Sehr geehrte Herren Dr. Semrau und Dr. Nürnberg,

wir nehmen gerne auf Ihren Brief Bezug, den wir am 09. Februar 2023 von Ihnen erhalten haben.

Die vorliegende Kritik bezieht sich auf ein zweites Update zur vergleichenden Evidenz der Defibrillator-Weste. Die Forschungsfrage war, welche Evidenz für den Einsatz der Defibrillator-Weste in breiten und unselektierten Patient*innengruppen (z.B. post-MI) vorliegt. Dabei begrenzte sich die wissenschaftliche Arbeit auf genau diese Frage und auch die Schlussfolgerung muss in diesem Kontext verstanden werden. Es ging nicht darum, bestehende enge Indikationen für die Defibrillator-Weste in Frage zu stellen (die sowohl durch Leitlinienempfehlungen, klinische Plausibilität und Daten zur technischen Performanz gestützt und Teil der klinischen Praxis ist), wenngleich auch dort weiterführende vergleichende Evidenz zur weiteren Stützung der Indikationen wichtig ist.

Wir freuen uns über inhaltliche Kritik, da diese – wenn fundiert und konstruktiv – einen wissenschaftlichen Diskurs ermöglicht. Leider mussten wir feststellen, dass in dem übermittelten Dokument auf Zitationen weitgehend – und Quellenangaben gänzlich – verzichtet wurde. Dies erschwert nicht nur die Nachvollziehbarkeit der Kritik, sondern auch einen wissenschaftlichen Diskurs erheblich. Wir versuchen dennoch auf die geschilderten Ansichten bestmöglich Bezug zu nehmen. Neben der inhaltlichen Kritik wurde uns unter anderem mangelndes Verständnis der Materie und eine methodologisch inkorrekte Durchführung des HTA Berichtes vorgeworfen. Diese Vorwürfe haben wir in der sachlichen Darstellung unten vollkommen entkräftet. Wir ersuchen, solche Behauptungen in Zukunft zu unterlassen. Allerdings freuen wir uns aber über einen inhaltlich-fachlichen akademischen Diskurs.

Die sachliche Darstellung wird in englischer Sprache aufgeführt, um ein möglichst breites Publikum erreichen zu können. Wie mit der ZOLL GmbH – stellvertretend durch Reimbursement Manager Dr. Semrau – vereinbart, wird dieser Diskurs auf unserer Website veröffentlicht. Die Ausführungen und Ansichten von Dr. Semrau (ZOLL Medical®) wurden deshalb mit dem Übersetzungsprogramm deepl.com übersetzt, sodass sich auch die internationale wissenschaftliche Community ein Bild machen kann.

Unsere HTA Berichte folgen den Prinzipien der evidenzbasierten Medizin – dem derzeit international höchsten Standard für die Zusammenfassung klinischer Evidenz. Im konkreten Fall wurde eine systematische Literatursuche in internationalen Forschungsdatenbanken durchgeführt, die klinischen Studien anhand von vorab definierten Einschlusskriterien ausgewählt und nach wissenschaftlichen Kriterien bewertet. Die randomisierte Kontrollstudie wird dabei als Goldstandard für die Evaluation von medizinischen Verfahren angesehen. Unsere grundlegende Vorgehensweise ist transparent und online einsehbar [1, 2] und richtet sich am neuesten Stand der Methodik für HTA durch Anlehnung an den EUnetHTA Leitlinien für HTA [3].

Innerhalb der evidenzbasierten Medizin basieren eindeutige Belege für oder gegen einen Zusatznutzen eines medizinischen Verfahrens auf Basis einer statistisch konservativen Interpretation der Daten aus randomisierten Kontrollstudien. Dabei ist der Fokus auf die Intention-to-Treat (ITT) Analyse gelebte Praxis medizinischer Forschung, weil nur diese Analyse die Randomisierung aufrecht erhält [1, 2, 4, 5]. Eine gut konzipierte Studie gewinnt ihre Glaubwürdigkeit aus der Einbeziehung einer vorab festgelegten Hypothese mittels Festlegung eines primären Endpunkts, die den Autor*innen dabei hilft, potenziell falsch positive Aussagen auf der Grundlage einer explorativen Analyse der Daten zu vermeiden [4]. Die weiterführende Sekundäranalyse von randomisierten Studien, die ihr Studienziel im primären Endpunkt verfehlt haben, sind mit hoher Unsicherheit behaftet und werden i.d.R. als Hypothesen-generierend gewertet [4]. Folgend dem aktuellsten Stand europäischer Leitlinien für HTA [5, 6] ist das Problem des Multiplen Testens im Kontext von Sekundäranalysen (etwa sekundäre

Endpunkte), zwar nicht formal lösbar, jedoch sollte dies bei der Interpretation der Ergebnisse jedenfalls entsprechend beachtet werden.

Es verwundert etwas, dass es neben der VEST-Studie so gut wie keine vergleichende Evidenz gibt. Neben der Durchführung von weiteren randomisierten Kontrollstudien könnten auch andere (einfacher durchführbare) vergleichende Analysen für die Evidenzgenerierung wertvoll sein. Es sollte methodisch prinzipiell möglich sein, anhand europäischer Kardiologie-Register halbwegs valide Vergleichsanalysen anzustellen. Daneben und noch viel einfacher in der Durchführung wären indirekte/ historische Vergleiche, um der Frage nachzugehen, ob dramatische Effekte in spezifischen Indikationen vorliegen [5]. Das Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) verweist hier mit einer ersten Annäherung zur Überprüfung ob ein dramatischer Effekt vorliegt, wenn dieser auf dem Niveau von 1 % signifikant ist und als relatives Risiko ausgedrückt den Wert 10 übersteigt [5, 7].

Des Weiteren wirkt die Sammlung der angeführten Kritikpunkte wie eine Wiederholung der – bereits mehrfach beantworteten – Kritik des EUnetHTA Berichts 2017 [8] bzw. des ersten AGENAS/LBI-HTA Updates aus 2019 [9]. Der dazugehörige wissenschaftliche Diskurs zu den Kritikpunkten[1] und eine entsprechende Erläuterung dieser seitens der Autor*innen des EUnetHTA Berichts ist in einem medizinischem Journal aufzufinden [10, 11] – dort, wo ein wissenschaftlich-fachlicher Diskurs stattfinden sollte. Zusätzlich dazu gibt es einen Brief von der ZOLL GmbH an österreichische Entscheidungsträger, der zumindest die inhaltlichen Kritikpunkte von Hrn. Dr. Semrau beinhaltet – eine entsprechende Stellungnahme der AGENAS/ LBI-HTA Autor*innen ist online einsehbar[2]. Unser Bericht ist methodisch ein weiteres zweites Update der Evidenz. Wir haben dabei die Evidenzanalysen der in den vorherigen Berichten bereits verwendeten HTA Berichte nicht verändert, sondern aktualisiert.

Wir stimmen den Ausführungen von Hrn. Dr. Semrau dahingehend zu, dass auf Basis von einarmigen Beobachtungsstudien Hypothesen über einen Zusatznutzen einer Defibrillator-Weste generiert werden können. Wie bei der Evaluation von medizinischen Technologien üblich sind diese Annahmen jedoch mit randomisierten Kontrollstudien zu überprüfen. Im besten Fall kann aus dem Unterschied in der Gesamtmortalität (der nach unserem GRADE-Rating niedrige Vertrauenswürdigkeit erzielte) ein erster Anhaltspunkt abgeleitet werden, jedoch muss hierbei berücksichtigt werden, dass dieser – wegen dem Problem des multiplen Testens – mit großer Unsicherheit behaftet ist und nicht als konfirmatorisch gewertet werden kann [12].

Auch wenn die bislang einzige randomisierte Kontrollstudie (VEST) ihr primär festgelegtes Studienziel verfehlt hat [13], zeigt diese Studie klar und unmissverständlich, dass eine Randomisierung im Kontext der Evaluation einer Defibrillator-Weste ethisch vertretbar und durchführbar ist. Registerdaten ohne Vergleichsgruppe sind aufgrund der darin inhärenten Verzerrungsmechanismen als Belege für oder gegen einen Zusatznutzen ungeeignet [5, 14].

Eine Einschätzung zur medizinischen Notwendigkeit einer Gesundheitstechnologie ist letztlich durch evidenzbasierte Leitlinien einzustufen und dabei werden a) Belege oder fehlende Belege aus randomisierten Kontrollstudien berücksichtigt und b) durch Konsensusverfahren der jeweiligen klinischen Expert*innen (z.B. im Zuge eines Delphi-Verfahrens) etwaige Indikationen bestimmt [15]. Eine Leitlinienarbeitsgruppe kann dabei klare Empfehlungen für/ gegen (ist indiziert/ ist nicht indiziert) oder reservierte Empfehlungen für/ gegen Therapien in spezifischen klinischen Szenarien aussprechen [16]. Für Entscheidungsträger*innen ist eine Kontextualisierung neben der komparativen Evidenz

[1] Im Sinne der Transparenz: Einige dieser Wissenschafter*innen erhielten finanzielle Unterstützung der Zoll GmbH für genau die Erstellung dieser Briefe an den Editor.

