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ORIGINAL ARTICLE

Extended follow-up after wearable cardioverter-defibrillator period: the PROLONG-II study

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Abstract

Aim The wearable cardioverter-defibrillator (WCD) is used for temporary protection from sudden cardiac death (SCD) in patients with newly diagnosed heart failure with reduced ejection fraction before considering an implantable cardioverter-defibrillator (ICD). However, the prognostic significance of the WCD remains controversial due to conflicting evidence. The aim of the present study was to evaluate prognosis of patients receiving life-saving WCD shocks.

Methods and results All patients receiving a WCD at Hannover Medical School for heart failure with reduced ejection fraction between 2012 and 2017 were included. Data were acquired at baseline, at 3 months and at last available follow-up (FU). Three hundred and fifty-three patients were included (69% male; age 56 ± 15 years; left ventricular ejection fraction 25 ± 8%). FU after the WCD was 2.8 ± 1.5 years with a maximum of 6.8 years. Daily WCD wear time was 22 ± 4 h. Fourteen patients (4%) received appropriate WCD shocks. Two patients (0.6%) died during the WCD period. Thirty patients (9%) died during extended FU. Mean estimated survival after the WCD was similar between patients with and without WCD shocks. Patients without an ICD recommendation after WCD prescription did not experience SCD during FU.

Conclusions Patients with WCD shocks showed a favourable survival. Patients without an ICD recommendation after WCD prescription had no SCD during FU. These findings support the practice of careful risk stratification before considering an ICD and the use of the WCD for temporary protection from SCD.

Keywords Heart failure; Sudden cardiac death; Wearable cardioverter-defibrillator; Implantable cardioverter-defibrillator

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Introduction

The wearable cardioverter-defibrillator (WCD) is currently used for temporary protection from sudden cardiac death (SCD) in patients with newly diagnosed heart failure with reduced ejection fraction (HFrEF) before considering an implantable cardioverter-defibrillator (ICD). These patients have a temporary risk for SCD, but their long-term risk is unknown at the time of diagnosis.[1] According to guidelines, decision on ICD implantation should not be made before 3 months of optimized heart failure therapy.[2] However, ICDs are often implanted earlier in clinical practice.[3]

In the PROLONG study, we have shown that a prolonged WCD prescription for optimization of medical therapy can avoid ICD implantations in certain patients.[4] However, whether these patients actually stay free from arrhythmia and SCD is currently unknown.

Data on long-term survival of patients wearing the WCD and receiving WCD shocks are limited. It is currently unknown whether WCD shocks convey a long-term survival benefit, a question that seems highly relevant in cost-effectiveness considerations regarding the WCD. The aim of the present study was to present longer term survival data of patients after the WCD period, especially those receiving appropriate WCD shocks. Furthermore, this study evaluated the

occurrence of ventricular tachyarrhythmias and SCD in patients without ICD recommendation, especially after the prolonged prescription period.

Methods

The PROLONG-II study included all consecutive patients receiving a WCD (LifeVest, Zoll, Pittsburgh, PA, USA) for newly diagnosed HFrEF at Hannover Medical School between 2012 and 2017. The study complies with the Declaration of Helsinki and was approved by the local ethics committee. All patients gave informed consent.

Baseline characteristics of all patients were acquired at the time of WCD prescription. The WCD was usually prescribed for 3 months, and ICD indication was evaluated afterwards, according to current guideline recommendations. Patients with CRT indication according to guidelines received a CRT device.[2] The prescription period was prolonged in cases where prolonged risk stratification was considered beneficial, based on previously published criteria from the PROLONG study: borderline left ventricular ejection fraction (LVEF) value at 3 months (30–35%), marked increase in LVEF compared with baseline (≥5%), and non-optimized heart failure therapy.[4]

The first outpatient visit was scheduled after 3 months. Further visits were scheduled according to the treating physician's discretion. In patients followed-up elsewhere, data were collected from medical records or structured telephone interviews. Data acquired at baseline, at 3 months, and last available follow-up (FU) were analysed. Patients who were alive at the last reported date were labelled as censored. Data included medication, electrocardiogram, left ventricular (LV) function and clinical status. WCD data were collected via the remote monitoring platform of the manufacturer (LifeVest Network, Zoll, Pittsburgh, PA, USA). Any WCD shock for haemodynamically unstable fast ventricular tachycardia (>200 bpm) or ventricular fibrillation was considered appropriate. The first and last authors had full access to all the acquired data in the study and take responsibility for its integrity and data analysis. Major endpoints were total mortality, LVEF, device implantations, and ventricular tachyarrhythmias.

