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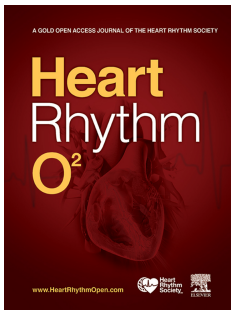

Sex Differences in Achieving Guideline-recommended Heart Rate Control among a Large Sample of Patients at Risk for Sudden Cardiac Arrest

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Sex Differences in Achieving Guideline-recommended Heart Rate Control among a Large Sample of Patients at Risk for Sudden Cardiac Arrest

Short title: Sex difference in heart rate control

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Conflict of interest

Valentina Kutyifa has received research grants from Boston Scientific, ZOLL Inc., Biotronik, NIH, and consultant fees from Biotronik, ZOLL Inc., Medtronic, and Abbott, as well as travel support from ZOLL Inc.

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Abstract

Background Despite known clinical benefits, guideline-recommended HR control is not achieved for a significant proportion of patients with HF and reduced ejection fraction. The Wearable Cardioverter Defibrillator (WCD) provides continuous heart rate (HR) monitoring and alerts that could aid medication titration.

Objective This study sought to evaluate sex differences in achieving guideline-recommended HR control during a period of WCD use.

Methods Data from patients fitted with a WCD from 2015 to 2018 were obtained from the manufacturer´s database (ZOLL, Pittsburgh, PA). The proportion of patients with adequate nighttime resting HR control at the beginning of WCD use (BOU) and at the end of WCD use (EOU) were compared by sex. Adequate HR control was defined as having a nighttime median HR <70 bpm.

Results A total of 21,440 women and a comparative sample of 17,328 men (median 90 days of WCD wear, IQR 59-116) were included in the final dataset. Among patients who did not receive a shock, over half had insufficient HR control at BOU (59% of women, 53% of men). Although the proportion of patients with resting HR ≥70 improved by EOU, 43% of women and 36% of men did not achieve guideline-recommended HR control.

Conclusions A significant proportion of women and men did not achieve adequate HR control during a period of medical therapy optimization. Compared to men, a greater proportion of women receiving WCD shocks had insufficiently controlled HR in the week preceding VT/VF and 43% of non-shocked women, compared to 36% of men, did not reach adequate HR control during the study period. The WCD can be utilized as a remote monitoring tool to record HR and inform adequate up-titration of BB, with particular focus on reducing the treatment gap in women.

Keywords: Ventricular tachyarrhythmia; VT; VF; women; wearable-cardioverter defibrillator; sudden cardiac death; heart rate control

Introduction

Increased heart rate (HR) is associated with adverse clinical outcomes in patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF ≤ 35%) including risk of all-cause death or HF hospitalization.[1,2] Regardless of the presence of structural heart disease, chronically elevated HR is related to mortality, [3,4] with a reported 14% increase in cardiovascular death for every 10 beats-per-minute (bpm) increase in HR in the general population.[5] A meta-analysis by Mc Alister and colleagues which included 19,209 patients with HF, found that the magnitude of HR reduction was significantly associated with the survival benefit of beta-blockers (BB).[6] Surprisingly, no significant relationship was found between the dose of BB and all-cause mortality.[6] As currently written, the focus of the clinical guidelines for HF management is to achieve BB dosages shown to be effective in clinical trials. [7,8] However, in clinical practice, HR is used during the optimization period to guide decisions on escalating BB dosage to achieve a resting HR of < 70 bpm among patients in sinus rhythm.[7-10]

Jungbauer et al. analyzed HR, recorded by a wearable cardioverter defibrillator (WCD), during rest and activity in 1,353 patients with a recent HF-related hospitalization.[11] Daytime and nighttime resting HR dropped significantly from the beginning to the end of WCD use (day: 72.5 bpm vs. 69.0 bpm, $p < 0.001$; night: 68.1 bpm vs. 64.3 bpm, $p < 0.001$). However, for 25% of patients, median nighttime HR remained ≥70 bpm during the last week of WCD use.[11] Another study assessing the utility of resting HR to predict posthospitalization mortality among patients with HF found that patients who died during the follow-up period had significantly higher HR compared to survivors.[12] Although their findings are noteworthy, these studies, as with most cardiovascular studies, included a majority of men (80% and 88%, respectively), and sex-related differences were not reported.[11,12]

The primary aim of the current study was to determine if there are sex differences in achieving guideline-recommended HR control among a sample of at-risk patients prescribed a WCD. The WCD, while primarily used for the monitoring and treatment of harmful ventricular

tachyarrhythmias/ventricular fibrillation (VT/VF), [10, 13-17, 19-20] also provides telemonitoring of several vital parameters including continuous HR measurement. [18,21] As a secondary aim, among patients who received an appropriate shock, we assessed sex differences in the proportion of patients achieving guideline-recommended HR control in the week preceding the shockable VT/VF event.

