart transplantation;
- Genetic (e.g., Brugada, Long QT, Short QT, etc.) and congenital inherited heart diseases.

Potentially suitable indications:

- Period of risk stratification in cases with syncope/cardiac arrest of unknown origin; cases with suspected inherited arrhythmia syndromes;
- Protection in patients with Left Ventricular (LV) assist device;
- Potentially dangerous Electrocardiogram (ECG) changes with drugs (e.g., QT prolongation).

However, since the present work focuses on post-MI and ICD explanted patients, details are reported specifically on these subjects. After titles, abstracts and references lists from the full-text publications were screened, we identified and reported in Table I all the eligible full-text publications in which the WCD was used in the target conditions, i.e., patients after MI and or patients with ICD explant. Some papers focused on only these patients (specified as "post-MI" or "explanted" in the "subjects" column), while others involved also patients with different conditions (identified as "Mixed indication"). We excluded from the present report all the publications in which we did not find information on the inclusion of post-MI and/or ICD explanted patients.

Overall, we found documents from original researches reporting on efficacy and/or safety and/or compliance of WCD [5,7,8,11,15,17,18,20-22,25,27,30,32,36,38,39,42,47,49,50,52-54,57], two original researches were on CEAs using a decision model [37,41], a HTA [23], several literature reviews [6,10,12,13,16,19,26,28,29,33,43,44,48,50,55] a meta-analysis [9], and guidelines [14,35,40], recommendations [34], consensus [45,46,56] a letter to the editor [31] and an editorial [24]. Generally, the main messages reported in these publications are that the WCD shows to be beneficial in patients with appropriate indications. The WCD can benefit patients in primary prevention, e.g., in patients after an acute MI, and for secondary prevention, i.e., in patients who survived SCA or sustained Ventricular Fibrillation (VF)/ Ventricular Tachycardia (VT), when the underlying cause might be treated or an implantation is impossible due to comorbidities or with ICD explant when immediate reimplantation is not possible. Because of its strict relationship with effectiveness, attention is to be paid to compliance, which might not be optimal in all patients. Taking into consideration patients' preferences and investing in good patient training can enhance the compliance rates. Finally, despite the many observations from real world use are useful, several authors underline the importance of conducting further research to gain evidence also from randomized controlled trials.

Overall, 5 publications focused on post-MI patients [5,15,38,41,49], 5 on ICD explanted patients [20,21,37,47,56] and the other 45 publications involved subjects with mixed diagnoses.

EFFECTIVENESS, SAFETY AND COMPLIANCE OF WCD IN PATIENTS WITH MI OR WITH ICD EXPLANT

In order to report details on effectiveness, safety and compliance on post-MI and ICD explanted patients, we further selected from Table I and describe in Table III the main characteristics of the original research in which these patients were involved, and their main demographic and clinical characteristics.

In total, 26 original researches were found, of which 4 focus on patients with MI [5,15,38,49] and 3 focus on those with ICD explant [20,21,47], while 19 (73%) studies evaluated the use of the WCD across various indications, specified as "mixed" [7,8,11,17,18,22,25,27,30,32,36,39,42,50-54,57].

Fifteen out of 26 studies were performed in the US and EU [5,7,8,17,20,21,25,39,47,49,51-54,57], 9 in European Countries [11,15,18,22,27,36,38,50,57], 2 in Japan [30,42],1 in Austra-

lia [32] and 1 in Israel [17]. No study was performed in, or included data from Italy. Overall, the observation was on data occurring from 2002 until 2017. Generally, all these studies covered aspects on effectiveness and/or safety and/or compliance and/or on optimization of WCD use in different indications and contexts. Eighteen studies were retrospective [7,8,18,20,21, 25,27,32,36,38,42,47,49,50,51-54], and 7 studies were prospective [11,15,17,22,30,39,57]. One study was a multicenter, randomized, controlled trial where eligible participants with a previous MI were randomly assigned in a 2:1 ratio to receive a WCD plus guideline-directed medical therapy (the device group) or to receive guideline directed medical therapy alone (the control group), at hospital discharge [5].

Tables IV and V show details on effectiveness and/or compliance found from the studies involving only patients with MI or with ICD explant, respectively. We did not find overlapping of participating subjects between these studies. Overall, the selected studies included a highly variable number of participants: overall, we found that patients with MI were 12,916 in total, and those with ICD explant were 10,169 in total. We note that the number of target patients was not specified in 3 studies performed on patients with MI [17,51,57].

Importantly, most of the studies with mixed samples reported results only in their full study sample, hence it was possible to gather specific results on our target patients from few studies. Furthermore, the studies described are difficult to compare because of differences in study designs, definitions of patients and observational periods. For instance, despite the fact that all studies were performed on patients who experienced MI, cohorts of the subjects were heterogeneous, since different characteristics of the study samples were adopted, e.g., in terms of LVEF (≤ 40%, 30% or 35%), time from MI event or revascularization for MI, follow-up (from 6 days to 2.6 years), etc. Accordingly, it was difficult to compare the results between the selected studies. Nevertheless, a general agreement was found from these studies, i.e., patients with MI at high risk of SCD may benefit from WCD therapy, which could be useful for preventing arrhythmic death and for optimizing guideline-driven ICD implantation, or to be used as a bridge to transplantation or ICD implantation in patients with appropriate indications.

Below we describe the main results of the 4 original researches [5,16,38,49] focusing on patients with MI occurring within 3 months.

The most recent study is the VEST randomized clinical trial conducted in the US by Olgin and colleagues [5]. It involved patients hospitalized for an acute MI and with EF <35%, discharged from hospital up to 7 days earlier. The patients were randomly assigned to receive WCD plus guideline-directed therapy (the device group involving 1524 patients) or to receive only guideline-directed therapy (the control group involving 778 patients). Participants in the device group wore the device for a median of 18.0 hours per day (interquartile range, 3.8 to 22.7). Arrhythmic death occurred in 1.6% of the participants in the device group and in 2.4% of those in the control group (relative risk = 0.67; 95% CI = 0.37-1.21; p=0.18). Death from any cause occurred in 3.1% of the participants in the device group and in 4.9% of those in the control group (relative risk = 0.64; 95% CI = 0.43-0.98; uncorrected p=0.04), and non-arrhythmic death in 1.4% and 2.2%, respectively (relative risk = 0.63; 95% CI = 0.33-1.19; uncorrected p=0.15). Of the 48 participants in the device group who died, 12 were wearing the device at the time of death. A total of 20 participants in the device group (1.3%) received an appropriate shock, and 9 (0.6%) received an inappropriate shock. Among the participants, 25 reported adjudicated arrhythmic death, 9 were wearing the WCD at the time of death, 4 of whom received appropriate shocks and 5 of whom had no ventricular tachyarrhythmias. In order to assess impact of wearing the WCD on sudden death, non-arrhythmic death, and total mortality, an "as treated" analysis was performed in the VEST trial to assess event rates per 100 person-months of wearing the WCD compared to not wearing the WCD and compared the two rates using Poisson regression. Based on this analysis, the VEST trial reported a total mortality rate of 0.50 per 100 person-months of patients wearing the device, and 1.91 per 100 person-months of patients not wearing the device, reporting a higher efficacy of VEST (rate ratio = 0.26; 95% CI = 0.14-0.48; Bonferroni corrected p<0.001). A study conducted in France [15], reported that WCD was life-saving in one patient (1/24) with prompt defibrillation shock delivery. During a mean wearing period of 3.0 ± 1.3 months, two episodes of VA occurred in two patients (8.3%): one successfully treated with WCD shock and one with spontaneous termination. The mean and median daily use of the WCD in these patients was 21.5 hours and 23.5 hours a day, respectively. The Authors' conclusions were that a high rate of VA occurred during the early period following myocardial revascularization with PCI in patients with low LVEF. The WCD was life-saving in 1 patient, considering also who used it <10 hours per day.

Kondo et al. [38], in their study conducted in Germany, analyzed the effectiveness of the WCD therapy in early post-MI patients. The median length of use was 33 days (20-67 days),

Reference	Country, period of data collection	Aim	Information on total study sample (unless otherwise specified)				
			Indication	Clinical characteristics of study sample	N	Male, %	Age Mean ± SD (Median, min-max)
Olgin et al. 2018 [5]	US, 2008-2017	To determine the efficacy of a WCD during the period before ICDs (in patients who have had a MI and have a reduced ejection fraction)	Post AMI	Patients who had been hospitalized with an AMI and who had an ejection fraction ≤ 35% or less	2,302	73.5%	60.9 ± 12.6 (Device Group) 61.4 ± 12.3 (Control Group)
Ellenbogen et al. 2018 [7]	US, 2011-2015	To assess the outcome of in-hospital VT and/ or VF arrest by time of day, day of week, and within-hospital location when using a WCD	Mixed: 14% explanted, 40% with ≥1 MI	Patients with in-hospital VT and VF arrest when using a WCD (72.0% and 11.0% primary and secondary)	234	74.0%	65 ± 12 (NR, NR)
Leyton-Mange et al. 2018 [8]	US, 2012-2013	To investigate all WCD prescriptions over 2-year period	Mixed: 23% explanted	Patients with a prescription of WCD at 2 large academic medical centers	147	80.0%	59 ± 14 (NR, NR)
Röger et al. 2018 [11]	Germany, 2012-2016	To determine the value of the WCD for therapy optimization of HF patients	Mixed: 14% explanted	Patients receiving a WCD at the tertiary care University Center	105	78.1% (93.3% in explanted pts)	NR ± NR (60, 26-79) (62, 29-79 in explanted pts)
Barraud et al. 2017 [15]	France, 2015-2016	To evaluate VA occurrence rate and patient's compliance with the WCD (90 days after myocardial revascularization)	Post AMI	LVEF <30% who had recent (<7 days) myocardial revascularization with PCI for an acute MI (100% primary prevention)	24	80.0 %	56 ± 10 (NR, NR)
Barsheshet et al. 2017 [17]	US and Israel, 2016	To provide clinical data on safety and efficacy of the WCD, data on VT and to assess a management strategy	Mixed: % NR	Patients with NYHA class III or IV during the past month with ≥1 hospitalization for cardiac decongestion and stabilization; advanced HF managed in an outpatient setting; AMI and Killip Class III/IV, coronary revascularization within 3 calendar months prior to enrollment; newly diagnosed HF of non-ischemic origin, or patients awaiting cardiac transplantation	75	69.0%	51 ± 14 (NR,NR)
Beiert et al. 2017 [18]	Germany, 2012-2015	To analyze the use and effectiveness of WCD in different patient populations delineating predictors of VT/VF occurrence or WCD shock delivery	Mixed: 11% explanted	Patients with newly diagnosed LVEF ≤35% and/or other high-risk criteria for occurrence of VT/VF and screened for the need of temporal protection by WCD	114	73.7% (92.3% in explanted pts)	NR ± NR (58, 46-71) (65, 58, 73 in explanted pts)
Castro et al. 2017 [20]	US, 2012-2015	To investigate the management and outcomes of patients with WCD (serious arrhythmic complications and reinfection)	Explanted	Patients underwent ICD or CRT-D removal due to local or systemic infection (47.6% and 52.4% primary and secondary)	21	76.0 %	65 ± 8 (NR, NR)
Ellenbogen et al. 2017 [21]	US, 2002-2014	To evaluate WCD use among ICD explant patients (in terms of VT/VF risk after ICD explant and VT/VF risk trend over time)	Explanted	Patients underwent ICD removal due to device-related infections and were prescribed a WCD	8,058	75.0%	62 ± 14 (NR, NR)
Erath et al. 2017 [22]	Germany, 2012-2015	To evaluate the efficacy, safety, and compliance of/to WCD use and subsequent medium-term outcome	Mixed: 25% explanted	Patients at high risk for VT/VF receiving a WCD	102	73.0% (72.0% in explanted pts)	59 ± 11 (61 ± 16 in explanted pts)
Naniwadekar et al. 2017 [25]	US, 2002-2015	To evaluate the efficacy and compliance of WCD	Mixed: 8% explanted 22% with AMI	Patients prescribed a WCD with recent MI, post-revascularization, with LVEF ≤35%, newly diagnosed NICM, VT/VF while awaiting ICD implantation, following ICD explant or genetic predisposition to SCD	140	62%	58 ± 16
Quast et al. 2017 [27]	Netherlands, 2009-2016	To describe the current use, number of prevented ICD implants and costs of WCD therapy	Mixed: 29.1% explanted	Patients, from two large tertiary heart centers, who were treated with the WCD.	79	74.9%	NR ± NR (54, 44-64)
Sasaki et al. 2017 [30]	Japan, 2014-2015	To describe the use of WCD in-hospital acute phase care	Mixed: 46% with prior MI	Patients at high risk of sudden arrhythmic death for a limited period, not candidates for an ICD and prescribed a WCD	50	92.0%	NR ± NR (56, 9-66)
Bhaskaran et al. 2016 [32]	Australia, 2013	To report the Australian experience with WCD	Mixed: 37.5% explanted	Patients with VT and VF prescribed a WCD	8	NR	NR

