Ludwig Boltzmann Institut
Health Technology Assessment

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Response to the letter from Dr. Semrau (dating April 18th 2019) on the health technology assessment (HTA) of the wearable cardioverter defibrillator (WCD)

We appreciate the critique expressed by Mr. Semrau, reimbursement manager of ZOLL Medical®. Rather than responding – bilaterally – to the letter in German language, we decided to engage in a scientific debate and answer the questions related to the EUnetHTA assessment conducted in 2016 [1] and the recent update 2019, conducted in collaboration with the Italian HTA institute AGENAS (project leader and 1st author of the update).

Due to the fact that the full report needed the approval of the Italian Ministry of Health before starting the public consultation, only a preliminary German executive summary was available online [2]. The full report was peer-reviewed by two experts (by a methodologist of LBI-HTA and by a cardiologist, representing the European Society of Cardiology) and is currently in public consultation: http://www.salute.gov.it/portale/temi/p2_6.jsp?id=1202&area=dispositivi-medici&menu=tecnologie (accessed on the 28.05.2019). Comments and critique can be put forward to be considered in the revision of the final report.

The results and the conclusions of the update (AGENAS/ LBI-HTA) assessment is in line with another recently conducted systematic review and meta-analysis published in the Journal of the American College of Cardiology. Masri, Altibi, Erqou, Zmaili, et al. [3] state that the finding of their systematic review

> *"(…) is that the available evidence from observational studies is fraught with poor methodology, selection bias, and confounding concerns. The available evidence from the only RCT, 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. These findings suggest that WCD should not be used in primary prevention until further RCT data support its use".*

Finally, the authors conclude that their analysis

> *"(…) highlights the limitations of the published data that justified the continued use of WCD for years. More RCT data, including cost analyses, are needed to justify the continued use of WCD in primary prevention".*

As mentioned previously, we appreciate the scientific debate that improves the quality of our and other HTA reports with the aim of delivering patients safe and effective technologies. Hence, we translated the critique from the e-mail sent by Dr. Semrau (April 18th 2019) into English and equally formulated our reaction to it. The criticism and our reaction are divided into six points:

1. the first four points of criticism concern the previous EUnetHTA HTA conducted in 2016 [1], authored by LBI-HTA;
2. the fifth point of criticism deals with the update assessment conducted by the Spanish HTA institute Avalia-t [4]; and
3. the sixth point concerns the most recent update assessment led by AGENAS [2] in collaboration with LBI-HTA.

Due to the fact that we did not co-author the update assessment of Avalia-t, we will answer only the points of criticism one to four and six.

No.	Point of criticism (translated)	Author's reply
1	Inclusion criteria were too strict. For the assessment of effectiveness, only RCTs were considered appropriate for inclusion. For the assessment of safety, only prospective studies were included.	The rationales for these decisions were outlined and explained accordingly in our two reply letters to the editor [5, 6].
2	The choice of comparators is not adequate: ICD, guideline directed pharmacological therapy, catheter ablation, external defibrillators.	In the 2016 EUnetHTA assessment [1], we selected the comparators based on discussions with clinicians and the broad list of indications that could be included in the WCD CE mark. The 2019 update AGENAS/ LBI-HTA assessment consulted Italian clinicians, who suggested narrowing down the list of indications. We have recognised the need for restricting the comparators in the update of the assessment to those that reflect current clinical practice in order to include more "realistic comparators".
3	Focus group analysis cannot provide any useable statements on the acceptance of the WCD (none of the patients had an experience with the WCD and it is not clear to what extent the patients were informed about the WCD).	We have also already commented on the focus group analysis in our two reply letters to the editor [5, 6] that were written as a reaction to two letters to the editor concerning the 2016 EUnetHTA assessment [6, 7]. We were transparent with the composition of the focus group participants and with the aim of the patient involvement. The aim was to understand the patients' perspective, to identify possible neglected outcomes, and to evaluate the *possibility* of the WCD use. We are aware of the limited number of patients. Our intention was to explore views and to learn about possible variations in experience and the meaning of this experience. We summarized the input from patients in a separate chapter of the 2016 EUnetHTA assessment [1] – separately from the evidence of high quality clinical studies. Patient input was used to merely complement the HTA and to enrich the information that can be extracted from the literature.

