Gender differences of patients treated with wearable cardioverter-defibrillator

Mohammad Abumayyaleh[1], Ibrahim El-Battrawy[2], Stephanie Rosenkaimer[1], Tobias C. Dreher [1], Juergen Kuschyk[3], Susanne Röger[4], Martin Borggrefe[3], and Ibrahim Akin[2]

[1]Ruprecht Karls University Heidelberg Faculty of Medicine Mannheim
[2]University Medical Centre Mannheim
[3]University Medical Center Mannheim
[4]University Medical Centre Mannheim, First Department of Medicine

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Abstract

Aims The treatment with the wearable cardioverter defibrillator (WCD) may protect against sudden cardiac death (SCD) as a bridging therapy until a cardioverter defibrillator may be implanted. Data regarding the impact of WCD on the outcome of patients according gender differences are limited. We analysed a consecutive patient cohort wearing WCD to explore gender differences. Methods and results We analysed 153 consecutive patients of whom were 118 males and 35 females (age, 60±13 vs. 60±16 years old; p=0.88). More males receiving WCD as compared to females suffered from ischemic cardiomyopathy (ICM) (41% vs. 23%; p=0.05), while females were diagnosed with non-ischemic cardiomyopathy (NICM) (60% vs. 42%); p=0.05). The wear time of WCD was equivalent in both groups (21±4 in males vs. 22±3 hours/days in females; p=0.18; and 65±42 in males vs. 65±43 days in females; p=0.96). In both groups, the left ventricular ejection fraction (LVEF) improved in males from 29±10% to 41±12% and in females from 28±12% to 45±13%; p=0.12. At 6-12 month-follow-up, the LVEF increased more in females as compared to males (40% vs. 17%; p=0.003). The rate of rehospitalization due to cardiovascular cause and all-cause-mortality were comparable in both groups at 6-12 month-follow-up (55% in male vs. 54% in female group; p=0.93) (9% in male vs. 11% in female group; p=0.71). Conclusion Compliance for wearing of WCD was excellent regardless of gender. During follow-up, LVEF improved more in females as compared to males. All-cause mortality and the rate of rehospitalization were comparable in both groups.

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Short title: Gender differences and wearable cardioverter-defibrillator

Mohammad Abumayyaleh, MD[1,2], Ibrahim El-Battrawy, MD[1,2], Stephanie Rosenkaimer, MD[1], Tobias C Dreher, MD[1,2], Jürgen Kuschyk, MD[1], Susanne Röger, MD[1], Martin Borggrefe, MD, PhD[1,2], Ibrahim Akin, MD, PhD[1,2]

[1]First Department of Medicine, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany

[2]DZHK (German Center for Cardiovascular Research), Partner Site, Heidelberg-Mannheim, Mannheim, Germany

Address for correspondence : Mohammad Abumayyaleh, MD, First Department of Medicine, University Medical Centre Mannheim, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany, E-Mail: mohammad.abumayyaleh@medma.uni-heidelberg.de, Phone: +49-621-383-1447, Fax: +49-621-383-1474.

Word account: 4230

Aims

The treatment with the wearable cardioverter defibrillator (WCD) may protect against sudden cardiac death (SCD) as a bridging therapy until a cardioverter defibrillator may be implanted. Data regarding the impact of WCD on the outcome of patients according gender differences are limited. We analysed a consecutive patient cohort wearing WCD to explore gender differences.

Methods and results

We analysed 153 consecutive patients of whom were 118 males and 35 females (age, 60±13 vs. 60±16 years old; p=0.88). More males receiving WCD as compared to females suffered from ischemic cardiomyopathy (ICM) (41% vs. 23%; p=0.05), while females were diagnosed with non-ischemic cardiomyopathy (NICM) (60% vs. 42%); p=0.05). The wear time of WCD was equivalent in both groups (21±4 in males vs. 22±3 hours/days in females; p=0.18; and 65±42 in males vs. 65±43 days in females; p=0.96). In both groups, the left ventricular ejection fraction (LVEF) improved in males from 29±10% to 41±12% and in females from 28±12% to 45±13%; p=0.12. At 6-12 month-follow-up, the LVEF increased more in females as compared to males (40% vs. 17%; p=0.003). The rate of rehospitalization due to cardiovascular cause and all-cause-mortality were comparable in both groups at 6-12 month-follow-up (55% in male vs. 54% in female group; p=0.93) (9% in male vs. 11% in female group; p=0.71).