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Reference	Country, period of data collection	Aim	Information on total study sample (unless otherwise specified)				
			Indication	Clinical characteristics of study sample	N	Male, %	Age Mean ± SD (Median, min-max)
Wäßnig et al. 2016 [36]	Germany, 2010-2013	To evaluate the use and effectiveness of WCD in preventing SD caused by VT or fibrillation	Mixed: 11.9% explanted	Cardiac patients currently receiving a WCD prescription (100% primary prevention)	6,043	78.5%	NR ± NR (57, 48-68)
Kondo et al. 2015 [38]	Germany, 2010-2014	To analyze the effectiveness of WCD (in terms of shock therapy from WCD, shock success for VF, LVEF improvement, compliance therapy) in early post- MI	Post-AMI	LVEF ≤35% and VT in the early post-MI phase who received a WCD (in the first 3 months post-MI) (48.5% and 51.5% primary and secondary prevention)	24	92.0%	69 ± 12 (NR, NR)
Kutyifa et al. 2015 [39]	US, 2011-2014	To characterize the patients prescribed with a WCD, to assess the risk for sustained VT and to identify the rate of EF improvement and subsequent ICD	Mixed: 40% with previous MI or CAD	Patients who had ischemic cardiomyopathy with previous MI or known CAD with a high risk for SC; Patients who had NICM with no known CAD and patients who had congenital/ inherited heart disease	2,000	70.0%	NR ± NR (62, IR 16)
Sasaki et al. 2014 [42]	Japan, 2014	To report patient compliance, and clinical efficacy of WCD	Mixed: 55.5% with > 1 MI	Patients at high risk of life-threatening VA prescribed a WCD	9	78.0%	NR ± NR (56, 51-63)
Tanawuttiwat et al. 2014 [47]	US, 2005-2009	To evaluate the effectiveness of WCD (in terms of shock, VT, mortality and compliance)	Explanted	Patients underwent ICD removal due to device-related infections and were prescribed a WCD in two tertiary cardiac centers	97	80.0%	65 ± 13 (NR, NR)
Epstein et al. 2013 [49]	US, 2005-2011	To describe usage of the WCD during mandated waiting periods following MI for patients at high risk for SCA	Post-AMI	LVEF ≤35% with a recent MI who had a WCD prescribed in the first 3 months post-MI or given an ICD-9v diagnostic code (acute MI)	8,453	73.0%	63 ± 13 (NR, NR)
Klein et al. 2013 [50]	Germany, 2013	To report the current clinical experience with WCD	Mixed: 39.0% with AMI, 10.0% explanted	Patients with AMI with LVEF ≤35% who received the WCD within 3-5 days after AMI	354	NR	NR
Zishiri et al. 2013 [51]	US, 2002-2009	To determine mortality risk in post revascularization patients with LVEF≤35%, to compare survival with those discharged with the WCD	Mixed: 1,283 with >1 prior MI event(s) out of 1,951 patients receiving PCI in the No WCD cohort. Data on MI patients not available for the WCD cohorts.	Hospital survivors after CABG surgery or PCI revascularization with LVEF≤35%	4,958	75.1%	66.6 ± 11.6 67.6 (54.0-78.5)
Kao et al. 2012 [52]	US, 2007-2010	To determine the incidence of SCD in selected population, and the efficacy of early defibrillation by a WCD	Mixed: 21.8% with prior MI	Patients listed for heart transplantation, with VT or LVEF ≤40%, and/or receiving inotropes	82	72.0%	61 ± 11.1 (NR, NR)
Chung et al. 2010 [53]	US, 2002-2006	To determine patient compliance and effectiveness of antiarrhythmic treatment by WCD	Mixed: 23.4% explanted 12.5% with recent or previous MI	Patients issued a WCD after market release in the US, entered into a database maintained by the manufacturer	2,720	74.0%	59 ± 15 (NR, NR)
Dillon et al. 2010 [54]	US, 2006	To determine the efficacy of the algorithm outside a clinical trial	Mixed: 31.4% with acute or old MI, 21.2% explanted	WCD detection algorithm has a low risk of inappropriate shocks	2,105	69.9%	NR ± NR (60, 12-93)
Feldman et al. 2004 [57]	US and Germany, 2003	To assess the effectiveness of the WCD	Mixed: % NR	The WEARIT Study enrolled ambulatory patients with NYHA functional Class III or IV, a LVEF <30%, VA within 48 hours of CABG but unable to receive an ICD, or ICD candidates who not expected to receive a device for at least 4 months. The BIROAD study enrolled patients who had experienced a recent MI that was complicated by VA, or an episode of syncope, or SCA but were not candidates for an ICD.	289	82.0%	55 ± 12 (NR, NR)

Table III. *Description of original researches on WCD in patients with MI and/or ICD explanted*

NR = Not Reported at all in the publication; VA = Ventricular Arrhythmia WCD = Wearable Cardioverter-Defibrillator AMI = Acute Myocardial Infarction LVEF = Left Ventricular Ejection Fraction PCI = Percutaneous coronary intervention MI = Myocardial Infarction VT/VF = Ventricular Tachycardia/ Ventricular Fibrillation SCA = Sudden Cardiac Arrest ICD = Implantable Cardioverter Defibrillators ICD/CRT-D = Implantable Cardiac Resynchronization Therapy CIEDs = Cardiovascular Implantable Electronic Devices HF = Heart Failure NICM = Non-Ischemic Cardiomyopathy EHRA EP = European Heart Rhythm Association European electrophysiology SD = Sudden Death SWIFT = Study of the Wearable Defibrillator In Advanced Heart-Failure Patients NYHA = New York Heart Association CAD Coronary Artery Disease

and the median daily WCD use was 23.1 h/day (range: 21.6-23.6 h/day). The use of WCD contributed to the goal of optimized guideline-driven ICD implantations, avoiding 42% (10 patients) of unnecessary devices. None of the patients died during the WCD therapy; however, two patients (8.3%) had a fatal non-arrhythmic event within 3 months after MI. The authors concluded that the WCD contributed to the goal of optimized guideline-driven ICD implantations. Furthermore, according to the opinion of most patients, the device was easy to handle after sufficient training before receiving the device.

Epstein et al. [49] from US retrospectively assessed the benefit of WCD use in 8,453 patients, from the database maintained by the manufacturer for American regulatory. Median daily use of WCD was 21.8 h per day and the mean length of use was 69 ± 61 days (median 57 days). In total 133 (1.6%) patients were appropriately treated with WCD and received 309 (3.7%) appropriate shocks (1.6%) with a resulting survival of 95% in revascularized and 84% in non-revascularized patients. The rate of inappropriate treatment was <1%. Ninety-six percent of the patients received the shock in the first 3 months of WCD therapy and 75% in the first month.

The actual survival analysis of all patients treated with a WCD showed that in the 3-, 6-, and 12-month intervals following WCD application, cumulative survival was 96%, 94%, and 93%, respectively, while for patients treated with appropriate shocks in the same 3-, 6-, and 12-month intervals, cumulative survival was 73%, 70%, and 65%, respectively. The authors concluded that 1.4% of patients may be successfully treated in the first 3 months with a resuscitation survival rate of 91%, implying that a select group of patients may benefit from defibrillation early after MI, particularly during the first 30 days following hospital discharge. The WCD may benefit individual patients selected for high risk of SCA early post-MI, particularly during the first 30 days following hospital discharge.

Results on WCD in patients undergoing ICD explant are reported in Table V. Overall, these studies recognized that the WCD could prevent SCD in patients who underwent ICD removals for CDI, however their results appeared difficult to compare and synthesize in terms of outcomes. Only 3 studies [20,21,47] were restricted to patients who were discharged after ICD removal, described below.

Castro and colleagues [20] reported data on WCD use in 24 German patients, who underwent ICD or Cardiac Resynchronization Therapy-Defibrillator (CRT-D) removal due to device-related local or systemic infections, during 392 ± 206 days. In contrast to previous published data by Tanawuttiwat et al. and Chung et al. [47,53], the authors observed no inappropriate shocks in their study. However, consistent with other studies [39,47,53], the mean daily wear time was 22.0 (15-24) hours. Castro and colleagues concluded that the WCD was a safe, comfortable and cost-effective bridging solution for the observed patients, with a survival rate of 100% and no recurrent device infection after a mean follow-up time of 454 days [20].

The biggest cohort of patients with ICD explant were reported from Ellenbogen et al. (n=8,058) [21]. While wearing the WCD, 334 patients (4%) experienced 406 VT/VF events, of which 348 events were treated. Shocks were averted in 54 VT/VF events by conscious patients. A low inappropriate shock rate was reported, similar to other studies [39]. After ICD explant, 78% of patients used the WCD for up to 3 months. Of the 22% who continued wearing the device after 3 months, 6% continued beyond 6 months, and 1% continued to use the WCD for more than 1 year. Previously published articles reported a mean length of use in all WCD patients of about 2 months [53]. Conclusions by Ellenbogen and colleagues [21] are that the WCD was effective against VT/VF mortality, with a low incidence of unnecessary shocks. Clinicians used the device as a short-term (up to 12 weeks) solution for SCA protection in the majority of patients, although 22% of patients used the tool for longer terms (>3 months). This device can offer clinician's flexibility in managing post-ICD explant patients during a vulnerable period until a long-term risk management strategy can be implemented.

Tanawuttiwat et al. [47] performed a retrospective study in patients who underwent ICD removal due to cardiac device infections at two American referral centers. Clinical characteristics and device information on 97 patients were analyzed. The median daily WCD use was 20 hours/day and the median length of use was 21 days. Three patients were shocked by the WCD: 2 patients had four episodes of sustained VT, successfully terminated by the WCD, while the third patient experienced two inappropriate treatments due to oversensitivity of the signal artifact. Three patients experienced sudden death outside the hospital while not wearing the device. Five patients died while hospitalized. The authors concluded that the WCD is useful in protecting patients during the gap between ICD removal and reimplantation. The mortality in this case series was 8.2%. All deaths occurred when the WCD was not in use;

Reference Study sample	Study sample, total number	N of target patients (post-MI)	Obs. Period Mean ± SD (Median)	Appropriate Shock Rate, % of pts	Inappropriate Shock Rate, % of pts	Ventricular Arrhythmia, % of pts	Survival, %	Compliance, h/d	Cumulative wearing time	Key message and conclusion on target patients
								Mean ± SD (Median, min-max)		
Olgin et al. 2018 [5]	2,302	2,302	84.3 ± 15.6 days	1.3 % (Device Group) vs 0.1 % (Control Group)	0.6% % (Device Group) vs 0.0 % (Control Group)	1.6 % (Device Group) vs 2.6 % (Control Group)	96.9 % (Device Group) vs 95.1% (Control Group)	14.0 (9.3) 18.0 (3.8-22.7)	Compliance is based on wearing the WCD for the full 90 days of study	WCD was effective at converting ventricular tachyarrhythmias, with successful conversion in patients who received an appropriate shock but did not lead to a significantly lower rate of the primary outcome of arrhythmic death than control.
Ellenbogen et al. 2018 [7]	234	93	6 days	NS	NS	NS	NS	NR	NR	NS
Barsheshet et al. 2017 [17]	75	NR	2.6 ± 1.0 years	NS	NS	NS	NS	NS	NS	NS
Barraud et al. 2017 [15]	24	24	3 months	4.1% (reported prompt defibrillation shock) delivery.	0.0%	8.3%	NR	21.5 (23.5, NR-NR)	3.0 (1.3 months)	WCD was a life-saving therapy in 1 target patient (4,1%), despite the fact that it was worn <10 h/day. However, patients' education can improve it the time of wearing.
Naniwadekar et al. 2017 [25]	140	31	NR	NS	NS	NS	NS	NS	NS	NS
Sasaki et al. 2017 [30]	50	23	NR	NS	NS	NS	NS	NS	NS	NS
Kondo et al. 2015 [38]	24	24	(8 months)	8.3%	0%	NR	0%	Mean value NR (23.1, 21.6-23.6)	Mean value NR (33, 20-67) days	WCD contributed to the goal of an optimized guideline-driven ICD implantation. Most of patients agreed that the device was easy to handle after sufficient training before receiving the device.
Kutyifa et al. 2015 [39]	2,000	805	NR	NS	NS	NS	NS	NS	NS	Compliance of WCD was very high and unrelated to disease etiology.
Sasaki et al. 2014 [42]	9	5	90 days	NS	NS	NS	NS	NS	NS	All patients were able to manage the battery system of the WCD by themselves.
Epstein et al. 2013 [49]	8,453	8,453	(24.7 months)	1.6%	1.3%	1.2%	93% (12-month intervals following the WCD (Cause NR)	Mean value NR (21.8, NR)	69 ± 61 days (57, NR)	During the 40-day and 3-month waiting periods in patients post-MI, the WCD successfully treated SCA in 1.4%, and the risk was highest in the first month of WCD use. The WCD may benefit individual patients selected for high risk of SCA early post-MI, particularly during the first 30 days following hospital discharge
Klein et al. 2013 [50]	354	138	NR	5.0%	NS	NS	NS	91.0 ± 13.0 days (NR, NR)	NS	LVEF (reassessed after 3 months) in patients with WCD was found significantly improved (to a mean LVEF of 33.6%). In all patients with non-improved LVEF, ICDs were implanted.
Zishiri et al. 2013 [51]	4,958	NR	3.2 ± 2.3 years	NS	NS	NS	NS	NR	NR	Non-arrhythmic deaths, overall mortality early after MI or revascularization in subjects with ICD implants, inflammatory reactions, or infectious complications associated with ICDs, could be avoided using a noninvasive bridging strategy. In this study, data on patients with prior MI event(s) are not available for the WCD cohorts. It is known that 1,283 patients with >1 prior MI event(s) out of 1,951 receiving PCI were present in the No WCD cohort. No further details are available on these patients.