Methods

Patient population. This retrospective investigation used a sample of 21,440 consecutive female patients prescribed a WCD from 2015-2018. Because females typically represent only 30 percent of WCD users, a random sample of male patients (one out of every 3, n=17,328) prescribed a WCD during the same time period served as the comparative group. All patients were fitted with a LifeVest system (ZOLL, Pittsburgh, USA) and registered into the LifeVest Network, a registry maintained by the manufacturer. At the time of WCD fitting, all patients consented to data collection for quality monitoring and research. Deidentified patient demographic data and the cardiac indication for WCD prescription were abstracted from physician medical orders. This secondary analysis of deidentified data was approved by the Institutional Committee on Human Research at the authors' institution. In order to have adequate data for analysis, >140 hours of WCD wear time and > 50% of HR data availability at nighttime was required during the first week and last week of WCD use.

WCD. Commercially available WCD devices were used. Worn around the chest like a vest, the WCD provides continuous recording of HR, activity, and body position through ECG electrodes and an accelerometer housed in the electrode belt. HR is one of the key parameters, along with morphology analysis, in the LifeVest arrythmia detection algorithm. Accuracy of the device's HR measurement has been demonstrated through validation testing using the Association for the Advancement of Medical Instrumentation EC57 arrhythmia database and a large proprietary database of ECG rhythms. The WCD as a remote monitoring tool to record HR has been validated in the multicenter HEAR-IT registry.[18]

Continuous HR data is collapsed into 5-minute intervals and retained for subsequent inspection and analysis. Previous publications provide a detailed description of the WCD. [13-17]

Data collection and follow-up. All patients were followed during WCD use for at least 30 days after the initiation of WCD therapy. Data were collected from the index hospitalization at the time of WCD fitting to the end of WCD use. Data collection included patient characteristics, initial indication for WCD therapy, all ECG recordings (initiated by the patient or during arrhythmias) as well as ECGs during WCD treatment. ECG recordings were reviewed by ECG technicians (blinded to this study) to determine whether the shock was appropriate (sustained VT/VF) or inappropriate (not VT/VF). Clinical circumstances for WCD therapy were retrieved by technical support representatives who investigated all WCD treatments and spoke directly with patients who received a WCD shock or with the treating physician.

Resting HR. European and American HF treatment guidelines[7,8] recommend BB use in patients with HF with reduced ejection fraction and recommend up-titration to the maximum BB dose.[7] European guidelines define resting HR according to the definition used in the SHIFT (Ivabradine and outcomes in chronic heart failure) trial.[1] For patients in sinus rhythm, a resting heart rate of 70 bpm or higher as measured on 12-lead electro cardiography (ECG), after at least 5-minutes of rest, performed on two consecutive visits.[1] Additionally, the target HR of 70 bpm is based on evidence that a HR of 75 bpm or lower is associated with a survival benefit in patients with HF with reduced ejection fraction (LVEF ≤ 35%).[22]

The WCD provides continuous HR monitoring. Investigators defined resting HR as median nighttime HR (midnight to 7:00 a.m.), as this period is most likely to capture HR recorded during a resting state. This decision is also based on results from a comparative study reporting nighttime HR might be the only HR parameter with prognostic importance.[4] HR is expressed as a weekly resting nighttime median, at the

beginning of WCD use (BOU) and at the end of WCD use (EOU). For patients who received a WCD shock, median resting nighttime HR is analyzed from the 7 days prior to VT/VF.

Data analysis. Descriptive statistics were used to summarize the datasets. Categorical variables were reported as frequencies (percentage), continuous variables as means (± standard deviation) or as medians (interquartile range (IQR) range). Baseline clinical characteristics were compared between women and men using the t-test for continuous variables and the $\chi 2$ test for categorial variables. Paired t-tests were performed to determine differences in HR at the BOU and EOU for non-shocked patients and BOU and the week preceding VT/VF among patients who received a shock. A repeated measures model was used to access change in HR during 12-weeks of WCD wear; an interaction term was included to determine the effect of sex on change in HR. All statistical tests were 2-sided, a *p* value of $p<0.05$ was considered statistically significant.