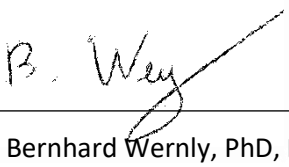
[2] vgl. https://eprints.aihta.at/1186/3/Stellungnahme_LBI-HTA_zu_Brief_von_Dr._Semrau_%28ZOLL_Medical%29.pdf

ebenso wichtig wie für Patient*innengruppen, um informierte Entscheidungen treffen zu können [17]. Dies entspricht der international etablierten Praxis der evidenzbasierten Entscheidungsfindung auf unterschiedlichen Ebenen [17]. Der AIHTA Update-Bericht ist dabei auf die Erstellung einer systematischen Übersichtsarbeit zu Wirksamkeit und Sicherheit (klinische Evidenz) aus komparativen Studien begrenzt und ersetzt dabei kein weiterführendes strukturiertes Konsensusverfahren von unabhängigen Leitlinienarbeitsgruppen bzw. weiterführende Kontextualisierung von Entscheidungsträger*innen [17, 18]. Letztlich stellen jedoch immer Ärzt*innen für einzelne Patient*innen Indikationen. Wir können mit der Evidenzsynthese nur eine Entscheidungsgrundlage anbieten; der klinische Kontext ist jedoch unersetzbar.

Abschließend halten wir fest, dass die von Dr. Semrau angeführten explorativen Sekundäranalysen aus wissenschaftlicher Sicht interessant zur Hypothesengeneration sind. Ein Zusatznutzen für ausgewählte Patient*innen ist auf Basis der vorhandenen Daten nicht auszuschließen. Darum würden wir es sehr begrüßen, wenn der gezeigte große Einsatz für das Medizinprodukt in weiteren Studien mündet. Wir stehen für den nächsten HTA Bericht zur Verfügung.

Mit freundlichen Grüßen,

Gregor Goetz, MSSc MPH



Priv. Doz-Dr. Bernhard Wernly, PhD, MScPH

Priv. Doz. Dr.in Claudia Wild

Response to the open letter from Dr Semrau (dating February 09th 2023) on the second update health technology assessment (HTA) of the wearable cardioverter defibrillator (WCD)

We appreciate the critique expressed by Dr Semrau, reimbursement manager of ZOLL Medical®. We are keen to engage in a scientific debate and address the comments point-by-point below. A scientific, constructive debate is essential to ensuring high quality scientific research results.

Evidence-based decision making is the sine qua non for a modern and rational health care system, informing both clinicians, patients and decision makers. Strong assumptions and postulations regarding treatments being highly effective (based on uncontrolled observational studies/ surrogate parameters or held beliefs of clinicians) need to be verified, ideally within randomised studies but definitely in the context of comparative trials [1, 2, 5, 14, 17-19]. This is crucial to avoid exposing patients to unnecessary risks (including from the omission of other, potentially more effective alternatives) and optimize the use of resources [1, 2, 5, 17-19].

Concluding that there is sound comparative clinical evidence for the broad use of WCD based on the VEST trial results is neither credible nor following basic bio-statistical methods for causal inference. The RCT [13] failed to show a statistically significant difference within the primary endpoint of the study arrhythmic mortality. We acknowledge, however, that there can be two scientific standpoints in the interpretation of the VEST trial results: either that the evidence is inconclusive [20] with still strong assumptions that some selected post-MI patients benefit from wearing the WCD or that there is no role for the WCD in post-MI patients [21]. In that respect, it regrettably appears that our report (and especially our discussion section) was read selectively and/or misunderstood: we have interpreted the VEST results as inconclusive evidence and highlighted that an absence of evidence of effect is not to be confused with evidence of no effect.

Further, we emphasized in the discussion chapter that the WCD may be regarded as a **medical necessity** in certain clinical settings, as acknowledged, for instance, by the Blue Cross Blue Shield Association (see p. 41 in our report [22]). In our discussion section, we intended to give a broad picture of the potential clinical utility of the WCD (see pp. 41,42 in our report [22]); this included the interesting tele-monitoring approaches with the WCD discussed by Blockhaus and colleagues [23] and Röhrer and colleagues [24]. We would like to emphasise that our description of potential further use-cases within the discussion may not be exhaustive, but we believe that – as highlighted by Dr Nürnberg – it is the task of cardiologists to determine in which contexts WCD could be used. These insights can be used for sound patient selection for future studies.

Our role as an HTA institute is to synthesise the available comparative evidence on the effects of health technologies [17] in line with best practice approaches of evidence-based medicine in order to inform decision-makers for coverage decisions for the benefit catalogue. Whether a therapy is a medical necessity for specific patients (and especially in which contexts) when only low-level evidence exists needs to be answered by independent clinicians within guideline working groups and steering committees. In their open letter, Drs Nürnberg and Semrau suggest that our report misquotes and/or misinterprets clinical practice guidelines on the WCD. However, evidence-based practice guidelines, such as those by the European Society for Cardiology taskforce clearly does not recommend the WCD for routine use in early post-MI patients based on VEST results [16]. Instead, it is recommended <u>in certain situations (indications) and selected patient groups:</u>

- **The ESC guideline (2021) on diagnosis and treatment of acute and chronic heart failure**, for instance, states the following [16]:

  *"A wearable cardioverter-defibrillator that is able to recognize and treat ventricular arrhythmias **may be considered for a limited period of time in selected patients** with HF who*

are at high risk for sudden death but otherwise are not suitable for ICD implantation. However, ***the large VEST trial failed to show that the wearable cardioverter-defibrillator reduced arrhythmic death in patients with an LVEF <_35% following a recent acute MI****" (Class 2b, LoE: B)*

- The recently published **ESC guideline (2022) for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death** states [25]:

  "The wearable cardioverter defibrillator (WCD) is an external defibrillator that has been shown to successfully detect and treat VT and VF. It is therefore ***suitable for patients who are at risk but temporarily not candidates for an ICD owing, for example, to extraction of an infected device and subsequent antibiotic treatment****. An unsolved problem is the protection of patients in the early phase (40 days) after an MI. The VEST trial enrolled 2302 patients with acute MI and an LVEF ≤35% and randomized them early in a 2:1 fashion to receive a WCD or not under guideline-directed optimal medical treatment (OMT). After a follow-up of 90 days there was no difference in the primary endpoint of arrhythmic death (1.6 vs. 2.4%; RR 0.67; 95% CI 0.37–1.21; P = 0.18). Concern was raised regarding the low median wear time of 18 h (IQR 3.8–22.7). The median wear time was higher (23.4 h, IQR 22.2–23.8) in a recent multicentre registry after structured patient education. However,* ***based on the available data, the task force does not recommend routine use of the WCD in the early post-MI phase****.* ***Nevertheless, the use of the device may be considered in selected post-MI patients deemed to be at high risk for SCD****.* ***Data on the benefit of the WCD for primary prevention of SCD in other clinical situations (e.g. acute myocarditis, primary prevention indication during pregnancy) are sparse and no recommendations can be currently made****."*

  The only available "should be considered" recommendation is for "adult patients with a secondary prevention ICD indication, who are temporarily not candidates for ICD implantation" and this is a class C recommendation, meaning that the recommendation is based on "consensus of opinion of the experts and/or small studies, retrospective studies, registries". As mentioned above, there is no universal recommendation, and "may be used" (class: 2b/ LoE: B) recommendations are formulated for selected patients in other clinical indications described within the aforementioned original text of the ESC guideline. In reading these guidelines [25] one should be aware that a class II recommendation means that (direct quotation from ESC): "conflicting evidence and/or divergence of opinion about the usefulness/ efficacy of the given treatment or procedure" exists.

  According to the aforementioned guideline [25] and our report (see p.41 in our report [22]), there is little debate about the utility of a WCD based on plausible reasons and technical performance data in niche indications, although the limitations of the available evidence should still be reflected as the ESC guideline did by formulating a class II recommendation with a LoE of C. We acknowledge that a randomised study would be challenging within this narrow patient group, but a comparative study using other methods that account for biases (control for confounders) to the utmost extent possible would be superior to the current evidence base. However, if it were true that the evidence be that clear and strong for all indications (as claimed by Dr Semrau), the ESC would clearly have formulated class I (= is recommended/ is indicated) recommendations with a higher level of evidence for all indications. If the comparative effectiveness were that unequivocal without a need for randomised studies (parachute analogy), it is very difficult to explain why the ESC did not formulate more "is indicated" recommendations.