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Reference Study sample	Study sample, total number	N of target patients (post-MI)	Obs. Period Mean ± SD (Median)	Appropriate Shock Rate, % of pts	Inappropriate Shock Rate, % of pts	Ventricular Arrhythmia, % of pts	Survival, %	Compliance, h/d	Cumulative wearing time	Key message and conclusion on target patients
								Mean ± SD (Median, min-max)		
Kao et al. 2012 [52]	82	17	from the time of WCD start until death (for those who died) or final date of data collection (for those who were still alive)	0.0%	0.0%	0.0%	100.0% (90 days)	NS	NS	NS
Chung et al. 2010 [53]	2,720	341	NR	2.9%	2.0%	NS	97.4% (VT/VF and Non-VT/VF deaths)	7.8 ± 38.9 days (NR, NR)	NS	The shocked events occurred in all non-traditional ICD indications groups, except the recent MI with LVEF>35% group. In patients with LVEF ≤ 35%, 12 events in 10 patients and 2 deaths occurred.
Dillon et al. 2010 [54]	2,105	660	NR	NS	NS	NS	NS	NS	NS	NS
Feldman et al. 2004 [57]	289	NR	NR	NS	NS	NS	NS	NS	NS	NS

Table IV. *Effectiveness and compliance of WCD in patients with MI from original studies*

NR = Not Reported at all in the publication; NS = not specified on the target patients SCA = Sudden Cardiac Arrest VT/VF = Ventricular Tachycardia/ Ventricular Fibrillation WCD = Wearable Cardioverter-Defibrillator MI = Myocardial Infarction MI = Myocardial Infarction

Reference Study sample	Study sample, total number	N of target patients (explanted)	Obs. Period Mean ± SD (Median)	Appropriate Shock Rate, % of pts	Inappropriate Shock Rate, % of pts	Ventricular arrhythmia, % of pts	Survival, %	Compliance (h/d)	Cumulative wearing time	Key message and conclusion on target patients
								Mean ± SD (Median, min-max)		
Ellenbogen et al. 2018 [7]	234	32	(6 days)	NS	NS	NS	NS	NR	NR	NS
Leyton-Mange et al. 2018 [8]	147	34	NR	0.7%	NR	2.0%	NR	Mean value NR (21.0, 15.0-22.8)	Mean value NR 50 (0-356) days	The wear duration varied by prescribing indication. The mean duration in explanted patients was lower than 50 days.
Röger et al. 2018 [11]	105	15	18.6 ± 12.3 months	NS	NS	NS	93.3% (non-arrhythmic reasons) 100.0% (arrhythmic reasons)	23.1 ± 1.1 (NR, NR)	92.5 ± 87.0 (NR, NR)	Patients with previous explanted ICDs had a higher mean daily use than did patients in the other patient groups. This was caused by the higher risk awareness in this patient group.
Beiert et al. 2017 [18]	114	13	NR	7.7%	0.0%	0.0%	100.0%	Mean value NR (23.4, 22.4-23.7)	Mean value NR (40, 12-64 days)	ICD explant due to CIEDI can be protected by a WCD
Castro et al. 2017 [20]	21	21	392 ± 206 days	4.7%	0.0%	4.7%	100.0% (procedures related death or other causes)	22.0, 15.0-24.0 (NR, NR)	NR	WCD seems to be a valuable bridging option for patients with ICD or CRT-D infections, showing no recurrent device infection
Ellenbogen et al. 2017 [21]	8,058	8,058	88 ± 148 days	4.2%	2.0%	4.0%	66.0% (fatal asystole and VT/VF)	NR	Mean value NR (53, 25-94 days)	WCD reported a high efficacy for protecting patients from VT/VF and it can be used as an ICD alternative in post-ICD explant patients.

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Reference Study sample	Study sample, total number	N of target patients (explanted)	Obs. Period Mean ± SD (Median)	Appropriate Shock Rate, % of pts	Inappropriate Shock Rate, % of pts	Ventricular arrhythmia, % of pts	Survival, %	Compliance (h/d)	Cumulative wearing time	Key message and conclusion on target patients
								Mean ± SD (Median, min-max)		
Erath et al. 2017 [22]	102	25	11 ± 8 months	NS	NS	NS	88.0% (cardiac and non-cardiac reasons)	23.7, 16.8-24.0 (NR, NR)	54, 1-131 days (NR, NR)	NS
Naniwadekar et al. 2017 [25]	140	11	NR	NS	NS	NS	NS	NS	NS	NS
Quast et al. 2017 [27]	79	23	(1.6, 0.1-3.3 years).	NS	NS	NS	96% (reason not specified)	NS	NS	WCD was safe and effective in outpatient setting for patients at high risk for SCD. Median WCD wear in patients bridging to ICD implant in case of device-related infection in this cohort is longer than the period of treatment recommended by current guidelines. This can be explained by the fact that these patients are not hospitalized, therefore there is no need for minimal recovery time to re-implantation to reduce the period of hospitalization
Bhaskaran et al. 2016 [32]	8	3	NR	0.0%	0.0%	NS	100.0%	23.5, 23.0-24.0 (NR, NR)	64 (18-119) days (NR, NR)	WCD was well tolerated and effective for SCD prevention in patients who are temporarily not suitable for ICD. The potential benefits of WCD, particularly allowing patients at risk for SCD but who cannot have an ICD implanted, to avoid the costs of prolonged hospitalization and be treated in an outpatient setting. The patients with explanted infected ICDs were able to be treated as outpatients while still having antibiotics because of the protection afforded by the jacket.
Wäßnig et al. 2016 [36]	6,043	717	NR	NS	NS	NS	99.4% (caused by VF or VT or asystole)	NR (23.4, 22.0-23.8)	NR (48, 27-78 days)	Half of the deaths occurred among ICD explant. WCD use was given for use directly after an ICD explant.
Tanawuttiwat et al. 2014 [47]	97	97	NR	3.1%	1.0%	2.1%	91.8%	Mean value NR (20.0, NR)	Mean value NR (21 days, NR)	WCD can prevent SCD in patients who underwent ICD removals for CDI. Compliance of WCD was relatively acceptable
Klein et al. 2013 [50]	354	35	NR	11.0%	NS	NS	NS	NS	NS	The WCD protects the patient during the time of temporary interruption of ICD therapy.
Chung et al. 2010 [53]	2,720	638	NR	5.2%	1.41%	NS	98.6% (VT/VF and Non-VT/VF deaths)	NS	56 ± 78 days (NR, NR)	WCD recorded events in the groups with ICD explant and history of VT/VF while awaiting ICD implant (49 events were reported in 33 patients)
Dillon et al. 2010 [54]	2,105	447	NR	NS	NS	NS	NS	NS	NS	NS

Table V. *Effectiveness and compliance of WCD in explanted patients, from original studies*

NR = Not Reported at all in the publication; NS = not specified on the target patients; VT/VF = Ventricular Tachycardia/ Ventricular Fibrillation; WCD = Wearable Cardioverter-Defibrillator; AMI = Acute Myocardial Infarction; ICD = Implantable Cardioverter Defibrillators; HF = Heart Failure; SCD = Sudden Cardiac Death; MI = Myocardial Infarction

Reference	AEs (%)			Frequency of discontinuation due to AEs (%)	Frequency of discontinuation due to death (%)
	Skin rash & itching	False alarms	Palpitations, light-headedness, & fainting		
Olgin et al. 2018 [5]	Rash:15.3 % (Device Group) vs 7.1% (Control Group) Itching: 17.2 % (Device Group) vs 6.4% (Control Group) (p<0.001)	Among 41 participants with an alarm indicating asystole, 6 events (all in the Device Group) were adjudicated as having had a true asystole event. No data for false alarms indicating arrhythmia were reported	Palpitations: 23.1% (Device Group) vs 25.7% (Control Group) Headache: 18.3% (Device Group) vs 19.2% (Control Group) Fainting: 4.2% (Device Group) vs 5.1% (Control Group)	NR	NR
Barraud et al. 2017 [16]	NR	0	NR	NR	NR
Kondo et al. 2015 [38]	NR	NR	NR	NR	0
Epstein et al. 2013 [49]	NR	NR	NR	NR	NR
Castro et al. 2017 [20]	0	0	NR	0	NR
Ellenbogen et al. 2017 [21]	NR	NR	NR	5,620/8,031 patients discontinued WCD for medical reason	523/8,031 patients discontinued use of WCD for death
Tanawuttiwat et al. 2014 [47]	NR	1/97	NR	16/97 were non-compliant and 9/97 were uncomfortable with wearing WCD. fourteen patients use the WCD for < 24 hours	No deaths directly related to WCD were reported
Ellenbogen et al. 2018 [7]	NR	NR	NR	NR	NR
Leyton-Mange et al. 2018 [8]	NR	NR	NR	NS	NS
Röger et al. 2018 [11]	NR	NS	NR	NS	NS
Erath et al. 2017 [22]	NS	NS	NS	NS	Three deaths not directly related to WCD were reported
Naniwadekar et al. 2017 [25]	NR	NS	NR	NS	NS
Quast et al. 2017 [27]	NR	NS	NR	NR	NS
Sasaki et al. 2017 [30]	NR	NR	NR	NR	NR
Bhaskaran et al. 2016 [32]	NR	NS	NR	NR	0
Wäßnig et al. 2016 [36]	NR	NS	NS	NR	NR
Beiert et al. 2017 [18]	NR	69.2%	NR	NR	0%
Sasaki et al. 2014 [42]	NR	NS	NR	NR	NS
Kao et al. 2012 [52]	NR	0%	NR	NR	0%
Chung et al. 2010 [53]	NR	NS	NR	NS	NS
Barsheshet et al. 2017 [17]	NR	NS	NR	NS	NS
Feldman et al. 2004 [57]	NR	NS	NR	NS	NS
Kutyifa et al. 2015 [39]	NR	NS	NR	NS	NS
Klein et al. 2013 [50]	NR	NS	NR	NS	NS
Dillon et al. 2010 [54]	NR	NS	NR	NS	NS

Table VI. *Safety of WCD for patients with MI and/or with ICD explant*
AE = Adverse Event; NR = Not Reported at all in the publication; NS = Not specified in target patients (post-MI or ICD explanted patients)

instead, no deaths occurred while a WCD was worn. Compliance in general was acceptable. Three SCA events occurred in one patient, and one conscious sustained VT occurred in another. Both were successfully treated with a shock by the WCD.

A further aspect to be considered as a possible benefit of the WCD is the potential capability to improve the selection of patients suitable to ICD Implantation. For instance, in Kutyifa and colleagues [39] showed a proportion of 40% of patients that did not need an ICD after the evaluation phase with the WCD.

An important aspect to be considered regarding WCD treatment is the patients' compliance, which can significantly influence the effectiveness. Generally, in the selected papers, we found positive findings on compliance, although it was not found very satisfactory in all of them [16,53]. For instance, Chung et al. [53] found that half of the patients wore the defibrillator continuously. Instead, according to other authors [16], patient education by specialized health caregivers can help to achieve good compliance to therapy, since patient's compliance with the WCD is closely linked to the understanding and knowledge of their cardiac disease as well as potential benefits associated with the appropriate use of the device. Appropriate training and education of the patient on how to properly wear the WCD, change the battery and respond to device alarms is a crucial part of the patient's education.

