Dissertation

Multiparameter monitoring and sudden cardiac death prevention with a wearable cardioverter defibrillator from diagnosis to cardiac rehabilitation

submitted by

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Statutory Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all those individuals and organizations that have contributed to the research of this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the guidelines of “Good Scientific Practice”.

Graz, July 30th 2023 *Ursula Rohrer, e.h.*

Disclosures

A publication of original data, a review as well as unpublished data served as basis for this thesis. I am the first author or co-author of these publications and included parts of it in my thesis. I informed all co-authors about the publication of this thesis. All co-authors have agreed to the inclusion of their illustrations, figures and published data in the dissertation and permission to reproduce illustrations and figures from own publications has been granted.

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Abbreviations and Definitions

Abbreviation	Definition
AAD	Antiarrhythmic drug
ACEi	Angiotensin-converting-enzyme-inhibitor
AF	Atrial fibrillation
AHA	American heart association
ALS	Advanced life support
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
ARVC	Arrhythmogenic right ventricular cardiomyopathy
BrS	Brugada Syndrome
CAB	Cardioacoustic biomarker
CAD	Coronary artery disease
CIED	Cardiac implantable electronic device
CMP	Cardiomyopathy
CPVT	Catecholaminergic polymorphic ventricular tachycardia
CR	Cardiac Rehabiliation
CR3	Cardiac rehabilitation retrospective review
CVD	Cardiovascular disease
DCMP	Dilated cardiomyopathy
DGK	German Society of Cardiology
ECG	Electrocardiogram

ERS	Early repolarization syndrome
ESC	European Society of Cardiology
GDMT	Guideline-directed medical therapy
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HNDCM	Hypokinetic non-dilated cardiomyopathy
HR	Heart rate
ICD	Implantable cardioverter defibrillator
ICMP	Ischaemic cardiomyopathy
LMNA	Lamin A/C
LQTS	Long QT syndrome
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MRA	Mineralocorticoid receptor antagonist
nsVT	Nonsustained ventricular tachycardia
OHCA	Out-of-hospital-cardiac-arrest
PA	Physicial activity
PVC	Premature ventricular contraction
SCA	Sudden cardiac arrest
SCD	Sudden cardiac death
SGLT2-i	Sodium– glucose co-transporter 2 inhibitors

SVT	Supraventricular tachycardia
TdP	Torsades-de-pointes
VA	Ventricular arrhythmia
VEST	Vest Prevention of Early Sudden Death Trial
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WCD	Wearable cardioverter defibrillator
WHO	World health organization

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Abstract in German

Hintergrund und Ziel: Patient*innen mit Risiko für plötzlichen Herztod (PHT) sind unter bestimmten Voraussetzungen nicht für einen implantierbaren Kardioverter-Defibrillator geeignet. Der tragbare Kardioverter-Defibrillator (WCD) wurde als temporäre Therapieoption entwickelt und diese Arbeit untersucht zwei verschiedene klinische Aspekte des WCD: (1) *PHT-Schutz nach akutem Myokardinfarkt (AMI):* Die "VEST" Studie konnte keinen Vorteil in Bezug auf die arrhythmische Mortalität bei Patient*innen mit AMI und eingeschränkter Linksventrikelfunktion (LVEF≤35%) durch einen WCD zeigen, wobei die Tragedauer niedriger als erwartet war. Das Ziel war es eine vergleichbare österreichische WCD-Kohorte mit guter Tragecompliance zu untersuchen. (2) *Kardiale Rehabilitation (CR) mit einem WCD:* Ziel war es, die Durchführbarkeit und Sicherheit zu beurteilen, da diese Kohorte von Patient*innen bisher noch nicht untersucht wurde.

Material und Methoden: 896 Patient*innen, die zwischen 2010 und 2020 in 60 Zentren eine WCD verordnet bekamen, wurden in das österreichische Register aufgenommen. Innerhalb des österreichischen WCD-Registers wurden zwei Kohorten identifiziert, um die Forschungsfragen zu beantworten: (1) Alle Patient*innen, die nach den Ein- und Ausschlusskriterien der VEST-Studie in Frage kamen, wurden analysiert und mit der ursprünglichen VEST-Kohorte verglichen. (2) Weiters wurden für die Beantwortung der zweiten Forschungsfrage alle Patient*innen, die sich einer CR mit einem WCD unterzogen haben, eingeschlossen und untersucht.

Ergebnisse: (1) 105/896 Patient*innen erfüllten alle Kriterien der VEST-Studie. Die arrhythmische und Gesamtmortalität unterschied sich trotz guter Tragecompliance der österreichischen Kohorte nicht signifikant von den Mortalitätsraten der originalen VEST-Kohorte. (2) 55/896 Patienten absolvierten eine CR mit einem WCD. Abgesehen von kleineren Anpassungen des Stoffteiles und der Geräteeinstellung traten während der CR keine schweren WCD-bezogenen unerwünschten Ereignisse auf. Nur 6% der im WCD-Register erfassten Patienten wurden zur CR überwiesen und unterzogen sich dieser.

Conclusio: (1) Die WCD ist eine sichere Behandlungsoption in einer gut selektierten Patient*innen-Kohorte mit einer LVEF ≤35% nach AMI. Trotz der exzellenten WCD-Tragedauer in unserer Kohorte war die arrhythmische Mortalität im Gegensatz zur VEST-Studienkohorte jedoch nicht signifikant niedriger als in der VEST-Studie. (2) Die Durchführung einer trainingsbasierten CR mit einer WCD scheint machbar und sicher zu sein, während die Verordnungsraten einer CR in dieser Kohorte trotz klarer Leitlinienempfehlungen sehr niedrig sind.

Abstract in English

Background and Aim: Patients at risk of sudden cardiac death (SCD) may not be eligible for implantation of an implantable cardioverter defibrillator either due to temporary contraindications or due to a transient SCD risk. The wearable cardioverter defibrillator (WCD) was developed to overcome these situations as a temporary treatment option. This thesis will cover two different clinical aspects: (1) *SCD protection after acute myocardial infarction (AMI):* The "VEST" trial failed to show a benefit on arrhythmic mortality in patients prescribed with a WCD after AMI with left ventricular ejection fraction≤35% (LVEF), having a lower-than-expected wearing compliance. The aim was to investigate outcomes in a well-compliant Austrian WCD cohort meeting all in- and none of the exclusion criteria. (2) *Cardiac rehabilitation (CR) with a WCD:* Patients undergoing CR with a WCD have not been studied so far. The aim was to assess feasibility and safety and describe outcomes in this cohort as CR is one of the therapeutic cornerstones in patients with an underlying disease.

Material and Methods: First, 896 patients prescribed with WCD in 60 Austrian centers have been included in the Austrian WCD registry between 2010 and 2020. Within the Austrian WCD registry two sub cohorts were identified to answer the research questions:

(1) All Austrian WCD patients being eligible according to the VEST trial in- and exclusion criteria formed the Austrian VEST cohort, were analysed, and compared to the original VEST cohort. (2) Last, all patients who underwent a CR with a WCD have been included and studied to answer the research question.

Results: (1) 105/896 patients received a WCD after AMI with a reduced LVEF. The arrhythmic and all-cause mortality did not significantly differ between the Austrian and the original VEST cohort, despite a good wearing compliance in the Austrian cohort. (2) 55/896 patients completed a CR of 28 days. Apart from minor adjustments of the fabric garment and device settings, no severe WCD-related adverse events happened during CR stay. Only 6% of the WCD registry were referred to and underwent CR.

Conclusion: (1) The WCD is a safe treatment option in a highly selected cohort of patients with LVEF ≤35% after AMI. However, despite excellent WCD wearing duration in our cohort, as opposed to the VEST study cohort, the arrhythmic mortality rate was not significantly lower as in the VEST study. (2) Completing an exercise-based CR with a WCD seems to be feasible and safe while CR is strongly underutilized in this cohort despite clearly stated guideline recommendations.

1 Introduction

1.1 Sudden Cardiac Death

The term “sudden cardiac death” (SCD) accounts for a death that occurs naturally but is unexpected and caused by a cardiac event. Different cardiac pathologies leading to SCD are summarized under this term. The cause of SCD is presumed to be either due to typical symptoms preceding the SCD or can be directly identified via autopsy. This needs to be distinguished from sudden cardiac arrest (SCA) that only describes the event of cessation of any cardiac activity itself but does not implicate the outcome. Furthermore, any sudden death in a child younger than one year is not counted as SCD but as sudden infant death syndromes.(2)

1.1.1 Epidemiology

Worldwide approximately 17.9 million people die each year of cardiovascular diseases (CVDs) according to the World Health Organization (WHO). All disorders of the heart and blood vessels are combined within this group according to the WHO definition of CVDs. Whereby, in addition to cardiac diseases such as coronary artery disease (CAD) and congenital heart disease, cerebrovascular and peripheral artery diseases are also included in this group. CVD accounts for around one third of all deaths worldwide and is therefore the leading cause of death.(3) In particular, SCD accounts for around 25-50% of CVD related deaths with a SCD incidence as high as 84/100.000 person-years in Europe. Hence, SCD is responsible for 10-20% of all deaths in Europe.(4-6) The majority of SCA events in Europe are out-of-hospital-cardiac-arrests (OHCA) with a survival of only 10.3% for at least 30 days or to hospital discharge according to the EuReCa ONE registry.(4)

The distinct features of SCD change over patient lifetime: starting with a low incidence in the childhood (1/100.000 person-years) that rises to a maximum of 200/100.000 person-years in the octogenarians. The probability of SCD not only increases over lifetime but also occurs predominantly in male subjects.(2, 7-9)

The number of favourable survivals after SCA remains low: only around 58% of bystanders perform advanced life support (ALS) resuscitation measures in OHCA and consecutively in only one third of SCA a primary return of spontaneous circulation is achieved. Moreover, only around 8-10% SCA victims leave the hospital or survive longer than 30 days after the index event in Europe.(4, 10) Therefore, OHCA and SCA not only

pose a burden on the SCA victim and their families but also on the health system due to long hospital stays and potential remaining physical disabilities.

As per definition SCD can occur with or without a previously known cardiac disease and with or without preceding symptoms as warning signs. Especially in the young, specific cardiomyopathies can manifest as SCA for the first time. In the younger population, inheritable cardiomyopathies and primary electrical diseases are the prevailing causes. Examples include long QT Syndrome (LQTS), Brugada Syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), early repolarization syndrome (ERS), idiopathic ventricular fibrillation (VF), hypertrophic cardiomyopathy (HCM), inherited forms of dilated cardiomyopathy (DCMP) and hypokinetic non-dilated cardiomyopathy (HNDCM), or myocarditis and congenital heart diseases. In the fourth decade CAD is the leading cause of SCD. The percentage of prior known structural heart diseases is rising with age and is associated with SCD in the elderly.(8, 11)

1.1.2 Screening and risk estimation

As morbidity and mortality in OHCA and SCA remain high, the main goal is primary prevention of SCD. Screening for SCD risk is, however, not recommended for the general population. In contrast, screening is recommended in specific subgroups such as first-degree relatives of patients affected with a known inheritable disease (LQTS, BrS, CPVT; ERS, idiopathic VF, HCM, DCMP and HNDCM) or first-degree relatives of a SCD victim with unknown cause of death at autopsy. Thus, effective screening measures in asymptomatic individuals of the general population still represent a gap in evidence and are not yet available. In certain cardiac diseases such as HCM, arrhythmogenic right ventricular cardiomyopathy (ARVC) and lamin A/C cardiomyopathy (LMNA) specific risk factors and calculators have been developed and implemented in clinical practice.(2)

Ischaemic cardiomyopathy (ICMP) is the most common cardiomyopathy associated with SCD. Patients with ICMPs have a high risk of SCD in the acute phase after acute myocardial infarction (AMI), as well as long-term especially if left ventricular dysfunction is present. AMI and the acute phase up until 48 hours after count as reversible cause for malignant ventricular arrhythmia (VA), when revascularization was achieved. Data suggest that early VF does indicate a higher SCD risk compared to patients with AMI without VF.(12, 13) Both arrhythmias don’t seem to have a negative impact on long-term mortality when occurring in the acute phase.(14) In ICMP the left ventricular ejection fraction (LVEF) is a sufficient surrogate parameter for the individual SCD risk and when reduced to 35% or below, the SCD risk is significantly increased.(2)

Contrarily, in non-ischaemic cardiomyopathy (NICMP) and inheritable cardiomyopathies, LVEF alone is not sufficient to estimate the SCD risk and usually additional risk factors can help to assess the individual SCD risk. Additional risk factors include clinical features like syncope or non-sustained VTs (nsVTs), specific high risk genetic mutations or imaging features like late-gadolinium-enhancement on cardiac magnet resonance imaging. Sometimes an electrophysiological study (EPS) is indicated for further investigations.(2)

After screening for estimating of the individual SCD risk, measures to prevent SCD risk largely depend on the underlying cardiac disease and may be composed of conservative measures, drug and device therapy. General measures like risk factor optimization and avoidance of arrhythmia triggers as well as exercise-based cardiac rehabilitation (CR) can be supportive in addition to drug and device therapy. Especially CR has shown to reduce mortality, the number of rehospitalizations and enhance QoL.(15, 16)

Hemodynamically stable idiopathic VTs originating from the ventricular outflow tracts are considered benign and are usually not associated with a SCD risk. Therefore, these arrhythmia are not further discussed in detail.(2)

1.1.3 Acute management

The acute management of VA primarily depends on patients' hemodynamically state and may either trigger resuscitation measures if in cardiac arrest or prompt measures for hemodynamic support when the patient is hemodynamically unstable. Concerning the acute management of VA, reversible causes need to be identified and corrected. Administration of antiarrhythmic drugs (AADs) or electrical cardioversion/ defibrillation may help to acutely terminate the arrhythmia. When patients are in cardiac arrest, the ALS treatment algorithm applies in accordance to the 2021 European Resuscitation Council ALS Guideline.(17, 18)

1.1.3.1 Reversible causes

Reversible causes are identified in up to 50% of SCA. A thorough work-up is necessary to properly determine correctable causes and identify patients with a low risk for recurrent SCA.

Myocardial ischemia in AMI is an important reversible cause of VA and consecutively prompt urgent coronary revascularization. VA ≥ 48 hours after AMI are not

considered a reversible cause provided that complete revascularization was performed. SCA in the acute phase at ischemia usually happens at physical exertion. SCA usually resolves itself when no structural substrate in the form of myocardial scar persist after revascularization or after having performed a negative EPS according to earlier studies.(19, 20) The approach from the current "*2022 European Society of Cardiology (ESC) Guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD*" do not recommend further investigations such as imaging or EPS and only distinguish whether VA persist for more than 48 hours after AMI and revascularization to recommend ICD implantation.(2)

Apart from myocardial ischemia, severe electrolyte disturbances in potassium and/or magnesium levels, hypoxaemia or fever may precipitate SCA. These factors are considered potential reversible causes. Not only acute correction of these triggers is recommended, but also a thorough SCD risk estimation. Even if the cause is corrected, these SCA survivors seem to have a persistent higher recurrence risk compared to the general population. Ladejobi et al. retrospectively analysed patients after SCA and identified that patients with a documented reversible cause like electrolyte abnormalities or newly initiation of an AAD. The patients that underwent ICD implantation had a much lower all-cause mortality.(21) According to current knowledge, AMI is not accounted for a reversible cause as patients after AMI have similar mortality rates irrespective of the presence or absence of an ICD.(19, 21)

Furthermore, several factors can prolong QTc intervals either in LQTS or even in structural normal hearts and lead to VA such as torsade-de-pointes (TdP) tachycardia. Electrolyte disturbances (hypomagnesemia, hypokalaemia, and hypocalcaemia), AADs like sotalol and amiodaron but also antidepressants, antibiotics and various other drugs can all prolong QTc intervals.(2)

Pre-excited atrial fibrillation (AF) leading to SCA, along with the identification and successful ablation of an anterograde conducting accessory pathway, may be considered curative. ICD implantation may not be necessary if VT/VF cannot be induced during the EPS according to the "*2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death*".(22)

1.1.3.2 Pharmacotherapy

Pharmacotherapy in the acute phase is only considered to help terminate arrhythmias in haemodynamically stable situations in addition to electrical cardioversion. In sustained monomorphic VT, procainamide and amiodaron are the AAD of choice in the

acute setting in previously known or suspected underlying heart disease. If the patient has no significant structural heart disease, flecainide, ajmaline, or sotalol may be considered. An electrical cardioversion should be performed If the risk of sedation is low or pharmacotherapy does not terminate the VA.(2)

Pharmacotherapy depends on the underlying pathophysiology in sustained polymorphic VT: if a reversible cause is identified (see chapter 1.1.3.1), the causal therapy should be initiated as soon as possible. If acquired long QT triggers VA, i.v. application of magnesium and potassium and/or increasing the patient's heart rate (HR) in sinus rhythm with either isoproterenol or pacing is indicated. Primary electrical diseases require specific therapies if the underlying disease is known beforehand. For example, isoproterenol or quinidine is the pharmacotherapy of choice in BrS or ERS, and idiopathic VF may be treated with isoproterenol, quinidine, or verapamil. VA triggered by LQTS or CPVT responds to betablockers, pacing or i.v. application of magnesium and potassium. In drug-resistant recurrent VA, deep sedation, intubation and or mechanical circulatory support may be necessary. Early catheter ablation may be considered in primary electrical diseases.(2)

1.1.4 Long-term management

1.1.4.1 Pharmacotherapy

Concerning long-term management, AADs do not reduce mortality, apart from beta blockers but play a role in addition to all disease-specific interventions. AADs also carry their own arrhythmic potential through means such as prolonging QT intervals or causing bradycardia. AAD may even be contraindicated in specific disease such as BrS.(2)

In patients with the phenotype "heart failure with reduced ejection fraction" (HFrEF), defined as LVEF≤40%, the well-established guideline-directed medical therapy can lower mortality due to SCD and heart failure (HF) regardless of the aetiology. This is true with the following substances: Angiotensin-converting-enzyme-inhibitors (ACE-i)/angiotensin receptor blocker (ARB)/angiotensin receptor neprilysin inhibitors (ARNI) combined with mineralocorticoid receptor antagonists (MRA), beta-blockers, and sodium-glucose co-transporter 2 inhibitors (SGLT2i).(2, 23)

Up titrating guideline-directed medical therapy to the maximum tolerated dose has a huge impact on both morbidity and mortality. The overall goal is to not only improve cardiac function, but also the functional status to decrease morbidity and improve quality of life (QoL) and hospitalizations due to HF.(24) Medical therapy needs to be up-titrated,

re-initiated or even expanded after the acute phase of being newly diagnosed with HF or after an acute decompensation of chronic HF,. Apart from the four recommended drug categories as initial therapy (ACEi or ARB or ARNI and betablockers and MRA and SGLTi), certain add-on drugs may have an effect on morbidity and the rate of HF hospitalizations: Ivabradin, digoxin, hydralazine, isosorbide dinitrate and vericiguat may serve as add-on in specific subgroups.(23)

1.1.4.2 Catheter ablation

In specific clinical situations, catheter ablation of premature ventricular contractions (PVC) triggering VTs or sustained monomorphic VTs is indicated as alternative to an ICD. This applies when an ICD is not available, medically contraindicated or declined by the patient. It can also be indicated as add-on therapy complementary to an ICD and AAD. Catheter ablation can help to modify or treat VA but is not considered an alternative to an ICD in regards to SCD prevention in current guidelines.(2) Ablation therapy for VF is even less established as a specific substrate is not defined, such as a scar-related re-entrant circuit in VT. PVCs may serve as triggers for VF and it has been studied whether catheter ablation targeting this localization decreases VF recurrence and SCD. A better understanding of the structural and electrical substrate may be needed to make catheter ablation more effective. Purkinje-triggered ectopies in ischemic heart disease or right ventricular PVC in BrS may be promising targets for ablation therapies in the future.(25, 26) Nevertheless, data from randomized-controlled studies opposing catheter ablation and ICD implantation are scarce. Data from a single arm trial of ablating well-tolerated VTs in patients with a structural heart disease show low mortality rates with randomized-controlled trials needed to confirm the result.(27, 28) A difference in mortality rate was not shown in a prospective registry including a low number of patients refusing ICD therapy but undergoing catheter ablation.(29)