Conclusion

Compliance for wearing of WCD was excellent regardless of gender. During follow-up, LVEF improved more in females as compared to males. All-cause mortality and the rate of rehospitalization were comparable in both groups.

Keywords: Wearable cardioverter-defibrillator; sudden cardiac death; gender differences; female; male.

Introduction

It is well known that an implantable cardioverter-defibrillator (ICD) improves survival and reduces the mortality rate due to ventricular tachyarrhythmias [1-3]. The Danish Cardiac Arrest Registry showed the superiority of early implantation of ICD in patients surviving myocardial infarction (MI) with cardiac arrest [4]. However, some patients don't meet the criteria for ICD implantation or are unable to receive an implantable device such as patients in the acute phase of MI or myocarditis. The wearable cardioverter defibrillator (WCD) may be considered to protect these patients against malignant ventricular tachyarrhythmias and as a bridge to ICD implantation [5]. However, compliance is impaired due to comfort issues [6]. The VEST trial showed no reduction of arrhythmic death as the primary endpoint in recent MI patients with reduced left ventricular ejection fraction (LVEF $< 35\%$) [7]. In this regard, one important and possible cause for this finding was non-compliance in wearing the WCD. However, being married, suffering from cardiac arrest during the index MI, and an increase of creatinine were independent predictors for a high WCD wearing time [8].

Concerning different percentages of etiologies in male and female patients, gender differences with a different rate of cardiovascular disease may have a different response to treatment. Randomized controlled trials and data on gender differences are lacking to determine patients in whom the WCD is prescribed and which gender benefits more from the WCD wearing. Real-world experience may provide helpful information to our clinical practice. Therefore, we analyzed a consecutive patient cohort wearing WCD to explore gender differences regarding compliance, rehospitalization, and mortality.

Methods

Between April 2012 and March 2019, we included 153 patients with HFrEF who received a WCD (ZOLL Life Vest system, Pittsburgh, USA) at our University Medical Centre in Mannheim, Heidelberg University.

Patients were treated according to the current European guidelines for heart failure [9].

WCD monitors the heart rhythm. If a life-threatening heart rhythm such as ventricular tachycardia (VT) or ventricular fibrillation (VF) is detected, it delivers a shock to restore sinus rhythm. The WCD consists of a two-channel electrocardiogram that records the front-back and left-right site as bipolar leading to continuous electrocardiographic analysis. The detection until shock delivery takes 45-55 s including initial detection of VT/VF 5 s to 10 s, tachycardia confirmation 10 s, and alarm time 25 s. Shock can be avoided by pressing the stop button. The WCD has a memory for ECG analysis from 30 s before starting the arrhythmia alarm until 15 s after the alarm stop [10].

We divided the collective into a male group (n=118) and a female group (n=35). Baseline characteristics of 153 patients with WCD such as indications for WCD use, clinical parameters, medication, medical history, and cardiovascular risk factors were gathered. The clinical outcome of patients was assessed by chart and/or telephone review at follow-up. Wear time of WCD and WCD shocks as well as arrhythmic episodes during WCD use were documented. LVEF $>$ 35% led to stop WCD wearing. ECG data and echocardiographic results were collected. Death and rehospitalization rate due to a cardiovascular cause during follow-up were evaluated.

LVEF was calculated by using biplane Simpson's method, using echocardiography and/or cardiac MRI. This study was executed in compliance with the fifth revision of the Declaration of Helsinki regarding investigations in human subjects and the study protocol was approved by the Ethics Committee of the Medical Faculty Mannheim, Heidelberg University [11].

Statistics

We present the data as mean +- standard deviation for continuous variables with a normal distribution. Median (interquartile range) was used for continuous variables with a non-normal distribution, and as frequency (%) for categorical variables. The Kolmogorov–Smirnov test was used to assess normal distributions. Student's t-test and the Mann–Whitney U-test were used to compare continuous variables with normal and non-normal distributions, respectively. Additionally, the Chi-squared-test or Fisher's exact test was used to compare categorical variables. The Wilcoxon signed-rank test was used for paired nonparametric quantitative variables. The McNemar test was used for paired qualitative variables. The cumulative probability of survival was determined by Kaplan-Meier analysis. We used repeated measurement analysis for serial quantitative parameters. Statistical analysis was performed using IBM SPSS Statistics for Macintosh (Version 25.0 Armonk, NY, USA: IBM Corp.).