The conclusions of our report are based on the available evidence and appear to be aligned with both the interpretation of clinical practice guidelines (above) and independently conducted systematic reviews. However, our conclusions are incorrectly recounted by Dr Semrau and Dr Nürnberg in their open letter. Just for clarity, this was our conclusion ([22], see p. 10 and p.15):

> *"The only available RCT failed to show that an add-on use of the WCD leads to a reduction in sudden cardiac death in patients with a recent myocardial infarction and impaired ejection fraction when compared to medical therapy alone.* ***Observational evidence shows that compliance with WCD is good in Austria, with poor compliance being a major limitation of the only available randomised evidence for WCD use****.*
>
> *Most of the evidence is observational and consists of studies including mixed populations in the analysis, leading to the inability to draw firm conclusions on indication-specific utility of the WCD. In the absence of comparative effectiveness evidence,* ***more RCT data are needed to justify continuing or expanding the use of WCD therapy in Austria****"*

Our conclusions are aligned with the only other independent systematic review and meta-analysis on the WCD, conducted by a team of researchers and cardiologists led by Ass. Prof. Ahmad Masri (MD). The authors used broader inclusion criteria (also all identified retrospective studies!) and concluded the following [26]:

> *"The rate of appropriately treated WCD patients over 3 months of follow-up was substantial; higher in-observational studies as compared with the VEST trial. There was significant heterogeneity.* ***More RCTs are needed to justify continued use of WCD in primary prevention****"*

Masri and colleagues [26] put their findings into perspective in the discussion section of their article published in the *JACC Clinical Electrophysiology*. Direct quotation (and cited sources from Masri et al. in footnotes):

> *"Our study puts into perspective the overall published evidence evaluating WCD use. All studies* were observational except VEST, in which the included WCD group was part of an interventional RCT[3]. ***Qualitative analysis shows that most studies were not indication-specific, thus diluting our knowledge on the indication-specific utility of WCD and in which patients it should be best used. Selection bias and including mixed indications in observational studies was likely the major determinant of the higher rate of appropriate treatment in patients prescribed a WCD as compared with the WCD arm of the VEST trial*** [3]*. This was also evidenced by the results of meta-regression showing a higher incidence rate of appropriate WCD therapy in patients with higher LVEF.*
>
> *In 2001, the FDA approved the first WCD manufactured by Lifecor (later acquired by ZOLL) based on 2 multi-center prospective observational studies (WEARIT and BIROAD), which enrolled 289 patients*[4]*. Both studies were grouped into one analysis based on FDA request, with each study treated as a subgroup. Over 901 patient-months, 6 out of 8 episodes of VT/VF were successfully treated by the WCD*[4]*. This was compared to historical controls who suffered SCD at home and called emergency services, in whom successful SCD resuscitation was 25%*[5]*. FDA concluded that the WCD device had greater efficacy than bystander resuscitation in the historical control group*[3]*. Besides the flaws of the design and the use of historical controls; only*

[3] Olgin JE, Pletcher MJ, Vittinghoff E et al. Wearable Cardioverter-Defibrillator after Myocardial Infarction. The New England journal of medicine 2018;379:1205–1215.

[4] Feldman AM, Klein H, Tchou P et al. Use of a wearable defibrillator in terminating tachyarrhythmias in patients at high risk for sudden death: results of the WEARIT/BIROAD. Pacing Clin Electrophysiol 2004;27:4–9.

[5] Feldman AM, Klein H, Tchou P et al. Use of a wearable defibrillator in terminating tachyarrhythmias in patients at high risk for sudden death: results of the WEARIT/BIROAD. Pacing Clin Electrophysiol 2004;27:4–9. [PubMed] [Google Scholar]

27% of patients in WEARIT were taking a beta-adrenergic antagonist, 34% were on anti-arrhythmic medications, and 45% were on inotropes. As such, the patients included in those studies do not represent the patients who are currently being prescribed WCD while on optimal medical therapy during the mandated waiting period prior to ICD consideration[6].

The recently published NHLBI and ZOLL-sponsored randomized VEST (Vest Prevention of Early Sudden Death) Trial would be the first RCT in 17 years testing WCD efficacy by randomizing patients post myocardial infarction with LVEF ≤35% to WCD or usual care. However, there was slow enrollment into the trial (2008 – 2017), leading to a change in the primary end-point from all-cause mortality to the less clinically relevant endpoint of SCD, which allowed for a decrease in sample size[3].The primary endpoint that the study was powered for (i.e. SCD) was not different between WCD + medical therapy arm (1.6%) vs. medical therapy only arm (2.4%), p=0.18. The secondary endpoint of all-cause mortality was advertised during the trial presentation to be lower in the WCD group as compared with no-WCD (3.1% vs 4.9%, p=0.04) which appeared to be driven partly by lower stroke rate in the WCD (monitored for atrial fibrillation in an open label study) group. However, the trial was not powered for all-cause mortality and multiple-comparisons correction, such as Bonferroni correction, was not presented [3].

***The WCD is one example in which evidence-based practice falls short**. In certain practices, the WCD has become the de facto standard of care for patients post MI with an EF ≤ 35% during the mandated 3 months waiting period for an ICD implantation for primary prevention. An online report in 2015 stated that >200,000 WCD have been prescribed[7]. This practice pattern is likely driven by the finality of SCD and partly by fear of litigation, despite the absence of data to support it. IRIS and DINAMIT both showed no overall mortality benefit to early ICD implantation [8,9] and DANISH showed no benefit of ICD on overall mortality over 5.6 years follow-up in NICM[10]*. The primary finding of our study is that the available **evidence from observational studies is fraught with poor methodology, selection bias, and confounding concerns**. The available evidence from the VEST trial shows that the rate of appropriate treatment by WCD was low (1 in 100 persons over 3 months) and that WCD was not associated with a decreased risk of SCD[3]. **These findings suggest that WCD should not be used in primary prevention until further RCT data support its use**."

It appears that numerous of the points of critique raised in the letter by Dr Semrau regarding the discussion section of our HTA report concern cited information from, among others, Ass. Prof. Masri and colleagues (instead of "personal opinions" of the AIHTA-authors, as attested by Drs. Semrau and Nürnberg). Especially the eighth point of critique (translated from German: "*own emotional/subjective expression of opinion, pre-emption of political decisions (exertion of influence)*") mostly regards quoted scientific discussion from cardiologists that we cited in the discussion section solely, and not "opinions" from AIHTA researchers. Therefore, instead of addressing each issue under the eighth section of critique in our point-by-point response, below, we provide references to the cited articles below. In case of disagreement with the systematic review results [26] or interpretation of evidence from our

[6] Al-Khatib SM, Stevenson WG, Ackerman MJ et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation 2017

[7] https://www.asahi-kasei.co.jp/asahi/jp/ir/library/business/pdf/150311.pdf. Accessed Nov 13th, 2018

[8] Steinbeck G, Andresen D, Seidl K et al. Defibrillator implantation early after myocardial infarction. The New England journal of medicine 2009;361:1427–36. [PubMed] [Google Scholar]

[9] Hohnloser SH, Kuck KH, Dorian P et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. The New England journal of medicine 2004;351:2481–8.

[10] Kober L, Thune JJ, Nielsen JC et al. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. The New England journal of medicine 2016;375:1221–30. [PubMed] [Google Scholar]

cited sources, we suggest an engagement in a scientific, constructive debate: we understand that the *JACC Clinical Electrophysiology,* for instance, accepts letter to the editors.

As we are an academic institute, we uphold scientific rigour, and the external validation of our systematic review results is essential. We therefore submitted a manuscript based on our research to *IJC Heart & Vasculature,* which was peer-reviewed by scientific cardiologists and subsequently accepted for publication [27]. For the sake of transparency, we will inform the editor in chief of the journal about this discourse.

In light of all of the above, based on the available evidence, the conservative perspective on WCD remains that more RCT data is needed to justify its routine use in primary prevention of SCD; this was highlighted by the independent systematic review conducted by Masri and colleagues [26] and our report. Based on the VEST trial results (incl. per-protocol analysis), it is unclear which patients should receive WCD therapy, because the evidence for benefit in post-MI patients was inconclusive. This is not to be confused with evidence of no effect, which is why we argue for further evidence generation. The primary authors of VEST themselves acknowledge in a very recent publication of VEST results that "it is unclear which patients should receive WCD therapy" to explain why they conducted a secondary analysis of VEST data to identify risk factors for arrhythmic death and overall mortality towards narrowing down selected patient groups that may benefit from wearing a WCD [28]. These are important analyses to both identify and select groups where WCD therapy is reasonable and inform patient selection also for future studies.

We sincerely hope to see more comparative trials of the WCD in promising selected patient groups. Such studies would enable guidelines with more specific, stronger recommendations of the use of WCD (=class I recommendations) and guide updated reimbursement decisions. We believe that supporting evidence generation is in the best interest of patients, cardiologists, and reimbursement decision makers to ensure that all those (and only those) who need the WCD have access.