All studies investigating catheter-ablation, as an add-on to ICD therapy show a decrease in the numbers of ICD therapies and benefit in mortality. Catheter ablation is not scientifically confirmed and therefore not recommended in current guidelines as initial therapy and as alternative to ICD therapy in preventing SCD.(2)

1.1.4.3 Cardiac rehabilitation

A multi-professional approach is needed in the process of up-titrating HF medication and modifying comorbidities such as obesity, hypertension or diabetes. Improving these aspects and consequently increasing LVEF may reduce the individual

SCD risk. An exercise-based CR is recommended in all patients with a cardiac disease such as HFrEF but also after surviving a SCA. The current "*2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure*" recommends either a self-guided approach or a supervised CR program for patients with frailty or comorbidities.(23) CR may decrease mortality and the rate of hospitalizations in patients with known CAD.(30) CR usually consists of various therapeutic columns supervised and performed by a multi-professional team. An integral part of CR is the medically supervised exercise training (ET) to improve functional capacity. Physiological counselling can be used to increase adherence to the medical therapies by enhancing understanding of the underlying disease. Behavioural therapy is added for lifestyle interventions when needed. These measures may help to obtain GDMT and reduce modifiable risk factors.(23, 24, 30, 31)

Recommendations for patients with heart failure with mildly reduced ejection fraction (HFmrEF, LVEF 41-49%) and heart failure with preserved ejection fraction (HFpEF, LVEF≥50%) have lower evidence classes due to a smaller number of large randomized controlled trials concerning medical treatment. Nevertheless, CR is also recommended in HFmrEF and HFpEF.(30, 32, 33)

1.1.4.4 Device therapy

All individuals surviving SCA or haemodynamically relevant sustained VA without reversible causes such as AMI have a persistent high risk of SCD and need to be protected from recurrent events.(2)

The most effective long-term therapy to prevent SCD in both primary and secondary prevention is the implantation of an ICD.(34-36) Apart from SCD risk estimation through thorough work-up incorporating clinical data, imaging, genotyping and additional risk factors, comorbidities, the estimated survival as well as the patients wish need to be taken into account when indicating device therapy.(2)

However, in specific clinical situations, an ICD might either not be indicated, or implantation may temporarily be unfeasible. The best example for a temporary contraindication of an ICD, with an existing not-reversible cause of SCD risk is in the acute phase after AMI. Large clinical trials like DINAMIT(37) and IRIS(38) found that ICD implantation within 40 days after AMI did not impact the overall mortality. The rate of SCD was lower in the device group in both studies but the rate of non-SCD was higher resulting in a neutral outcome.(37, 38) If the SCD risk persists, ICD implantation may be safer after

this episode. Moreover, patients are unprotected from SCD if an ICD explantation due to a device infection is needed. When endocarditis is present a several weeklong run of antibiotics may be needed before a re-implantation is safe. Contrary to temporary contraindications for ICD implantation with a persistent SCD risk, there might be no contraindications but rather a temporarily elevated SCD risk.(2, 39, 40) Hence, the WCD was developed years ago to address this problem.(40-42)

1.2 Wearable cardioverter defibrillator

1.2.1 Technical composition and algorithm

A WCD is a device consisting of the following components: An adjustable fabric vest adjacent to the wearer's chest contains four electrodes recording an electrocardiogram (ECG) and three defibrillation electrodes (one apical, two posterior) containing the heart sounds sensor to observe the heart rhythm and deliver externally applied shocks, if needed (see *Figure 1*). Furthermore, the vest is equipped with a three-axis accelerometer to assess parameters like step count, body position and activity level.(43)

Analogous to implantable devices, a feature of the WCD was studied to assess surrogate parameters called "cardioacoustic biomarkers" (CAB). CABs are analysed by a complex algorithm to identify a decline in cardiac function.(44) This sensor is placed close to the defibrillation electrode sitting at the apical position. Additionally, the device monitors the wearing time, all the captured measurements, and as well relevant ECGs. This information is transmitted to an online platform accessible by the treating physician. All these components are connected to a monitor containing a rechargeable lithium-ion battery and the shock unit.

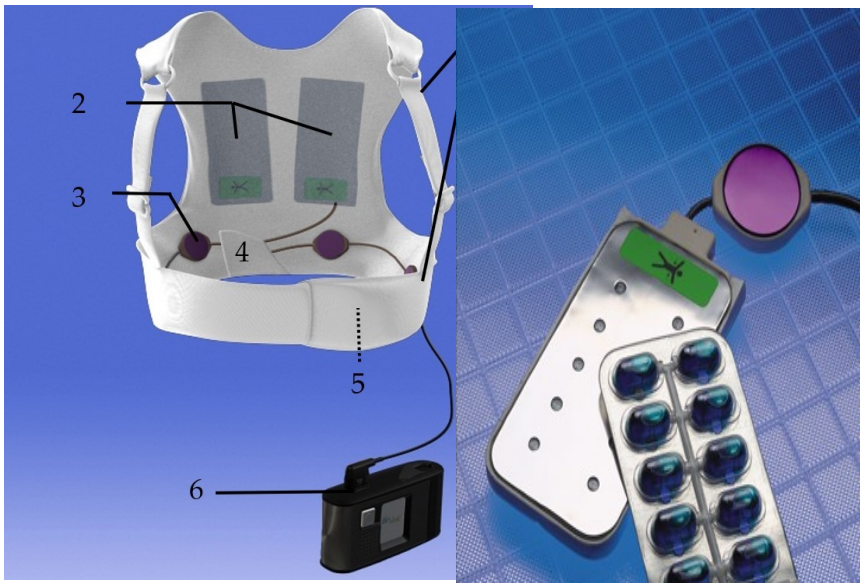

Figure 1: left: (1) fabric garment, (2) two posterior defibrillation electrodes, (3) electrode belt, (4) vibration box, (5) apical positioned defibrillation electrode with heart sounds sensor, (6) monitor unit; right: self-gelling defibrillation electrodes (44), © ZOLL CMS GmbH(1)

Prior to a WCD shock, a vibrational alarm from the vibration box located close to the dorsal part of the electrode belt and an acoustic and visual alarm from the monitor box inform the patient and potential bystanders about an event detection (see Figure 1). The underlying software discriminates harmless rhythms from VA and HR. When a VA is detected, a biphasic direct current shock with 75 to 150 joules will be applied after sending out the above-mentioned warnings. The detection algorithm for VA starts when the patient's HR exceeds the predefined HR limits for VT/VF. The HR algorithm is based on the Fourier transformation frequency plot and the treating physician sets separate thresholds for VT and VF, which may be helpful if the HR of a prior VA is already known, or higher thresholds are needed for younger and/or more active patients. When HR criteria are met, the ECG quality and the concordance of HR between the two leads is assessed to potentially reject the QRS morphology as criterion or to downgrade the importance of HR when the quality is assumed to be insufficient. Additionally, the onset and stability of the suspected arrhythmia are assessed for discrimination (see *Figure 2*). Since the ECG is captured by an externally worn electrode belt, the discrimination between atrial and ventricular origin of signals is not possible and the ECG is therefore subject to external interferences to a higher extent compared to intracardiac electrograms of an ICD. To overcome the issue of inappropriate detection and inappropriate shocks,

two reaction buttons situated on the monitor unit can be pressed by the wearer to abort a treatment when an alarm appears.

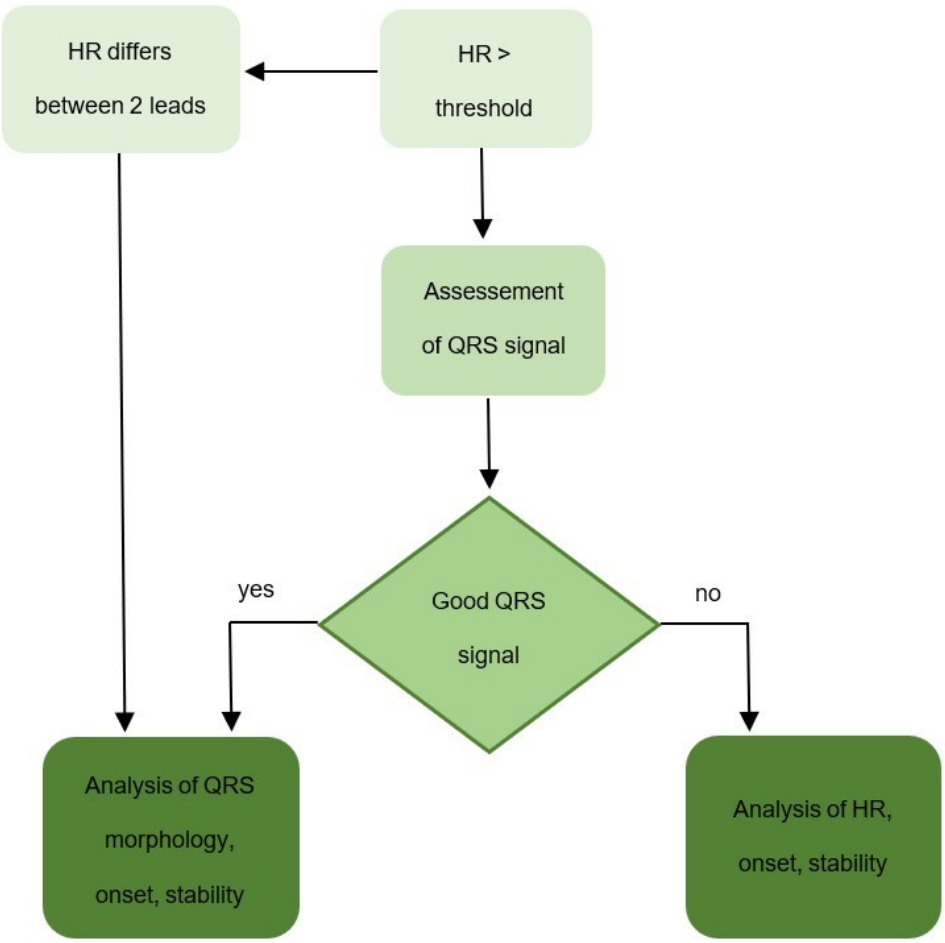

Figure 2: ECG detection algorithm(1)

Apart from so called “physiological alarms” triggered by the above-described algorithm preceding an imminent WCD shock, both technical and informative alarms are depicted at the monitor unit to inform about technical problems, low battery status, and loose sitting ECG electrodes etc.(45, 46) The WCD, its technical composition, the underlying software and algorithms were priorly described in more detail.(45-48)

1.2.2 Device functions

The WCD is fitted individually to each patient. After fitting, education is needed to inform the patient on all device functions and handling to achieve the maximum level of

safety. As soon as the device is fitted and the baseline ECG confirms good signal quality, various functions are available as subsequently described.

1.2.2.1 Wearing duration

The compliance to wear the WCD as continuously as possible is monitored through device itself. One of the most important factors for the effectiveness of the device is the daily wearing compliance as the WCD can only detect and treat arrhythmia when worn. The wearing duration in hours/day is counted if at least 1 of 2 ECG leads capture electrical activity and is available for the treating team in the online platform (see *Figure 3* and **Fehler! Verweisquelle konnte nicht gefunden werden.**).

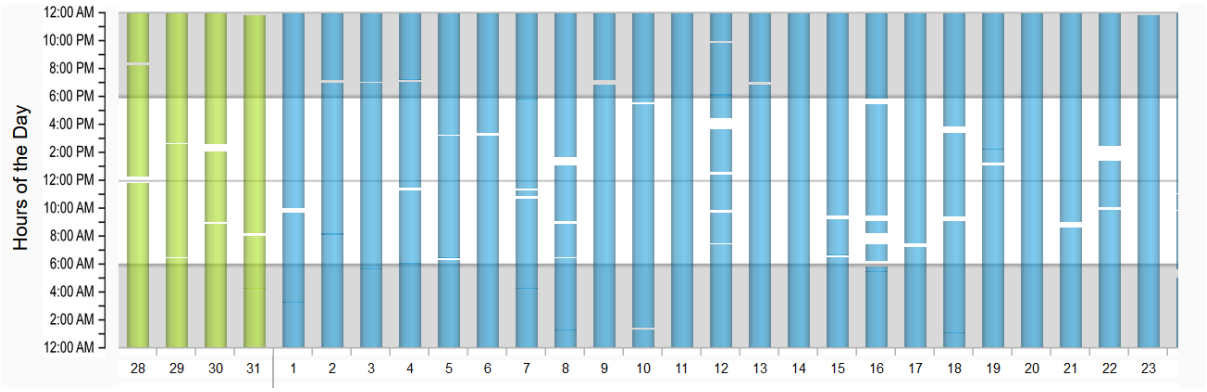

Figure 3: The documented wear-time of a patient with a good compliance. The date is plotted on the x-axis and the time (24h/day) is plotted on the y-axis from 12:00 a.m. to 12:00 p.m. The blue or green columns show the duration of WCD wearing, with only short interruptions during the days resulting in a wearing duration of 23.6 hours/day. The change of color from green to blue highlights the transition to a new month.(1)

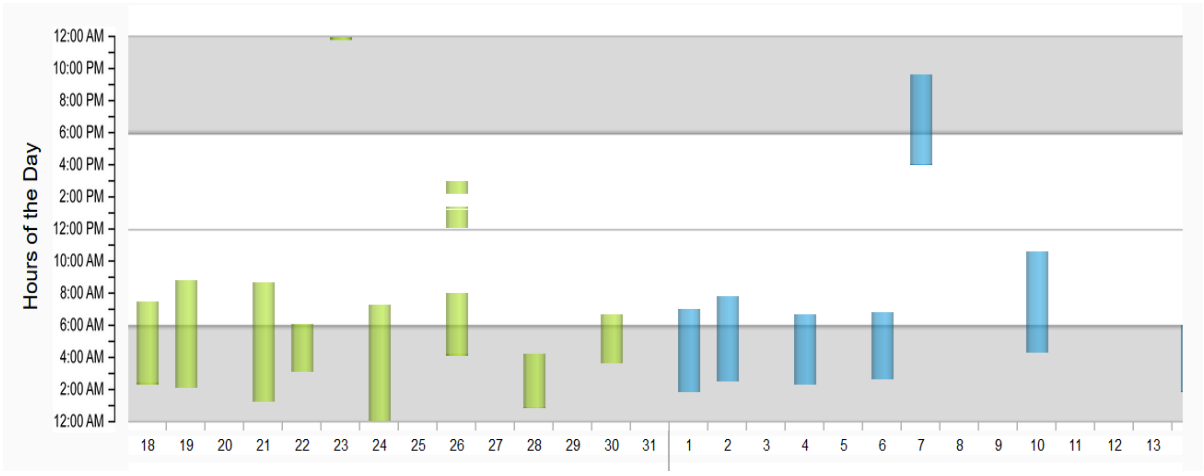

Figure 4: The documented wear-time of a patient with a low compliance and a wearing duration of 5.3 hours/day (1)

The duration the WCD is prescribed can vary widely and depends on patient-related factors such as the desire to stop wearing the device, device-related factors as for example skin reactions to the device and medical reasons that are usually at the physician's discretion. To improve compliance, patients need intense education. The German position paper for WCD use additionally recommends active surveillance of the actual wear-time through the online network. The suggested threshold that seems to be sufficient is 20 hours/day. The position paper even proposes to stop WCD prescription if the compliance remains low despite thorough patient education.(49) The wearing duration is reported to be >20 hours/day in most patients under real-world circumstances in large nationwide registries.(50-53) Few factors influencing the compliance have been identified such as younger age to decrease wear-time.(53, 54) Other factors such as gender, BMI or the number of alarms does not seem to have an impact.(53)

In the only randomized-controlled trial, the VEST trial (41) patients showed a below-average wearing compliance of median 18 hours/day. Only 53% of patients of the device cohort wore the device ≥22 hours/day within the planned three months of prescription. One third stopped wearing the device two month ahead of schedule, 43% one month too early and almost one third did not wear the WCD at all. Four of five patients did not wear the WCD for the intended 90 days of prescription. Concerning outcomes, 9/25 patients with a fatal outcome did not wear the WCD at the timepoint of their death. A correct adjudication of the cause of death is impossible without having the ECG from the timepoint of death. Furthermore, the WCD could not have treated a VA whether there was one while not being worn. (13,19) Following long discussions about the influence of the wearing compliance on the outcome, a per-protocol analysis of the VEST data was published two years later. The authors state, that the arrhythmic mortality is decreased in this analysis in patients of the device cohort who had a good wearing compliance (>90%, 21.6h).(55)

1.2.2.2 ECG monitoring and alarms

Via the ECG electrodes, the ECG is continuously surveyed and automatically classified with the algorithm explained in section 1.2.1.. When the algorithm identifies a VA, the ECG will be recorded and sent to the online platform to analyse the underlying rhythm and to take further action. The automatic alarm and a potential necessary treatment will be prepared and applied parallelly to this action. Apart from automatically triggered alarms, the patients have the possibility to record ECGs when pressing the buttons on the small monitor of the WCD whenever they feel arrhythmia-related symptoms. As the WCD has no pacing-facility and is primarily made to treat tachycardia,

bradycardia may trigger symptoms and potentially lead to syncope or even death but cannot be treated by the WCD. In this clinical situation, the WCD serves as ECG monitor and can be used to correlate symptoms to the underlying ECG. For example, a patient experienced dizziness and the manually triggered ECG revealed underlying third grade AV block (see *Figure 5*).

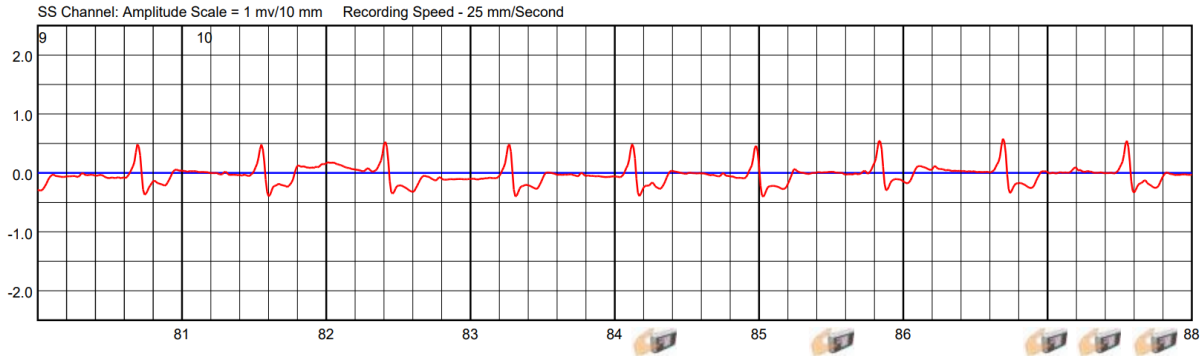

Figure 5: A manually triggered alarm showing a third-degree AV block (1)

Apart from manually recorded ECGs, automatically recorded ECGs following the predefined algorithm are more sensitive to interfering signals. Interferences can lead to oversensing, such as supraventricular tachycardia (SVT) and AF with bundle branch block (BBB), pre-existent cardiac pacemakers that have been implanted earlier due to bradyarrhythmia, high t-waves or external noise when ECG electrodes lose contact to the patient's chest. Pacing spikes and t-waves can not only lead to oversensing in sinus rhythm but can also lead to misclassification of SVT or AF (see *Figure 6*) due to the QRS deformation of ventricular pacing.