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4	Two letters to the editor have been published by Sperzel et al. that both question the 2016 EUnetHTA assessment [1] by the LBI.	We appreciate the scientific discussion on the assessment that was created in collaboration with several HTA bodies in EUnetHTA. Two reply letters were sent to the editor that can be accessed (open access): • 1st reply letter Sperzel J, Staudacher I, Goeing O, et al. Critical appraisal concerning "Wearable cardioverter defibrillators for the prevention of sudden cardiac arrest: a health technology assessment and patient focus group study". Med Devices (Auckl). 2018;11:201–204." • 2nd reply letter Ettinger S, Stanak M, Szymański P, et al. Reply to: Comments on the authors' reply to the critical appraisal concerning "Wearable cardioverter defibrillators for the prevention of sudden cardiac arrest: a health technology assessment and patient focus group study". Med Devices (Auckl). 2019;12:129-131
5	Update of the EUnetHTA report by the Spanish ACIS [4]	See rationale above: since LBI-HTA was not part of this assessment, no statement on this report can be given. The report is published in Spanish language.
6	Substantial errors from the 2016 report [1] (e.g., comparators) were also made in the new update assessment [2, 8]. The consensus process between AGENAS and LBI-HTA to use "realistic" comparators was nebulous, showing that the comparators used in the 2016 assessment are incorrect. The reason is that the comparators mentioned in the 2019 update were corrected to reflect "realistic" comparators.	The selection process of comparators in 2016 was done with the partners as well as clinical experts consulted in the assessment. In 2019, the selection process was based on AGENAS researchers consulting their clinical expert from the Italian context. Based on this information, there was a dissent between AGENAS and LBI-HTA: between "realistic" indications and indications based on the broad CE-mark. After a meeting of both institutes, we finally chose the narrow, more realistic indication group that can be found in Table 1 in chapter 2 of the 2019 report - currently in the public consultation phase [8].

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	The term "Wirksamkeit" was confused with the term "Effektivität" in the assessment. In the context of the WCD, the "Wirksamkeit" would have long been proven by case series studies, while the "Effektivität" is to be evaluated.	In medical literature, the term "efficacy" and "effectiveness" is neither defined in a standardised way, nor is there a definite German translation [9]. Windeler and Antes [9] discuss these problems and suggest that the term "Wirksamkeit" and "Nutzen" may be good, yet still not perfect, terms to translate efficacy and effectiveness respectively. Regardless of the precise terminology used, RCTs are essential to establish the "Wirksamkeit" of an intervention (and whether a clinical benefit can be proven). Especially in the context of the WCD, Masri, Altibi, Erqou, Zmaili, et al. [3] discussed the FDA approval process in 2001 (that Dr. Semrau mentions): "The FDA approved the first WCD manufactured by Lifecor (later acquired by ZOLL) based on 2 multicenter prospective observational studies (WEARIT and BIROAD), which enrolled 289 patients (…). Both studies were grouped into 1 analysis based on FDA request, with each study treated as a subgroup. Over 901 patient-months, 6 of 8 episodes of ventricular tachycardia/ventricular fibrillation were successfully treated by the WCD (…). This was compared to historic controls who suffered SCD at home and called emergency services, in whom successful SCD resuscitation was 25% (…). The FDA concluded that the WCD device had greater efficacy than bystander resuscitation in the historic control group (…). Besides the flaws of the design and the use of historic controls; only 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 before ICD consideration" (see page 7, 8 in [3]). For further references of the case series studies and the FDA approval, the reader is referred to Masri, Altibi, Erqou, Zmaili, et al. [3].

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		In addition, also a guideline by the European Society of Cardiology [10] stated in 2015 that "(…) this device can save lives in vulnerable patients, but its efficacy has not been validated" (see p. 19). Therefore, it was a class IIb recommendation meaning that the "(…) usefulness/efficacy is less well established by evidence/opinion" (see p. 6).
	The definition of primary endpoints within an HTA is not common and is a bit astonishing.	Please see page 5 in the EUnetHTA guideline about endpoints used for relative effectiveness assessments [11]: "In any REA a hierarchy of endpoints should be established (e.g. primary endpoints, secondary endpoints) even if all endpoints will be simultaneously assessed."
6.1.	No presentation of the as-treated analysis and "wrong" interpretation that the significant difference in all-cause mortality may be a chance finding.	**Ad. as treated analysis**: The results of the as-treated analysis were not extracted due to inferiority grounded in a higher likelihood of bias when compared to the intention-to-treat analysis. It is true that the favourable results of the as-treated analysis may indicate that poor compliance may have had an influence for the fact that there was no statistical difference in arrhythmic mortality. It was, therefore, stated in the report that it is essential to conduct further data analysis to explain factors contributing to the low compliance and identify who wore the device. It would then be potentially feasible to elaborate on the reasons for compliance/non-compliance (ev. in subgroups). **Ad. Chance finding:** We did not claim that the significant difference in overall mortality was a chance finding. Rather, we highlighted that the risk of the difference being a chance finding is increased because it is uncorrected for multiple testing, with a p-value for comparison of 0.4. In fact, Olgin, Pletcher, Vittinghoff, Wranicz, et al. [12] clearly stated