No.	Point of critique (translated)	AIHTA response
1.	**Selective Reporting** In the HTA of Goetz, Wernly and Wild, so-called "selective reporting" is regularly applied. Publications, text passages or data and results that contradict the own opinion are not mentioned	This was an update systematic review: our selection criteria were, hence, based on the EUnetHTA report 2017 and AGENAS/LBI-HTA update report 2019 [8, 9]. A systematic review is based on a search and multiple databases and on a selection of studies (with pre-defined in-/exclusion criteria) that represent the best available [29].
1.1	**Exclusion of retrospective studies** - Goetz et al. categorically exclude retrospective studies, but at the same time criticize that there are not enough studies on the WCD and also resort to "personal opinion" in the discussion to support their views. ("Personal opinion" i.e. an opinion of any person, is the lowest level of evidence and does not require verifiable data).	It is correct that a personal opinion is the lowest level of evidence. We have excluded any kind of opinions – regardless whether these were held by scientific/ clinical experts, ZOLL or both – from the analysis and narrative synthesis of evidence (see results section of our report). Our inclusion criteria were pre-defined and were based on previous EUnetHTA 2017 and AGENAS/LBI-HTA 2019 reports [8, 9]. The rationale for exclusion of retrospective studies was explained in-depth in numerous Zoll-sponsored letter to the editors of the EUnetHTA report 2017: inclusion of retrospective studies would have not changed the comparative evidence [10]. The only other independently conducted systematic review [26] on the topic included all available studies (incl. retrospective studies) and did not derive at a different conclusion and critiqued the inability to draw firm conclusions on indication-specific utility of the device.
1.2	**Shortness of breath** - The RCT VEST reports several side effects that could potentially occur (clustered) with WCD. Goetz et al. correctly mention that skin irritation was significantly more common in the WCD group. Furthermore, it is mentioned that all other parameters were not different. The equally relevant side effect of shortness of breath, which occurred significantly less frequently in the WCD group, is not addressed. This can be considered critical, since shortness of breath is a parameter that can be caused by anxiety or other discomfort and thus is actually given special attention by the authors as a "Patient Reported Outcome".	Methodologically, this was a second HTA update of the EUnetHTA report and AGENAS/LBI-HTA report [8, 9]. The evidence synthesis from the last report conducted by AGENAS/LBI-HTA was not changed, but updated. Dr Semrau has already critiqued this point within the past assessment and the rationale was provided within the last letter we received on 18th of April 2019: [11].
1.3	**No overall appraisal of the results of the various analyses on the RCT** - Detailed presentation or discussion of the results of the ITT, as-treated, and per-protocol analyses is largely omitted on the part of the authors, Goetz et al. The opinion is expressed that an ITT analysis is basically the best form of analysis and that other results are negligible. This is in contrast to a scientific approach that basically considers all available analyses with an open mind. In the few sentences, which are to be found to the accomplished analysis forms, characteristics of As-treated analysis with those of the Per-Protocol analysis are mixed up and assigned to a large extent wrongly.	*We quote directly from a New England Journal of Medicine (NEJM) methods paper on primary outcomes in clinical research written By medical statistician Prof. Stuart Pocock and Prof. Gregg W. Stone (MD) [4]:* *"Analysis conducted according to the intention-to-treat principle is the main method used to make a valid comparison between two treatment strategies according to the treatments that were actually delivered to all patients who underwent randomization. When an intention-to-treat analysis fails to reach statistical significance, arguments are advanced that nonadherence and treatment crossovers may have masked real treatment effects and that as-treated or per-protocol analyses may get closer to the truth. Unfortunately,* ***the use of as-treated or per-protocol populations introduces selection bias, because patients who do not adhere to the treatment regimen and those who cross over to the other treatment strategy may have a different prognosis that is unrelated to actual treatment.*** *Hence, such analyses rarely influence conclusions regarding treatment efficacy that are based on the intention-to-treat principle. However, on-treatment analyses may be considered appropriate when safety issues are examined"* As seen within the ESC guidelines above [16, 25], these post-hoc analyses did not affect the interpretation of the VEST results from guideline groups either. And the Cochrane handbook [30] writes the following:

[11] please see https://eprints.aihta.at/1186/3/Stellungnahme_LBI-HTA_zu_Brief_von_Dr._Semrau_%28ZOLL_Medical%29.pdf

		*"An **ITT analysis maintains the benefit of randomization**: that, on average, the intervention groups do not differ at baseline with respect to measured or unmeasured prognostic factors. Note that the term 'intention-to-treat' does not have a consistent definition and is used inconsistently in study reports"* *Patients and other stakeholders are often interested in the effect of adhering to the intervention as described in the trial protocol (the 'per-protocol effect'), because it relates most closely to the implications of their choice between the interventions. However, two approaches to estimation of per-protocol effects that are commonly used in randomized trials may be seriously biased. These are: 'as-treated' analyses in which participants are analysed according to the intervention they actually received, even if their randomized allocation was to a different treatment group; and naïve 'per-protocol' analyses restricted to individuals who adhered to their assigned interventions. **Each of these analyses is problematic because prognostic factors may influence whether individuals adhere to their assigned intervention**. If deviations are present, it is still possible to use data from a randomised trial to derive an unbiased estimate of the effect of adhering to intervention (…). However, appropriate methods require strong assumptions and published applications of such methods are relatively rare to date. When authors wish to assess the risk of bias in the estimated effect of adhering to intervention, use of results based on modern statistical methods may be at lower risk of bias than results based on 'as-treated' or naïve per-protocol analyses."*
1.4	**Failure to find important literature** - Goetz et al. also criticise the fact that quality of life data was collected in the RCT but not published. However, corresponding results were already published in 2020. These were not addressed by the authors. (Cheung CC, Olgin J, Pletcher MJ, Hue T, Vittinghoff E, Lin F, Lai M, Lee BK. (2020) Abstract 14913: The Impact of Wearable Cardioverter-defibrillators on Quality of Life: Insights from the Vest Trial. Circulation 142, Issue suppl 317).	Conference abstracts do not fulfil our inclusion criteria that were defined a priori. Abstract 14913 was, hence, excluded from the synthesis. We explicitly state that conference abstracts are not subjected to peer review.
1.5	**Non-reporting of the patient survey of an included study** - Goetz et al. attach particular importance to patient-reported outcomes. Thus, two of the five defined endpoints of the HTA refer to corresponding outcomes (health-related quality of life/QoL and patient satisfaction). The prospective study by Garcia et al. included by the authors contains data on precisely this question (Europace 2021). However, the results of this publication were not discussed.	After carefully reading this paper again, we still could not find data on quality of life or satisfaction **measured with a validated instrument**. It appears that Garcia et al. [31] used a questionnaire with regard to user satisfaction using a **tool that was not scientifically validated** but – rather – created by Zoll[12]. Please see footnote 49 and our PICO question – a rationale was provided why these data did not meet our inclusion criteria.
1.6	**Incomplete/incorrect citation from European guidelines** - When listing WO indications from guidelines, certain indications were not reported. One of the indications not mentioned received an "IIa" recommendation in the cited guideline, (meaning: "should" be done). Goetz et al., on the other hand, incorrectly report that only "IIb" recommendations (meaning: "can" be made) were made in the guidelines.	Although Dr Semrau did not provide us with a reference of the specific guideline, we assume that he means the ESC guideline for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death [25]. It appears that the guideline was published/ available on Pubmed on the 21st of October 2022. At this time, the AIHTA update report was already published. Also, neither did we conduct a guideline synopsis nor was there room for a systematic search for guidelines within this update systematic review. After careful inspection of the mentioned guideline, it appears that there is a misunderstanding when it comes to the correct interpretation of evidence-based guideline recommendations: The mentioned **IIa** recommendation is applicable for a niche indication (adult patients with a secondary prevention ICD indication, who are temporarily not candidates for ICD implantation) and has **a level of evidence of C** (based on consensus of opinion of experts and/or small studies, retrospective studies, registries).

[12] It appears that the utilised questionnaire within the study was self-defined/ created by Zoll Medical. The questions were (for instance 5 point likert agreement scale: strongly agree to strongly disagree): "The LifeVest gives me peace of mind", "I sleep significantly better knowing I am protected by the LifeVest", "LifeVest has given me confidence to perform exercise or cardiac rehabilitation". Garcia et al. quote the following source for their questionnaire on patient satisfaction: https://www.innovationsincrm.com/cardiac-rhythm-management/2012/april/224-health-benefits-wcd