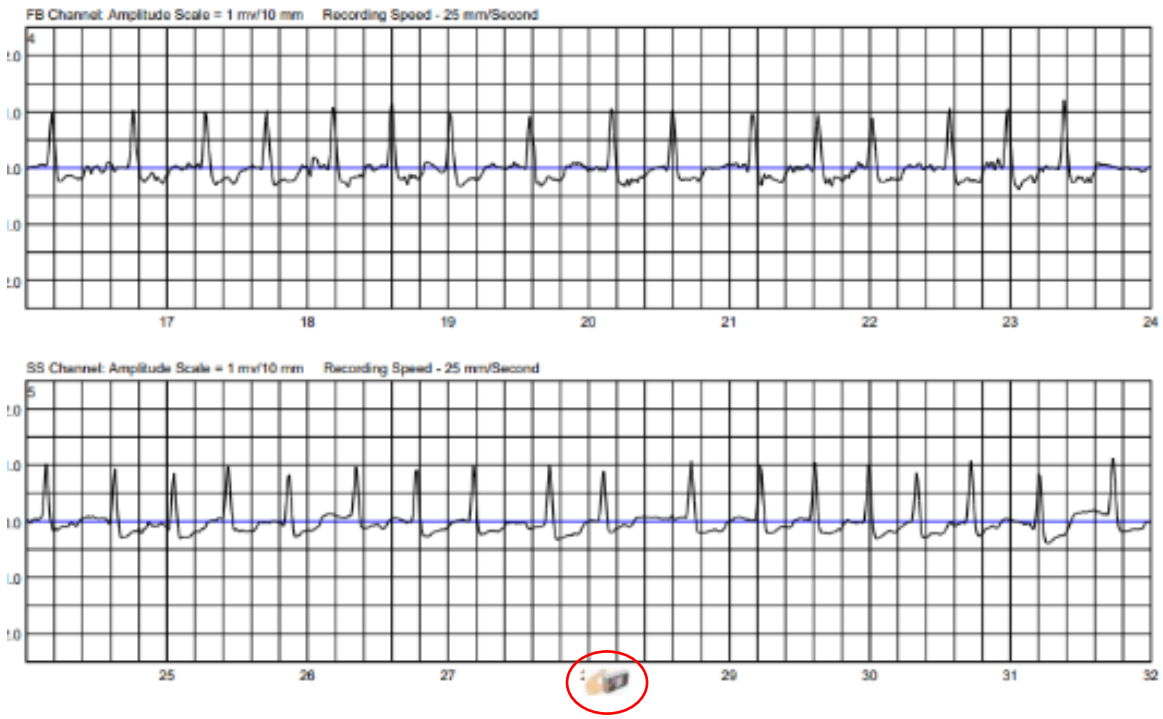

Figure 6: Tachycardic atrial fibrillation triggering an automatic alarm, red circle on sign for patient pushing buttons to terminate.(1)

Further on, this may lead to inappropriate detection and finally to inappropriate shocks. See *Figure 7* for an example of an inappropriate WCD shock due to t-wave oversensing of a patient in the Austrian WCD registry.

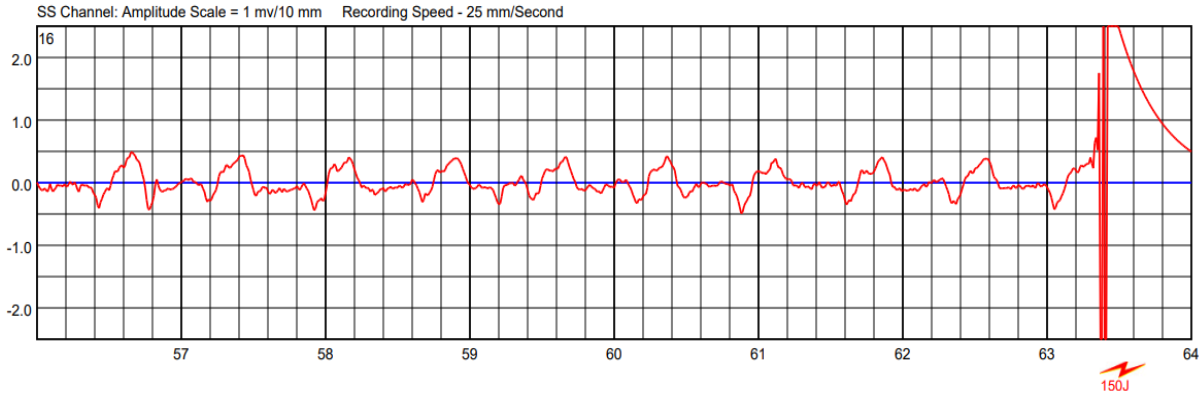

Figure 7: T-wave oversensing due to high t-wave voltage leads to inappropriate arrhythmia detection and eventually to an inappropriate shock with 150J (see red flash sign) on the right end of the figure.(1)

Furthermore, patients with a previously implanted Cardiac implantable electronic device (CIED) may also experience oversensing when the stimulation is programmed unipolar. Additionally, t-wave voltage can increase during ventricular pacing and lead to double counting also in bipolar pacing.(56) According to previous studies, unipolar programmed devices lead to inappropriate VA detection in up to ten percent.(57) Reprogramming to bipolar pacing whenever available and recording an ECG during

ventricular pacing should be considered for early detection of t-wave oversensing during ventricular pacing.

Nonetheless, artefacts due to poor electrode-to-skin contact are the most frequent cause for inappropriate alarms. Looking into data from the Austrian WCD registry, 95.6% of all inappropriate alarms can be identified as ECG artefacts while the underlying rhythm is sinus rhythm (see *Figure 8*). Other publications observed inappropriate alarms due to artefacts in almost 60% of patients. More active patients with a low body weight seemed to suffer from a higher number of inappropriate alarms. The authors suggest that insufficient skin contact of the ECG electrodes may be more frequent in these patients. In this case the authors proposed to reprogram the VT heart rate threshold from the preset rate of 150bpm to 180bpm. Analogously to ICD programming, the WCD programming can be modified to reduce the rate of alarms. The proposed thresholds have been studied and proposed for ICD patients in the MADIT-RIT trial and transferred to recommendations in WCD patients in this publication.(58, 59)

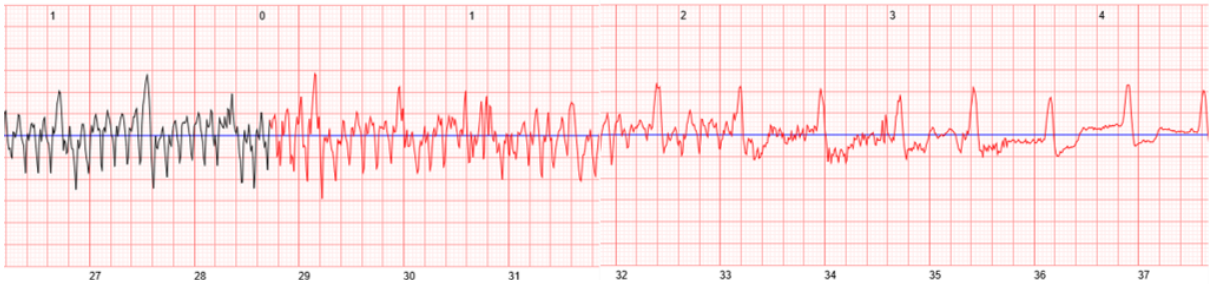

Figure 8: Regular high frequent artefacts triggering an alarm for ventricular arrhythmia on the left side (ECG turns from black to red). On the right side, when artefacts vanish an underlying sinus rhythm can be seen.(1)

Apart from the above-mentioned factors, several influencing factors have been studied to identify patients with a high risk of inappropriate alarms and shocks and modifiable factors. In contrast to earlier data and case reports, neither wearing compliance, gender, a CIED and/or ventricular pacing, previously known other arrhythmias such as SVTs or AF, QRS duration, BMI nor age showed significantly higher rates of inappropriate alarms.(53)

Inappropriate alarms are considered to pose a burden on the treating physicians to review the ECGs as well as on patients being confronted with the multi-level alarming of the WCD. In clinical practice, patients are educated to react adequately and abort inappropriate shocks by pressing the response buttons. Aborting the treatment may help to prevent an inappropriate shock but would still lead to a significant number of alarms.

This leads to an inappropriate shock rate ranging from less than 1% in registries (54, 60) and prospective cohorts (50) to 1,9% in real-world cohorts with smaller numbers of patients.(53)

1.2.2.3 Treatment function

Following the appropriate detection of a VA, the WCDs main function is to apply shocks to VT/VF (see *Figure 9*) prevent SCD. Patients are educated to abort treatments when they feel well. These events are usually adjudicated as hemodynamically stable VA. The WEARIT-II registry showed that only 25% of events required shocks compared to 75% sustained VAs being aborted by the patients.(50) Once a shock is applied, the efficacy of the new WCD generation is between 90% and 100%.(15, 17-19)

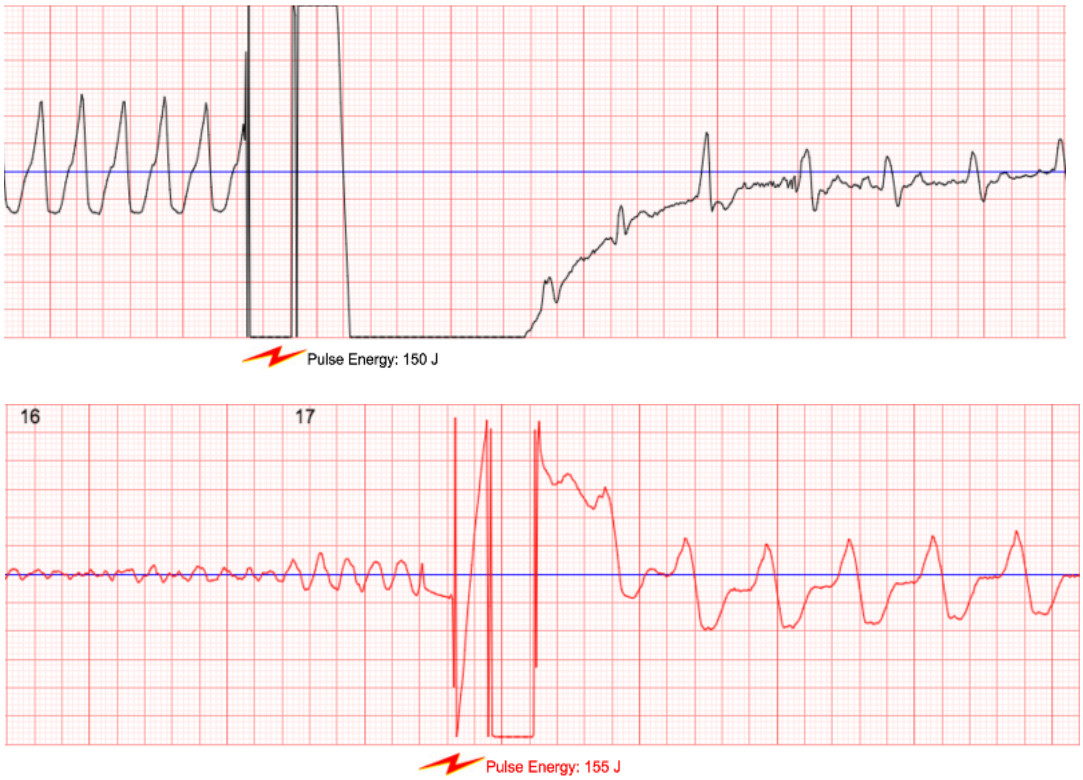

Figure 9: Appropriate detection of ventricular tachycardia (figure above) and ventricular fibrillation (figure below) and a WCD shock (flash pictogram below)(1)

Rare situations still require immediate external medical actions such as mechanical resuscitation or complex interdisciplinary management in ventricular storm. Hemodynamically unstable bradyarrhythmia or asystole can be detected by the WCD but not treated as it is not equipped with a pacing function.

For now, the events are transmitted to the online network and need to be actively opened and viewed. A German initiative proposed timely transmission so that early WCD-

detected life-threatening arrhythmias could start the rescue chain over a telemedical link from the device to a local emergency call center. The authors suggest that this would reduce the time to detect cardiac arrest and enhance chances of survival especially in out-of-hospital cardiac arrest. The target would be ineffective WCD shocks or arrhythmia that may not be terminated by a shock such as bradyarrhythmia and asystole.(61) This has not yet reached clinical application.

1.2.2.4 Monitoring heart failure

Patients being prescribed with a WCD often suffer from left ventricular dysfunction. Apart from arrhythmia detection, monitoring of surrogate parameter of cardiac compensation or decompensation is routinely detected in implantable devices, such as ICDs or cardiac resynchronisation therapy with defibrillators and can support early detection and anticipation of imminent decompensation to avoid re-hospitalizations. Telemedical monitoring of CIED can help to detect early signs and changes before clinical symptoms and signs are present and need hospitalization. This has been studied in CIED patients and has proven to improve clinical outcomes predominantly in HFrEF patients.(23, 62)

The WCD is often prescribed shortly after index hospitalization for acute decompensation or due to newly diagnosed heart failure (HF) when the risk of re-hospitalization is greatest.(63, 64) The non-invasive character of the WCD implicates that invasive measurements cannot be performed. The WCD has different functionalities to support early detection of an imminent cardiac decompensation: a raise in resting HR or in atrial arrhythmia burden can be an early sign as well as decreased physical activity (PA) that may be detected by the WCD. These factors need to be actively monitored through the online network.

The “TRENDS” option records several different parameters that depict the PA such as the daily step count as well as parameters indicating increased filling pressures such as the body position and angle in different situations. Each parameter is either graphically and numerically available for a specific timepoint or as a trend over a timespan (see *Figure 10*). The PA plays a prognostic role to predict HF events and cardiovascular death in cardiac patients independently of the way it is detected, whether self-reported (65) or device detected.(66, 67)

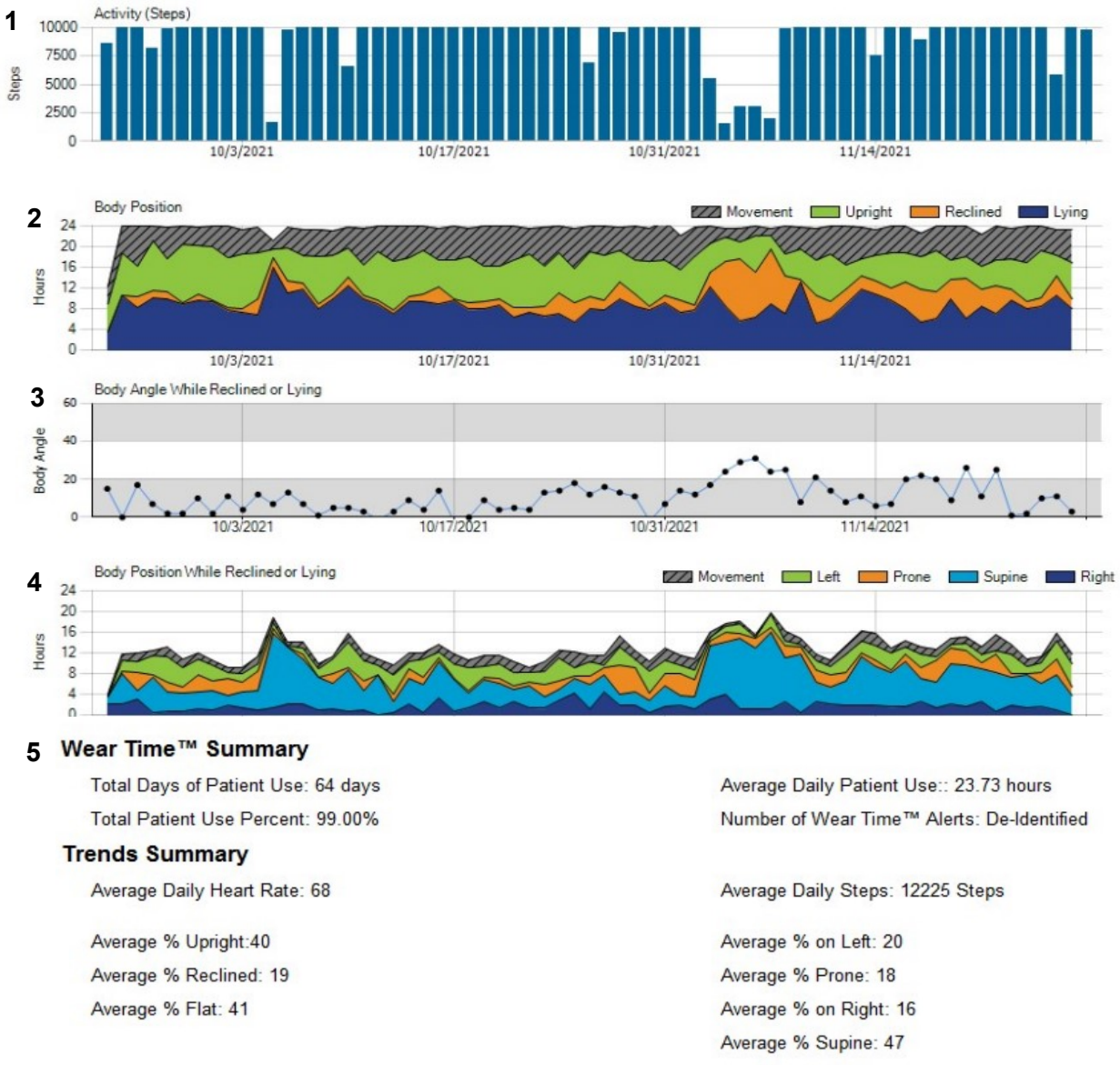

Figure 10: TRENDS data of a patient with ongoing WCD prescription showing the daily step count (1), the body position (2), the body angle while reclined or lying (3) and the body position while reclined or lying (4), a wear-time summary and the TRENDS summary (5) below.(1)

The clinical application of the TRENDS data have been studied in the PROLONG II trial in patients with a newly diagnosed HFrEF.(68) In this specific study in patients with severely reduced LVEF (mean LVEF 25.3 ± 8.5%), a multivariate analysis of combined parameters (HR, step count and five-minute HR variability approximate) suggested that the change of the HR variability approximate is an independent predictor for LVEF improvement. This parameter may potentially indicate an early treatment response in patients with newly diagnosed cardiomyopathies with reduced LVEF. This specific parameter is not routinely available in the online network but has been calculated only for this study.(69)

Another surrogate parameter of PA that can be detected and telemedically monitored by the WCD is the average daily step-count that was studied in several trials.(43, 70, 71) A retrospective, observational study of more than 4000 patients showed that a decrease in PA is prognostic for worse outcomes. Patients were more likely to receive a shock when the PA was low within the first seven days after index hospitalization.(43) A prospective female cohort of almost 5000 patients confirmed that a PA decline is a surrogate parameter of a WCD shock.(71)

Furthermore, a randomized clinical trial assessed the performance of a WCD-mediated 6-minute walk test (6MWT) and confirmed the feasibility of this home-based approach. The 6MWT is a quick and well-established test for the functional capacity of a HF patient. It was compared to a group that completed an in-clinic clinician guided 6MWT and showed consistent result that confirms reliable and objectifiable results in the WCD-guided approach.(72) This approach combined with the daily step count was used for remote monitoring of patients during CR and suggested the clinical application of a WCD to support active surveillance of rehabilitation measures and serve as surrogate parameter of cardiopulmonary exercise capacity.(73)

Cardioacoustic biomarkers (CAB) were studied to monitor HF in HFrEF. The CABs record cardiohaemic vibrations from heart sounds via sensors included in the defibrillation electrodes on the harnish of the WCD adjacent to the patient’s chest close to the tip of the heart. Additionally, information from the accelerometer and the simultaneously registered ECG were summarized to a combined parameter. More specifically the electromechanical activation time (EMAT) and the third heart sound (S3) strength were combined. The HEAR-IT study included patients with a LVEF ≤35% to apply a newly suggested multiparameter monitoring approach.(44)

The EMAT itself is a parameter measured on the WCD recorded surface ECG from the Q wave onset to the peak of the first heart sound. This accounts for the systolic function. When this parameter is prolonged, the third heart sound, which is a known sign of HF and increased filling pressures, is measured. The combined approach and the thresholds were gathered from data from the HEAR-IT study and analysed in a multivariate approach to study, which parameter account for a HF event risk. HF events such as cardiovascular death, arrhythmias, hospitalizations, or emergency department visits for HF happened in 81/671 (12%). The CABs decrease to a value above the threshold in 69% of the events at least 2 weeks and in 90% of HF events at least 3 days before the event happened. As mentioned before, the CABs not only served to predict an event but also helped to classify patient groups at high risk. The groups where classified due to CAB values of the first 7 days after hospital discharge from the index event. The CABs combined with the HR had a negative predictive value of 94% for HF events. The trend of this parameter showed a correlation not to acutely identify imminent decompensation but to early identify patient groups at low or high risk for a HF event such as a re-hospitalization. The results suggested the CABs as tool to predict patients at risk and to further prevent HF events. The CABs are not routinely available in clinical practice.(44)

1.2.3 Clinical applications

The clinical application and clinical use of the WCD changed over time. The initial patient cohorts that were studied consisted of patient with a high SCD risk: the WEARIT study included patients with symptomatic HFrEF and the BIROAD study included patients after a coronary intervention with risk factors and the studies were conducted parallelly. (74) The coronary intervention of the BIROAD study was either performed percutaneously or surgically and patients needed additional risk factors for SCD such as HFrEF, experienced syncope or documented VA. The included patients either had a contraindication for ICD therapy or declined ICD implantation. The results of these first 289 patients suggested that the WCD is safe for further clinical investigations and showed that the shocks were efficient with a 75% success rate. After these first clinical trials, the device and its functions evolved over time. The initial device applied shocks with a monophasic waveform and a maximum output of 285 joules and could not transmit any ECGs or events via telemonitoring compared to the current used device. (74)

After the initial studies, larger prospective trials such as the WEAR-IT II registry collected results from 2000 patients with various underlying cardiac diseases in a real-world setting. The shock efficacy improved to 100% first shock success with the new

generation of WCD provided with biphasic shocks and a maximum of 150J shock energy. The results showed low appropriate (2%) and inappropriate shock rates (0.5%) in this non-selected study population. Congenital or ischemic aetiology showed a tendency to higher shock rates compared to NICMP. Nevertheless, this study supported the efficacy and safety of this device.(50)

These subgroups have further been analysed: A German Single Center study of 114 patients showed a significantly higher event rate in ICMP patients (16.7%) compared to NICMP (3.8%) as well as compared to the overall shock rate (9.6%). These data suggested a high risk in ICMP patients and especially in patients after AMI.(75) Patients with congenital CMP (76) and patients with peripartum CMP (77, 78) were also studied in dedicated trials.