Results

Patient characteristics. Patient characteristics by sex and shock status are detailed in Table 1. A total of 38,768 patients (55% women) were included in the sample and the median patient age was 67 years (IQR 58-75 years). Patients wore the WCD for a median duration of 90 days (IQR 59-116 days), which was not significantly different between men and women. The most common indication for WCD prescription was newly diagnosed HF in patients with non-ischemic heart disease (65%), which was significantly more common in women ($p<0.001$). An indication of ischemic heart disease with new-onset HF, including interventional or surgical revascularization (29%) was more common in men ($p<0.001$). Less frequent indications were documented VT/VF with/without cardiac arrest (5%), familial or congenital heart disease with arrhythmogenic potential (0.2%) and other or unknown indications (1%). A total of 251 patients (118 women and 133 men) received a WCD shock for VT/VF.

Change in HR during WCD use by sex. Among patients who did not receive a shock, a higher proportion of women had a median nighttime HR ≥70, compared to men at the BOU (women: 59%, men 53% (Figure 1). By EOU, the proportion of patients with insufficient HR control decreased among both women and men. The median nighttime HR in women was 73.3 ±11.79 bpm at the BOU and decreased to 69.0 ±11.63 bpm at the EOU suggesting therapy optimization (p<0.001). Similarly, nighttime HR among men decreased from 71.8 ±12.35 bpm at the BOU to 66.9 ±12.15 bpm at EOU (p<0.001). However, as shown in Figure 1, the proportion of women with inadequate HR control remained higher than the proportion of men (women: 43%, men 36%).

Heart rate profiles one week before shock. At BOU, inadequate HR control was seen among 64% of the women and 62% of men who would experience a sustained VT/VF (Figure 2). BOU nighttime HR was higher among shocked patients compared to patients who did not receive a shock, regardless of sex, though reached statistical significance only for males (shocked women: 75.4 ±13.18 bpm, non-shocked women:73.3 ±11.79 bpm, p=0.089; shocked men: 74.1, ±13.11 bpm, non-shocked men: 71.8, ±12.35 bpm, p=0.042). In the week preceding VT/VF, 55% of women had inadequate HR control compared to 53% of men.

Changes in heart rate over time by sex. Repeated measures analysis confirmed a significant decreasing trend in heart rate over the initial 12 weeks of guideline-recommended therapy (F=1554.34, p<0.001) (Figure 3). The decrease in heart rate over the 12-week period was present for women and men. However, a significant interaction between sex and week suggests that the improvement in heart rate control over time was greater for men compared to women (F=11.81, p<0.001).

End of use outcomes in the study. For the full sample, the most common WCD end of use reason was LVEF improved (n=14,687 (37.88%)), followed by received an ICD (n=11,844 (30.55%)), early return of

187 the WCD by patients choice (n=6,141 (15.84%)), planned WCD finish (n=3,274 (8.45%)), other (n=1,996
188 (5.15%)), and patient died (n=826 (2.13%)) (Table 2).

189 **Discussion**

190 This large retrospective study comprising 38,768 patients fitted with a WCD yields several important
191 findings. First, while median nighttime HR dropped significantly for both women and men, at EOU a
192 greater proportion of men (64%) than women (57%) achieved a median nighttime HR<70 bpm. Among
193 patients who did not receive a WCD shock, at EOU median HR did not meet guideline recommendations
194 in 43% of women and 36% of men. Regardless of sex, patients who received a WCD shock had a higher
195 nighttime HR at BOU compared to those who did not receive a shock. In the week preceding the VT/VF
196 event necessitating WCD shock therapy, the median nighttime HR for women and men was above the
197 guideline-recommended <70 bpm and a greater proportion of women, relative to men, had
198 insufficiently controlled HR profiles in the week preceding VT/VF. Although causality cannot be
199 evaluated in this retrospective study, consistently elevated median nighttime HR is associated with
200 sustained VT/VF leading to appropriate WCD shock in women and men at risk for sudden cardiac death.