Statistical analysis

Data are presented as mean ± standard deviation for continuous variables and as numbers and percentages for categorical variables. For comparison of nonparametric continuous variables, Wilcoxon test or Kruskal–Wallis test were used, as appropriate. For comparison of categorical variables, χ^2 test or binary logistic regression analysis was used, as appropriate. Survival analysis was performed using Kaplan–Meier method, log rank test, and Cox regression analysis. P values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA).

Results

Three hundred and fifty-three patients were included in the analysis. There were 244 (69%) male patients. Mean age was 56 ± 15 years. Mean baseline LVEF was 25 ± 8%. Underlying heart disease was non-ischaemic cardiomyopathy (NICM) in 227 patients (64%) and ischaemic cardiomyopathy (ICM) in 126 (36%). Baseline characteristics are presented in *Table 1*.

Wearable cardioverter-defibrillator wear time and shocks

Wearable cardioverter-defibrillator data are summarized in *Table 2*. Mean total wear time per patient was 104 ± 76 days

Table 1 Baseline characteristics

Baseline characteristics	n = 353
Age, years	56 ± 15
Male, *n* (%)	244 (69)
WCD indication, *n* (%)	
NICM	227 (64)
DCM	169 (48)
Myocarditis	24 (7)
PPCM	27 (7)
Other	7 (2)
ICM	126 (36)
LVEF, %	25 ± 8
NYHA functional class	2.7 ± 0.7
NT-proBNP, ng/L	6549 ± 8565
Pacemaker, *n* (%)	10 (3)
Comorbidities, *n* (%)	
Arterial hypertension	196 (56)
Diabetes mellitus	81 (23)
Family history of CV diseases	57 (16)
Dyslipidaemia	119 (34)
Smoking	157 (45)
Renal failure	77 (22)
Medication at WCD prescription, *n* (%)	
Beta-blocker	332 (94)
Renin–angiotensin system inhibitor	338 (96)
Mineralocorticoid receptor antagonist	310 (88)
Ivabradine	77 (22)
Digitalis	32 (9)
Amiodarone	21 (6)
Diuretic	284 (81)
Electrocardiogram	n = 344
Atrial fibrillation (%)	58 (17)
Heart rate, bpm	82 ± 23
QRS duration, ms	116 ± 29
Left bundle branch block, *n* (%)	65 (19)

CV, cardiovascular; DCM, dilated cardiomyopathy; ICD, cardioverter-defibrillator; ICM, ischaemic cardiomyopathy; LVEF, left ventricular ejection fraction; NICM, non-ischaemic cardiomyopathy; NT-proBNP, N terminal pro brain natriuretic peptide; NYHA, New York Heart Association; PPCM, peripartum cardiomyopathy; WCD, wearable cardioverter-defibrillator.

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Table 2 WCD data

WCD data	*n* = 353
Wear time	
Prescription for 3 months, *n* (%)	265 (75)
Prescription >3 months, *n* (%)	88 (25)
Total wear time, days	104 ± 76
Daily wear time, h/day	22 ± 4
WCD shocks	
Total appropriate shocks, *n*	15
Patients with appropriate shock, *n* (%)	14 (4)
NICM	9 (4)
DCM	6 (4)
Myocarditis	0
PPCM	3 (11)
Other	0
ICM	5 (4)
Time to shock, *days*	49 ± 49 (1–158)
Inappropriate shocks, *n*	0
Death during WCD period, *n* (%)	2 (0.6)

DCM, dilated cardiomyopathy; ICD, cardioverter-defibrillator; ICM, ischaemic cardiomyopathy; NICM, non-ischaemic cardiomyopathy; PPCM, peripartum cardiomyopathy; WCD, wearable cardioverter-defibrillator.

and daily wear time was 22 ± 4 h. The WCD was prescribed for 3 months in most patients (75%) and was prolonged in 88 patients (25%).