Additionally, nationwide registries studied the clinical application in real-world settings like the German WCD Registry with over 6000 patients from 404 centers (54), the US WCD registry included more than 3500 patients (79) and the Austrian WCD registry with around 900 patients from all 56 Austrian centers (51). All these registries added longitudinal data on the clinical applications, event rates and outcomes.

Apart from general registries and as event rates remained low in studies and registries that included allcomers, specific subgroups suspected to be at high risk of SCD were investigated on: patients experiencing an acute HF deterioration (80, 81) or during the evaluation phase of a newly diagnosed LV dysfunction (82). In newly diagnosed HFrEF, the calculation of SCD risk should be postponed until after implementation of GDMT following the current ESC HF guidelines.(23) In the evaluation phase. patients are at risk for SCD and are considered to be unprotected. The PROLONG trial studied this cohort in order to avoid early and potentially unnecessary ICD implantations during establishment and up-titration of HF medication.(83) 156 Patients with HFrEF due to various cardiac diseases, but mainly NICMP were scheduled for a follow-up after 3 months to assess not only the LV function but also the functional status of the patients. Both parameters are needed to indicate an ICD implantation. If the LVEF increase to a value between 30 and 35% with an increase of more than 5% within the first evaluation phase or the HF medication was not yet fully established, the WCD prescription was prolonged for further 3 months. At the end of the study, 42% of patients improved LV function to a value above 35% after 3 months and another 19% improved after the prolonged evaluation phase of 6 months. The study enhanced a longer evaluation phase than recommended by the guidelines with almost one fifth of patients improving within the

prolonged phase and stated that patients are still at risk within this timespan due to the fact that WCD shocks occured throughout the course of six months.(83)

Besides patients with newly diagnosed HF, patients with a prior implanted device needing an explantation and/or lead extraction due to electrode infection or material failure can be potential candidates for a WCD. A WCD can be indicated when a reimplantation needs to be avoided or immediate reimplantation is contraindicated to minimize the risk of an infection.(42) Results suggest that a WCD may reduce length of hospital stays. The potential benefit on health care economics and the physiological impact on patients through reduced hospitalization length was not specifically studied before.

All these data did not result in specific recommendations in the current guidelines but added information on the clinical application of the device.

The setting of patients after AMI and/or after revascularization came back repeatedly in several studies as these patients seemed to be at temporary high SCD risk supported by high event rates in several registries compared to other aetiologies. Prospective randomized controlled trials showed that ICD implantation shortly after AMI decreases arrhythmic death but does not improve all-cause mortality.(2, 37, 38) This led to the specific recommendation from the ESC guidelines (2) against ICD implantation at that early timepoint. This cohort seemed to potentially benefit from WCD prescription, at least following results from registries and non-randomized trials suggested.(75, 84, 85)

As these suggestions needed confirmation, the controlled "VEST”(41) trial (*Vest Prevention of Early Sudden Death Trial*) was designed to randomize patients after AMI with left ventricular dysfunction (LVEF ≤35%) to either WCD and GDMT or to GDMT alone. The results published in 2018 failed to show a significant difference on the chosen primary outcome arrhythmic mortality between the two groups (1.6% device group and 2.4% control group, p=0.18) in the as-treated analysis. The secondary outcome including non-arrhythmic mortality and death from any cause showed a significant difference between the groups (3.1% device group and 4.9% control group, p=0.04). The results showed a high number of crossovers (>5%) as the WCD is commercially available in the US where most patients were recruited. Furthermore, a low wearing compliance (median 18 hours/day) in the device group and 34% randomized to a WCD not wearing it at all were stated reasons for the unexpected negative result. The difference in non-arrhythmic and total mortality was interpreted as chance finding as the result was not corrected for multiple testing.(41)

As the results were expected to show a benefit considering the high event rates in this cohort in earlier studies, the authors performed a post-hoc analysis of patients treated per protocol that stated a benefit on arrhythmic mortality.(55) However, this publication neither changed clinical practice nor lead to a guideline recommendation in this indication.

The current ESC guidelines recommend to consider a WCD in the early phase after an AMI (IIb recommendation, Level of Evidence LoE Class B) for selected patients with a high SCD risk due to incomplete revascularization, having a pre-existent LV dysfunction or arrhythmias more than 48 hours after the index myocardial infarction.(2) Other indications following the guidelines may be in patients with a permanent SCD risk due to secondary prevention but a temporary contraindication for ICD implantation (IIa recommendation, LoE Class C). Specific subgroups that showed high event rates and were studied in small registries without randomized-clinical trials, such as patients with a peri-partum cardiomyopathy or inflammatory heart disease and LVEF≤35% are not provided with specific recommendations with the data being too sparse. The WCD is considered as an option in the first 3-6 months after diagnosis until either restitution of LV function or definite ICD implantation takes place. In the waiting time for heart transplantation (Class IIb, LoE C) a WCD may be considered.(2)

Apart from clinical considerations concerning the underlying cardiac disease, the prerequisites for a WCD candidacy are suggested to be similar to ICD patients: the ESC Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (2) as well as the AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (22) recommend an expected survival of more than one year with a good functional status and a reasonable QoL. As the specific recommendations for WCD are missing, national societies have drafted advisories. The American Heart Association (AHA) does not recommend a WCD when the risk for non-arrhythmic fatal events significantly exceeds the arrhythmic mortality risk, with an expected survival of less than 6 months (Class III recommendation, LoE C).(86) The German Society of Cardiology (DGK) states the following contraindications for WCD prescription (49): Patients either declining or not being eligible for an ICD or not being capable of handling a WCD.

1.3 Gaps in evidence and objectives

The goal of this thesis, and the incorporated studies is to analyse the most important functions of the WCD in different clinical settings in which gaps in evidence still exist.

1.3.1 SCD protection after acute myocardial infarction

Following results of the IRIS and DINAMIT study, prior trials did not show a benefit on mortality when a prophylactic ICD is implanted shortly after AMI.(37, 38) In the weeks after AMI patients seem to be unprotected from SCD. The VEST trial (41) published in 2018, included 2302 patients after AMI and LVEF≤35% and randomized them in a 2:1 ratio to study to WCD and GDMT versus GDMT only to study whether a WCD was beneficial concerning arrhythmic mortality. The trial could not show a significant reduction in arrhythmic mortality in patients prescribed with a WCD (1.6% with WCD vs. 2.4% with GDMT, p=n.s.). Apart from a relevant number of crossovers between the intervention and the control group, a lower than expected wearing compliance was one of the reasons that might account for the result. Analysis suggest that a higher WCD wearing compliance might have positively influenced the outcomes.(87) The current ESC guidelines (2) incorporate data from the VEST trial did not change the prior recommendation concerning this clinical application. The guidelines set a class IIb recommendation to consider a WCD for SCD prevention in the acute phase after myocardial infarction. The guidelines mention that real-world registries capture a much higher wearing compliance if a WCD is not prescribed under the conditions of a randomized study. The question whether there would be a benefit on arrhythmic mortality in a cohort with a better compliance than in the VEST trial is not answered yet.

We used data from the Austrian real-world WCD registry incorporating patients with an overall good wearing compliance and compared these to the original VEST(41, 55) cohort with a significantly worse wearing compliance. The objective is to analyse the real effect on arrhythmic mortality in patients during the acute phase of AMI and with reduced LVEF.

1.3.2 Cardiac rehabilitation with a WCD

CR aims to improve cardiac function und functional capacity in patients with a cardiac disease. CR as add-on to specific interventional and/or medical therapy can reduce mortality, re-hospitalizations and improve QoL in different clinical settings as in

newly diagnosed HF after myocardial infarction or with a cardiomyopathy of other origin.(23, 24, 30, 31)

Patients undergoing a CR with a CIED have been studied previously. There is Evidence shows that CR can be performed safely and outcomes concerning exercise capacity and psychological distress levels improve similarly. Additionally, rates of total and exercise-related shocks decrease after CR.(88, 89) To support CR measures and improve safety in CIED patients, few considerations are mentioned in the guidelines. Exercise testing is recommended to see whether arrhythmias are provoked and to detect the needed exercise HR to adjust CIED programming to avoid inappropriate shocks for sinus tachycardia. (class IIa, LoE C).(30, 90) General considerations are to avoid any local trauma and to postpone any PA concerning the upper extremities including exercise-based CR within the first weeks after newly implantation of a device including leads. Apart from that, myopotential-induced oversensing and either inhibition of pacing or triggering of inappropriate shocks through exercise is scarce.(30, 91, 92) In contrast to CIED patients, corresponding data on patients undergoing CR with a WCD are not studied thoroughly until now, only observational data exist about this specific cohort.(73, 93)

Data from patients completing a CR program with a WCD will be analysed. We aimed to investigate the feasibility and safety of patients undergoing a regular in-patient exercise-based CR program with a WCD.

2 Materials and Methods

2.1 Austrian WCD registry

The Austrian WCD registry enrolled 896 patients in 60 centers who received a WCD within 2010-2020 (see *Figure 11*). All patients were informed about the nationwide WCD registry at the timepoint of WCD prescription and asked for informed consent by their treating physician. All Austrian clinical centers and all Austrian rehabilitation institutions received institutional review board approval from the ethic committee (*EK 27-057 ex 14/45)*.

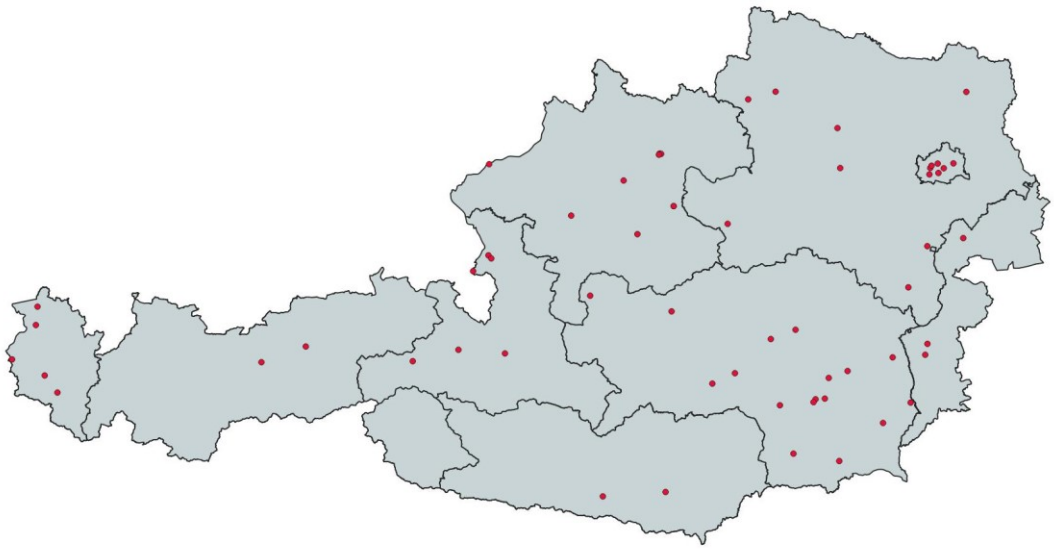

Figure 11: 60 centers all over Austria contributed 896 WCD patients to the registry

Baseline characteristics and follow-up data were recorded from medical records; compliance, wearing duration, VT/VF programming as well as all alarms and WCD treatments were collected from the ZOLL Patient Management Network (ZPM) and correlated with medical records via electronic hospital systems. The ZPM is a website maintained by the manufacturer of the WCD (ZOLL, Pittsburgh).

2.1.1 SCD protection after acute myocardial infarction

Within the Austrian WCD registry, we performed a retrospective analysis of all patients being eligible according to the in- and exclusion criteria of the original VEST trial between 2010 and 2020 (see *Table 1*, reproduced from the original publication).(41) For inclusion in the retrospective analysis, all three main inclusion criteria and none of the exclusion criteria have to be met.

Inclusion criteria	Exclusion criteria
1. Patients identified in the hospital or within 7 days after discharge with a diagnosis of an AMI (STEMI or Non-STEMI)	1. Existing ICD or indication for an ICD
	2. Existing unipolar pacemakers/leads
2. LVEF ≤35%, determined at the following time point: • if no PCI ≥8h after AMI • if acute PCI occurs, ≥8h after PCI if CABG is planned (before or within 7 days of discharge), most recent assessment at least 48h post CABG	3. Chronic renal failure requiring haemodialysis after hospital discharge
	4. Chest circumference too small/large for WCD
	5. Participants discharged to a skilled nursing facility with anticipated stay >7 days
	6. Pregnancy
3. Age ≥18 years	7. Inability to consent
	8. Any condition/circumstance that makes the participant unsuitable for the study

Table 1: Inclusion and exclusion criteria of the VEST trial (41), Abbreviations: AMI – acute myocardial infarction, CABG - coronary artery bypass grafting, ICD - implantable cardioverter defibrillator, LVEF - left ventricular ejection fraction, MI - myocardial infarction, PCI - percutaneous coronary intervention, STEMI - ST-elevation myocardial infarction, VEST - "Vest Prevention of Early Sudden Death" trial, WCD - wearable cardioverter defibrillator

2.1.2 Cardiac rehabilitation with a WCD

This is a multi-center, retrospective, observational cohort study of patients prescribed with a WCD (from the manufacturer ZOLL CMS GmbH.) between 2010 and 2020 and completed an exercise-based CR following the current recommendations.(30,

31) The study is called “Cardiac Rehab Retrospective Review – CR3” and is registered at ClinicalTrials.gov (NCT04675957).

The following criteria were used to enrol subjects in the study:

- Partial (>50%) or full completion of CR when wearing the WCD
- ≥18 years old and able to give informed consent

2.2 WCD diagnostics and treatments

ECG recordings during different alarms, either triggered by an automatically working algorithm with predefined detection limits or those manually recorded by the patient, were reviewed in the online network.

Automatically triggered alarms: The physicians can decide the HR limits for VT and VF detection, the default programming for the detection threshold is 150 bpm for VT and 200 bpm for VF. These automatically detected ECGs trigger an alarm so the patient can react to avoid inappropriate WCD shocks of stable VA or due to false alarms. When VA are captured but the WCD treatment is aborted by the patient, these arrhythmias are counted as hemodynamically stable VA unless the correlated medical records disagree.

Manually recorded alarms: These alarms are captured by patients pressing the buttons on their WCD when they feel symptoms that may be arrhythmia associated but may not trigger WCD treatments.

Appropriate and inappropriate treatments: The appropriateness of applied WCD shocks was assessed by three independent cardiologists, independently assessing the blinded ECG stripes. Sustained VTs (>30 sec), VF, TdP were adjudicated as appropriate. Asystole, bradycardia, artefacts, pacemaker oversensing, sinus tachycardia, AF with rapid ventricular response, or non-sustained ventricular tachycardia (nsVT, <30 sec) triggered events were categorized as inappropriate.

Follow up: All available medical reports and additional information from telephone follow ups by treating physicians were reviewed. Data concerning arrhythmic events like WCD treatments, VA, SCD or cardiovascular death/death from any cause were documented in the registry as well as clinical follow ups after WCD termination. The cause of death was categorized as arrhythmic death or death from any cause following medical reports. When the WCD was worn during the event, the ECG recording was included in

the adjudication.(51) The adjudication of the outcome events and mortality was assessed by three independent cardiologists.

2.3 Data analysis

The mean ± standard deviation and/or interquartile range, or median and range (min; max) when relevant, were calculated for all continuous variables. Categorical variables are presented as percentages (%) and counts. Continuous variables were compared either using a student t-test or the Wilcoxon Rank-Sum test. Frequencies were evaluated with a Chi-square analysis or Fishers' exact test. For comparing two or more samples, the Kruskal-Wallis test was used as appropriate. Relationships were assessed via correlation and linear regression, tested with the one-way ANOVA. Two-tailed P-values <0.05 were considered to indicate statistical significance. Statistical analyses were performed using SPSS 27 (IBM, Armonk, New York, USA).

3 Results

3.1 Austrian WCD registry

All patients who have been prescribed a WCD in Austria are part of the Austrian WCD registry. There are no inclusion criteria other than having a WCD fitted. 896 patients were treated in 56 different centers for various cardiac diseases.

3.1.1 Baseline characteristics

The 896 patients prescribed with a WCD had a mean age of 60±14 years and 21% were female. 561/896 patients (63%) had a WCD due to a potentially reversible SCD risk, bridge to a therapeutic procedure such as VT ablation. 254/896 patients (28%) were waiting until an ICD implantation could be performed. In 78/896 (8%) were waiting for ICD implantation with a temporary existing contraindication for implantations. The smallest population consist of 5/896 patients (1%) with a terminal non cardiac disease during risk stratification. All these cohorts are divided in subcategories as seen in *Table 2*.

In the registry, 56% (499/896) of patients received a WCD due to secondary prevention compared to 44% being primary preventive supplied with a WCD. The baseline LVEF of the whole population was 32±14%. Almost 90% of the population (779/896) had a prior history of CAD at baseline. Around 75% (672/896) were diagnosed with arterial hypertension. 246/896 (27%) have documented AF in their medical history.

WCD prescription duration was 62 days (1;675). Patients with a very short duration either stopped the treatment due to their own request, received shocks very early on that required hospitalization and/or an ICU stay. A patient with myocarditis and prolonged immunosuppression resulted in the longest wearing duration of almost two years. During the median 62 days of wearing the device, the daily wear-time was median 23,5 (0;24) hours.