Overall, good compliance rates were found especially in recent studies: e.g., the median daily wear time was 23.1 and 22.5 hours from the observation of patients involved in registries [36] and [39], respectively. This may be the result of increased comfort seen with newer generations of WCDs, which are smaller and weigh less than the initial WCDs used in earlier studies.

Finally, details on safety are reported in Table VI, which shows that few results were found from the literature on safety related with the use of WCD by subjects with MI or with ICD explant.

ECONOMIC IMPLICATIONS OF WCD

In the context of constrained health care resource availability, it is important to assess the ratio between costs and effectiveness, as well as to identify the driving factors that influence the upper and lower bounds of sensitivity when evaluating the use of WCD therapy in patients who are at risk of SCD and SCA. The results of economic studies will be useful for health policy and access stakeholders making reimbursement and funding decisions.

We found 4 studies assessing the cost and cost-effectiveness of WCD use, published between 2015 and 2017. Overall, the WCD reported a good value for money. However, some differences in the results of the available studies can be explained by the fact that different methods were used, heterogeneous populations were involved and they were conducted in different settings, using different perspectives, different time horizons and analyzing different types of data.

Among the main differences, 1 study was targeted to subjects with ICD explant [37], 1 focused on patients with early MI [41], while the other 2 studies involved subjects with different indications including cases of ICD explant due to infection and those who are early post-MI [27,32].

The two studies by Healy & Carrillo [37] on patients who underwent ICD removal and by Sanders et al. [41] on early post-MI patients, were conducted using a Markov economic model applied in the US healthcare system, adopting the perspective of the society [37] and the perspective of Medicare [41]. Accordingly, Healy & Carrillo [37] analyzed direct costs (e.g., cost of the WCD device, hospital costs, cost of laboratory tests, cost of follow-up visits and costs related with ICD implantation and management) and indirect costs (loss of income and loss of productivity for premature death), while Sanders et al. [41] included only direct costs. A lifetime simulation period was considered in the model. Healy & Carrillo [37] estimated the cost effectiveness of the WCD in patients who underwent ICD explant and were deemed to require reimplantation due to SCA risk but in whom immediate reimplantation was not possible. For these patients, the authors assumed 4 management options: 1) discharge home with WCD until reimplantation; 2) discharge home without WCD until reimplantation; 3) discharge to a Skilled Nursing Facility (SNF) without a WCD until reimplantation; and 4) remain in the hospital without WCD until reimplantation. The efficacy of alternatives was reported in terms of SCA mortality, non-SCA mortality and post-reimplantation mortality. QALYs and LYs gained were used as parameters of effectiveness between the alternative strategies. In the analysis by Healy & Carrillo, the ICER of the WCD strategy, compared to discharge home without a WCD was $ 20,300 per LY or $ 26,436 per QALY gained [37]. In the other options,

discharge home with WCD versus discharge to a SNF without WCD and versus in-hospital stay without WCD, was dominant; since WCD was less costly and more effective than alternatives. One-way and two-way sensitivity analyses were performed to account for result uncertainties. SCA event rate, WCD treatment efficacy and time to reimplantation had the highest impact on the ICER. Overall, WCD cost effectiveness decreased as SCA event rates decreased. The WCD cost effectiveness is also positively impacted by higher WCD efficacy. The ICER ranged between $ 15,392/QALY and > $ 50,000/QALY if the WCD efficacy of 95% and <69% was considered, respectively. Further, with regard to time to reimplantation, the WCD remained cost-effective, considering 5.6% 2-month SCA risk, as long as the time to reimplantation was at least 2 weeks.

Similar to the previous one, another study explored the cost-effectiveness of WCD in early post-MI patients [41]. The model tracked a cohort of patients during their lifetime who were considered at an increased risk for SCD but not yet eligible for prophylactic ICD implantation since they were within either 40 days from their MI or 90 days from coronary revascularization. Patients received either the WCD or current standard of care (no therapy). The authors included directs costs associated with WCD use, emergency medical services, ICD implantation and follow-up. They assumed $ 2,754/month for WCD patients and an additional physician visit for patients who received an inappropriate shock. A cost of $ 18,500 for patients within the standard of care strategy and subsequent hospitalization was considered. Additional costs related to ICD implantation ($ 36,034), generator replacement ($ 27,271), and lead replacement ($ 15,595) were included. The model results were reported in terms of costs, quality of life, survival and the incremental cost-effectiveness of WCD, compared with usual care. In the Sanders analyses, the WCD strategy was more expensive than usual care (incremental cost of $ 11,503), but improved life expectancy by 0.261 life years or 0.190 QALYs. The incremental cost effectiveness of the WCD was $ 44,100/LY or $ 60,600/QALY.

The authors explored the sensitivity of model predictions to uncertainty in model parameters in sensitivity analysis, using ranges of values for key parameters. Overall, the ICER of WCD was more favorable in higher-risk patients. With higher probability of SCA, the WCD was more cost effective. Use of the WCD cost < $ 100,000/QALY gained as long as the rate of cardiac arrest in the first month post-MI was > 1.16%. This suggests that patients at low risk of SCA would be unlikely to obtain sufficient benefits from the WCD. The efficacy of WCD in successfully terminating SCA events is another model parameter of key importance. The use of the WCD costs less than $ 100,000/QALY, even if the WCD was only successful in terminating 80% of events. The authors concluded 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 US [41].

In the Netherlands, Quast et al. described the costs of WCD therapy in 79 patients. However, the population was heterogeneous: newly diagnosed cardiomyopathy was reported in 58.2% of patients and the remainder (42.8%) had an indication for device extraction due to ICD infection or other reasons [27].

A previous study was conducted in Australia and reported some considerations on the cost of WCD. The study included only 8 patients with a wide range of indications for WCD use. Of these patients, 3 suffered a device infection, 3 suffered a cardiomyopathy, 2 patients had myocarditis and aortic stenosis, respectively [32].

The small sample size and the heterogeneity among patient indications makes it difficult to generalize results from one study to another. The benefits of WCD are dependent on patient selection [29]. Therefore, other analyses in selected populations are strongly needed to demonstrate the true benefits and to secure a cost-effective use of WCD.

No specific economic evaluations for the Italian setting were retrieved by the literature review. To fill this gap, two decision analytical models were developed to estimate the economic implications attributable to the use of WCD in target patients with post-MI (Model 1) and target patients with ICD explant for an infectious indication (Model 2). A Cost Effectiveness Analysis (CEA) was performed with Model 1, to estimate the Incremental Cost Effectiveness Ratio (ICER) attributable to the use of WCD in post-MI patients, since the WCD showed to be more effective and more costly than standard care. The ICER shows the incremental cost per unit of additional effectiveness attributable to the use of WCD in the target patients. A Cost Minimization Analysis was performed with the Model 2, assuming an equivalent effectiveness between the WCD and the standard of care in Italy (hospitalization in a low intensity hospital after ICD removal) among patients with ICD explant due to infection. Under this assumption, we do not include clinical consequences but only economic consequences in

the model, in order to estimate the difference in costs between WCD and standard of care in target patients. This is a conservative approach because "Hospitalization in a low intensity hospital" does not guarantee that patients are adequately protected from SCD unless they are on a monitored bed.

Both the models were performed simulating a lifetime time horizon and adopting the point of view of the Italian National Health Service (NHS). The data used to populate the models were obtained from the extensive literature research conducted for this HTA and from a specific literature research based on the data required by the models.

Cost effectiveness of WCD used in patients with MI in Italy

We developed a decision-analytic Markov model to assess the cost-effectiveness of the WCD compared with the current standard of care for post-MI patients. The decision-analytic model simulated the period of 90 days where the WCD is used and the patients are not yet eligible for prophylactic ICD implantation. The Markov model simulated the period after the 90 days post-MI, including the effect of ICD, in which patients were followed whose LVEF had improved to >35% treated with optimal medical therapy. Patients with an LVEF ≤35% had an ICD implanted for primary prevention. During the simulation, patients were at risk of dying and this risk decreased based on ICD therapy. Patients who had an ICD implanted were at risk for ICD infections, lead failure, explants, inappropriate shocks and subsequent hospital stays, as well as the need for generator replacements over time. The model assessed patient survival, their HRQoL, and the costs related to their state of health. From the model we estimated the (ICER) of WCD use vs standard of care expressed as € per Quality Adjusted Life Year (QALY) gained.

Study Design

We developed a decision-analytic model to estimate the lifetime costs and benefits of WCD versus medical therapy alone at hospital discharge in patients who had been hospitalized with an acute myocardial infarction with a left ventricular ejection fraction (LVEF) of 35% or less (assessed ≥8 hours after myocardial infarction).

To build the model, we used the data from the recent VEST randomized clinical trial [5]. When data necessary to build a model appropriate for our healthcare system were not available, we used other published and referenceable sources of data (Table VII).

We discounted costs and benefits at an annual 3% rate [127,128] and performed the analysis from the perspective of the Italian National Health Service (NHS). We expressed outcomes in terms of 2018 euro (€), life-years (LYs), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) expressed as € per LY gained and € per QALY gained.

Decision-Analytic Model

We built a state-transition Markov model to assess the overall outcomes associated with the use of WCD, using a lifetime time horizon and monthly cycle (Figure 3). A hypothetical cohort of patients post-MI was considered, using the data from the recent VEST randomized clinical trial [5]. Accordingly, the cohort under study had a mean age of 61 years, received the WCD or only a medical therapy at hospital discharge. Patients stayed in this health state for 3 months or received an implantable cardioverter defibrillator (ICD) before the end of this period if a condition requiring an ICD was developed. After 3 months, patients who were alive and had not already received an ICD, were re-evaluated to determine their eligibility for a primary prevention ICD implantation (LVEF≤35%) or for only medical therapy (LVEF>35%). ICD implantation could be successful or result in procedural death. Patients who had received an ICD entered in the post-ICD health state in which they

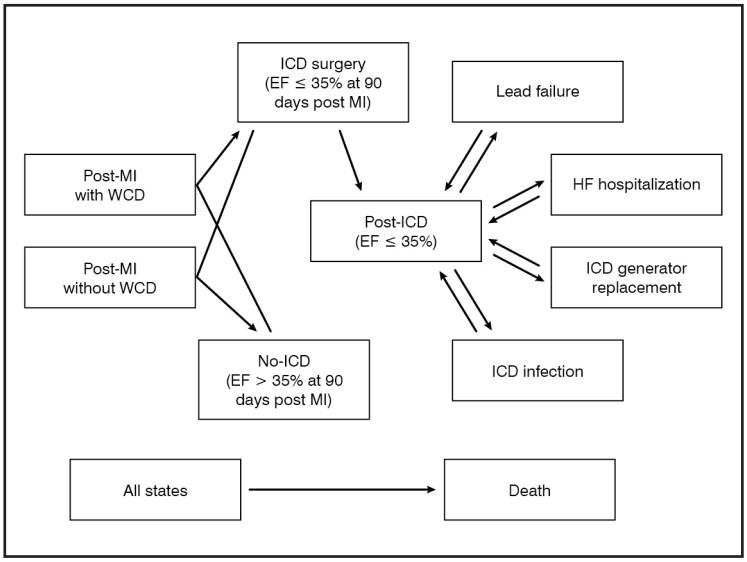

Figure 3. *Markov model for cost-effectiveness evaluation in post MI*
EF = Ejection Fraction; HF = heart failure; ICD = Implantable Cardioverter Defibrillator; MI = Myocardial Infarction; WCD = Wearable Cardioverter Defibrillator

Parameter	Value	References
Cohort mean age (years)	61	Olgin 2018 [5]
Discount rate of efficacy	0.030	Sanders 2016 [127], Cortesi 2018 [128]
Discount rate of cost	0.030	Sanders 2016 [127], Cortesi 2018 [128]
90 days post MI with WCD		
Mortality – monthly probability	0.0104 (0.0084-0.0125)	Olgin 2018 [5]
Inappropiate shock – monthly probability	0.002 (0.0016-0.0024)	Olgin 2018 [5]
ICD implantation within 90 days post-MI – monthly probability	0.0149 (0.0119-0.0178)	Olgin 2018 [5]
Probability EF ≤35% at 90 days	0.4070 (0.3256-0.4884)	Sjoblom 2014 [129]
90 days post MI with Medical therapy		
Mortality – monthly probability	0.0166 (0.0133-0.0199)	Olgin 2018 [5]
ICD implantation within 90 days post-MI – monthly probability	0.0194 (0.0155-0.00232)	Olgin 2018 [5]
Probability EF ≤35% at 90 days	0.4070 (0.3256-0.4884)	Sjoblom 2014 [129]
ICD		
Procedural death – monthly probability	0.0020 (0.0016-0.0024)	van Rees 2014 [130]
Cardiac mortality in patients with ICD – monthly probability	0.0044 (0.0035-0.0052)	Bardy 2005 [131], Greenberg 2004 [132]
Probability of lead failure – monthly probability	0.0015 (0.0012-0.0018)	Kremers 2013 [133]
Probability of ICD infection – monthly probability	0.0007 (0.0006-0.008)	Kremers 2013 [133], Uslan 2007 [134], Margey 2010 [135], Johansen 2011 [136]
Death from lead failure – monthly probability	0.0130 (0.0104-0.0156)	Cheng 2010 [137]
Death from ICD infection	0.0500 (0.0400-0.0600)	Margey 2010 [135], Sohail 2007 [138]
Battery life (replacement)	0.0113 (0.0091-0.0136)	Kramer 2013b [139], Gandjour 2011 [140]
Hospitalization for HF	0.0080 (0.0064-0.0096)	Moss 2009 [141], Tang 2010 [142]
No ICD		
Cardiac mortality in patients without ICD – monthly probability	0.0019 (0.0015-0.0022)	Solomon 2005 [87]

Table VII. *Clinical data input for cost-effectiveness model on post MI*

could become hospitalized for heart failure, experience lead failure, ICD infection, ICD generator replacement or die for cardiac death or other causes. Patients with LVEF>35% who had received only medical therapy entered in the No-ICD health state where they could die for cardiac death or other causes. We constructed the model by using Microsoft Excel.