Results

Baseline characteristics of 153 patients with WCD

In our population, the male group had an average age of 60+-13, and the female group 60+-16 years old. The indication for WCD use was various,**figure A** . 41% of males who received WCD suffered from ischemic cardiomyopathy (ICM) with LVEF [?]35%. On the other hand, among females in the population who received WCD, only 23% had ICM; p=0.05. In addition, 60% of females received WCD who had non-ischemic cardiomyopathy (NICM). However, 42% of males suffered from NICM who received WCD, **figure B** . Accordingly, coronary artery disease (CAD) was more observed in the male as compared to the female group (45% vs. 23%; p=0.02). Other indications for WCD were myocarditis, device explanation cause of device infection, hypertrophic cardiomyopathy (HCM), takotsubo syndrome (TTS), and channelopathies such as Long-QT syndrome. Primary and secondary prevention indications are listed in the supplementary appendix. Baseline characteristics are presented in **table 1** .

Comparison of follow-up clinical data of male versus female patients

At baseline, a mean LVEF was in both groups comparable (29%+-10% in males vs. 28%+-12% in females; p=0.59). At follow-up, a mean LVEF increased during 6-12 months to 41%+-12% in males and 45%+-13% in females; p=0.12). By contrast, the value of NT-ProBNP decreased significantly after 3 months from 3098

pg/ml (200-12896) at baseline to 1025 pg/ml (76-4748) at 3-month-follow-up in males; p=0.03 and from 8181 pg/ml (1496-84474) at baseline to 1333 pg/ml (190-18369) in females; p=0.03. ECG's and rhythm data at baseline and 6-12-month-follow-up were comparable, **table 2** . Data about echocardiography and NT-ProBNP levels at admission and follow-up are presented in the supplementary appendix.

Follow-up data of patients after WCD use

The wear time of WCD was comparable in both groups, 21+-4 in male vs. 22+-3 hours/days in females; p=0.18 and 65+-42 in males vs. 65+-43 days in females; p=0.96. The rate of appropriate shocks was similar in both groups, 4% in the male and 3% in the female group; p=0.71,**table 3** . The most presented tachycardia during WCD use was VT's (3% in males vs. 3% in females; p=0.88). This led to appropriate shocks in 4% of male and 3% of female participants; p=0.71. Different reasons led to stop WCD wearing, one of these was an improved LVEF, incompliance, and later the implantation of the electronic cardiac device at follow-up time, **table 3** .

The improvement of LVEF was revealed in both groups, more in females as compared to male participants at follow-up during 6-12 months (40% vs. 17%; p=0.003). After using WCD, the number of device implantations in both groups was comparable, 40% of the male in comparison to 43% of female patients; p=0.75. The most favorable implanted device in both groups after WCD use was subcutaneous-ICD (24% in males vs. 26% in females; p=0.81), transvenous ICD (8% in males vs. 11% in females; p=0.48), and cardiac resynchronization therapy with defibrillator (CRT-D) (9% in males vs. 6% in females; p=0.59). The indication of device implantation after WCD was the not improvement of LVEF despite optimal heart failure medication.

The rehospitalization rate due to the cardiovascular cause was equivalent in both groups (55% in a male group vs. 54% in a female group; p=0.93). All-cause mortality was comparable at 6-12 month-follow-up (9% in male vs. 11% in female; p=0.71). Data of patients at follow-up are presented in **table 3.**

Discussion

We present the clinical outcome including rehospitalization rate and all-cause mortality in WCD patients divided into male and female groups up to 1 year. The main findings of the study are (1) The improvement of LVEF was revealed in both groups more in female than male participants; (2) The rehospitalization rate due to the cardiovascular cause was comparable in both groups; (3) All-cause mortality was similar in both groups; (4) The wearing time is comparable in male and female participants.