		No/896 (%)
Risk stratification		**561 (63)**
	Unclear CMP	254 (28)
	Recent AMI, LVEF<35%	105 (12)
	Recent PCI/CABG	100 (11)
	Myocarditis	96 (11)
	Rare/genetic CMP	8 (1)
Bridge to a therapeutic procedure		**254 (28)**
	Delayed ICD implantation	140 (16)
	Bridge to reimplantation after ICD associated infection	75 (8)
	Bridge to ablation	19 (2)
	Bridge to CABG	11 (1)
	Bridge to HTX	9 (1)
Bridge to ICD implantation		**76 (8)**
	Recent PCI/AMI	49 (5)
	Acute infection	19 (2)
	Ventricular thrombus	7 (1)
Terminal non cardiac disease		**5 (1)**

Table 2: Indications for WCD prescription: different main categories with the associated subcategories; Abbreviations: AMI – acute myocardial infarction, CABG – coronary artery bypass graft, CMP- cardiomyopathy, HTX – heart transplantation, ICD – implantable cardioverter defibrillator, LVEF – left ventricular ejection fraction.

3.1.2 Alarms and events

Altogether, 607/896 patients (68%) experienced 24.296 automatically triggered alarms (median 3 (0;2292) events per patient) and 668/896 (74%) triggered 5501 alarms manually.

3.1.2.1 Manual alarms

Within these more than five thousand ECGs, 88% (4833/5501) were classified as sinus rhythm. Only five ECGs showed slow sustained VT that had a cycle length below the programmed detection thresholds (0.09%) and therefore not been automatically detected. 22 ECGs showed nsVTs (0.4%) and 51 triggered ECGs detected AF. Almost

600 ECGs (11%) showed other non-malignant arrhythmia that were not detected by the automatic algorithm such as bradycardia, PVCs, or SVTs (see *Table 3*).

		No of alarms (%)	Patients, n (%)	Events/patient
Manual alarms		5501 (100)	668 (74)	2 (9;579
	Sinus rhythm	4833 (88)	497 (55)	1 (0;579)
	Others (PVC…)	483 (8.8)	482 (54)	1 (0;2)
	Sinus tachycardia	80 (1.5)	9 (1)	2 (0;57)
	AF/-flutter	51 (0.9)	26 (3)	1 (0;8)
	SVT	23 (0.4)	20 (2)	1 (0;3)
	NsVT	22 (0.4)	9 (1)	1 (0;10)
	Sustained slow VT	5 (0.1)	4 (0.4)	1 (0;2)
	Bradycardia	4 (0.1)	4 (0.4)	1 (0;1)

Table 3: Manual alarms, Abbreviations: AF - atrial fibrillation, nsVT – non-sustained ventricular tachycardia, VT - ventricular tachycardia, PVC - premature ventricular contraction

3.1.2.2 Automatic alarms

Only around six percent of patients (55/896) had adequate automatic alarms compared to 65% of patients experiencing inadequately triggered alarms. Several patients experienced non-sustained events and sustained events and or shocks later on. VT and VF separated by a short time interval was documented in a few patients. Inappropriate automatic alarms (22.282/24.296) were caused by oversensing of artefacts in 92% of cases. Apart from that, 275 (1%) sustained VTs were appropriately detected. Only 32 VT events required a WCD treatment. These cases were further classified as 243 hemodynamically stable VTs where patients aborted the WCD treatment. Malignant arrhythmias such as VT and VF that received a shock will be discussed in chapter 3.1.2.3. Several events were triggered due to non-malignant arrhythmias as seen in *Table 4*.

		No of alarms (%)	Patients, n (%)	Events/patient
Ventricular arrhythmia		**305 (1.3)**	**55 (6)**	**0 (0;72)**
	Sustained VT (stable)	243	50 (5.6)	0 (0;72)
	Shocked VT	32	19 (2.1)	0 (0;5)
	Shocked VF	30	17 (1.8)	0 (0;4)
Other arrhythmia and artefacts		**23.991 (98.7)**	**583 (65)**	**2 (0;2292)**
	Artefacts	22.282	572 (64)	2 (0;2292)
	NsVT	1028	62 (7)	0 (0;636)
	AF/-flutter	343	32 (4)	0 (0;137)
	SVT	197	36 (4)	0 (0;72)
	PM/t-wave oversensing	77	2 (0.2)	0 (0;71)
	Others (atrial runs, PVCs…)	50	10 (1)	0 (0;10)
	Bradycardia	9	9 (1)	1 (0;1)
	Asystole	5	5 (0.6)	1 (0;1)

Table 4: Overview of automatically triggered alarms; Abbreviations: AF – atrial fibrillation, nsVT- non-sustained ventricular tachycardia, PM – pacemaker, PVC – premature ventricular contraction, VF - ventricular fibrillation, VT – ventricular tachycardia

Concerning potential predictors for an increased number of inappropriate alarms, former studies and registries suggest, that the wearing compliance, gender, having a previously CIED device, QRS duration or age do not have an impact. Vice versa, skinny and more active patients have been identified to trigger a significant higher number of alarms.(53, 58) Similarly, in the Austrian registry, younger patients have a higher amount of alarms (p=0.023), while BMI, wearing compliance and previously known AF do not have an influence (p=n.s.).

3.1.2.3 Shocks

Of the 896 patients, 36 (4%, mean age 67±14 years, 11% female) received a total of 72 automatically triggered shocks (median 2; range 1-5). 33/896 (3.7%) patients received 62 appropriate shocks (median 1, range 1-5), whereas 7/896 (0.8%) patients received 10 inappropriate shocks (median 1, range 1-2).

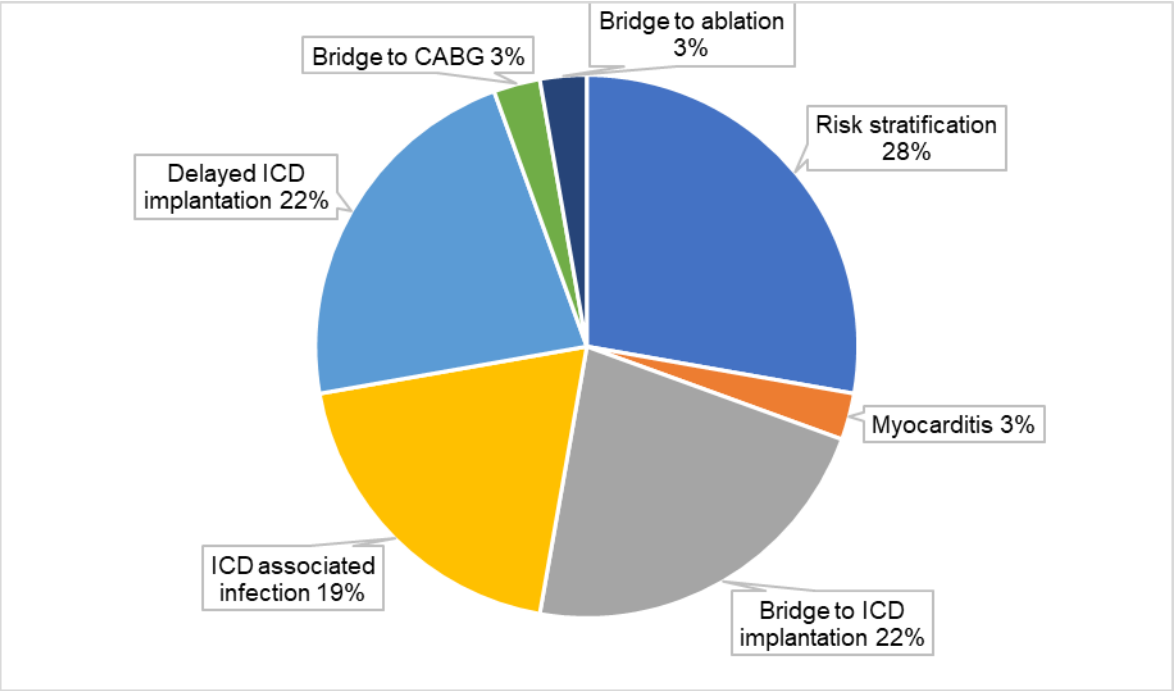

Figure 12: WCD indications of patients who received an appropriate shock; Abbreviation: CABG – coronary artery bypass graft, ICD - implantable cardioverter defibrillator.

WCD indications in patients with an appropriate shock were SCD risk stratification (10/33, 28%), delayed ICD implantation (8/33, 22%) or as bridge to ICD implantation (8/33, 22%), ICD associated infections with the need for explantation (7/33, 19%), bridge to CABG, bridge to ablation or myocarditis (each 1/33, 3%) (see *Figure 12*). Four patients with inappropriate shocks had a WCD as bridge to ICD, one patient during risk stratification one due to an explanted ICD until reimplantation and one due to delayed ICD implantation.

The median time from WCD prescription to a shock event was 7 days (1-151). 46/69 (67%) shocks happened within 30 days after prescription, see Figure 13.

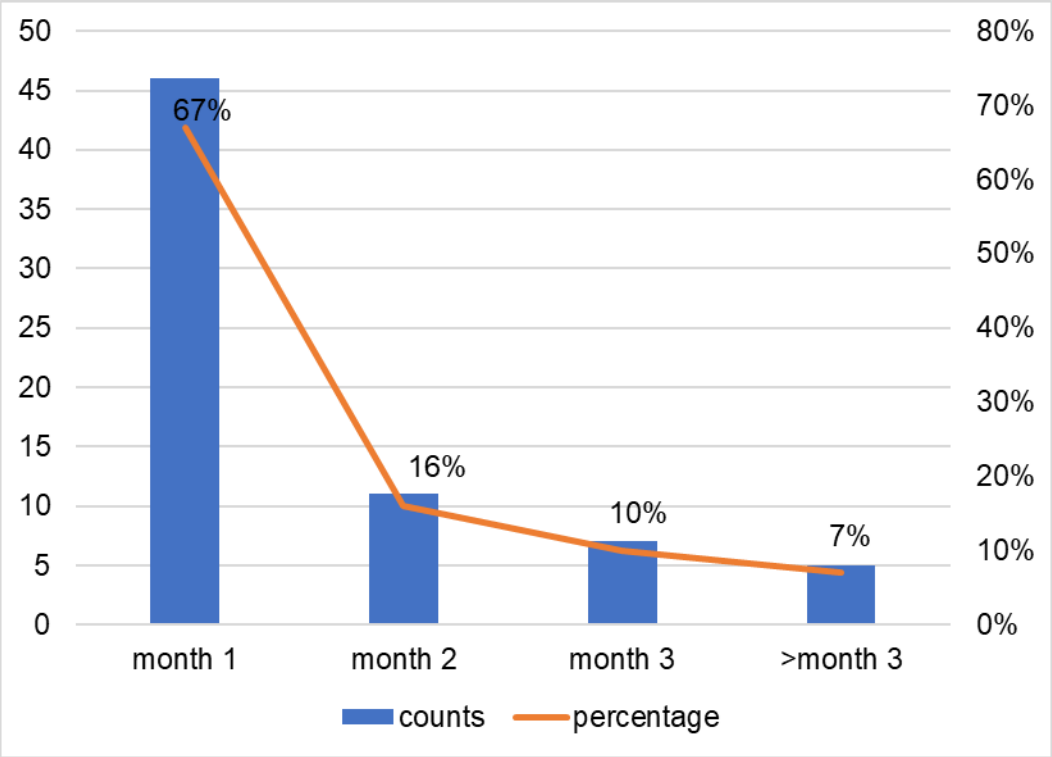

Figure 13: Timepoint of first shock after WCD prescription

In total, 57 events (27 VT/30 VF) could be successfully treated with WCD shocks. The overall shock rate in our cohort was 0.03 shocks (3.9%) per patient-month. The mean HR of all shocked events was 243 (range 130-340) beats per minute. 49/62 events were converted to SR with the first shock (79%), 5 events were appropriately terminated with the second shock. In one patient, VF was appropriately detected and treated by the WCD however, the arrhythmia reinitiated after 5 shock attempts (3 of them initially effective and 2 ineffective) and he was admitted to an ICU and treated for electrical storm. 1 patient with a VT received one appropriate but ineffective shock and terminated spontaneously after that episode (see *Figure 14*).

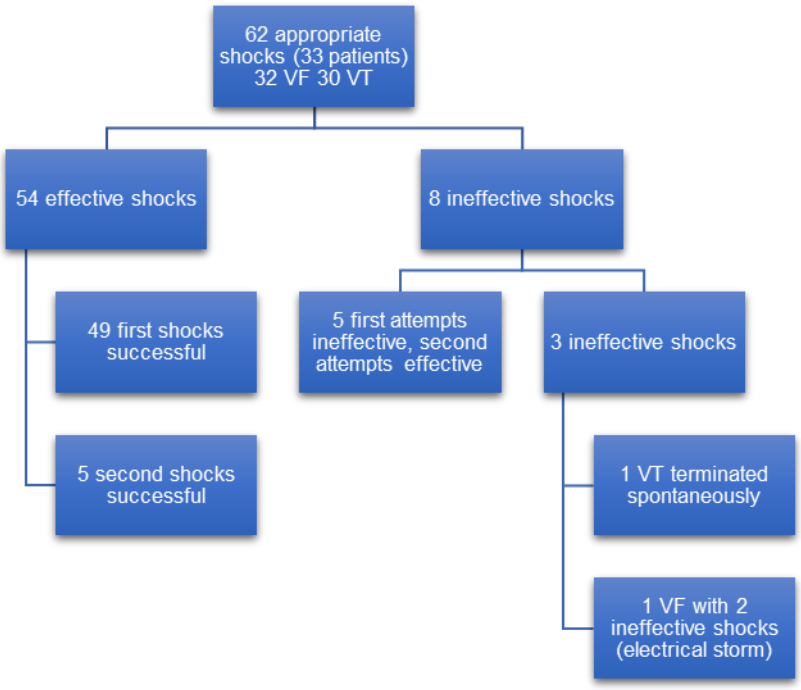

Figure 14: Appropriate shocks in 33 patients for VT or VF; Abbreviations: VF - ventricular fibrillation, VT - ventricular tachycardia

The time from event onset to shock was median 60 (40;1187) seconds, while the longest time to shock results from an initial haemodynamic stable patient aborting the indicated treatment.

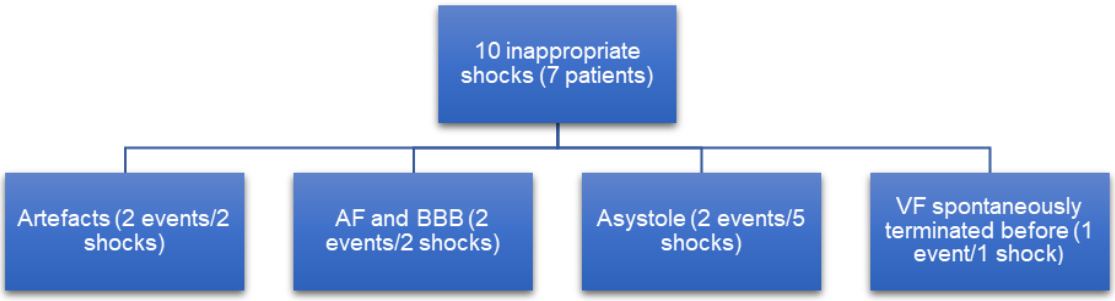

Figure 15: Reasons for inappropriate shocks; Abbreviations: AF – atrial fibrillation, BBB - bundle branch block, VF - ventricular fibrillation

Seven patients (0.8%) received a total of ten inappropriate shocks with a per patient shock rate of 1 (1;2): inappropriate shocks were applied either due to artefacts with underlying sinus rhythm or non-shockable rhythms (asystole or AF with BBB). In one patient, VF converted to sinus rhythm spontaneously before the WCD treatment was delivered (see *Figure 15*). None of the inappropriate treatments converted a benign rhythm to a malignant arrhythmia or asystole.

Looking through the automatically recorded alarms preceding a WCD shock, shocked patients experienced significantly more often non-sustained VTs (23.5% vs. 6.5%, p<0.0005) and hemodynamically stable sustained VTs (p<0.0005). Compared to the total cohort, shocked patients were older (mean age 67±14 vs. 60±14 years, p=0.001) and the percentage of female patients was lower without statistical significance (11% vs. 21%, p=0.262). The mean baseline LVEF at prescription was 33±15% in the population with appropriate shocks compared to 32±14% in the all-over cohort (p=n.s.). Cohorts that seem to predict a higher likelihood to receive shocks is the cohort of secondary prevention (p=0.007), the cohort of octogenarians (p=0.008), when WCD was indicated due to an ICD associated infections with the need for temporary explantation (p=0.001), when used as bridge to ICD (p=0.042) and in patients with ongoing risk stratification (p=0.009).

3.1.3 Follow-up

The WCD prescription ended after 62 (1;675) days due to various reasons. 883/896 (98.5%) were still alive at the end of prescription while 13/896 (0.5%) died during this time. Four patients had a non-terminable or recurrent arrhythmia, five patients died in asystole and four patients were adjudicated to have a non-cardiac cause of death. Only three of these patients received shocks beforehand. One patient received an inappropriate schock due to asystole and two patients for VF. One patient had VF with intermittent effective shocks but recurrent VF. These patients were 63±13 years (25% female) old at the time of death. The fatal events happened 82±154 days after WCD start and all of them had a reduced LVEF at the beginning (30±12%).

On the contrary, a majority of patients (444/896, 49.6%) were supplied with an ICD, whereas almost one third of patients (282/896) had a restitution of their cardiac function to a LVEF of 45±9% (see *Figure 16*).

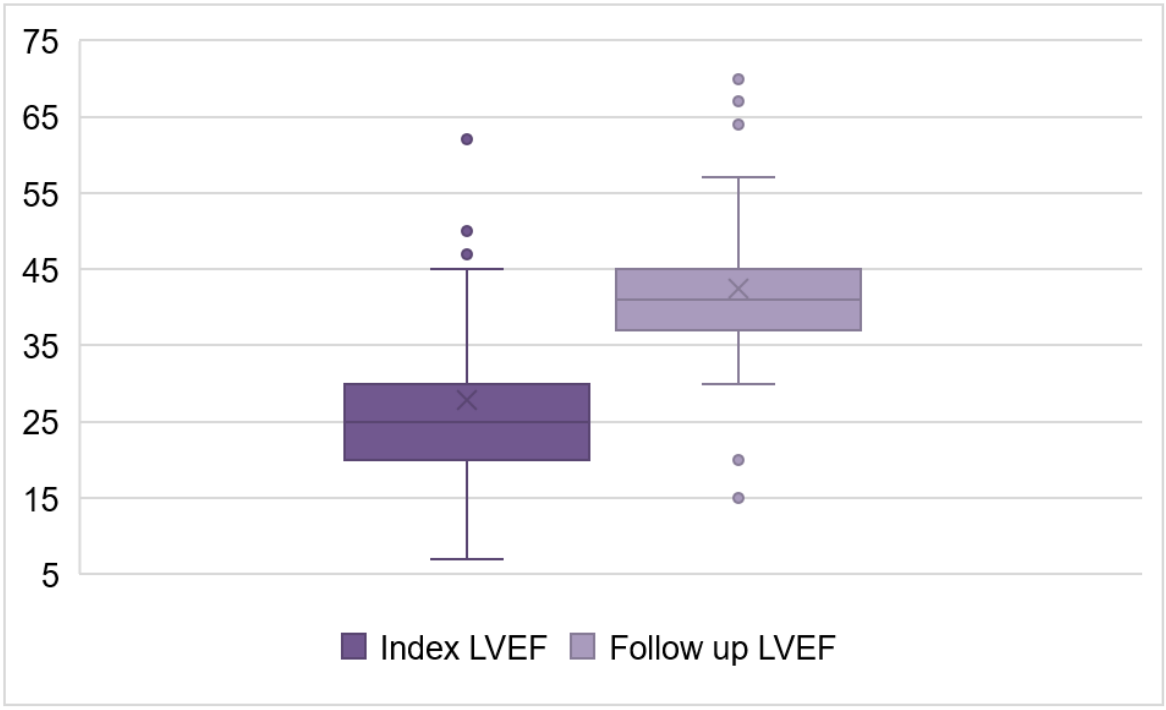

Figure 16: Change in LVEF at the start (left) from 29±11% and end (right) of WCD prescription to 45±9%

69/896 (7.7%) patients refused to continue WCD treatment due to side effects or technical problems. A very small cohort (4%, 36/896) underwent a therapeutic procedure and stopped wearing the WCD afterwards: 12 patients had catheter ablation, 11 patients improved after PCI and 9 patients after CABG. Only 4 patients with end-stage HF received a heart transplantation. 6 patients had an acute event and WCD was stopped due to being monitored at an ICU. In the all-over cohort the LVEF improved to median 32±14% (see *Figure 17*).