Efficacy

In the base case (VEST ITT) scenario, using the ITT data reported in the VEST trial [5], we modeled the efficacy of WCD on the basis of the overall survival at 90 days: 3.1% in the WCD group and 4.9% in the medical therapy. We used these data to estimate the monthly probability of death in the patients treated with WCD and in the patients treated with medical therapy alone (Table 7). We also determined the risk of receiving an ICD before the 90 days, based on VEST trial: 4.4% in the WCD group and 5.7% in the medical therapy group, even if it was forbidden by the VEST trial protocol, apart from secondary prevention (Table VII).

Mortality and adverse events

In the 90 days post-MI, we accounted for all-cause mortality using the VEST trial [5], considering the short time horizon and the possible misclassification bias associated to the definition of cause of death in medical therapy group within the trial. The VEST trial was also used to estimate the WCD risk of inappropriate shock (Table VII).

While for the long-term mortality associated to a patient after 90 days post-MI, we separately modeled non-cardiac and cardiac death respectively, following the approach used by Woo et al. [143]. Because the risk for death from general (non-cardiac) causes increases with age, we separated the risk for death into general population and excess cardiac components. We based our general population mortality on the age specific risks for death from the Italian National Institute of Statistics [144]. In the patients who received an ICD, the excess of cardiac mortality (Table 7) was estimated based on the overall mortality in the ischemic ICD group of SCD-HeFT (Sudden Cardiac Death in Heart Failure) Trial [131] and on the prevalence of cardiac death in the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial) [132]. In the patients without ICD, the excess of cardiac mortality (Table VII) was estimated based

on the patients with LVEF >30% of VALIANT (Valsartan in Acute Myocardial Infarction Trial) [87]. We held the excess cardiac mortality constant while allowing the general population mortality to rise with age; cardiac death therefore comprised a gradually decreasing fraction of the overall risk for death.

Further, we included in the model a risk of death associated to ICD implantation and ICD adverse events (lead failure and ICD infection) [135,137,138,145]. We obtained the probabilities of lead failure, ICD infection based on published registry data [134-138,146].

Costs

In the first 90 days of the simulation, we included WCD cost and overall cost associated to post-MI patients based on a study of MI economic burden conducted on an administrative Italian database [147] (Table VIII). This study reported a cost per patient-month post MI of € 760 (excluding the cost of the index event hospitalization) in the first year that decreased to € 327 per patients-month in the 2nd and 3rd year post MI. For both WCD and medical therapy treatment simulated, we assumed the same monthly cost considering no difference in the medication use and rehospitalizations reported in the VEST trial for both arms. In the WCD simulation we also account for the cost associated to the use of WCD, € 10,800 for the first 90 days after MI, based on the Italian mean price provided by ZOLL.

For the ICD implantation and the related interventions associated to ICD adverse events, we applied the cost associated to the appropriate Italian DRG (Table VIII) [148]. The same approach was used to estimate the cost associated to HF hospitalization in ICD patients.

We estimated the expected battery lives of ICD devices according to previously reported data [139], assuming a mean battery life of 5 years and assuming no battery failure in the first 2 years after ICD implantation [140]. For patients with or without ICD, we associated the mean monthly costs associated to patients after MI based on a study of MI economic burden conducted on an administrative Italian database (Table VII) [147].

Because the utility value decreases with age, we based our utility value on the age specific utility from the EQ-5D utility score reported for the Italian population [149]. In the model, the utility values associated with the age-specific Italian general population were adjusted based on the disutility values associated to the health states and events simulated.

Parameter	Value	References
Costs (€)		
WCD – monthly cost	3,600 (2,894-4,306)	Assumption
Monthly cost in the 90 days after MI with WCD	761 (609-914)	Mantovani 2011 [147]
ICD implantation	16,573 (13,258-19,888)	DRG 515 – G.U. 2013 [148]
ICD replacement	16,573 (13,258-19,888)	DRG 515 – G.U. 2013 [148]
Revise due to lead problem	3,547 (2,837-4,256)	DRG 515 – G.U. 2013 [148]
Revise due to infection	16,573 (13,258-19,888)	DRG 515 – G.U. 2013 [148]
Monthly cost after ICD implantation	327 (261-391)	Mantovani 2011 [147]
HF hospitalization	4,898 (3,918-5,878)	D'angiolella 2019 [151]
Monthly cost after 90 days post-MI without ICD	327 (261-391)	Mantovani 2011 [147]
Utility		
Disutility WCD	0.050 (0.040-0.060)	Assumption
Disutility MI	0.0626 (0.0501-0.0751)	Borisenko 2015 [150]
Disutility inappropriate shocks[1]	0.5 (0.4-0.6)	Sanders 2015 [41]
Disutility ICD surgery	0.0164 (0.0131-0.0197)	Smith 2013 [152]
Disutility lead failure[2]	1.0	Woo 2015 [143]
Disutility ICD infection[3]	1.0	Woo 2015 [143]
Disutility ICD replacement	0.0164 (0.0131-0.0197)	Smith 2013 [152]
Disutility HF hospitalization[4]	0.4830 (0.3864-0.5796)	Woo 2015 [143]
Disutility post ICD	0.1167 (0.0187-0.2157)	Borisenko 2015 [150]
Disutility post-no ICD	0.0368 (0.0294-0.0442)	Borisenko 2015 [150]

Table VIII. *Cost and utility data inputs for cost-effectiveness model on post MI*

[1] Apply for 0.5 (0.4-0.6) days
[2] Apply for 2 (1.8-2.2) days
[3] Apply for 5 (4-6) days
[4] Apply for 12 (9.6-14.4) days

For the patients in the first 90 days post-MI, we used the disutility associated to MI [150] with an additional disutility for the patients with WCD based on the inappropriate shock events and on a conservative assumption on the impact of WCD in daily life (Table VIII). In the patients who received an ICD after 90 days, we assumed a disutility associated to ICD implantation, ICD lead failure, ICD infection, and hospitalization for HF and ICD battery replacement (Table VIII). The ICD disutility data and approach for their estimations were retrieved from the study by Woo et al. [143].

For patients in the post-ICD health state, we assumed the disutility associated to heart failure, while for the patients with no ICD, we assumed the disutility value associated to post-MI due to a better LVEF associated to this patient (Table VIII) [150].

Analysis

A base case (VEST ITT) analysis was performed based on the results of the ITT analysis of VEST trial [5] and on the data input and assumption described above, while an alternative scenario was assessed as a sensitivity analysis to address the impact of WCD cost, reducing and increasing the 90-day WCD cost from -30% to +30%.

Finally, we performed a one-way sensitivity analysis to assess the impact of each parameter (Table VII and Table VIII) on the model results and a probabilistic sensitivity analysis to account for the influence of simultaneous changes in correlated and uncertain model inputs on the cost-effectiveness of WCD. In the probabilistic analysis, we randomly sampled model inputs from distributions based on their expected values and uncertainty distributions derived from a literature review and clinical judgment and ran 1,000 independent simulations to estimate the probability that WCD would meet a particular willingness-to-pay threshold.

Results

In the base case (VEST ITT) scenario l, the WCD was the most effective yet the more costly treatment with 0.19 QALYs gained compared to Medical therapy and an incremental cost of € 9,048 per patient. (Table IX) The ICER estimated was € 47,709 per QALY gained that is lower than the highest cost-effectiveness threshold (€ 60,000 per QALY gained) reported in the economic-evaluation conducted in Italy [153-156]. In the base case (VEST ITT), the WCD also reported an improvement of 0.24 LYs compared to Medical therapy. Based on the improved survival, and on the incremental cost of € 9,048 per patient, the WCD reported an ICER of €38,276 per LY gained.

Another scenario assessed in the analysis was the impact of WCD price on cost-effectiveness results (Figure 4). In this analysis, we observed a linear relationship between ICER and WCD price, with an ICER range from around € 37,000 to € 58,000 per QALY assuming a WCD cost from € 2,700 to € 4,500 per month.

Besides WCD costs, the other parameters with a higher impact on cost-effectiveness results were mortality at 90 days in WCD and medical therapy treatments and the probability of ICD implantation before 90 days, as shown by the one-way sensitivity analysis (Figure 5). Based on these results, the cost-effectiveness of WCD could be higher in the base-case (VEST ITT) scenario considering the higher rate of ICD implantation before 90 days observed for

Cost (€)	Cost d (€)	LYs	LYs d	QALYs	QALYs d
WCD					
97,961.78	76,808.64	15.78	11.71	12.95	9.65
Medical therapy alone					
88,566.24	67,759.84	15.46	11.48	12.69	9.46
Δ Cost (€)	**Δ Cost d (€)**	**Δ LYs**	**Δ LYs d**	**Δ QALYs**	**Δ QALYs d**
WCD vs Medical therapy alone					
9,395.53	9,048.80	0.33	0.24	0.26	0.19
		ICER € x Lys (€)	**ICER € x Lys d (€)**	**ICER € x QALY (€)**	**ICER € x QALY d (€)**
		27,786.84	**38,275.53**	34,245.49	**47,709.07**

Table IX. *Base-case (VEST ITT) scenario*
Δ = Delta/difference; d = Discounted; ICER = Incremental Cost-Effectiveness Ratio; Lys = Life Years; QALYs = Quality-Adjusted Life Years

the patients without WCD in the clinical practice compared to what was reported in the VEST trial, where participants were prohibited from receiving an ICD before 90 days [38].

A cost-effectiveness acceptability curve was also estimated. The cost-effectiveness acceptability curve (CEAC) is a graphical method for summarizing the impact of uncertainty on the results of an economic evaluation, frequently expressed as an ICER or willingness to pay. The CEAC, derived from the joint distribution of costs and effects, illustrates the Bayesian probability that the data are consistent in relation to possible values of the cost-effectiveness threshold.

Figure 6 shows that in the case of the WCD, given a maximum acceptable ratio of € 60,000, the probability that the WCD therapy is cost-effective compared with routine medical treatment is 0.55. This is equivalent to stating that, given the data, there is a 55% chance that the additional cost of WCD therapy, compared with routine medical management, is less than the willingness to pay threshold of € 60,000 per QALY gained reported in the economic-evaluation conducted in Italy [153-156]. Note the comparative nature of both statements. It is *not* equivalent to stating that the WCD therapy has a 55% chance of costing less than € 60,000.