		There is no single class I (=is recommended) recommendation on the WCD. All available recommendations are class II recommendations meaning more broadly that (direct quotation from ESC terminology): "conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure" is present. While a IIa recommendation means that weight of evidence/opinion is in favour of usefulness/efficacy, a class IIb recommendation means that the usefulness/efficacy is less well established by evidence/opinion. Usually, guideline recommendations are only sporadically mentioned within these systematic update reviews of the clinical evidence. A guideline synopsis [17] would be the method of choice if one wanted to synthesise (and potentially contrast) available guideline recommendations with regard to the WCD. We urge the importance, however, to consider not only the recommendation, but also the level of evidence which was omitted by Dr Semrau.
2.	**Inadequate use of Risk of Bias (ROB) assessment tools GRADE**	
2.1	**Assessment** The GRADE group is a highly esteemed group of international scientists who have made a special contribution to evidence-based medicine. One of the basic approaches is to independently determine the confidence in effects for each parameter analysed. The GRADE tool used by Goetz et al. also serves this purpose. The evaluations derived by Goetz et al. from this tool, in relation to the WCD, show serious errors in places. However, the reason for this can only be understood to a limited extent, as it is not discussed in detail in the course of the study. For example: The total mortality together with the arrhythmic mortality" is assessed together. This cannot be considered adequate for various reasons. While all-cause mortality is the most reliable of all conceivable parameters, since there are no two opinions on death or non-death, the classification "arrhythmic mortality" is dependent on regularly incomplete data in the case of a (usually unobserved) sudden cardiac death, which, moreover, must be interpreted by people from a distance. So there are at least two relevant uncertainty factors here. One would therefore most likely place high confidence in all-cause mortality and possibly moderate confidence in arrhythmic mortality. Goetz et al., on the other hand, assign equal low confidence to both mortality parameters in this large randomised trial. This is incomprehensible because both the ITT and the as-treated and per-protocol analysis of the RCT consistently show significantly reduced all-cause mortality. Thus, while the most reliable parameter is given a low confidence rating, Goetz et al. give a high confidence rating to compliance, which in their own assessment was a major shortcoming of the study. This assessment is not consistent and not comprehensible.	We have separately GRADED these endpoints (please see previous AGENAS/LBI report [9] for a nuanced description). In order to be more concise for the update report (and given that this RCT evidence was not newly identified), we have shortened the GRADE evidence profile, by combining arrhythmic and all-cause mortality. It is still separately GRADED (all explanations are inserted in footnotes). Main reasons for downgrading **arrhythmic mortality**: deviation from intended intervention (especially due to poor compliance) and statistical imprecision. Main reasons for downgrading **all-cause mortality**: Besides the aforementioned reasons for downgrading, the endpoint "death from any-cause" was set as a **secondary outcome** in the included RCT. In addition, the study did not statistically correct the analysis for **multiple testing** (please see footnote c in GRADE table)" If Bonferroni-correction was applied, the endpoint all-cause mortality is not statistically significant anymore. We quote the NEJM methods paper again [4]: "If the primary outcome is negative, positive findings for secondary outcomes are usually considered to be hypothesis-generating." It appears that the opinion of Dr Semrau (regarding considering unadjusted stat. difference in all-cause mortality as moderate or high certainty evidence for strong additive benefit of WCD in post-MI) is not only in stark contrast to the AIHTA report using GRADE, the NEJM methods paper, but also to other scientific interpretation of how the stat. difference in all-cause mortality (note: unadjusted for multiple testing; not significant after adjustment for multiple testing) can be interpreted. Dr C. Israel – a cardiologist and advisory board member of Zoll – and colleagues [32], for instance, discussed, among others, VEST results within a narrative review: the difference within all-cause mortality was hereby addressed (although without GRADE assessment): *"(…) Perhaps, the most unexpected finding of the VEST trial was the observation that the secondary endpoint all-cause mortality was apparently reduced by the WCD.* ***This finding has to be considered hypothesis-generating and not confirmatory as the primary end point was not significantly different****. Even though it can only be speculated what the underlying mechanism for this observation might be, it is reasonable to assume that the WCD affected some patients' compliance*." We agree with Dr Semrau that generation of scientific hypotheses, speculations and assumptions are generally important. C. Israel and colleagues hereby further formulated very interesting hypotheses: The WCD could serve as a tool to increase patient awareness of a heart disease and improve compliance (e.g., within live-style modification). "Potential reductions in non-arrhythmic mortality related to better compliance, combined with a significant reduction of arrhythmic mortality, could result in reduced total mortality". Although interesting, these are defined by

		authors themselves – and need to be regarded as – hypotheses. [13] The authors correctly concluded that "(…) these hypotheses derived from the VEST trial merit validation in future, prospective studies". From a statistical standpoint, we agree that VEST was statistically underpowered (which was reflected within the domain "imprecision" within our GRADE assessment) and agree with the appraisal of Stuart J. Pocock and Tim J. Collier, when stating the following [12]: *"The hypothesis posed for VEST (Vest Prevention of Early Sudden Death Trial) (…) is: can a wearable cardioverter-defibrillator (WCD) reduce the risk of sudden death in the immediate post-MI period (up to 90 days) in patients with reduced ejection fraction (EF)? The trial recruited 2,309 patients within 7 days of hospital discharge after acute MI who had EF ≤35%. They were randomized in a 2:1 ratio to WCD + guideline treatment (n = 1,524) versus guideline treatment only (n = 778) and were then followed for 90 days.* *Results for the primary outcome (sudden death) and several pre-defined fatal and nonfatal secondary outcomes are shown in Table 2[note: within the publication of [12]]:. There is not a significant reduction in sudden death (p = 0.18), and hence, some have called this a "negative" trial. This we find too dismissive, because the observed difference in incidence of sudden death (1.6% vs. 2.4%) is in favor of WCD: a 32.8% relative reduction, but with a wide 95% CI ranging from a 21.2% increase to a 62.8% decrease.* ***A better term is to call the trial "inconclusive."*** *The problem is that the trial only has good statistical power to detect very marked treatment differences. For instance, had the total of 44 sudden deaths split 22 (1.4%) on WCD and 22 (2.8%) on control, then this hypothetical 50% risk reduction would have been significant with p = 0.02. Even if the trial had been twice as big (n = 4,604) the observed 32.8% reduction would still only have p = 0.06. It would require 3 times as many patients (n = 6,906) for such a risk reduction to achieve p = 0.02. This is the dilemma we face when undertaking trials of an intervention strategy (9), such as wearing a WCD in the VEST trial. Patient recruitment is much harder than in drug trials (in VEST it took almost 10 years to recruit 2,302 patients), so that definitive evidence of efficacy is much harder to achieve. A further issue is patients' compliance with wearing the WCD; this averaged around 18 h/day initially and declined to around 12 h/day by 90 days (including nonusers). Such reduced compliance over time must inevitably compromise the ability to prevent sudden deaths.* *Among the pre-defined secondary outcomes (…), the one that really matters is all-cause death, with a 90-day incidence of 3.1% on WCD versus 4.9% on control. This is a 35.5% relative risk reduction with 95% CI: 2.2% to 57.5% reduction; p = 0.04. It is a natural instinct to now label VEST as a "positive" trial. After all, surely a significant result for all-cause death justifies such a claim? But a more cautious interpretation is warranted. First, the result is statistically fragile: if there had been just 1 less death in the control arm, the p value becomes >0.05. Second, all-cause death is not the primary outcome. Third, it seems illogical that the WCD is equally effective in preventing both sudden and nonsudden deaths. Thus,* ***although it is plausible that a WCD really does reduce mortality, the VEST trial's evidence is not sufficiently convincing*** *by itself."*
2.2	IHE tool Assessment When using the RoB assessment tool for single-arm observational studies, Goetz et al. make two methodological errors, each of which leads to a systematically worse rating of all studies. In this tool, 20 questions are given on the quality of the studies to be assessed. Each positively assessed question results in one point. While the developers of the tool (IHE) remove certain questions that do not fit the context (and thus would always have to be answered with NO) before the analysis, Goetz et al. leave such questions in their analysis, so that - regardless of the quality of the study - all studies are already assigned negative points in advance. The IHE states in its guidance, for example, on the question: "Were outcome assessors blinded to the intervention that patients received": "Answer YES, when blinding is not applicable or is unnecessary ".	Assessing the validity of single-arm observational studies needs harmonisation throughout the health technology assessment world. As no clear guidance is available to reach overall bias by using the IHE-20 tool, we used the point system clearly and transparently that can be seen on page 25 within our report. In future HTA assessments throughout Europe, the risk of bias of single arm clinical trials will not be assessed anymore by following EUnetHTA guidance. Instead a high RoB will be assumed for these studies by default. Direct quotation of EUnetHTA new practical guideline 2022 [14]: *"**Uncontrolled trials per se are of very limited value for performing relative effectiveness assessment**. Although the (partial) use of some tools for RoB assessment is possible, the overall conclusion on the (very limited) internal validity of uncontrolled studies is very unlikely to be changed by RoB assessment. Therefore, RoB assessment is not required"*

[13] For the sake of transparency, it needs to be mentioned that the first author of the report and a significant proportion of all authors of this narrative review disclosed a potential conflict of interest in form of, inter alia, travel grants, lecture fees/ honoraria and being within advisory board of Zoll CMS.