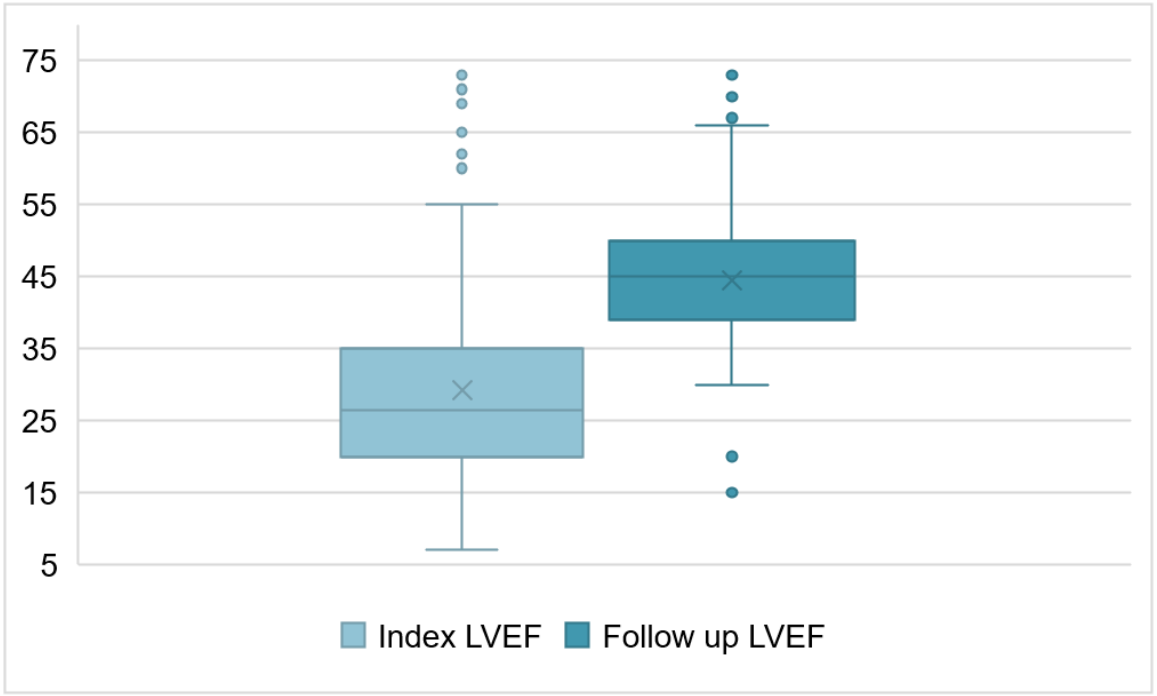

Figure 17: Change in LVEF at the start (left) from 32±14% and end (right) of WCD prescription to 38±13%

3.2 SCD protection with a WCD after acute myocardial infarction

Within the national WCD registry consisting of 896 patients from the whole country, around ten percent (105/896) received a WCD shortly after experiencing AMI and additionally being diagnosed with a reduced LVEF of ≤35%. All inclusion criteria from the original VEST study were applied and all patients were checked for exclusion criteria. The Austrian cohort that fit into these criteria will be called “Austrian VEST cohort” in the further course. When comparisons with data from the original VEST patients that were randomized to WCD as add-on to OMT are done, this cohort will be called “original VEST cohort”:

3.2.1 Baseline characteristics

The Austrian VEST cohort (64±11 years, 12% female) received a WCD 7 (0;21) days after AMI with an initially measured LVEF of 28±6%. These patients presented with typical cardiovascular risk factors like arterial hypertension (96/105, 91%) and diabetes (27/105, 25%). 72% (76/105) had a history of a vascular disease, either peripheral, central, or CAD or a large vessel disease like aortic sclerosis documented. A smaller cohort has experienced a stroke (5/105, 5%) or a thromboembolic event (9/105, 9%) before. Furthermore, 61/105 (58%) patients experienced malignant VA before their WCD supply.

Comparing these baseline characteristics with the original 1524 VEST cohort, the LVEF (28±6% in Austria vs. 28±6% in the VEST group) and age shows similar values (64±11 years in Austria vs. 61±13 years in the original VEST group) without significant differences (p=n.s.). The percentage of female patients was even lower in the Austrian VEST cohort (12%), compared to 27% in the original VEST cohort (p=0.001). On the contrary, Austrian patients were more likely to have a history of arterial hypertension (91% in the Austrian vs. 65% in the original VEST cohort, p<0.05).

Concerning the coronary intervention, 103/105 (98%) underwent PCI and 1/105 (1%) underwent CABG. One patient (1%) should have received surgical revascularization but declined the procedure. During the VEST trial, each option was accepted for inclusion, whether revascularization was performed or not, and irrespective of the method that was chosen. The rates of PCI were high in both cohorts with an even higher rate in the Austrian VEST cohort (98% vs. 84% in the original VEST cohort, p<0.05). The percentage of surgical revascularization was comparable (1% in the Austrian and 0.9% in the original VEST cohort, p=n.s.). Eight percent of original VEST patients have been treated with

thrombolytics while none of the Austrian VEST patients was treated medically ($p<0.05$). Moreover, a similar number of patients (8%) from the original VEST cohort did not undergo any revascularization strategy.

3.2.2 Wearing duration and compliance

In the Austrian VEST cohort, the actual wearing duration in days was 69 (1;277) days. Due to the real-world character of this registry, the whole prescription duration was analysed, which differs from the preset prescription duration of three months that was scheduled in the VEST trial.(41)

Moreover, in the original VEST trial the prescription duration varied despite the preset duration of three months: one third of patients stopped wearing the WCD after the first month and accumulating to 43% of patients who stopped prescription within the first two months. 34% of patients randomized to the device group did not wear the device at all. Within the small percentage of patients wearing their device for the intended timespan of 90 days, 13% had a daily wearing compliance of less than 22 hours/day.(41, 55) Thereafter, the investigators of the VEST trial published a per-protocol analysis, that analysed 525 well-compliant patients with a mean wear-time of 21.6 hours. The authors state that older age, female gender, Caucasian ethnicity, patients that were married and patients with a lower BMI seemed to predict good compliance, defined as wearing the WCD >90% of the day. Also patients being recruited in Poland seem to be more compliant compared to patients recruited in other countries (US, Germany and Hungary).(55)

As the daily wearing compliance is one of the most relevant factors of the WCD, patients undergo an either nurse-based or technician-based training at the timepoint of WCD fitting to support the patients' compliance in Austria. Hence, the wearing compliance is as high as 23.5 (0;24) hours/day in the Austrian VEST cohort (see *Figure 18*). In comparison and frequently discussed, patients from the original VEST cohort wore their device only 18.0 (3.8;22.7) hours/day. There is no specific threshold to determine the quality of compliance but the more hours/day the device is worn, the higher the probability to detect and treat VA. Eighty percent of Austrian VEST patients (83/105) wore the WCD at least 22 hours/day (see Figure 18) compared to only half of patients in the original VEST cohort. In the Austrian VEST cohort only around seven percent (7/105) had a wearing duration below 18 hours/day.(41)

The shortest wearing duration of one day is because one patient was shocked on the first day shortly after fitting the device as further elaborated in chapter 3.2.3. The 78-years-old male patient that wore his device almost ten months was the only patient

declining being revascularized surgically. Together with his physician, a prolonged period of risk stratification and ICD evaluation was determined to evaluate a potential restitution of his cardiac function under OMT before the decision for an ICD was made. Over ten months he did not receive any WCD treatments and wore the device around 21 hours/day. His LVEF improved from 20% to 35% and eventually he stopped the WCD prescription due to his own desire without any further scheduled therapeutic measures.

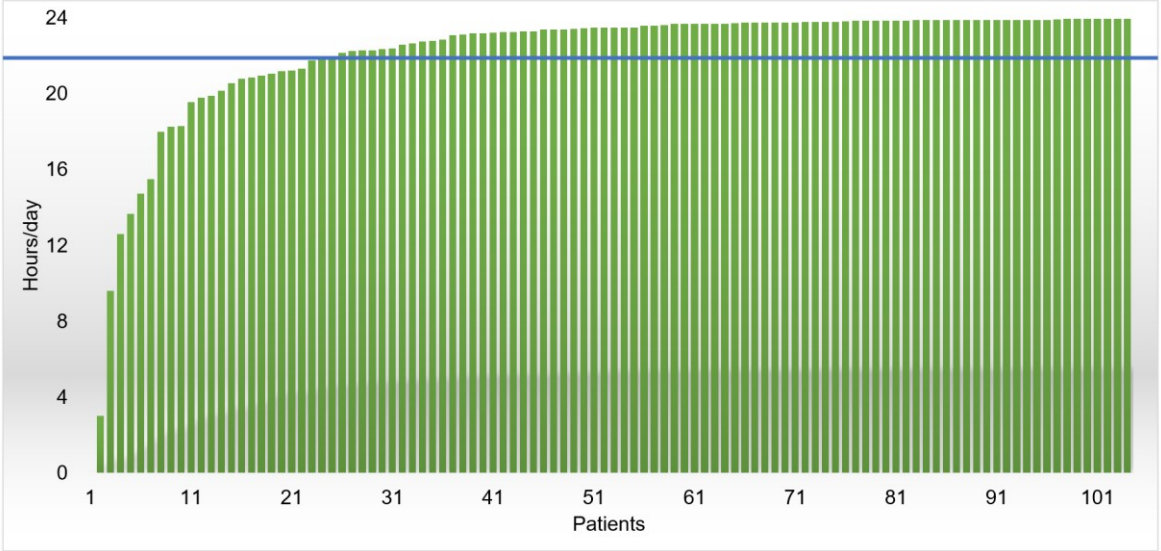

Figure 18: The daily wearing compliance of 105 patients in the Austrian VEST cohort is as high as 23.5 (0;24) hours/day; the blue line indicates a wearing compliance of >22 hours/day

3.2.3 Alarms and events

Ahigh number of manually triggered ECGs (617) were recorded in 61% (65/105) of patients. Comparably to the overall cohort, 99.5% of these ECGs were interpreted as sinus rhythm and in one tenth of these cases with a HR above 100bpm. Singular ECGs revealed AF or atrial flutter (2/617). In one ECG a nsVT was detected. No sustained VT or VF was detected by these manually triggered ECGs (see *Table 5*).

In 72% (76/105) of patients, almost 2800 alarms were automatically recorded with an average number of alarms per person of 37±79. The range of these numbers was a single alarm to a maximum of 565 alarms in one patient. As in manual alarms, the majority 97.5% was adjudicated as inappropriate alarms due to either normal sinus rhythm or non-malignant arrhythmia. Six patients experienced 190 nsVTs, while 169/190 nsVTs appeared in only one patient. Very few patients experienced SVTs, AF, atrial flutter, or oversensing as a cause of automatically triggered alarms. One patient had asystole and

deceased due to this event. Apart from this one fatal event, no bradycardia was detected (see *Table 5*).

		No of alarms (%)	Patients, n (%)
Manual alarms		**617**	**65 (61)**
	Sinus rhythm	607 (98.4)	45 (43)
	Sinus tachycardia	7 (1.1)	1 (1)
	AF/-flutter	2 (0.3)	2 (2)
	NsVT	1 (0.2)	1 (1)
Automatic alarms		**2788**	**76 (72)**
	Shocked VT	7 (0.25)	2 (2)
	Shocked VF	2 (0.07)	2 (2)
	Sustained VT	25 (0.9)	5 (5)
	Artefacts	2550 (91.5)	68 (65)
	NsVT	190 (6.8)	6 (6)
	AF/-flutter	10 (0.4)	4 (4)
	SVT	2 (0.07)	2 (2)
	PM/t-wave oversensing	1 (0.04)	1 (1)
	Asystole	1 (0.04)	1 (1)

Table 5: Alarms and the underlying rhythms in the Austrian VEST cohort. Abbreviations: AF – atrial fibrillation, nsVT – nonsustained ventricular tachycardia, PM – pacemaker, SVT – supraventricular tachycardia, VT ventricular tachycardia, VF – ventricular fibrillation

The 34/2788 (1.2%) appropriate automatic alarms consisted of 5 patients with 25 hemodynamically stable VTs without shocks and four patients (3.8%) within the Austrian VEST cohort that received in total nine shocks (median 2 (1;5). Seven VT and two VF events required therapy and all shocks happened within the first two weeks after prescription, with a median time from prescription to shock of 7 (1;12) days. Moreover, the shocks were applied 35 (29;110) seconds after event onset all shocks were effective at first attempt. In the further course, three of these patients stopped wearing the WCD early and were implanted with an ICD 15±4 days after WCD prescription. The fourth patient receiving initially effective shocks for VF stopped wearing the WCD because he was monitored at the ICU afterwards and died one day after the initial event in refractory electrical storm. No inappropriate shocks happened in the Austrian VEST cohort

compared to a still very low number of shocks in the original VEST cohort (9/1524; 0.6%; p=1.0).

Just like in the Austrian VEST cohort, a large number of automatic alarms (57.451) occurred in 72% of patients. Comparing the underlying arrhythmia from the Austrian cohort to the events in the original VEST cohort, the number of patients with hemodynamically stable VTs (5/105; 5% in the Austrian vs. 69/1254; 5.5% in the original VEST cohort, p=n.s.), asystole events (1/105; 1% in one Austrian patient vs. 6/1524; 0.4% in original VEST patients, p=n.s.) and the number of shocks was not significantly different (4/105; 4% in the Austrian vs.20/1524; 1.3% in the original VEST cohort, p=n.s.).

Even though high numbers of inappropriate alarms triggered by artefacts still pose a problem with the wearable character of the device, this does not seem to impact the wearing compliance in the Austrian VEST cohort. There was no significant correlation between a high number of alarms measured as average number per hour and low compliance as measured by average daily wearing time (Spearman's rho=-0.11, p=0.28). In contrast, patients being confronted with the highest number of alarms indeed show a good compliance (Figure 19).

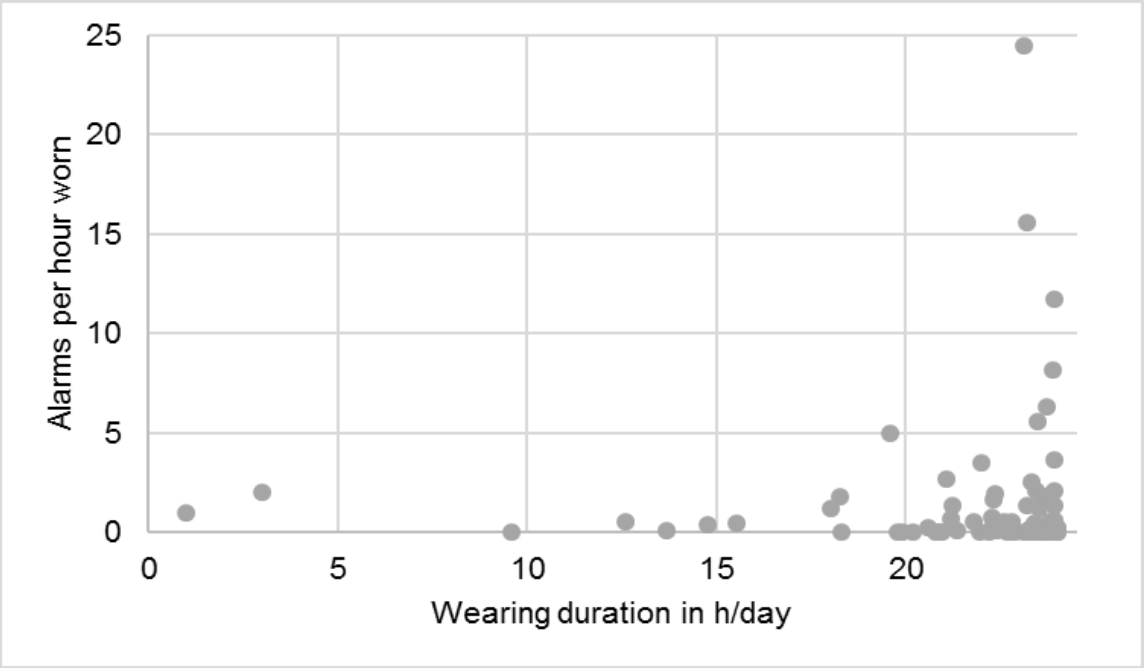

Figure 19: There is no correlation between a high number of alarms and low wearing compliance in the Austrian VEST cohort (Spearman's rho=-0.11, p=0.28)

3.2.4 Total mortality

Within the Austrian VEST cohort, the total mortality was 2.9% (3/105) during a follow-up of 69 (1;277) days. These three events were carefully assessed and thereafter subdivided into arrhythmic (2/105, 1.9%) and non-arrhythmic mortality (1/105, 1%). Only one patient wore the WCD during the fatal event and was adjudicated as non-arrhythmic event, while no autopsy took place to identify the exact cause of death. The other two patients did not wear the WCD because they were monitored at an ICU due to electrical storm.

3.2.4.1 Non arrhythmic mortality

One 57 year-old male patient had an out-of-hospital cardiac arrest due to asystole as his primary rhythm while wearing the WCD and died despite intense resuscitation attempts. At the timepoint of the initial prescription, he presented with AMI and a LVEF of 35%. He had a 3-vessel CAD and was fully revascularized. No bradyarrhythmia was documented before the fatal event.

3.2.4.2 Arrhythmic mortality

As mentioned above, two patients died due to ventricular storm after experiencing sustained VA while wearing their WCD: The first patient was a 34-years old male patient that was diagnosed with a large ventricular aneurysm, a severely reduced LVEF of 15% and thrombi in both ventricles after AMI with a single-vessel CAD. He initially experienced recurrent monomorphic VTs after revascularization still monitored at the ward and was prescribed with a WCD. A few days later, he experienced recurrent monomorphic VTs (300ms tachycardia cycle length) and aborted the WCD treatments while being hemodynamically stable. He was then admitted to the local ICU and transferred to a university hospital for VT ablation and left ventricular assist-device (LVAD)/HTX evaluation. He was not eligible for endocardial VT ablation and/or LVAD implantation due to the ventricular thrombi and the cardiac surgeons stated that the ventricular aneurysm was too large to be removed. The heart-team also declared him not eligible for HTX because of ongoing drug abuse. Without any further therapeutic options, the patient died in refractory electrical storm shortly after.

The second patient was a 64-years old male patient that had a non-STEMI with a two-vessel-CAD. He was fully revascularized and a LVEF of 25% was measured in the echocardiography. He experienced nsVTs and finally VF with a WCD shock that he was prescribed with while he was still in-patient at the ward more than 48 hours after the initial

event. The recorded ECG showed short-coupled R-on-T PVCs that induced VF. The initial WCD treatment was appropriate and effective. Nevertheless, he suffered and finally deceased in electrical storm at the ICU the day after.