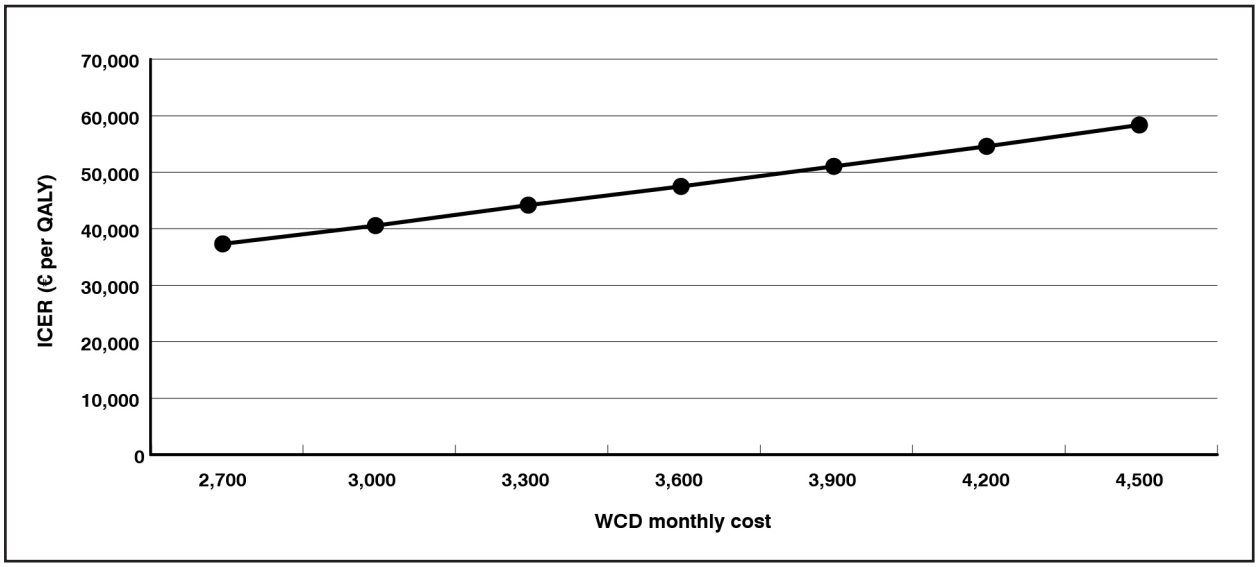

Figure 4. *Cost-effectiveness of WCD in relation to WCD cost in the base-case (VEST ITT) scenario*
ICER = Incremental Cost-Effectiveness Ratio; QALY = Quality-Adjusted Life Year; WCD = Wearable Cardioverter Defibrillator

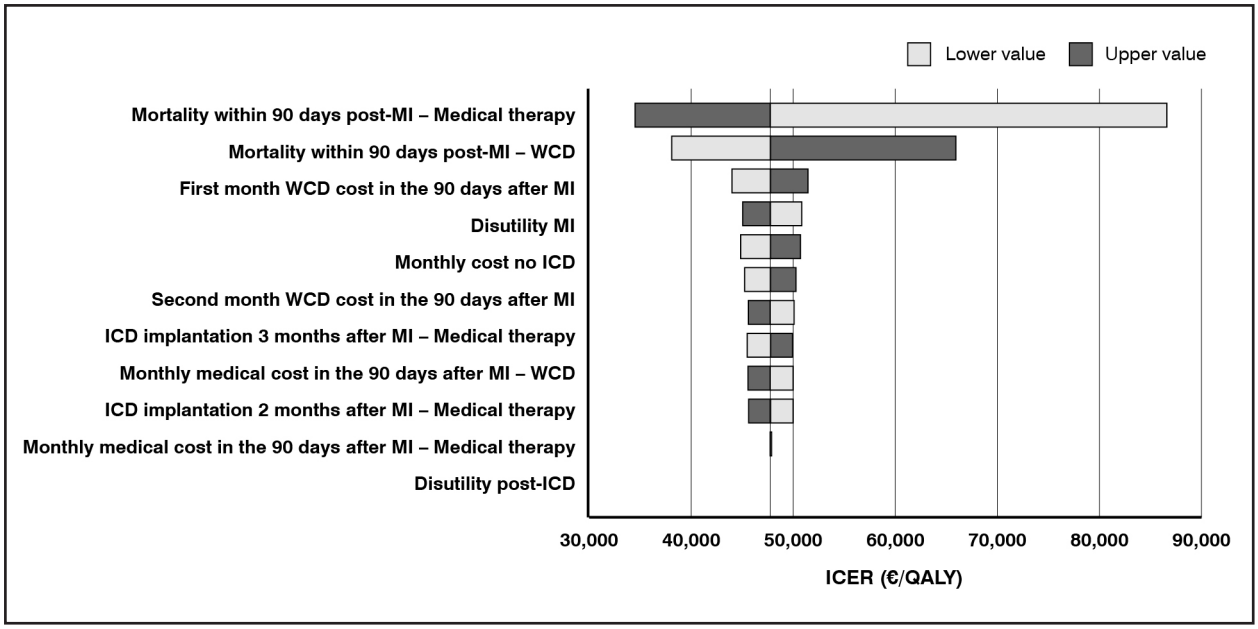

Figure 5. *Tornado Diagram (Post-MI C/E Model) – one way sensitivity analysis*

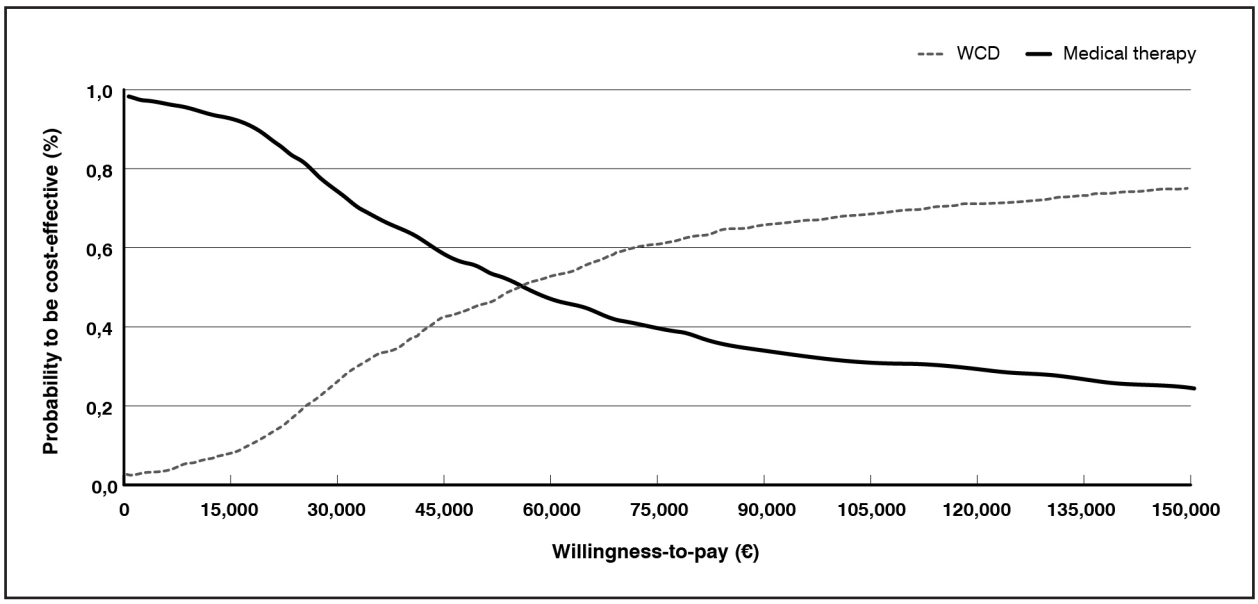

Figure 6. *Cost-effectiveness acceptability curve*

COST EFFECTIVENESS OF WCD USED IN PATIENTS WITH ICD EXPLANT IN ITALY

We developed a decision-analytic Markov model to estimate the lifetime costs of WCD versus standard of care in patients with implantable cardioverter defibrillator (ICD) removed due to infection.

Study Design

We decided to perform a cost-minimization analysis instead of a cost-effectiveness analysis assuming the same efficacy between the WCD and the standard of care in Italy (hospitalization in a low intensity hospital after ICD removal). The decision was based on a conservative approach considering that the only previous economic evaluation reported in the literature and conducted by Healy & Carrillo [37] used a WCD efficacy higher than hospitalization and clinical experts, involved in this HTA, suggested a higher efficacy for WCD.

The difference associated between the two compared interventions are related to the management of time spent by patients without an ICD. In the time between the ICD explantation and the new ICD implantation (assumed 1 month based on clinical practice), patients can use a WCD and be discharged from the hospital waiting for the new implantation or be hospitalized in a low intensity hospital until the new ICD implantation.

We discounted costs at an annual 3% rate [127,128] and performed the analysis from the perspective of the NHS. We expressed outcomes in terms of 2018 euro (€).

The data used to populate the model were obtained from the extensive literature research conducted from the present work (Table III).

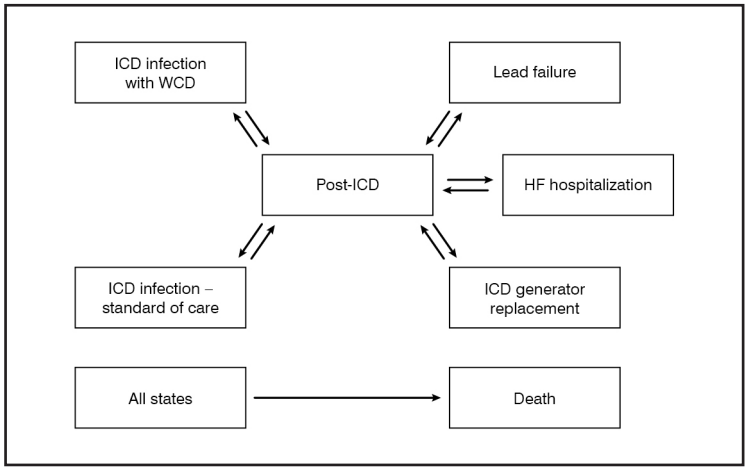

Figure 7. *Markov model for cost-minimization evaluation in ICD explant*
ICD = Implantable Cardioverter Defibrillator; WCD = Wearable Cardioverter Defibrillator

Decision-Analytic Model

We built a state-transition Markov model to assess the overall costs associated to the use of WCD, using a lifetime time horizon and monthly cycle (Figure 7). A hypothetical cohort of patients with implantable cardioverter defibrillators (ICD) removed due to infection, with a mean age of 61 years [37], can receive the WCD after the ICD removal or be hospitalized in a low intensity hospital. Patients stay in this health state for 1 month; after this time-period, we assumed the resolution of infection and the implantation of a new ICD.

The new ICD implantation could be successful or result in procedural death. Patients

with ICD entered in the post-ICD health state where they could be hospitalized for heart failure, experience new ICD infection, ICD generator replacement and die for cardiac death or other causes. We constructed the model by using Microsoft Excel.

Efficacy and Mortality

Based on the cost-minimization analysis approach, we assumed the same efficacy between WCD and the standard of care (Table X). We modeled the efficacy of this intervention based on Sudden Cardiac Arrest (SCA) rates in the first month after ICD explantation and the WCD event survival of 85.5%, reported in the WCD registry. Event survival rate was defined as SCA rate due to VT/VF events as a part of all SCA events including e.g., asystoles, with a termination-success of VT/VF events by the WCD of 100% [37,53]. This is a conservative approach because "Hospitalization in a low intensity hospital" does not guarantee that patients are adequately protected from SCD unless they are on a monitored bed.

While for the long-term mortality after the new ICD implantation, we modeled separately the non-cardiac from the cardiac death following the approach used by Woo et al. [143]. Because the risk for death from general (non-cardiac) causes increases with age, we separated the risk for death into general population and excess cardiac components. We based our general population mortality on the age specific risks for death from the Italian National Institute of Statistics [144]. In the patients who received an ICD, the excess of cardiac mortality (Table X) was estimated based on the overall mortality in the ICD group of SCD-HeFT (Sudden Cardiac Death in Heart Failure) Trial [131] and on the prevalence of cardiac death in the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial) [132]. We held the excess cardiac mortality constant while allowing the general population mortality to rise with age; cardiac death therefore comprised a gradually decreasing fraction of the overall risk for death.

Further, we included a risk of death associated to ICD implantation and ICD lead failure in the model. [137,145]. We obtained the probabilities of lead failure from published registry data [134-138,146]. Finally, based on these registry data, we also estimated the probability of ICD reinfection.

Costs

In the 30 days after ICD explanation, we included the cost of WCD and the cost of new ICD implantation for the WCD intervention and the cost of hospitalization in a low intensity hospital and the cost of a new ICD implantation for the standard of care (Table XI). In the analysis, we assumed a WCD cost of € 3,600 (based on Italian mean price provided by ZOLL) and a cost of € 5,250 for the hospitalization in a low intensive hospital (based on daily hospitalization cost of € 250 and 21 days of hospitalization).

For the ICD implantation and the related interventions associated to ICD adverse events, we applied the cost associated to the appropriate Italian DRG (Table XI) [148]. The same approach was used to estimate the cost associated to HF hospitalization in ICD patients.