	In a single-arm study, blinding is not appropriate because all patients receive the same intervention. Goetz et al. nevertheless answer the question with NO throughout. If only this one question were taken out of the evaluation, according to the evaluation scale of Goetz et al. there would already be 7 studies with moderate and only 3 with high bias risk (instead of 7 with high and 3 with moderate risk). Another factor to be questioned is how Goetz et al. chose the scaling for assessing very high, high, moderate or low bias risk. (It would also have been possible to add very low risk as a 5th grade). The easiest to understand would be 25% fulfilled conditions each to move from one risk class to the next (0-5 points very high risk, 6-10 points high risk, 11-15 points moderate risk, 16-20 points low risk). With this classification, all included studies fell at least into the moderate bias risk, three even into the low risk. In contrast, the classification chosen by Goetz et al., in which 57.5% are necessary to be considered a high bias risk (<57.5% a very high risk), in which 80% of the points are necessary to be considered moderate and 92.5% to be considered a low risk, does not seem comprehensible. This classification is not intuitive. Only because of the combination of these non-intuitive modulations, together with the retention of inadequate questions/questions not applicable to the underlying studies, the majority of studies appear to be at high risk of bias.	So we see this point of critique obsolete, as new HTA guidelines [14] will consider these studies to be of high risk of bias by default in future (without RoB assessment using a tool such as the IHE-20 checklist).
3.	**Inaccurate allegations** Furthermore, Goetz et al. make several claims which, on closer examination, are not technically or factually correct. For example, they suggest that the authors of the VEST study themselves "suspected" that the overall mortality in VEST was only significantly reduced by chance. In fact, as is usual and correct according to scientific standards, Olgin et al. merely noted that, if interpreted conservatively, one could just as well say that the result was due to chance. In reality Olgin et al. stated several times, including in the original publication, that a misclassification of arrhythmic mortality was the most likely explanation for the non-significant primary endpoint. It can be assumed that Goetz et al. were aware of this fact, since they cite a "personal opinion" in which Olgin holds this opinion. Furthermore, it must be noted that the results obtained in this HTA, which are already quite negative in themselves, are presented even more negatively in the course text. Some statements are therefore not covered by the reported results. For example, Goetz et al. state: "The trustworthiness of the trustworthiness of the evidence from observational studies was very low". This statement cannot be derived from the results presented.	As systematic review authors, we summarise evidence from randomised trials. We do not speculate. Clear evidence for superiority based on randomised studies is needed [4]. We wrote: "*The statistically significant reduction in all-cause mortality could also occurred due to chance, as suggested by the authors of the VEST study in the course of the first publication*" (see p.41). Olgin et al. [13] write that *"(…) the uncorrected P value for comparison was 0.04 in favor of the wearable cardioverter–defibrillator. However, this result was not corrected for multiple testing, and given the use of most such corrections, the difference between the device and control groups would not be significant.* ***Thus, the conservative interpretation is that this result was a chance finding****."* By writing that it "could also" have occurred due to chance, we meant that the authors discussed that the conservative interpretation is that this result was a chance finding. We apologise if this was not clear enough to the reader of our report. Regarding misclassification, the following is written by Olgin et al. [13]: *"The trial may have been underpowered to detect a beneficial effect of the wearable cardioverter–defibrillator on the primary outcome. Our power calculation anticipated a 58% lower rate of arrhythmic death with the device than without it. The power was, in part, reduced because 5% of the deaths were adjudicated as being of indeterminate cause and were thus removed from the primary analysis.* **Misclassification of the adjudicated cause of death may have further reduced the power for the primary outcome***. It is difficult to determine an arrhythmic cause of death accurately for unwitnessed deaths or deaths with limited documentation."*
3.1	**There is an additional and not comprehensible negation of the actual results** At best, the evidence of the studies was low (as shown above, it was rather moderate from an objective point of view), but by no means very low. Similar negative overstatements can be found in other parts of the HTA. For example, a study with "critical" ROB is mentioned as a result of the assessment. This study and/or the assessment of "critical risk of bias" does not exist within this HTA. The statement	Thank you for highlighting this import issue within GRADE methods. When following GRADE guidelines [33], the lowest certainty of evidence on the outcome level reaches the overall certainty of evidence for the whole body of evidence. We agree that the "overall certainty of evidence" to be derived from the endpoint with the lowest certainty of evidence does not perfectly reflect the actual findings of a systematic review more broadly. We believe that a range (certainty of evidence ranged from … to …) would be a good

	made therefore does not correspond to the documented results and therefore appears to have no relation to reality.	methodological improvement within GRADE. In so doing, the GRADE methods may be enhanced. Thanks for this valid point of critique that we may use in future HTA reports for deriving overall certainty of a body of evidence. For the credibility to consider results of a secondary endpoint as high certainty of evidence, please see answer to 2.1 For the term "critical RoB", please see explanation to the utilised ROBINS-I tool (answer to point 4.3)
3.2	**Another study is said to have shown an association between WCD and anxiety (Weiss 2019**). In fact, anxiety was asked before assignment to the groups and issuance of the WCD. Thus, there may be no association at baseline between a patient's level of anxiety and wearing the WCD. Goetz et al., on the other hand, incorrectly suggest that the WCD was causal for an increased level of anxiety and repeat this view in various places.	We appreciate our reports are read in-depth, but it appears that there is a significant misinterpretation of our text. Errare humanum est: We are happy to clarify what we have written/ not written. It is correct that we included the comparative registry-analysis of Weiss 2019 for our evidence synthesis**. It is incorrect that we suggested the WCD to be causal for increased level of anxiety based on this registry.** The only thing that a registry can provide are data for associations (not for causation!). We recommend the article of Altman and Krywinski for a detailed description of distinctions of these two terms [34]. Mingling association and causation is scientifically incorrect. As systematic review authors, we generally try to minimise interpretation of data within the results section and use the description of data used from the respective included studies instead. In the context of the registry, we have written the following: *"One registry study found **a statistical (positive) association between WCD and baseline anxiety** when comparing the anxiety score and rate of anxiety between WCD therapy (n=85) to standard care (n=38), with 41 ± 11 vs 39 ± 13 (p = 0.22) and 58.9% vs 29.2% (p = 0.02), respectively (State-Trait Anxiety Inventory). Further, there was a non-statistical trend toward better improvement of depression scores in patients with WCD, with a mean change in score points of -4.1 ±6.1 and -1.8 ±3.9 (p =0.09) in patients receiving WCD* and patients receiving no WCD, respectively. The change in anxiousness score was not statistically significantly different between patients enrolled in the WCD registry compared to patients receiving no WCD." The authors of the study themselves stated (direct quotation!) [35]: "Patients with subsequent WCD prescription showed a higher baseline state anxiety score (41 ± 11) compared to those without WCD (39 ± 13, p = 0.22), and had a significantly higher rate of anxiety (58.9% versus 29.2%, p = 0.02). **The association between WCD and baseline anxiety was still significant when adjusting for significant differences in baseline characteristics** between patients with and without WCD such as age, education level and history of malignancy (p = 0.02)."
3.3	**In addition, reference should be made again to an issue already briefly mentioned above**. Goetz et al. are of the opinion that intention to treat is the superior form of analysis to all others. This leads them to the assumption and statement that no attention should be paid to other types of analysis, as already noted above. This is not a scientifically defensible view. The aim of science is to ask questions openly and to consider them logically, neutrally and objectively. For example, ITT and Per-Protocol Analysis (PPA) have different questions: ITT asks what the outcome is after allocation of a therapy, while PPA asks what the outcome is after application of a therapy (similar to as-treated analysis). Both questions have their scientific justification. In case of ambiguity, it is always useful to look at different sides - in this case analyses. This is omitted by Goetz et al. or cannot be understood on the basis of the published HTA.	In the results section, we have both reported the ITT results and the results of the PPA and as-treated analysis. Please have a look at page 34 and the data-extraction table (Table A-1). We agree that all these analyses have their own purpose. This is exactly why we have both extracted and synthesised the evidence with regard to ITT and other analyses. But as correctly stated by Dr Semrau, each form of analyses has their own strength and limitations. While forms of on-treatment analyses (for instance) may be considered appropriate when safety issues are examined, the ITT is still the main method used to make a valid comparison between treatments. We quote the NEJM methods [4] paper again: *"**Analysis conducted according to the intention-to-treat principle is the main method used to make a valid comparison between two treatment strategies** according to the treatments that were actually delivered to all patients who underwent randomization. When an intention-to-treat analysis fails to reach statistical significance, arguments are advanced that nonadherence and treatment crossovers may have masked real treatment effects and that as-treated or per-protocol analyses may get closer to the truth**. Unfortunately, the use of as-treated or per-protocol populations introduces selection bias, because patients who do not adhere to the treatment regimen and those who cross over to the other treatment strategy may have a different prognosis that is unrelated to actual treatment**. Hence, such analyses rarely influence conclusions regarding treatment efficacy that are based on the intention-to-treat principle. However, on-treatment analyses may be considered appropriate when safety issues are examined."*