During the WCD wearing period, 14 patients (4%) received a total of 15 appropriate WCD shocks for haemodynamically unstable fast ventricular tachycardia or ventricular fibrillation. Inappropriate shocks did not occur. Diagnosis of the patients with appropriate shocks was NICM in 9 cases (4% of NICM patients) and ICM in 5 (4% of ICM). Two of the 14 patients (1 with NICM and 1 with ICM) received their appropriate shock during the prolonged prescription period (2% of all patients with a prolonged WCD prescription). Mean time to WCD shock was 49 ± 49 days. None of the baseline characteristics predicted WCD shocks. Two patients (0.6%) died during the WCD wear period for non-cardiac causes, 40 and 53 days after prescription. These patients had not received WCD shocks.

Implantable cardioverter-defibrillator indication

At 3 months FU, mean LVEF was 34 ± 10%. 113 patients (32%) met ICD indication criteria and were scheduled for implantation. These patients included the patients with appropriate WCD shocks. Implantations were performed 105 ± 54 days after WCD prescription. Eighteen patients (5%) met ICD indication criteria but refused implantation.

Of the patients who had a prolonged WCD prescription >3 months, 31 (35%) met ICD indication criteria after the WCD, including the two patients with WCD shocks during that time. Implantations occurred 241 ± 99 days after WCD prescription. Three patients (3%) refused implantation after the prolonged WCD period.

Of all patients, 188 (53%) did not meet ICD indication criteria after the WCD period. During extended FU, 11 of them (6%) received an ICD for primary prevention, after 2 ± 1.2 years. None of the patients without an ICD recommendation experienced life-threatening arrhythmias or SCD.

Appropriate ICD therapies occurred in 10 (9%) of the patients who received an ICD at 3 months, 1 (3%) of the patients who received an ICD after the prolonged prescription, and none of the patients who received an ICD during extended FU. The patients with ICD shocks included four patients who had had appropriate WCD shocks during the WCD period (29% of patients with WCD shocks). WCD shocks were associated with future ICD therapies ($P = 0.01$). Four patients (3%) received inappropriate ICD shocks.

Survival during extended follow-up

Survival data were available for 333 patients (94%), while 20 patients were lost to FU. None of the patients with WCD shocks were lost to FU. Cumulative observation period adds up to 931 patients-years. Mean FU was 2.8 ± 1.5 years with a maximum of 6.8 years.

Thirty patients (9%) died during FU after a mean of 1.7 ± 1.1 years. These were 21 (9%) of the patients with NICM and 9 (7%) of the patients with ICM. Overall mean estimated survival time after WCD prescription was 6.2 ± 0.1 years (95% confidence interval 6–6.4 years). Baseline characteristics associated with higher mortality were a longer QRS duration ($P = 0.02$), higher BNP ($P = 0.01$), renal failure ($P = 0.01$), and a trend for atrial fibrillation ($P = 0.08$).

Cause of death was cardiac in five patients (17%) with one autopsy-confirmed acute myocardial infarction in a patient who had refused ICD implantation for primary prophylaxis. Cause of death was non-cardiac in 17 patients (57%). Cause of death was unknown in eight patients (26%).