Parameter	Value	References
Cohort mean age	61	Olgin 2018 [5]
Discount rate – cost	0.030	Sanders 2016 [127], Cortesi 2018 [128]
30 days after ICD explanation		
Mortality WCD probability	0.0404 (0.0325-0.0484)	Chung 2010 [53], Healy 2015 [37]
Mortality Standard of Care	0.0404 (0.0325-0.0484)	Chung 2010 [53], Healy 2015 [37], assumption
ICD		
Procedural death – monthly probability	0.0020 (0.0016-0.0024)	van Rees 2014 [130]
Cardiac mortality in patients with ICD – monthly probability	0.0044 (0.0035-0.0052)	Bardy 2005 [131]; Greenberg 2004 [132]
Probability of lead failure – monthly probability	0.0015 (0.0012-0.0018)	Kremers 2013 [133]
Probability of ICD infection – monthly probability	0.0007 (0.0006-0.008)	Kremers 2013 [133], Uslan 2007 [134], Margey 2010 [135], Johansen 2011 [136]
Death from lead failure – monthly probability	0.0130 (0.0104-0.0156)	Cheng 2010 [137]
Battery life (replacement)	0.0113 (0.0091-0.0136)	Kramer 2013b [139]; Gandjour 2011 [140]
Hospitalization for HF	0.0080 (0.0064-0.0096)	Moss 2009 [141], Tang 2010 [142]

Table X. *Clinical data input for cost-minimization model in ICD explant*

Cost	Value (€)	References
Cost of WCD	3,600 (2,894-4,306)	Assumption
Cost of low intensity care	5,250 (4,221-6,279)	ASST rhodense, Expert opinion
Cost of ICD explanation due to non-fatal infection	21,634 (17,394-25,874	DRG 515 – G.U. 2013 [148]
30 days after ICD infection – WCD CD	25,234 (20,288-30,180)	Assumption, DRG 515 – G.U. 2013 [148]
30 days after ICD infection – Standard of care	26,884 (21,615-32,153)	ASST rhodense, Expert opinion, DRG 515 – G.U. 2013 [148]
Cost of ICD reimplantation after non-fatal infection	0	-
Cost of ICD replacement	16,573 (13,258-19,888)	DRG 515 – G.U. 2013 [148]
Cost of revise due to lead problem	3,547 (2,837-4,256)	DRG 515 – G.U. 2013 [148]
Monthly cost after ICD implantation	345 (149-541)	Madotto 2015 [157]
HF hospitalization costs	4,898 (3,918-5878)	D'angiolella 2019 [151]

Table XI. *Cost data inputs for cost-minimization model in ICD explant*

We estimated the expected battery lives of ICD devices according to previously reported data [139], assuming a mean battery life of 5 years and assuming no battery failure in the first 2 years after ICD implantation [140]. For patients after ICD implantation, we associated the mean monthly costs after ICD reported by Smith et al. (Table X) [152].

Analysis

A base case analysis was performed based on the data input and assumptions described above, as sensing the cost of WCD and standard of care interventions, and the difference of overall costs associated to these interventions.

Further, we assessed the impact of WCD and hospitalization in a low-intensive care hospital cost reducing and increasing their cost from -30% to +30%. To assess the reliability of results, we also performed a one-way sensitivity analysis to test the impact of each parameter on the model results.

Treatments	Cost (€)	Cost discounted (€)
WCD	105,175.35	86,035.52
Standard of care	106,997.92	87,817.92
	Δ Cost (€)	**Δ Cost discounted (€)**
WCD vs Standard of care	-1,822.58	-1,782.40

Table XII. *Base-case (VEST ITT) scenario*
Δ = delta/difference

Results

In the base case scenario, the WCD resulted as the less expensive treatment compared to Standard of care. Based on the cost-minimization analysis, the WCD reported a cost reduction of € 1,782 per patient. (Table XII) Both the value of WCD and the Standard of care costs reported a high impact on the results. In Figure 8 we observed a change in the

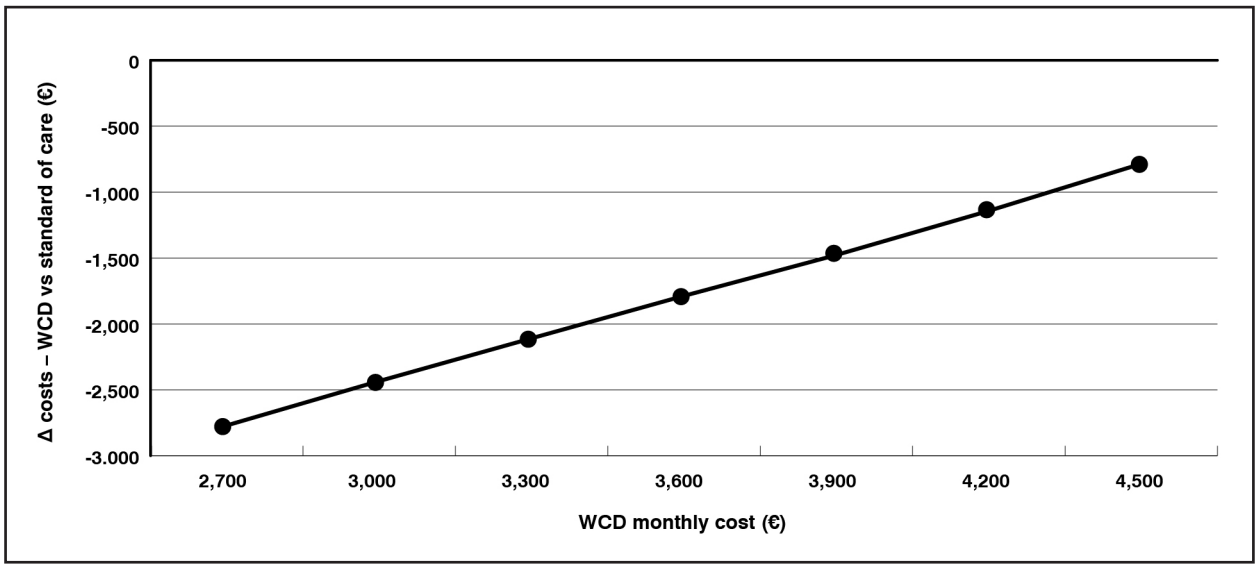

Figure 8. *Cost-minimization of WCD in relation to WCD cost*

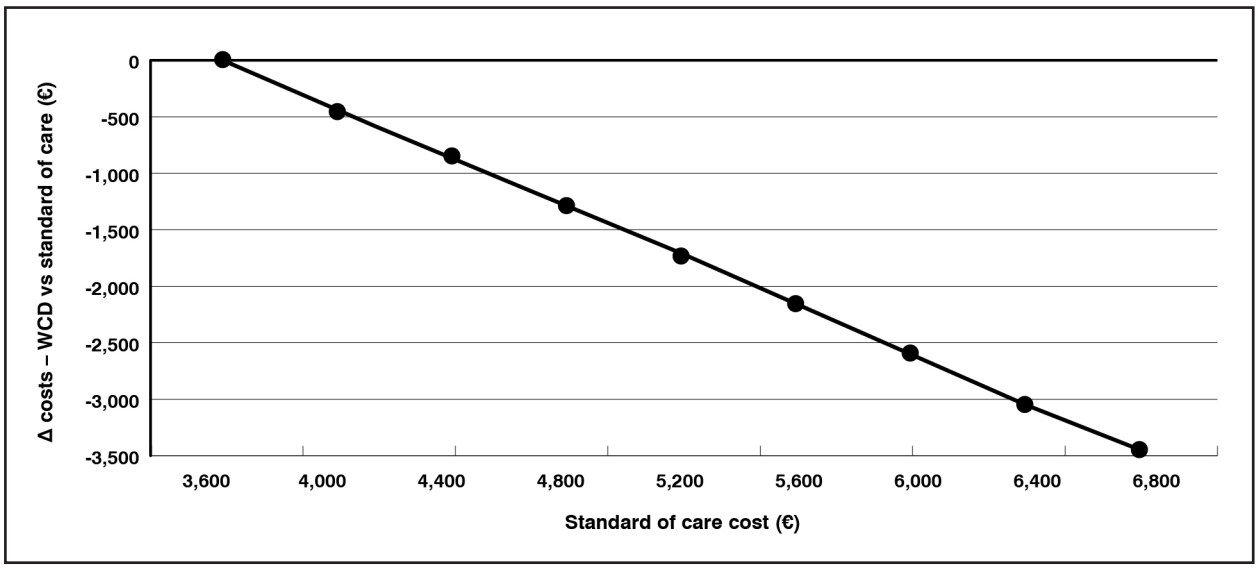

Figure 9. *Cost-minimization of WCD in relation to Standard of care cost*

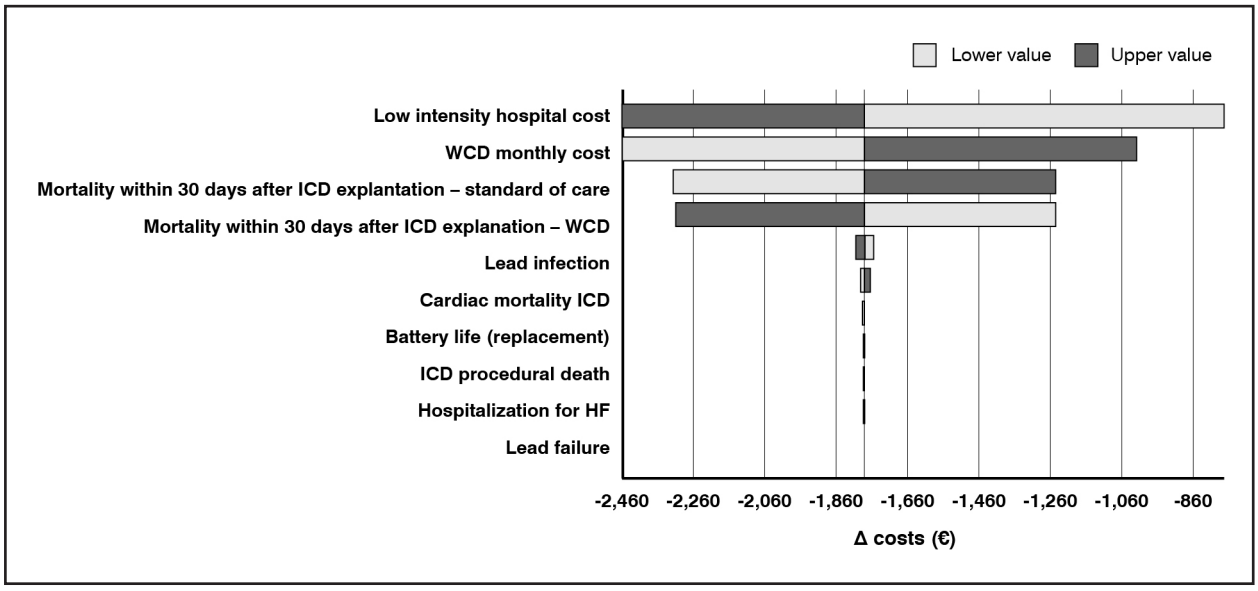

Figure 10. *Tornado Diagram (ICD Explant C/M Model) – one way sensitivity analysis*

cost saving from € 2,800 to € 810 assuming a WCD cost from €2,700 to €4,500. The same impact was found changing the Standard of care costs (Figure 9), with a cost saving associated to WCD ranging from € 3,500 to € 0 assuming a standard of care cost from € 6,800 to € 3,600.

WCD and standard of care costs resulted also as the parameters with a higher impact on the cost-minimization results, based on the one-way sensitive analysis (Figure 10).

Discussion and recommendation

In the European guidelines, published in 2015 [40], it is specified that "the WCD may be considered for adult patients with poor LV systolic function who are at risk of sudden arrhythmic death for a limited period, but are not candidates for an implantable defibrillator (e.g., bridge to transplant, bridge to transvenous implant, peripartum cardiomyopathy, active myocarditis and arrhythmias in the early post-myocardial infarction phase).

More recently, the authors of the AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death [158] recommend the use of WCD in two categories of patients: those "with an ICD and a history of SCA or sustained VA in whom removal of the ICD is required (as with infection), in whom the WCD is reasonable for the prevention of SCD"; and "in patients at an increased risk of SCD but who are not eligible for an ICD, such as awaiting cardiac transplant, having an LVEF of 35% or less and are within 40 days from an MI, or have newly diagnosed NICM, revascularization within the past 90 days, myocarditis or secondary cardiomyopathy or a systemic infection, wearable cardioverter-defibrillator may be reasonable".

An HTA is a useful informative instrument to guide healthcare policymaking. It consists of a systematic evaluation of properties, effects, and/or impacts of a health care technology compared with its possible alternatives, for the management (diagnosis, prevention, treatment, care) of a specific condition. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences.

We conducted an HTA work on the use of WCD in two categories of subjects: adult patients with a recent MI, and adult patients with an ICD explant.