The WCD may be considered in selected patients with a high risk of SCD, if the implantation of conventional ICD is temporarily contraindicated (e.g. poor LVEF after acute myocardial infarction until LV function improves, before heart transplantation) [12]. Therefore, the American Heart Association (AHA), American College of Cardiology (ACC), Heart Rhythm Society (HRS), and European Society of Cardiology (ESC) provide class II, level of evidence C for the use of WCD in these selected patients [13, 14].

Epidemiological data

Both groups had a similar average age of 60+-13 in males and 60+-16 years old in females. While 41% of males suffered from ICM with LVEF [?]35%, only 23% of females received WCD with ICM. Following our data, the Israeli-ICD registry showed comparable epidemiological frequency regarding gender differences. The average age in both genders was similar, 64+-14 in female and 64+-13 in male participants. In addition, ICM was significantly more observed in males as compared to the female group (79% vs. 46%; p=<0.01). On the other side, more women suffered from dilated cardiomyopathy (DCM) in comparison to men's participants (38% vs. 18%; p=<0.01) [15]. In the VEST trial, the device group consisted of 72.8% male participants with the percutaneous coronary intervention (PCI) during the index hospitalization [7]. To summarize, our real-world data corresponds with previously published ICD data.

Adherence

The wear time of WCD was comparable in males with 21+-4 and female group with 22+-3 hours/days, the rate of incompliance was revealed in 8% of male and 9% of female participants, there were no significant

differences in this regard. One observational study has presented a similar adherence rate with daily use of 23 h per day in 6043 patients [16]. The wear time in the VEST trial was 18 h, also less than the wear time in our patients [7]. Most cases of death occurred in patients who were not using the WCD [7]. In addition, the indication for WCD in one large cohort was equivalent in accordance with our study concerning the different number of cases including ICM or DCM, genetic or congenital disease, ICD explanations, or myocarditis [16].

Clinical Efficacy

In our cohort, we observed VT's in both groups that led to appropriate shocks. In 1998, Auricchio et al. presented successfully arrhythmia detection and defibrillation in 9 patients from 10[17]. Other randomized trials showed the safety and efficacy of WCD in the termination of VT/VF. In this regard, first shock success was in 79 of 80 (99%) among all patients from whom were 74% male participants, respectively [18].

Impact on hospitalization and mortality

The hospitalization due to cardiovascular cause and all-cause mortality was equivalent between both genders in our cohort. For this purpose, one large trial investigated gender differences after ICD showed no differences between males and females regarding hospitalization cause of heart failure and death during follow-up [15]. In the United States (US) registry, WCD use reduced the rate of mortality up to 67% reduction analyzed with the propensity-score-matching method [19]. In this trial, 19% of all participants were female and 3-month-mortality was 2.2% in all patients. In the VEST trial, the mortality rate was 3.1% and the rate of hospitalization due to cardiovascular cause was 22% [7]. These rates are less than in our trial. However, the VEST trial had high selected exclusion criteria as compared to our real-world experience.

To summarizing, in a real-world setting, we don't observe any differences in adherence, efficacy, and impact on hospitalization and mortality in male and female patients after WCD use. The improvement of LVEF was more observed in females as compared to the male group.

Limitations

Our trial has several limitations. The number of cases in this study was too small and the majority of patients were male to make qualitative assessments. We did not evaluate other diagnostic methods as MRI to identify patients with a high risk for arrhythmias and SCD. The order of WCD was based on individual patient risk. In the follow-up time, the cause of death was not reported and could not be analyzed.

Conclusion

The same level of patient compliance for wearing WCD was revealed in both groups regardless of gender differences. At follow-up, LVEF improved more in females than in male patients concerning different etiologies. All-cause mortality and the rate of rehospitalization were comparable in both groups.

Conflict of interest

The authors declare that they have no conflict of interest.

Clinical perspectives

WCD is a good treatment approach in patients suffering from reduced left ventricular ejection fraction for example after myocardial infarction or myocarditis to avoid unnecessary implantation of implantable cardioverter-defibrillator regardless to genders.

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Figure legend

Figure A: Indication for WCD Use in males vs. females

Figure B: ICM and NICM in males vs. females with HFrEF

Table legend

Table 1: Baseline characteristics in males vs. females with Wearable Cardioverter Defibrillator (WCD)

Table 2: Follow up diagnostic data in males vs. females

Table 3: Follow up data in males vs. females after Wearable Cardioverter Defibrillator (WCD) use

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