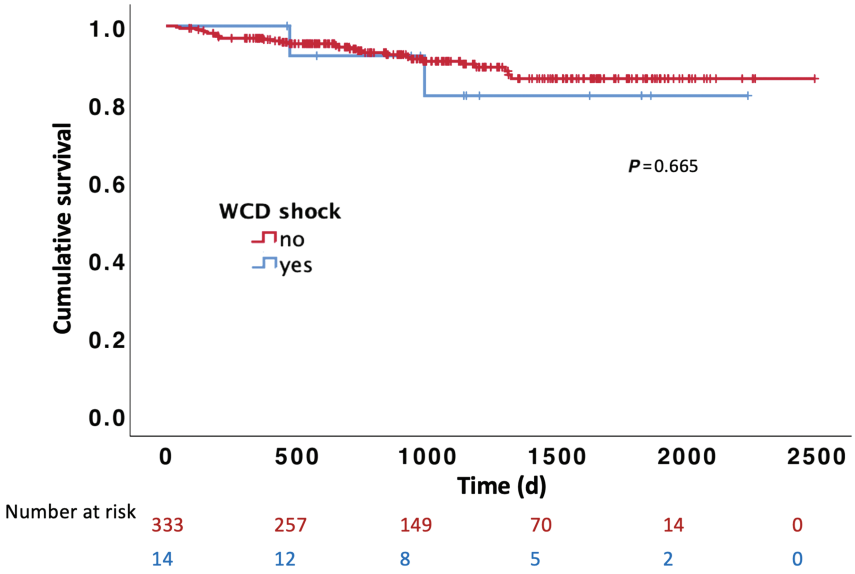
Two (14%) of the patients with WCD shocks died, both female patients with NICM. One died 1.3 years after WCD prescription at the age of 54 of biventricular heart failure; the other died 2.7 years after WCD prescription at the age of 77 of unknown cause. Mean estimated survival of the patients after WCD prescription was 5.4 ± 0.5 years. WCD shocks did not represent a predictor for mortality (*Figure* 1).

Discussion

The PROLONG-II study investigated survival of patients with HFrEF after WCD prescription. To date, this is the study with the longest available FU in a larger cohort of WCD patients: 353 patients were followed for 2.8 ± 1.5 years.

The main findings of the PROLONG-II study were (i) survival after WCD prescription was 91% within the extended FU period; (ii) WCD shocks were not associated with poorer survival; and (iii) no SCD or haemodynamically unstable

Figure 1 Survival during extended follow-up. Kaplan–Meier survival curves of patients with newly diagnosed heart failure with reduced ejection fraction with and without appropriate wearable cardioverter-defibrillator (WCD) shocks during WCD wear time. Numbers next to curves indicate mean estimated survival times.



ventricular tachycardias occurred in patients without an ICD recommendation after the WCD period.

Baseline characteristics and wearable cardioverter-defibrillator period

Three hundred and fifty-three patients receiving the WCD for HFrEF were analysed. The baseline characteristics such as underling cardiomyopathy, LVEF, age, and gender were comparable with other large WCD registries.[5–8] The present study cohort can be considered a representative real-world WCD patient population.

Wearable cardioverter-defibrillator compliance was excellent. Daily wear-time of 22 h was comparable with those of prior observational studies.[6,7] In contrast to the general assumption that patient adherence is better in randomized controlled trials compared with observational studies,[9] the only trial showing a much lower median daily wear-time of 18 h/day was the randomized VEST trial.[8] In contrast to VEST, patients in PROLONG-II were closely monitored via LifeVest Network. If wear compliance decreased, patients were contacted and encouraged to increase wear time.

The incidence of appropriate WCD shocks in the present study was 4%. Mortality during the WCD prescription period was low with 0.6%. These numbers are also similar to previous observational studies.[5,7,10] In the VEST trial, however, the number of WCD shocks was lower, and mortality was higher, which may be related to patient selection, poorer compliance, adherence, and treatment in VEST compared with the observational studies.[8]

The low patient compliance is a major drawback of the VEST trial and limits its validity. The as-treated analysis of the trial did demonstrate a significant reduction in overall and arrhythmic mortality in patients wearing the WCD, supporting the results from the present and previous observational studies.[5,6,11]

Survival after the wearable cardioverter-defibrillator

While several observational trials and one randomized controlled trial have addressed short-term survival of patients wearing the WCD, there are limited data on long-term survival. The longest previously available FU from the large observational studies was 1 year in the WEARIT-II[12] and WEARIT-II-Europe[13] registries.