Recently, Ettinger and colleagues [23,159] published an HTA on the use of the WCD to prevent SCA. However, there are some aspects that make this HTA work little useful to understand the value of WCD used in our healthcare system. Apart from a number of methodological drawbacks discussed between the authors of this work and Sperzel and colleagues [160,161], we specify below the aspects that are more significant to motivate the conduction of the present HTA work. First, the target patients considered and the criteria adopted to select the publications during the literature research were different than ours; second, no economic evaluation was conducted; Third, the approach of consulting a focus group is very interesting to collect information from the perspectives of interested individuals like patients, however, the authors involved only patients with no actual experience with the WCD, while it is recognized that having or not having an experience (i.e. using the WCD) can have significant implications on individuals' opinions. The opinions reported only by subjects with no experience on the use of the WCD cannot be balanced, and would be better reported together or compared with the opinions of subjects with experience. Furthermore, they did not take the opportunity to involve clinicians as well, who would have contributed with their expert opinions in obtaining a more complete picture of implications of use of the WCD.

To perform the present HTA, we conducted a literature research, with the contribution of HTA and clinical experts. Further, due to the lack of specific economic evaluations conducted for the Italian setting, a cost-effectiveness and a cost-minimization analysis were conducted for the Post-MI and ICD explant population, respectively. The main results are summarized and discussed below.

The main key messages from the most recent reviews [6,10,12,13,16,19,26,28,29] or meta-analysis [9] in which studies involving subjects with previous MI or subjects with previous ICD explant were involved are specified below: the WCD effectively bridges a limited time period in patients with a high risk for SCA and may become a helpful tool for risk stratification to better select patients for primary prevention implantable cardioverter-defibrillator placement. The WCD can be considered when a transient contraindication to ICD is present, such as endocarditis or device related infection. The WCD is recommended in several cases, including patients with an ICD and a history of SCA or sustained VA in whom removal of the

ICD is required, and patients at an increased risk of SCD but who are not eligible for an ICD, such as having an LVEF ≤ 35% and are within 40 days from an MI. The WCD is a feasible bridge to ICD therapy and/or safe observation for patients at high risk for SCD, especially in the acute recovery phase of cardiac diseases. Additionally, the WCD might provide a safe environment for long-term observational studies even in patients at higher risk for SCD. The clinical value of the WCD must be measured not only by the number of terminated arrhythmic events, but also by successfully performed risk assessment and by the number of prevented non-optimized guideline-driven ICD implantations. Despite the fact that more recent studies have reported the clinical benefits in the target population, further research could be done to identify potential areas of improvement in terms of clinical outcome with the WCD. Data from long-term experience with the WCD are needed to confirm these initial findings.

In regards to patients having experienced an MI, Barraud and colleagues [15] stated that the WCD was life-saving in one patient after MI, although he used the device < 10 hours a day. The small sample size limits the generalizability of the findings; however, the study confirms that the patient training is crucial to achieve good compliance. Kondo and colleagues [38] affirmed that early post-MI patients at high risk of sudden cardiac death may benefit from WCD therapy, hence the WCD can contribute to prevent non-optimized guideline-driven ICD implantation. If persistent arrhythmia is detected, the WCD notifies the patient via a responsiveness test, allowing a conscious patient to prevent treatment. Most patients agreed that the device was easy to handle after sufficient training before receiving the device. Sanders et al. [41] reported that in patients with a recent MI and reduced LVEF, the use of a WCD could reduce the rate of SCD during the recovery period at a cost that appears to be economically attractive. In 2013, Epstein and colleagues [49] stated that a select group of patients may benefit from defibrillation early after MI, particularly during the first 30 days following hospital discharge (1.4% of patients were resuscitated by the WCD in the early weeks post-MI). However, they suggested the conduction of further studies in the critical period early post-MI.

Castro and colleagues [20] reported that the WCD is a safe and efficient solution to protect patients from SCA while waiting for re-implantation of a new ICD/CRT-D device. The WCD reported a high efficacy for protecting patients from VT/VF and it can be used as an ICD alternative in post-ICD explanted patients. Healy and Carrillo [37] affirmed that the WCD is likely cost-effective in protecting patients against SCA after infected ICD removal while waiting for ICD reimplantation compared to keeping patients in the hospital or discharging them home or to a skilled nursing facility. In 2014 Tanawuttiwat and colleagues [47] specified that in their study, compliance, which is essential for the effective use of the device, in general was relatively acceptable, and that WCD can prevent SCD, until ICD reimplantation is feasible in patients who underwent device removals for ICD. In 2009, Wilkoff and colleagues [56] reported that when there is concern for ongoing infection, alternatives to early re-implantation (after 2-3 days) include wearable defibrillators, epicardial lead implantation and surgical debridement of vegetations. However, at that time there was little published data and no consensus regarding the best approach for patients needing device re-implantation.

Findings from the studies indicate that the WCD, though the cost of the device is usually high in most health systems, may be a cost-effective option in appropriately selected patient groups. The cost-effectiveness ratios appear to be acceptable. However, cost effectiveness is highly related to factors such as patient risk profile and device cost. The studies imply that to ensure cost-effective use of WCD therapy, more and continuous research is needed. The cost of the device may be partly offset by reductions of hospitalizations and other resource use (costs due to device follow up, monitoring, complications, and replacement) and avoiding unnecessary ICD implant. However, generalizing the study results or trying to transfer them between settings remain complex. The diversity in the methods used in such studies, differences in the patients involved, unit costs and resources utilized among different countries clearly affect the way in which costs and benefits of the treatments are accounted for and hence may also affect the conclusions.

In conclusion, despite the numerous advances, many gaps in knowledge about the costs and real-world outcomes of WCD are recognized in the existing literature. These gaps include:

- Identification of patients who are most likely to benefit from a WCD among all eligible patients;
- Characterizing the role of the WCD in patient subgroups not well-represented in the trials;
- Evaluation of the impact of WCD use in clinical practice and introduction in treatment guidelines.

Since patient selection is fundamental to high value care in using the WCD to prevent SCD, further evidence is needed to better define the appropriate patient group for the device and the target indication group [23,32]. Randomized trials for some of these indications with cost analyses would help the clinician in deciding the potential extended benefits of this device and arguing the case with hospital and health fund administrators [32]. Although the cost-effectiveness of WCD therapy is still to be confirmed, it is expected that the WCD will reduce the costs and improve the outcome in appropriately selected patients [30].

To conclude: SCA and SCD leads to serious health consequences for individuals and burden for the health care system [118-121]. The experience on the use of WCD shows promising results, although some crucial points like costs, may interfere with the use of the WCD when clinically indicated. The overall benefits of the WCD, in terms of both safety and effectiveness, relate to patient acceptance and compliance. Acceptance and compliance can depend on communication between clinicians and patients and on appropriate training of patients. Communication and training require expertise and resources (human and financial). Investing on expertise and training could optimize compliance, hence effectiveness and safety. Information on compliance in Italy derives from the LifeVest Network database (registry maintained by manufacturer, ZOLL, Pittsburgh, PA), reporting 23.6 median hours of daily use, equivalent to those registered in Germany (median = 23.1 hours [36]) and in France (median = 23.4 [162]). Details on ethical/legal aspects and on organization implications of Life Vest are not deeply discussed in this HTA and further researche is needed to fully address these issues. However, the use of a wearable device generally reports few issues for the organization and ethical/legal aspects; indeed, WCD has the possibility to improve the organization and management of post-MI and ICD explant patients with positive implication from the ethical point of view. For example, the use of WCD can avoid the hospitalization for ICD explant patients and the relative organizational and management issues, providing more coverage (if used appropriately) from SCA and SCD.

In the post-MI patients, the base-case (VEST ITT) analysis performed with our cost-effectiveness model, reported an ICER of € 47,709 per QALY gained and of € 38,275 per LY gained comparing WCD vs medical therapy; an ICER that is below the highest cost-effectiveness threshold of €60,000 per QALY gained reported in the economic-evaluation conducted in Italy [153-156]. This analysis was based on the overall mortality data estimated in the VEST trial by the Intention to Treat Analysis that reflects the low adherence to WCD of the patients involved in the trial [5]. Among 25 participants with adjudicated arrhythmic death, 9 were wearing the WCD at the time of death, 4 of whom received appropriate shocks and 5 of whom had no ventricular tachyarrhythmia. In order to assess the impact of wearing the WCD on sudden death, non-arrhythmic death, and total mortality, an "as treated" analysis was performed in the VEST trial to assess event rates per 100 person-months of wearing the WCD compared to not wearing the WCD, and compared the two rates using Poisson regression. Based on this analysis, the VEST trial reported a total mortality rate of 0.50 per 100 person-months of patients wearing the device, and 1.91 per 100 person-months of patients not wearing the device reporting a higher efficacy of VEST (rate ratio, 0.26; 95% CI, 0.14 to 0.48; Bonferroni corrected $p<0.001$).

Although an economic model calculating WCD cost-effectiveness was not conducted on the "As Treated" results; a "As Treated" Scenario Analysis is reasonable considering the higher adherence of WCD reported in the clinical practice. It is clear that cost calculations conducted with this data would be lower than those already reported for the ITT economic analysis.

However, the VEST trial, used as the main WCD efficacy data source in post-MI patients, failed to provide a higher efficacy in reducing SCD compared to medical therapy. Many issues are associated to the solidity of these results based on the difficulty to classify SCD. Being aware that this issue requires further investigation to improve the assessment of WCD efficacy in post MI patients, we based the analysis on the overall mortality data following the opinions of clinical experts involved in this HTA. However, even considering the need of further studies with a better design to improve WCD adherence and cause of death identification, the cost-effectiveness analysis provided in this HTA report could help decision makers to better understand the potential value of WCD in post MI patients.

The other Italian NHS specific economic evaluation on WCD reported in this HTA was a cost-minimization analysis in patients with infected ICD explantation. In this analysis, the WCD provides a cost saving of € 1,782 per patient. These results were obtained assuming equal efficacy of WCD and Standard of care (3 weeks hospitalization in a low intensity hospital), a conservative approach considering the only previous economic evaluation by Healy &

Carrillo [37] where WCD efficacy was considered higher than hospitalization. However, even with this conservative approach, the WCD resulted as the less expensive treatment option with cost savings for the NHS budget. These results were confirmed in the sensitivity analysis.

The cost-effectiveness acceptability curve (CEAC) seen in Figure 6 shows the probability that the WCD is cost-effective compared with standard medical management, for a range of monetary values that a decision-maker might consider the maximum acceptable to avoid sudden cardiac arrest or death. This range of maximum monetary values, expressed as Euros per the probability of being cost-effective, is given on the *x*-axis. Given a specified value of this 'acceptable' cost-effectiveness ratio (a point on the *x*-axis), the CEAC shows the probability that the data are consistent with a true cost-effectiveness ratio falling below a willingness to pay value (read off the *y*-axis).

In the case of the WCD, given a maximum acceptable ratio of € 60,000, the probability that the WCD therapy is cost-effective compared with routine medical treatment is 0.55. This is equivalent to stating that, given the data, there is a 55% chance that the additional cost of WCD therapy, compared with routine medical management, is less than the willingness to pay threshold of €60,000 per QALY gained reported in the economic-evaluation conducted in Italy [153-156]. Note the comparative nature of both statements. It is *not* equivalent to stating that the WCD therapy has a 55% chance of costing less than € 60,000.

The use of WCD in post-MI patients or with an ICD explant and demographic and clinical characteristics that are typically observed and similar to those used in the two economic models applied in the present HTA, was found to be cost-effective in the first and cost-saving in the second group of patients. The two present some limitations, deriving from the use of data from different literature sources to make assumptions for the construction of the two models, which would deserve to be confirmed by more robust data obtained from a real-world application experience for a long-time horizon in the different regional health services of Italy.

In conclusion, the use of WCD according to guidelines can therefore contribute not only to an improvement in patient care in clinical practice, but also to a more effective utilization of resources in the Italian NHS. In addition, further research on risk factors for SCA and SCD should be conducted to continue to improve the identification of the target population. All evidence provided in this HTA was considered reliable by Italian clinical and HTA experts. Accordingly, the results can be considered applicable within the Italian NHS.

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Conflict of interest

- PAC reports research grant from Angelini, outside the submitted work; lectures fee from Pfizer, outside the submitted work; speakers bureaus from Roche, outside the submitted work.
- GLB reports consulting fees from Biotronik, outside the submitted work; speaker fees from Zoll, Biotronik, and Boston Scientific, outside the submitted work.
- RDP reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Biotronik, outside the submitted work.
- RDP is President of Italian Association of Arrhythmology and Cardiac Pacing.
- LSD, LS have nothing to disclose.
- GB reports speaker's fees from Medtronic, Boston Scientific, Bayer, Boehringer Ingelheim, outside the submitted work.
- LGM reports grants from Bayer, Boehringer Ingelheim, and Daiichi Sankyo, outside the submitted work; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Bayer and Pfizer, outside the submitted work; Participation on a Data Safety Monitoring Board or Advisory Board from Bayer and Pfizer, outside the submitted work, outside the submitted work.

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