3.4	**Instead, attempts are made to discredit forms of analysis other than ITT** This leads to confusion between the properties of As-treated and Per-Protocol analysis. When looking objectively at the results for all-cause mortality - the most objective parameter imaginable - it is significantly reduced in the WCD group in ITT, as-treated and per-protocol analysis. (This parameter was assessed by Goetz et al. in the GRADE assessment as the only parameter with a high risk of bias or low confidence).	See above. ITT is the gold standard → confirmatory [4].
4.	**Inconsistency of assessment and reporting**	
4.1	The risk of bias in the RCT is assessed inconsistently and logically incomprehensible. Thus, parameters with high confidence are assessed as low confidence (total mortality), parameters with different confidence are assessed as the same (total mortality, arrhythmic mortality) and, for various reasons, less confidence is assessed as the highest confidence (compliance). In addition, parameters that are always automatically recorded in the same way and are independent of the study type or of a control group (e.g. compliance) are assessed with two levels of higher trustworthiness in the RCT than in the observational studies.	We do not fully understand this point of critique. But we believe answer to 2.1. gives justification to our reasoning that can also be found in our report. It is aligned with the interpretations of VEST by both renowned guidelines such as the ESC (see above) and the other independently conducted SR by Masri and colleagues [26].
4.2	In the RCT, the Risk of Bias tool states "some concerns" with regard to the measurement of the outcome parameters, with the indication that the assessors of the Adjudication Committee may have known which intervention which patient had received (Table A-4). This statement is a serious, incomprehensible accusation, as the RCT was apparently conducted correctly and the adjudication committee was also fully blinded. The original paper by Olgin et al. explicitly states: "The cause of death was adjudicated by an independent panel of experts Who were unaware of the group assignments (and therefore did not have any data from the wearable cardioverter-defibrillator)". The assumption on which the authors' statement is based is not explained further in the text. Because of this, it is also not comprehensible how Goetz et al. arrive at the overall assessment "Overall risk of bias: high".	Please see Table A-4 in our report. The risk of bias for the ITT effect of VEST is high due to bias due to deviations from intended intervention (low compliance). The risk of bias for the PP effect in VEST was high due high bias due to missing data and the fact that PP/as-treated analyses represent inadequate methods to fully estimate the effect of assignment to intervention (= the effect of interest for the systematic review at hand).
4.3	In general, it should be noted that Goetz et al. make several unspecific, general criticisms without specifying them further or clarifying the underlying problem and its potential impact (quote: "Some concerns were additionally found with bias in the measurement of outcome and selection of reported results."). In addition, the reporting of own results seems inconsistent in parts. For example, the result of the ROB assessment of the observational studies (tool of the IHE) is reported differently in two places in the HTA.	We used the terminology of the respective risk of bias tools. These consider the following options for domain specific and overall bias of a study: RoB v.2 for RCTs [36]: low, some concerns, high [36] ROBINS-I for comparative studies [37]: low risk, moderate risk, serious risk, critical risk IHE-20 for single-arm studies [38]: Low, moderate, high, very high using a self-defined scoring system.
4.4	Elsewhere, the term "critical risk of bias" was used for a study in the text, although this term can be found neither in the document itself nor in the corresponding table.	See above (ROBINS-I checklist) and table A-5
5.	**Omission of scientific discussion of results**	
5.1	A decisive factor for a scientifically sound, neutral evaluation of a study is an open discussion of the results at the end. Thus, in the case of the VEST study, it is of course possible that, as Goetz et al. assume, the reduction in all-cause mortality may have been random. However, it is just as likely that this can be assumed to be real. This is supported by various facts listed above. An open discussion of the results of all points speaking for and against was omitted or at least not documented in the HTA. Furthermore, it must be noted that Goetz et al. do not consider or discuss effects	Basic biomedical research tests hypotheses [39, 40]. Scientifically, we can either a) reject H0 and accept H1 as there is sufficient evidence (based on primary endpoint and ITT) or b) not reject H0 because of insufficient evidence [6, 39, 40] As an HTA institute, we assess the evidence – from randomised studies – that are able to sufficiently show that H0 can be rejected and write a report based on this evidence. We do not speculate and postulate what would have happened if… The facts are: VEST [13] failed its primary endpoint (h0 cannot be rejected = insufficient evidence) with poor compliance being a major limitation. Secondary post-hoc analyses on VEST [41] can be used to formulate hypotheses, as done by numerous authors. These need to be confirmed in future trials. Based on real-world evidence

	(such as arrhythmic mortality or total mortality) and their influence (direction of influence) in the sense of a sensitivity analysis. Goetz et al. rightly criticise the relatively poor compliance in the RCT. However, the consequence of a possible better compliance on the mortality outcome is not considered or included and discussed. It can be assumed that with better compliance, the reduction in mortality would have been even greater. Sixteen patients with adjudicated sudden cardiac death were not wearing the WCD at the time of death. With an effectiveness of around 95% (Nguyen 2018), it is legitimate to postulate that a large proportion of these patients would have remained alive if they had been wearing their WCD. This would correspond to up to 1% absolute further mortality reduction in an already significantly reduced overall mortality (at best WCD 2.1% vs. control 4.9% instead of 3.1% vs. 4.9%).	[31, 35, 42-54], we know that the compliance with WCD is good (which is in fact stated within our conclusion of the report), being a major limitation of VEST [13]. We acknowledge, however, that there are different standpoints with regard to what VEST results indicate. After VEST failed its primary endpoint, there were essentially two scientific standpoints/ opinions what VEST implies: 1. Although VEST failed its primary endpoint, evidence is still **inconclusive** and **VEST does not provide evidence against the WCD** as highlighted by, for instance, Lee et al. [20]. In this context, results of the secondary endpoints and per-protocol analyses could be used as data for the hypotheses that some selected patients within the post-MI patient group would still benefit from the WCD, although VEST failed to show an arrhythmic mortality benefit. Fauchier et al. [55] hereby also state the need to optimise patient selection and highlight that the risk for sudden cardiac death could be considered. OR 2. VEST results are similar to DINAMIT and IRIS and would "(…) provide **robust evidence showing no role for defibrillators,** whether implantable or wearable, **within 40 days after myocardial infarction** in the absence of sustained ventricular tachycardia or fibrillation (…)" as Stecker and colleagues [21] point out. We fully agree with Dr Semrau when saying that one can postulate and hypothesise about the add-on benefit of WCD in selected post-MI patients. We also agree that it would be an oversimplification to discredit the utility of the WCD fully on the basis of VEST. In fact, we have clearly written this in the discussion of the update report 2022: Absence of evidence should not be confused with evidence for no effect. We even highlighted that there are plausible indications for WCD use despite sufficient RCT evidence (please see p. 41 in our report [22]). It appears that guidelines also interpret the evidence as inconclusive instead of evidence favouring the null hypothesis: The ESC guideline task force, for instance, "(…) does not recommend routine use of the WCD in the early post-MI phase. Nevertheless, the use of the device **may be considered in selected post-MI patients deemed to be at high risk for SCD**" [25]. So we would agree with the standpoint of Lee et al. [20] and Fauchier et al. [55] that VEST results do not necessarily provide evidence against the role of a WCD (as highlighted also in our report). But in fact, it does not matter which opinions from cardiologists we agree upon. There are no further RCTs that can confirm one or the other assumption. It is beyond our remit to speculate and put weight on numerous assumptions, as suggested by Dr Semrau that we should do. This is not how scientific evaluations are conducted. Sensitivity analysis are important, if decisions are made based on assumptions (e.g., had they worn their WCD, if assuming that, something can be postulated). We acknowledge that modelling approaches do exist. We are not modellers, we are systematic review authors summarising clinical comparative evidence solely. However, hypotheses are important and can encourage further randomised controlled studies – for instance in selected post-MI patients that would in theory benefit most from WCD. Given the excellent compliance shown in real-world evidence, it seems unlikely that patient compliance is as poor as it was in VEST again.
6.	**Criticising data that is missing but actually exists and has been ignored**	
6.1	As already described under "selective reporting", Goetz et al. do not report on the patient-reported outcomes (PROs). outcomes (PRO) of the study by Garcia et al. included in the HTA. This is not comprehensible, especially considering the fact that QoL and PRO are declared to be among their most important five outcomes. Moreover, it does not seem logical to criticise the lack of corresponding data when these are demonstrably available in the included studies. Goetz et al. complain about selective reporting because the QoL data of the RCT were not included in the original paper by Olgin et al. This fact, too, seems hardly understandable, since the QoL data of the RCT had already been published in a separate publication when they prepared their HTA	This first point is repetitive. Answers above. In May 2022, we contacted the study authors of VEST and were informed that, while there was no publication available yet, a manuscript was in preparation. With regard to the rationale for not including retrospective studies, please see the answers to the letter to the editors (four out of nine authors received financial support from Zoll GmbH for the submitted work) [11] published within the Dove press. The authors of the EUnetHTA report [10] clearly provided a sound rationale for their selection criteria. Hence, we did not see a need for including retrospective studies.