The present study followed a larger HFrEF patient population after WCD prescription for 2.8 ± 1.5 years. Ninety-one per cent of the patients survived. QRS duration, BNP, and renal failure at baseline were associated with mortality. Our data confirm previous findings on the prognostic significance of these comorbidities.[12,14,15]

The overall survival in the present study was more favourable in comparison with epidemiological data on patients with newly diagnosed heart failure not wearing the WCD.[16]

Importantly, WCD shocks were not a predictor for mortality. This is unexpected after the WEARIT-II registry, where 1 year survival of patients with ventricular arrhythmias during WCD wearing was lower compared with patients

without arrhythmias.[12] However, unlike the present study, which analysed WCD shocks for life-threatening ventricular tachyarrhythmias, the WEARIT-II registry included haemodynamically tolerated arrhythmias, which have different pathomechanisms and prognostic significance.[17,18]

The results of the present study also stand in some discrepancy to the results from IRIS and DINAMIT. Early ICD shocks did not positively impact overall survival in these studies. Early ICD shocks were associated with increased mortality, leading to a shift in the cause of death instead of a survival benefit.[17,19,20] However, these studies have limited validity today, as management of HFrEF has substantially changed. Survival of HFrEF patients experiencing life-threatening ventricular arrhythmias early after diagnosis may be more favourable today.[21] In fact, a recent study showed a survival benefit for early ICD therapy in certain high-risk patients after myocardial infarction.[22] In the present study, patients with life-saving WCD shocks had a mean estimated survival similar to patients without WCD shocks. These data speak against a mere mortality shift from SCD to other causes.

Our findings seem crucial in the debate about further justification of the WCD after the VEST trial. In contrast to observational WCD studies,[4–6,23] the VEST trial did not confirm a reduction of SCD in patients after myocardial infarction in the intention-to-treat analysis.[8] Recruitment, compliance, and WCD shock rate, as well as the subsequently published as-treated analysis, suggest that the study design contributed to this negative result, and the evidence on WCD prescription therefore remains unsatisfying.[11] While further randomized controlled trials are called for, none has been launched so far.

Wearable cardioverter-defibrillator for risk stratification in newly diagnosed heart failure

Patients with newly diagnosed HFrEF have an increased risk of SCD. However, the risk may be temporary, and ICD therapy for primary prevention is not indicated until stable heart failure therapy is established.[2] In clinical practice, a relevant number of ICD implantations occur too early and are non-indicated,[3] although a more thoughtful use of the ICD seems reasonable in the light of its associated risks, costs, and the growing evidence for its reduced benefits in selected cohorts.[24,25] A more thorough, personalized risk stratification is also addressed in the current PROFID project.[26]

We have previously shown that ICD implantations can be avoided by prolonging the period of risk stratification and therapy optimization beyond 3 months.[4] Following this practice, less than half of the patients in the present study met ICD indication criteria after the WCD. Importantly, none of the patients not receiving an ICD experienced SCD or had malignant arrhythmias during extended FU. These results support a prolonged waiting period for risk stratification and uptitration of heart failure therapy to avoid untimely ICD implantations.

Limitations

One limitation of the current study is its single-centre retrospective design. However, after the VEST trial, it is uncertain if a second randomized controlled trial will ever be conducted. The study population was a heterogeneous real-world WCD patient population. The fact that only patients with WCD prescription were included in the study represents a selection bias, even though standardized prescription criteria were applied. Six per cent of the patients were lost to FU. This number is not unusual in clinical trials with HFrEF populations.[27] Multivariate analyses were limited by the small number of patients receiving WCD shocks. Our study did not address cost-effectiveness, which was not possible with the acquired data.

Conclusions

This real-world cohort of patients wearing the WCD after diagnosis of HFrEF showed a favourable survival during extended FU, including patients who received appropriate WCD shocks for early haemodynamically unstable ventricular arrhythmias. Early WCD shocks were not associated with increased mortality. The findings speak against a mortality shift from SCD to other causes of death and support the use of the WCD for temporary protection from SCD. Patients who did not receive an ICD after the WCD period neither died of SCD nor suffered from ventricular arrhythmias during extended FU. Thorough uptitration of heart failure medication and risk stratification should be performed before considering ICD implantation.

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Conflict of interest

All authors have participated in the research and approved the manuscript. D. D. received lecture honorary, travel grants, and/or a fellowship grant from Abbott, Astra Zeneca, Biotronik, Boehringer Ingelheim, Boston Scientific, Medtronic, Microport, Pfizer, and Zoll. C. V. received lecture honorary, travel grants, and/or a fellowship grant from Abbott, Astra Zeneca, Bayer, Biotronik, Boehringer Ingelheim, Boston Scientific, Medtronic, Pfizer, and Zoll. J. B. received honoraria for

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