Comparing these event rates with the mortality rates from the original VEST cohort, the total mortality (3/105; 2.9% vs. 48/1524; 3.1%, p=n.s.) the non-arrhythmic mortality (1/105; 1% vs. 21/1524; 1.4%, p=n.s.) and the arrhythmic mortality (2/105;1.9% vs. 25/1524; 1.6%, p=n.s.) did not show any significant difference. Whereas 9/25 patients adjudicated as arrhythmic death of the original VEST cohort died while wearing their WCD. The adjudication of the other patients was without documented arrhythmia.(41, 55)

3.2.5 Follow-up

After the WCD prescription period, 44% (46/105) of patients in the Austrian VEST cohort have received an ICD, 36% (38/105) had a restitution of their LVEF, 10/105 (10%) had the desire to stop wearing the WCD, 3/105 (3%) died, 8/105 (8%) had no documented reason for stopping their WCD. The follow up LVEF in the patient that were alive at the end of prescription was 35% (15;59) compared to the baseline LVEF of 28% (10;35) at baseline (Figure 20).

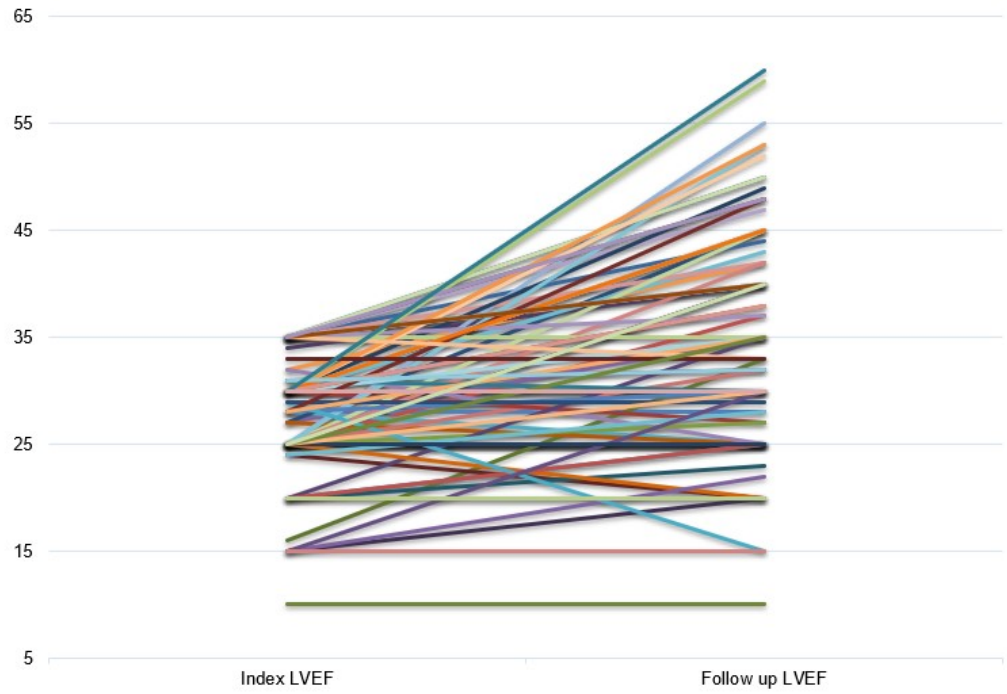

Figure 20: Index LVEF 28% (10;35) at the timepoint of prescription compared to the follow up LVEF of 35% (15;59) of the Austrian WCD cohort. Every coloured line stands for the LVEF in an individual patient.

Finally, in the original VEST cohort 67/1524 (4.4%) VEST patients received an ICD implantation during the first 90 days what was practically not intended according to the study protocol and represented a protocol deviation. An ICD-implantation after the predefined 90 days of follow-up was not documented in the VEST trial. Hence, these numbers are not reliably comparable.(41)

3.3 Cardiac rehabilitation with a WCD

The CR3 study recruited patients from the Austrian WCD registry who have completed at least 50% of the CR with a WCD. Within 896 patients, 55 (6%) patients fulfilled all inclusion criteria. The patients underwent CR for 28 (18;42) days compared to their total WCD prescription duration of approximately three months (94 days (26;294). The median daily wearing compliance was as high as 23.4h (12.6;23.9) which is like in the overall WCD cohort of the Austrian registry (see chapter 3.1.1).

Moreover, 76% (41/55) of patients had a WCD 43 (23;178) days before CR start and completed the whole period with it. On the other hand, not all patients were supplied with a WCD beforehand: CR physicians prescribed a WCD during CR in 22% (12/55) of patients due to newly diagnosed reduced LVEF. Furthermore, LVEF recovered during CR in 2/55 and WCD was stopped thereupon.

3.3.1 Baseline characteristics

55 patients were included in the CR3 study (age 60±11 years, 1% female patients). The median baseline LVEF at start of CR was 36% (12;80%) and all patients had modifiable cardiovascular risk factors at the beginning of their CR. 76% of patients were overweight or obese at the beginning of CR with only 20% of patients classified as having a normal body mass index (BMI), 4% were classified as underweight (see *Figure 21*). The overall median body weight was 82 (52;118) kg and the BMI 28 (18;40) kg/m². Around 70% (38/55) had a prior medical history of arterial hypertension with a baseline blood pressure at CR start of systolic 126±18mmHg, diastolic 79±11mmHg. One third (19/55, 35%) had a medical history of diabetes, more than half of the patients (31/55, 56%) had a vascular disease, and 28/55 (51%) also had a history of prior PCI. AF or atrial flutter had been previously diagnosed in 20% (11/55) and 4/55 (7%) had a prior stroke.

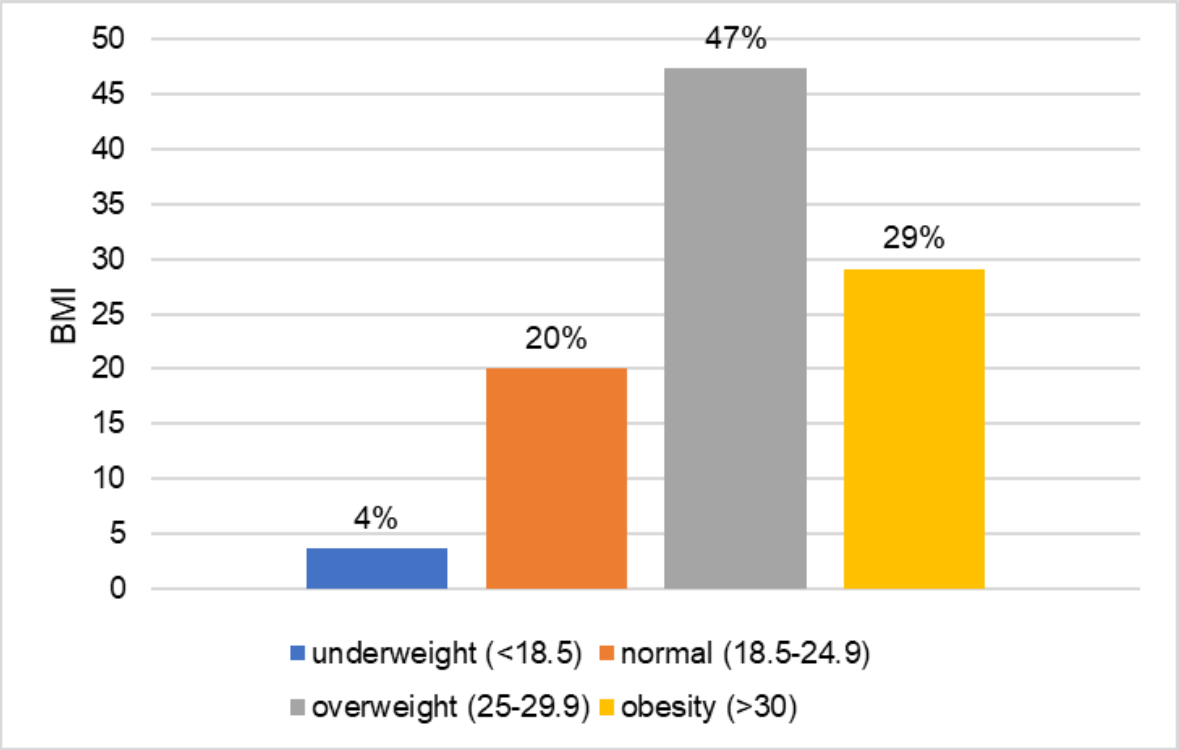

Figure 21: BMI of patients in the CR3 study

The patients received a WCD due to various underlying cardiac diseases. Almost half of the patients (27/55) had ICMP, one third (15/55) was previously diagnosed with DCMP, and 10/55 (18%) patients had myocarditis. One patient had valvular CMP or tako-tsubo CMP. One patient experienced an aborted SCD without known cardiac disease with suspicion of a primary electrical disease (each 1.8%) (see *Figure 22*). Similarly, the reasons for WCD prescription were varied: the WCD was prescribed to bridge the time to ICD implantation due to a temporary contraindication, to bridge the time to a potential restitution of LVEF or during risk stratification.

The majority (40/55; 72%) received the WCD as primary prophylaxis. In 15/55 (28%) patients earlier experienced VA was VT in 4/15 patients and VF in 9/15 patients, 2/15 patients experienced both arrhythmias.

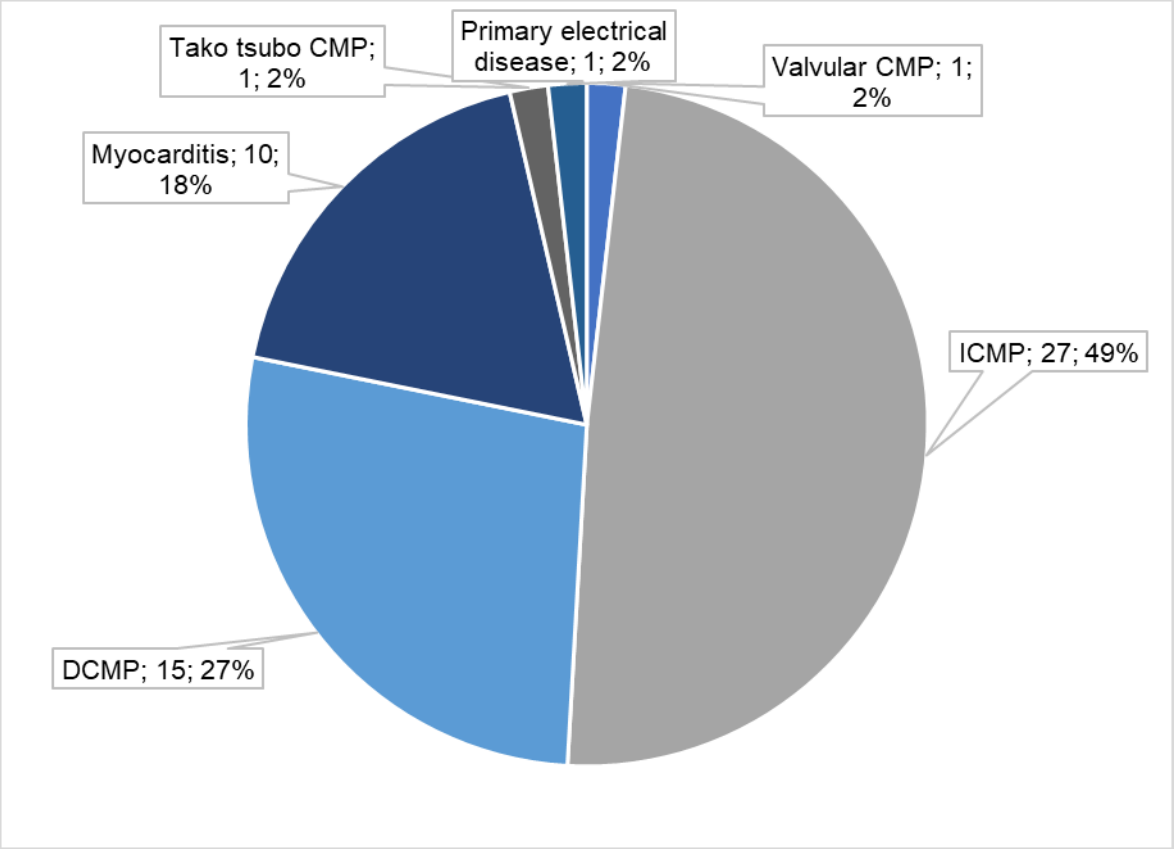

Figure 22: Underlying cardiac diseases that led to WCD prescription in CR3 study patients; Abbreviations: DCMP – dilatative cardiomyopathy, ICMP – ischemic cardiomyopathy

To assess physical capacity, exercise testing was performed at the CR start. Due to preexisting severe LV dysfunction seven patients (13%) did not undergo any exercise testing. Most patients (42/55; 76%) performed a classical cycle ergometry, 6/55 (11%) performed a walking test. The target value in cycle ergometry was reached to 65±17% in these patients at the baseline testing.

3.3.2 Alarms and events

Within the 94 (26;294) days of prescription, 2848 automatic alarms (64±116/patient) and 340 manual alarms (7±9/patient) were generated. All manual alarms in 53/55 (93%) patients were adjudicated as sinus rhythm, no arrhythmias were detected.

On the other hand, 99.2% (2826/2848) of all automatically triggered alarms accounted for artefacts. Less than one percent (14/2848) were triggered by 2 nsVTs in one patient and 12 AF episodes in 3 patients and were counted as inappropriate automatic alarms. No bradycardia or asystole was detected. Only 0.3% of alarms appropriately detected 8 sustained VA (7 VT, 1 VF) in four patients which subsequently led to four shocks in two patients (see *Table 6*). Two patients with hemodynamically stable

VTs were medically treated with AAD while only one patient had the VTs documented during CR.

Furthermore, the above mentioned two patients (4%) experienced four (1;3) shocks for VA while none of them happened during CR. One 58-year-old male patient had an effective shock for VF. A 76-year-old male patient had three VT events that converted to sinus rhythm with the first shock, respectively. The shocks took place one and 13 days after WCD prescription and 48 days and one day before CR. Moreover, no inappropriate shocks were detected.

		Number of events (%)	Patients (%)
Automatically recorded alarms		2848	44 (80)
	Shocks for VT	3 (0.1)	1 (2)
	Shocks for VF	1 (0.04)	1 (2)
	Sustained VT	4 (0.8)	2 (4)
	Artefacts	2826 (99.2)	44 (80)
	Non-malignant arrhythmia	14 (0.5)	4 (7)
Manually recorded alarms		340	51 (93)

Table 6: Overview of automatically and manually recorded alarms and underlying heart rhythm and shocks for VT/VF events; Abbreviations: AF – atrial fibrillation, nsVT – nonsustained VT, VF - ventricular fibrillation, VT - ventricular tachycardia

3.3.3 Adverse events

The documented adverse events were carefully adjudicated and categorized as WCD-related and general adverse events. Concerning general adverse events, three patients had a hypotension-associated syncope during CR. All of them wore the WCD at that timepoint confirming that no symptom-related underlying arrhythmia.

Regarding WCD-related adverse events, one patient experienced an increase of automatically recorded alarms. He was sent to an out-patient clinic from the CR institution to investigate that further. It turned out that the increased number of alarms was due to artefacts. The artefacts appeared because of a loosening of his fabric garment subsequently resulting in poor skin-electrode-contact. A relevant weight loss through CR measurements seemed to be the cause of this. The manufacturer provided him with a

smaller size and the high number of artefact-related false alarms resolved. Another patient had repeatedly inappropriate automatic alarms due to sinus tachycardia during his exercise training and needed a re-programming of the detection thresholds. No severe adverse events such as inappropriate shocks happened.

3.3.4 Follow-up

After 28 days (18;42) of CR, the LVEF showed an increase from the baseline LVEF of 36% (12;80) increased to 42% (23;73) (see ***Fehler! Verweisquelle konnte nicht gefunden werden.***).

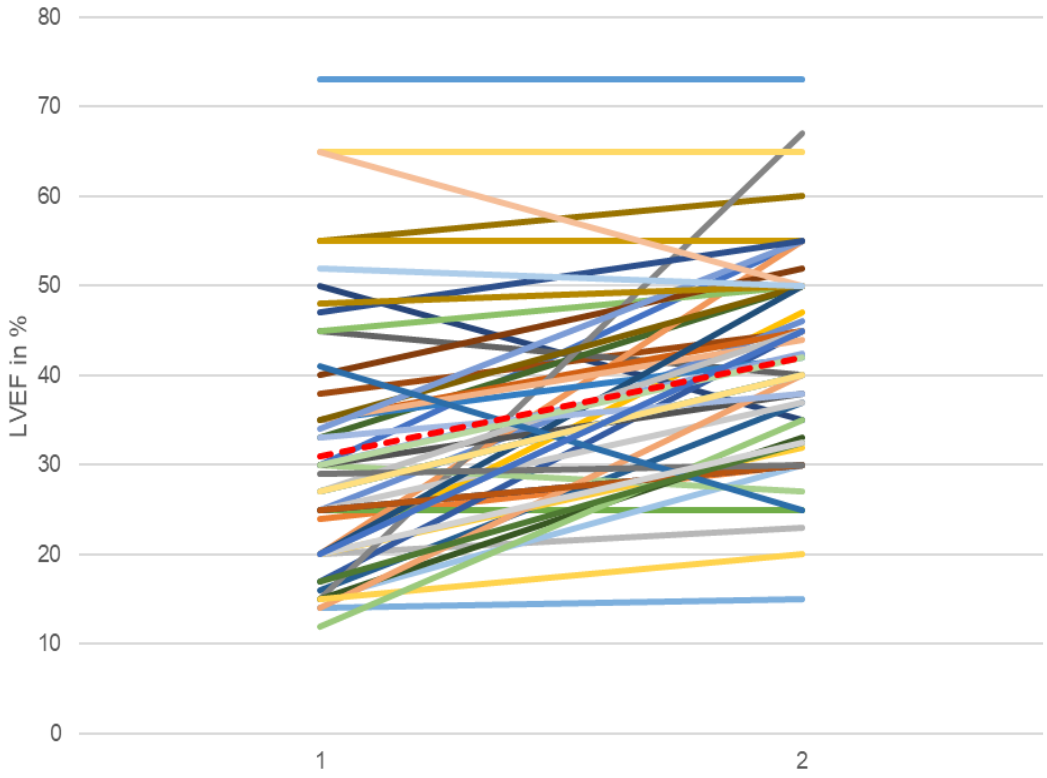

Figure 23: Baseline LVEF of 36% (12;80%) (1) before CR improved to 42% (23;73) at the end of CR (2); red dotted line – mean LVEF over time; Abbreviations: CR – cardiac rehabilitation, LVEF – left ventricular ejection fraction

More than half of the patients (30/55, 55%) patients had a restitution of their cardiac function and were not supplied with an ICD, one third (19/55, 35%) underwent ICD implantation after all performed measures. Three patients (5.5%) had an improved LVEF after PCI and one 28-years old patient had a heart transplantation after a severe myocarditis. One patient (1.8%) was diagnosed with a terminal carcinoid syndrome and WCD was stopped then. One patient (1.8%) declined wearing the WCD for a longer time and therefore it was stopped.

The modifiable cardiovascular risk factors have been re-assessed at the end of the CR: the median body weight remained stable at around 81kg (50;114) compared to 82 kg (52;118) at baseline evaluation as well as the median BMI (27 (19;39) kg/m² compared to the median baseline BMI 28 (18;40) kg/m²). Mean blood pressure decreased from 126±18mmHg systolic to 117±17mmHg and from 79±11mmHg diastolic to 72±12mmHg.