	update, but were not identified by them. A request for this to the study leader (Olgin et al.) was apparently not made. Goetz et al. excluded retrospective studies in principle (analogous to the predecessor HTAs of LBl/aihta). At the same time, they criticised the fact that there were predominantly studies with mixed indications for WCD and that only a few small studies with homogeneous indications were available. In fact, there are many large register studies. The largest of these include the one by Epstein et al. Ellenbogen et al. (JACC 2017). Both included more than 8,000 patients each and both only include patients from one indication each.	Again, it makes it really hard to follow the point of critique if no source is adequately referenced. We assume that the following articles are meant by Dr Semrau: **Epstein AE**, Abraham WT, Bianco NR et al. Wearable cardioverter-defibrillator use in patients perceived to be at high risk early post-myocardial infarction. J Am Coll Cardiol 2013;62:2000–2007. **Ellenbogen KA**, Koneru JN, Sharma PS, Deshpande S, Wan C, Szymkiewicz SJ. Benefit of the Wearable Cardioverter-Defibrillator in Protecting Patients After Implantable-Cardioverter Defibrillator Explant. JACC: Clinical Electrophysiology These single-arm retrospective studies were included in the only other independently conducted systematic review from Masri and colleagues [26] and there is no notable change with the overall conclusion and interpretation of the evidence from these researchers (in fact, these researchers saw the observational evidence as even more flawed as we have). Selection bias and including mixed populations (diluting the ability to draw firm conclusion on indication-specific utility) was first concluded by Masri et al. Our conclusion may be seen as a confirmation of conclusion of SR conducted by Masri et al. in 2019 [26].
7.	**Lack of understanding of the therapy to be evaluated, inadequate questions**	
7.1	Goetz et al. repeatedly criticise that the studies do not explicitly state whether the WCD is used for primary or secondary prevention of sudden cardiac death. However, this deficiency only appears to exist. The indications mentioned in the publications themselves contain the answer to the question of whether it is primary or secondary prevention. For example, patients after explantation are always counted as secondary prevention, whereas the protection of patients with myocarditis or after a myocardial infarction is initially considered primary prevention. It is generally recommended to involve specialists, in this case a cardiologist, in the preparation of an HTA for supportive assessment.	We would never presume lack of understanding out of politeness within the framework of an academic discourse, but: "Homo sum, humani nil a me alienum puto". However, there is a misunderstanding regarding primary and secondary prophylaxis on the part of Dr Semrau. Primary prevention involves the use of ICDs in patients who have not yet experienced a life-threatening arrhythmia but are at high risk of developing one. These patients may have a history of heart disease or other risk factors that increase their likelihood of developing a dangerous arrhythmia. ICD placement is recommended for primary prevention in patients who have a reduced ejection fraction (EF) of less than or equal to 35% and who meet other criteria as outlined in guidelines. Secondary prevention, on the other hand, involves the use of ICDs in patients who have already experienced a life-threatening arrhythmia, such as ventricular fibrillation or ventricular tachycardia. These patients are at high risk of recurrent episodes and benefit from ICD placement to prevent future events. So, to use the examples given, myocarditis or a previous myocardial infarction do not represent primary prophylactic indications. Rather, these entities are etiologies. Similarly, explanted ICD systems do not necessarily represent a secondary prophylactic setting, as the initial ICD placement may have been for primary prophylaxis. These are indeed delicate clinical situations where it is essential for clinically active physicians to be involved, as was the case in this review.
7.2	Furthermore, Goetz et al. repeatedly criticise the fact that it is not regularly stated whether the prescription of the prescription of the WCD is a supplement to pharmacological therapy or a substitute for hospitalisation. However, the question is neither technically nor factually correct, because the WCD does not treat the underlying disease, which is done by the individually prescribed drugs that are necessary in every case, but it protects against death in the event of sudden cardiac arrest (VT/VF). The question of whether a hospital stay is replaced, which can be asked completely independently of this, depends solely on how high a patient's individual risk of sudden cardiac death is assessed by the attending physician.	The position paper of the DGK [56] on the wearable cardioverter defibrillator states clearly that in certain situations, a WCD can replace hospital observation/ monitoring in the hospital. If the argument of Dr Semrau is to be true (that WCD monitoring cannot replace hospital monitoring), it would mean that the use of the WCD is always used in addition to standard care. It appears that this is in stark contrast to both the DGK position paper [56] and common clinical experience. We urge the need for more clarity with regard to specific use cases of the WCD. Evidence-requirements for strong utility are highly dependent on the question whether something is given as an add-on treatment or as a replacement.
7.3	Goetz et al. repeatedly point out that most studies only report on mixed populations. They deduce from this that no indication-specific conclusions can be drawn. Against the background of the purpose of WO therapy, the question does not seem reasonable. The WCD does not treat indications, but arrhythmic events that are absolutely comparable for different indications. It is possible that different indications have a different risk. However, this is irrelevant to the question of how high the success rate is after adequate WCD therapy. Goetz et al. could answer this question based on their own collected data or by referring to other HTAs and meta-analyses. However, there is no reference to this in the document.	This point is essentially a repetition of the second part of point 6.1. Please see answer above.

8.	**Own emotional expression of opinion, anticipation of political decisions (exertion of influence)**	
8.1	By definition, an HTA should collect, document, and qualitatively evaluate the available evidence on a specific therapy in a neutral, open-ended, and factually correct manner, e.g., to provide political decision makers with a neutral basis for decisions. Goetz et al. overstep their boundaries as HTA authors and thus move even more obviously away from an independent, scientific claim. It can be implied that with their formulations they take decisions out of the hands of policy makers and give their personal understanding and thus the line of march. In addition, in their opinion, they denounce inadequate behaviour on the part of governments, health systems, physicians, and industry. Thus, their HTA manifestly becomes indicative of pre-established particular interests. Goetz et al. generally attack medical technology assessment and approval in Europe (CE mark) and present the WCD as a prime example of a product that has entered the European market virtually untested. Interestingly, however, the WCD does not serve as an example, because the WCD was initially approved in the USA by the U.S. Food and Drug Administration (FDA) on the basis of the results of clinical studies. The argumentation of Goetz et al. reveals throughout that not data and facts, but emotions and misconceptions underlie and shape their work.	A discussion is structured in the following way: Summary of findings, Embedding new knowledge into existing knowledge, contextualisation, limitations of report, conclusions For contextualisation only, we have also cited opinions from clinical experts/ cardiologists with an evidence-based medicine approach (note: these were neither our opinions/ "emotions" nor are these "attacks"): "**WCD as an example in which evidence-based practice falls short" (incl. FDA-approval):** **A. Masri**, A. M. Altibi, S. Erqou, M. A. Zmaili, A. Saleh, R. Al-Adham, et al. Wearable Cardioverter-Defibrillator Therapy for the Prevention of Sudden Cardiac Death: A Systematic Review and Meta-Analysis. JACC Clin Electrophysiol. 2019;5(2):152-161. Epub 2019/02/21. DOI:10.1016/j.jacep.2018.11.011. **Discussion of new medical device regulation replacing the old CE mark regulation:** **A. G. Fraser**, R. A. Byrne, J. Kautzner, E. G. Butchart, P. Szymański, I. Leggeri, et al. Implementing the new European Regulations on medical devices—clinical responsibilities for evidence-based practice: a report from the Regulatory Affairs Committee of the European Society of Cardiology. Eur Heart J. 2020;41(27):2589-2596. DOI: 10.1093/eurheartj/ehaa382 **Spin bias in VEST**: **J. Mandrola**. The VEST Trial Failed, and So Did the Press Release. 2018 [cited 15.04.2022]. Available from: https://www.medscape.com/viewarticle/893756[14]
	This HTA was conducted contrary to the applicable standards and the requirement for an HTA to present a comprehensive, neutral picture of the data on a therapy. It is neither open-ended nor neutral or objective. Rather, it can be classified as tendentious. This inadequate approach deprives various parties of the opportunity to form an objective, neutral picture of a product, such as the WCD in this case. Politicians in particular trust that an appropriate institute such as AIHTA will produce careful, neutral, scientifically correct analyses that do not have to be subjected to further scrutiny. Due to the manuscript here, which does not meet scientific standards, it is not possible for politicians to make a scientifically sound, neutral decision for or against a life-saving therapy.	It is incorrect to say that the HTA does not meet applicable standards, and we kindly request such statements to be avoided. Our HTA reports follow the principles of evidence-based medicine - currently the highest international standard for summarizing clinical evidence. In this specific case, a systematic literature search was conducted in international research databases and the clinical studies were evaluated according to scientific evidence-based medicine criteria. The randomized controlled trial is thereby considered the gold standard for the evaluation of medical procedures. In this context, we would like to remind the reader that we cannot emphasise on unproven assumptions based on single-arm studies, expert opinions or opinions from Zoll, but apply strict evidence based medicine principles. Our job is to synthesise the available evidence with strict and neutral evidence-based medicine criteria. Such an assessment does not change if assumptions and low-level single-arm evidence is promising, which is essentially what Dr Semrau is suggesting. Scientific and independent scrutiny is highly important and should take place within an editorial of an academic journal and independent researchers (ideally without potential conflict of interests) job is to scrutinise the rigour of a scientific article. As we uphold a high scientific standard and engage within an independent peer review process, we have submitted a scientific manuscript to IJC Heart & Vasculature. The referees (independent cardiologists) critiqued the systematic reviews minimally and provided us with valuable constructive scientific feedback before suggesting to accept the article for publication [27].

[14] And Spin bias more broadly: https://catalogofbias.org/biases/spin-bias/

	A direction is being set that, in the worst case scenario, will hinder or even prevent adequate care for patients at high risk of sudden cardiac death. Flawed or knowingly influenced policy decisions may also limit doctors' treatment options. This happens, for example, when a product is withdrawn from the market due to a refusal to reimburse it, thus depriving treating physicians of a treatment option. Therefore, a trustworthy and absolutely neutral evaluation of the evidence, and thus of the safety and effectiveness of a product, is essential, as is that of the economic components.	Adequate care is to be defined by evidence-based guidelines (indication-specific as highlighted by guidelines above): We acknowledge that WCD might and should be indicated in some selected patients [25]. We assessed the comparative evidence. We did not judge in which scenarios the WCD is adequate and necessary when randomised evidence confirming superiority of add on use of WCD in post-MI patients is missing (= job of guidelines for clinicians)! Our evidence synthesis is based on available research and our interpretation of evidence is aligned with evidence based guidelines and the only other available recent systematic review without industry-sponsoring [26]. We agree that neutral and objective communication about the facts of the WCD is key for adequate shared decision making. Nobody would disagree that the WCD technically works. Otherwise the device would have never received CE marking. We have also highlighted that the technical performance and safety of WCD are adequate. But evidence confirming superiority based on hard endpoints is a completely other research question. Evidence-based guidelines correctly interpret VEST results hereby (= by concluding only on the statistically conservative interpretation of VEST), as highlighted above.

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