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		themselves in the discussion of their article in the NEJM that the conservative interpretation is that this result was a chance finding.
6.2.	Incidence of VT/VF was extracted and presented in the review, yet the RCT did not report on this data. Also, the 2018 assessment team used VT/VF as an endpoint even though the WCD could not influence the incidence of VT/VF.	We appreciate this point of critique. Indeed, we wrongly extracted the incidence of VT/VF, where in fact, this data only refers to the rehospitalisation due to VT/VF. Therefore, this will be corrected accordingly. We did, however, not claim that the WCD has an influence on the incidence of VT/VF. We selected the outcome in analogy with the previous EUnetHTA report [1]. We did so, even though in our opinion, the incidence of VT/VF is not an outcome per se (WCD does not influence it), but it may still be an outcome of interest (e.g., showing the denominator for the number of appropriate shocks and withheld shocks).
6.3.	No difference in ICD implantation between intervention and control group in the VEST study is not surprising.	We did not state that no statistical difference in ICD implementation between device and control group is surprising.
6.4.	The overall safety results are not comprehensible because it is unclear which data belongs to which study (apart from the RCT).	We remind that only a preliminary German summary is currently available online. Summaries are by default less comprehensible and the reader is referred to the full report that is currently under public consultation in Italy [8].

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	The authors state that the RCT does not provide information on SAE that lead to death, whereas the publication mentions every diseased patient in the WCD group.	To our understanding, Olgin, Pletcher, Vittinghoff, Wranicz, et al. [12] did not specifically report on this outcome. However, in the Appendix 4 of the full report [8] we stated (footnote 35): "*One patient died while he was wearing the device. The authors state that this death could be possibly related to the WCD use. The authors also state that it was deemed likely to not be an arrhythmic death*".
	Six of the studies had 0% unsuccessful shocks (it is incorrect to state that only two out of ten studies reported on unsuccessful shocks).	This point of critique is unclear to the authors. It is incorrect that six of the studies had 0% unsuccessful shocks. Rather, six out of ten studies reported on inappropriate shocks and two out of ten studies reported on unsuccessful shocks. First shock success was reported by five studies (83.3%-100%). This data can, to our understanding, not be used to calculate the percentage of unsuccessful shocks.

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	Authors were reporting the outcomes selectively because rash and itch from RCT was reported, but the difference in shortness of breath that favours patients wearing the WCD was not. On those grounds, safety of the WCD is questioned by authors.	It is correct that the following is stated in the VEST study [12]: "*a lower proportion of participants in the device group than in the control group reported shortness of breath (P = 0.004)*". However, we were not able to find a plausible clinical reason explaining how/why the WCD would influence shortness of breath. If we are provided with (non-placebo-related) explanations why the WCD would reduce shortness of breath, we are happy to reflect on the possibility to add this outcome into the assessment. On the contrary, there are good reasons to believe that rash and itch may be caused by the WCD. This is the reason why we chose rash and itch as an outcome, but not shortness of breath.
6.5.	Discussion: The 2018 assessment team stated that the significant reduction of the all-cause mortality is a chance finding.	We never stated that the difference in all-cause mortality is a chance finding. **We stated that the risk of this difference being a chance finding is increased.** This is the conservative interpretation of the difference as pointed out by the primary investigators of the VEST study in the article published in the NEJM [12]. After the VEST study was published, a letter to the editor was published by Stecker and Walsh [13] in which it is argued that the studies VEST, DINAMIT, and IRIS – 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". It is further stated that

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		"(…) aggressive marketing, without clinical evidence, does a disservice to patients. Under the exceptional circumstances in which the use of wearable cardioverter–defibrillators may still be considered, the negative results of these three randomized trials should be made clear to patients" [13].
6.6.	Compliance: The 2018 assessment team did not highlight that there is a discrepancy between the compliance data in the RCT when compared to the compliance in clinical practice (e.g., to be seen in case series studies). There are good reasons to think that compliance should be higher in case series studies (e.g., motivation is lower when the treatment arms are presented as being equivalent – as in the RCT, the LifeVest-Network was not allowed in the RCT – the use of the LifeVest-Network increases compliance because the doctor is informed early and thus can counteract to increase compliance, and a 24/7 hotline is available).	We remind that only a preliminary German summary is currently available online. Summaries are by default less comprehensible and the reader is referred to the full report that is currently under public consultation in Italy [8]. In the final report [8], the discussion section in the clinical effectiveness domain explicitly deals with the issue of compliance and its comparison to data from observational studies.

References

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