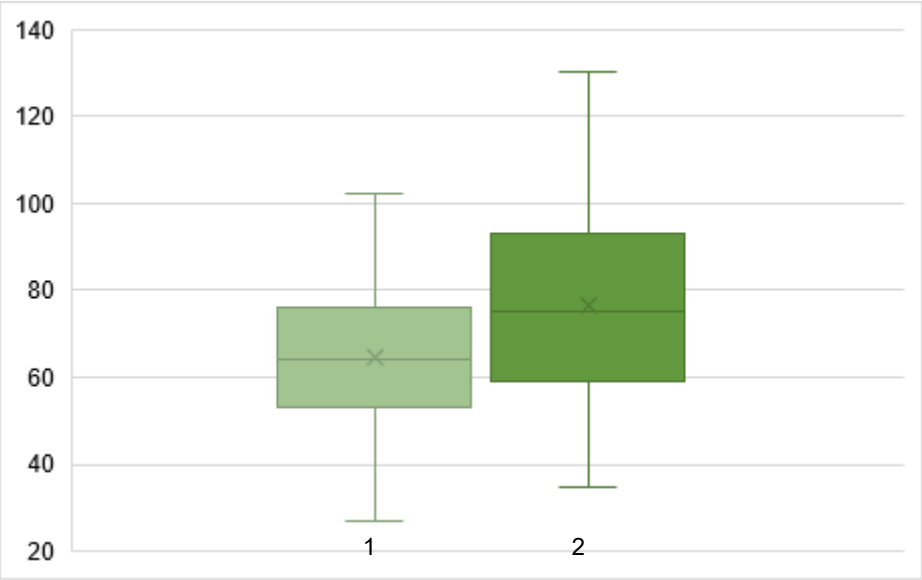

Figure 24: (1) Baseline cycle ergometry (65±17% of watt goal reached) compared to (2) final cycle ergometry (77±22% of watt goal reached)

To assess functional capacity, another exercise testing was done at the end of CR: Around half of the patients (27/55) underwent a cycle ergometry and another three patients (5.5%) underwent a walking test. Within the performed testing an approvement could be acknowledged, (see *Figure 24*). The final report of the CR facility stated that 65% (36/55) fully reached their set goals, one third (18/55, 33%) partly fulfilled and one patient did not fulfil the goals.

4 Discussion

4.1 SCD prevention with a WCD after acute myocardial infarction

The original VEST trial investigated a presumably high-risk cohort of SCD but failed to prove a benefit of a WCD on arrhythmic mortality. As the guidelines do not recommend implanting an ICD within the acute phase after AMI, patients with a LVEF≤35% seem to be unprotected. A lower-than-expected compliance was widely discussed as a potential reason for the negative study as several patients did not wear the device at the timepoint of their death despite being randomized in the WCD group.

We therefore compared the results from the original VEST cohort being randomized to OMT and WCD with results from a well-compliant population retrospectively identified within the Austrian WCD registry. Previous retrospective and prospective registries showed consistently high WCD compliance in real-world settings compared to patients in the only randomized-controlled VEST trial, which might be interlinked with the randomization process within the VEST trial. (50, 79, 85, 94)

The results reported in the Austria WCG registry demonstrated similar shock rates and arrhythmic mortality to those in the VEST trial. The primary outcome of arrhythmic mortality (1,9% vs. 1.6%, p=0.52) and the secondary outcome all-cause mortality (2.9% vs. 3.1%, p=0.42) did not differ significantly between Austria and the Vest trial, respectively, although the compliance of these two cohorts is different. Apart from the numbers not proving a benefit some aspects of the original VEST trial need to be considered.

WCD-wearing compliance

The low wearing compliance suggests that some cardiac events were potentially missed, treatable VAs were not detected, and some deaths could have been prevented. In principle, data from registries proved effectiveness of WCD shocks for malignant VA (51, 58, 80, 85, 95). On the other hand, a device cannot detect, prevent, or prevent death due to arrhythmia when it is not worn.

A previous meta-analysis supports the hypothesis that more VA would have been captured and potentially treated with a higher all-over wearing compliance. This analysis confirmed a higher shock rate in registries and observational studies compared to the randomized-controlled VEST trial.(96) The rate of appropriate WCD shocks was not statistically higher in numbers in the Austrian WCD cohort than in the original VEST cohort

(3.8% vs. 1.3%, p=0.64). . The low number of patients being supplied with a WCD after AMI in Austria may account for a relatively low event rate.

Moreover, the adjudication whether the death was caused by a VA or due to another cause is more difficult without the underlying ECG tracings at that timepoint. The number of patients wearing a WCD at the timepoint of death were drastically low: Only one fourth of all deceased patients within the cohort that were randomized to a WCD in the VEST trial wore a WCD at the time of death. This means 12 patients and only half of these patients (6/12) had a documented VT or VF detected and treated by their WCD. These 6 patients account for 0.4% of all 1524 patients in the WCD arm of the study. One would think that patients included in a trial with probably more frequent follow-ups compared to clinical routine and study stuff having dedicated time for patient education would suggest a good wearing compliance.

On the other hand, low wearing compliance might be interlinked with the randomization process of the trial.(50, 79, 85, 94) There is a specific trial that shows that patient education influences their wearing compliance and eventually increases the likelihood of appropriate detection and treatment of malignant VA.(95) Moreover, a good patient compliance not only to wearing the WCD but also adherence to drug therapies improve prognosis, especially in the post-AMI population where adherence to medication is essential.(97) In comparison to the Austrian VEST cohort, only one out of the three patients that died wore their WCD. The two patients did not wear the WCD because they were hospitalized. Hence, all events could be correlated with the underlying ECGs and no patient died at a timepoint when they simply did not want to wear the device.

Event adjudication

Apart from low wearing compliance, the adjudication within the VEST trial needs to be discussed. The publication states that all arrhythmic deaths were adjudicated by an independent panel of experts, but they also report that the process took place without reviewing the WCD-derived ECGs (see Supplementary Appendix of VEST trial, (41, 51) Furthermore, outcomes of several original VEST patients are derived from reports of the emergency medical system that captured non-shockable rhythms. The WCD could not record ECGs as it was not worn at that timepoint. While shockable rhythms will eventually develop into non-shockable rhythms and therefore can be the result of a delay between emergency medical call and first medical contact and or ECG recording.(41, 55) In contrast, the cardiologists adjudicating outcomes of the Austrian VEST cohort relied on

WCD-derived ECGs when available and correlated the outcomes with medical reports when available.

As an answer to all discussions and criticism of the original trial, the VEST investigators published an as-treated and per-protocol analysis. Within this publication, they state a statistically significant reduction in arrhythmic mortality when patients had a compliance of >90% of the time what applies for one third of the original cohort in the WCD arm.(55) Nevertheless, in 9/525 patients wearing a WCD, arrhythmic death was adjudicated while the appendix of the VEST trial publication mentions that the WCD of 4/9 patients did not record malignant VA at timepoint of death.(41) Hence, only 5 patients had a VA detected and treated by the WCD and eventually died despite the treatment. These five patients would consecutively fit into the definition of an arrhythmic death that was established for the Austrian VEST cohort. To summarize, within two well-compliant cohorts applying a strict definition of arrhythmic deaths 5/525 (1%) arrhythmic deaths in the original VEST cohort would be opposed to 2/105 (2%) in the Austrian VEST cohort.

Female patients

One fact that needs to be considered is that the percentage of female patients in both trials is low with only 12% in the Austrian VEST cohort and only 27% in the VEST cohort. A factor for a low rate of women may be the lower incidence of CAD and AMI in premenopausal women. Lower rates of cardiovascular risk factors like arterial hypertension and hyperlipidaemia in premenopausal women, a different pathophysiology of AMI and atypical symptoms in female patients at any age could account for lower and/or later detection rates.(98) Hence, women are less likely to receive revascularization or undergo CIED implantation what also might account for a lower number of patients in this cohort.(99) AMI in female patients might be underdiagnosed and potentially not treated in the acute setting. Females potentially present at a later timepoint and with chronic ICMP instead of AMI. The incidence of CAD and AMI raises later and exceeds male incidences after the age of 75, while in the Austrian VEST cohort only 7 patients (7%) were ≥75 years. Moreover, the age group of ≥75 years-old when woman a higher incidence of AMI will be less likely to be considered for a CIED due to their life expectancy.

Automatic alarm detection algorithm

Concerning the WCD itself, the automatic arrhythmia detection treatment algorithm produces a high number of inappropriate alarms that still pose a problem. The

inappropriate alarms are mainly triggered by artefacts, sinus tachycardia, AF or SVT. Presumably, patients can manage the alarms after a thorough patient education as for the 72% of patients confronted with alarms, not a single patient had an inappropriate shock. The high alarm rate also did not appear to negatively impact the wearing compliance in the Austrian VEST cohort. In addition, the results from the VEST trial which stated that the WCD arm had a lower rate of overall mortality raised the idea that a worn device might positively influence medication adherence and disease awareness.

Identifying predictors

Several reviews analysing the VEST study, and sub cohorts from large nationwide registries that receive a WCD after AMI, suggest specific additional factors that should be present for WCD prescription apart from a reduced LVEF. One suggestion was to prescribe a WCD only until an ICD supply is possible. This would implicate that the indication for an ICD was already established beforehand like in patients with a reduced LVEF ≤35% without potential to recover or hemodynamically unstable VA more than 48 hours after AMI.(100) Additional risk factors in the context of AMI could be a low LVEF already before AMI, patients that could not be fully revascularized or detected nsVTs while still hospitalized. Another factor that will be of rising importance is incorporating information from imaging such as cardiac MRT to identify a potential substrate for re-entries.

Another suggestion was to identify the expected compliance of patients as well-compliant patients seem to benefit the most from WCD treatment. The post-hoc analysis of the VEST cohort have identified the following predictors of a low wearing compliance: LVEF≤25%, a prior diagnosis of HF or diabetes, a WCD shock within the first week of prescription and patients that were recruited in Poland.(55, 101) Whether it is still an unanswered question to withhold a therapy if indicated based on potential predictors. Vice versa, all indications are based on one negative randomized-controlled trial and several registries or observational studies.

WCD as a monitoring device

Apart from the classical shock function, the newer WCD generation has multiple additional functions. If the treating physician would actively log on to the online network and assesses the recorded ECGs, early detection of non-malignant arrhythmias which might require further treatment or monitoring of PA is possible. CABs or other surrogate parameters for HF and PA that have been studied in the TRENDS study have not found

their way into clinical practice until now.(43, 44, 70-72) A review suggested to focus on these additional monitoring functions as they may add a benefit on mortality, but further prospective studies to confirm this hypothesis is recommended.(101)

Reimbursement

Another important part in all patients prescribed with a WCD, irrespective of the underlying cardiac disease, is that the reimbursement for the WCD is still not regulated in all countries. Weak guideline recommendations due to scarce data from randomized-controlled trials do not help to solve this problem.(97, 102)

4.1.1 Limitations

There are several limitations of this study, respectively of the comparison between the Austrian VEST cohort and the original VEST cohort. The Austrian VEST cohort has been identified retrospectively out of the Austrian WCD registry and patients did not undergo a randomization process. The alarms and events have been adjudicated from three independent cardiologists, but only two of the three did the analysis without prior background information. This limitation, however, lies within the nature of a real-world registry to assess the everyday benefit of this patient cohort. The observational retrospective study design influences the result by the lack of control groups and the diversity of the reported patients.

Furthermore, a different system of patient education or a different health care systems where the WCD is commercially available may result in a different wearing duration and compliance. The approach on how to train and educate patients in Austria is either nurse-based or technician-based to ensure good adherence. However, this may not reflect different health care systems and centers outside of Austria. The compared original VEST cohort recruited patients from the US, Germany, Poland, and Hungary but none from Austria.

Another factor is that women are underrepresented throughout this trial due to various reasons. . On one hand, CAD and AMI occur more often in male patients until the age of 75. The reported cohort is 64±11 years so most patients were at an age when CAD and AMI concerns men predominantly. Also, clinical trials and real-world registries about SCD and CIED report lower numbers of female patients and it is known that women are less likely to be considered for cardiovascular interventions and procedures. (103, 104) In specific analyses or subgroup analyses, female patients with a WCD seem to have higher event rates.(105) Our real-life registry data shows only 12% of females in the Austrian

cohort, which is consistent with rates in large trials. Female patients seem to be generally underrepresented and it is unclear whether results apply to female patients to the same extent.

4.1.2 Summary and perspective

This study included 105 well-compliant patients being prescribed with a WCD after AMI with a LVEF≤35% and fitting into the in- and exclusion criteria of the VEST trial. These patients were identified within the Austrian WCD registry retrospectively. The goal was to compare outcomes concerning event rates and mortality rates to data from patients that have been recruited in the original VEST trial and randomized to the WCD arm. The results confirm that the WCD wearing compliance in real-world cohorts is high in patients after AMI with reduced LVEF. These results stand in contrast to the only randomized-controlled trial, the VEST trial, where compliance rates were below average. The rate of alarms and events seem comparable to other international reports and to the all-over Austrian WCD population. Within this cohort, VA were adequately detected and acutely effectively treated. On the other hand, no VA was missed by the automatic algorithm. Despite primarily effective shocks the WCD could not improve the arrhythmic mortality in this post-MI cohort compared to the original VEST cohort.

Higher selected sub cohorts including additional risk factors may still benefit from a WCD. Furthermore, the pre-emptive assessment and estimation of the patients' compliance should increase in importance when the decision for or against a WCD is made. The WCD will still be prescribed for patients at very high risk, for example to bridge the time to a definitive ICD implantation after AMI when an implantation is temporarily contraindicated. Further randomized-controlled trials are needed to study risk factors and predictors to identify optimal candidates. That would help to strengthen recommendations for well-defined subgroups and help reimbursement.

4.2 Cardiac rehabilitation with a WCD

Concerning patients undergoing a WCD, singular case reports and observational studies are published.(73, 93) The CR3 study is the first to demonstrate that no severe WCD-related adverse events happened during exercise-based CR in a cohort of 55 patients. These results should support and promote a higher referral rate of cardiac patients with and without a WCD to exercise-based CR to improve patient outcomes.

CR referral

The referral rate to CR of patients with a WCD seems far below average and below the expected numbers that guideline-driven indications would suggest. Only 6% of the Austrian WCD registry have completed an exercise-based in-patient CR program. Referral rates of patients after AMI and/or PCI without a WCD are reported as around 50-60% in the US and a little bit lower rates for Europe (40-50%).(106-108) Hence, CR seems to be underutilized in this clinical situation while the reported rates are still almost ten times higher than the reported referral rate in this study.

The reported causes for non-referral are based on different levels and factors such as logistical and time barriers and declining the suggested referral by the patient. The treating physicians may lack information about CR, starting with the potential indications, the potential benefit, the referral process, or the local rules of reimbursement. Reasons for not-referral on a system-level are different regulations concerning the reimbursement.(106) At least reimbursement should not be the main issue as patients after AMI or revascularization procedures are on the indication list for CR and subsequently full reimbursed in Austria. WCD-related reasons can also be lack of knowledge about the device and fear of potential severe adverse events. Data from the CR3 study confirm underutilization of CR measures while no adverse events would confirm a hazard through the device itself.

Alarms, malignant arrhythmias

The number of generated alarms and ECGs was high but comparable to other registries. Also, the distribution of the underlying rhythms detected in the recorded ECGs was internationally comparable.(41, 51, 55, 58, 73) The rate in numbers did not seem to be higher due to the exercise-based CR program. Moreover, no patient stopped the WCD during the CR period due to a high number of alarms.

Adverse events

No severe WCD-related adverse events happened during and/or due to CR. It could be expected that exercise training could trigger more inappropriate alarms and therefore increase the risk of inappropriate shocks, while the overall inappropriate shock rate in the Austrian WCD registry is very low. A larger study on exercise-based CR with a WCD would be needed to detect inappropriate shocks. Two patients reported minor WCD related adverse events that could easily be solved with an ambulatory visit and could have been solved on site with a WCD technician and supervised by a CR physician. So far, no specific recommendations exist. Compared to an ICD, the WCD has the advantage that the patients are informed and/or warned of an automatically triggered alarm via an acoustic, tactile, and visual warning sign to have the opportunity to abort an imminent treatment for a non-malignant tachycardia. This could be the case when sinus tachycardia during exercise training exceeds the detection threshold, and the remaining algorithm is not able to distinguish the underlying rhythm.

Outcomes

The data from this study show that no WCD shock was necessary during CR. The rehabilitation measures in patients with a WCD resulted in improvement of blood pressure and exercise capacity without WCD-related hazards. The exercise training early after an acute event can improve PA while protected from VA by the WCD. Early improved PA is reported to be associated with improved survival rates and can be promoted by a WCD.(89)

4.2.1 Limitations

The retrospective design and small sample size that might result from underutilization of CR in Austria are a clear limitation of this study. Neither a randomization nor a control group were established. The goal of this study was to simply assess feasibility and safety of patients undergoing a CR with a WCD in a real-world data. As the patient number is small and the underlying cardiac diseases and other patients' characteristics, for example age and percentage of gender vary widely, the specific results may not apply to all patients.

4.2.2 Summary and perspective

To summarize, 55 patients underwent a stationary CR program with a WCD that has been prescribed due to various underlying cardiac diseases. The study showed high wearing compliance and a low shock rate without any severe WCD-related adverse event. WCD patients successfully finished the program with an improvement of their modifiable

cardiovascular risk factors. As a perspective for future studies or clinical indications, the WCD may support CR measures in an ambulatory setting as wearing the device is safe during exercise-based CR. The WCD-guided 6-minute walking test (72, 73) and parameters like the daily step count and average HR could help monitor the PA and therapy success telemedically.(43, 70, 71) Furthermore, the current/past pandemic helped to accelerate establishing technical infrastructure and financial reimbursement of telemedical approaches. This approach could further help to reduce in-patient visits and on the long run reduce hospitalizations to counteract shortness of medical staff and improve patient outcomes.

4.3 Conclusion

The WCD is an established treatment option in selected patient groups with a high risk of SCD not being eligible for an immediate ICD implantation despite lacking data from randomized-controlled trials. The prescription of a WCD may help to avoid unnecessary ICD implantation, can cover the period of establishing OMT or bridge the waiting time to therapeutic procedures. The WCD is effective in preventing SCD and an important risk stratification tool.

- **CR is underutilized in patients with a WCD:** CR is an important measure and recommended to improve outcomes and QoL and is still underutilized. CR with a WCD is feasible and safe without severe WCD-related adverse events. The WCD can enhance early referral to CR and support early PA. There is no need for a time delay after an acute event compared to a newly implanted CIED with electrodes that need several weeks after surgery to settle.

- **Reprogramming and adjustment of the WCD during CR**: The patient, the device and the appearing number of alarms needs to be monitored to detect a potential need for readjustment of the garment and/or reprogramming of the detection thresholds if needed. So far there are no specific recommendations on WCD adjustments during CR but these could be similar to the recommendations made for ICD patients. The detection threshold should be adjusted after initial exercise testing to a HR higher than the planned exercise HR. If a high or increasing number of alarms appear, a check-up should be scheduled and can be performed at the CR facility as no specific technical device would be needed for adjustments.

- **WCD after AMI:** the Austrian VEST cohort showed appropriate detection of VA and a high effectiveness of WCD treatments but could not prove a benefit on arrhythmic mortality in a well-compliant cohort. Sub analysis of the original VEST trial suggest assessment of additional risk factors for further WCD prescriptions to identify patients that benefit the most from this treatment.

- **Wearing compliance is key:** A good wearing compliance improves the effectiveness of this treatment and therefore is one of the key components of therapy success. Physicians or a nurse-based approach could survey the patient's wearing compliance and offer follow-up trainings to enhance compliance and to increase the likelihood of VA detection.

- **WCD and its monitoring function:** As data to justify the WCD as a tool to prevent SCD are scarce, at least when it comes to randomized-controlled trials, other functions like surrogate parameters to detect a deterioration of HF or PA may promote positive outcomes. Parameters like CABs and TRENDs data give the possibility to intervene early and help to prevent imminent CV events while only partially available. While big data are available the clinical implementation and role on outcomes are still matter of future investigations.

- **Female patients are underrepresented:** In all reported studies, female patients are largely underrepresented, and study data may not apply to this cohort. Future clinical practice and studies should focus on treating and recruiting more female patients as treatments seem to be equally effective.

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