201 **WCD and HR monitoring.** The WCD is an established therapy for safe and effective treatment of patients
202 at-risk for sudden cardiac death. [13-17, 19-20] Recently, a number of studies have reported on the diagnostic
203 utility of HR monitoring in patients with HF or myocardial infarction fitted with the newest generation
204 WCD. [11-12, 18] Jungbauer and colleagues found that 40% of 1,353 patients fitted with a WCD had a median
205 nighttime HR ≥ 70 bpm at BOU and by EOU, HR control remained inadequate for 28% of patients.[11]
206 However, their sample consisted primarily of male patients (80%) and they did not report differences in
207 HR due to sex or shock status. Another retrospective study of patients fitted with a WCD investigated
208 the relationship between HR and HF-related mortality in the early posthospitalization period.[12] Of the
209 4,590 patients included in the study, 88 patients (2%), died during the study period. In comparison to

patients who survived, those who died during WCD wear had a higher median nighttime HR and a greater proportion of patients who died had a median nighttime HR ≥ 70 bpm at both BOU and EOU (deceased, BOU: 64%, EOU: 70%; survived, BOU: 44%, EOU 29%). However, as is often the case in cardiovascular studies, this sample consisted primarily of men (88%) and the investigators did not examine differences based on sex.

Insufficient HR control and arrhythmia risk. The current study adds to the existing evidence demonstrating the utility of the WCD in monitoring HR among patients at risk for sustained VT/VF. In addition, we build upon previous work to show that among women, an elevated median nighttime HR is associated with sustained VT/VF. Moreover, in comparison to men, a greater proportion of women lacked adequate HR control three months after the initiation of guideline-recommended medical therapy. Results from the Framingham Heart Study suggest that the cause for death in HF patients with inadequate HR control might be cardiac-arrhythmic in a significant proportion of patients.[2] Therefore, guideline-recommended medical therapy, and specifically sufficient beta-blockade in HF patients, is of paramount importance in this patient population as indicated by current guideline recommendations.[7-10] This author group previously investigated safety and efficacy of the WCD in women at-risk for SCD[19-21] and reported that the majority of women receiving shocks had newly diagnosed heart failure or non-ischemic heart disease.[19] In a post-hoc analysis of the WEARIT-II US registry comprising 2000 patients (598 women; 30%), the burden of ventricular tachycardia or ventricular fibrillation was even higher in women, with 30 events per 100 patient-years compared with 18 events per 100 patient-years in men (p=0.02), with similar findings for treated and non-treated ventricular tachycardia/ventricular fibrillation. Also, recurrent atrial arrhythmias/sustained ventricular tachycardias were more frequent in women than in men (167 events per 100 patient-years vs 73 events per 100 patient-years; p=0.04).[20]

Need for guideline-recommended medical therapy in women with cardiovascular disease. Our study findings indicate that among patients at risk for sudden cardiac arrest women, like men, with

inadequate HR control may be at greater risk for sustained VT/VF. Lacking medication prescription and adherence data, we can only speculate that our sample of women were prescribed BB and adhered to this treatment, however, adequate up-titration to achieve significant HR reduction (< 70 bpm)[7-10] may not have been performed clinically. Women are underrepresented in cardiovascular trials, especially regarding sudden cardiac death/defibrillator therapy[23-24] and in clinical trials supporting FDA approval of cardiovascular drugs.[25] For example, in the PARADIGM-HF trial (angiotensin-neprilysin inhibition versus enalapril in heart failure), evaluating sacrubitril/valsartan versus enalapril for medical HF therapy among patients with HF with reduced ejection fraction, only 22% of the total patients enrolled were women yielding a participation to prevalence ratio of only 0.4.[25] Therefore, initiatives like the Get-With-The-Guidelines-Registry collecting real-world data on daily clinical practice regarding cardiovascular treatment in the USA is one approach to gain adequately powered data to assess sex differences in the treatment of cardiovascular disease. Another solution to improve the representation of women in clinical trials of cardiovascular disease is by setting goals for sex-based equity in enrollment (e.g., a 50% male/50% female recruitment goal). This author group aims to close the evidence gap on BB treatment to gain sufficient HR control in women at risk for sudden cardiac arrest fitted with the WCD in an outpatient setting using HR monitoring data in the international multicenter prospective trial "Optimizing Beta-Blocker Dosage in Women using the Wearable Cardioverter-Defibrillator (OPT-BB Women)" that is currently enrolling patients.

Limitations. Our study is retrospective in nature, hence all potential limitations of such a design apply to this analysis. We analyzed abstracted medical records data as given by the treating physician on the WCD prescription and did not have access to the full medical records or data on follow-up, echocardiographic data, or HF medication, including beta-blocker and ivabradine use.

Conclusion

This large retrospective study on patients at-risk for sudden cardiac arrest fitted with the WCD demonstrates, for the first time, that inadequate HR control (≥70 bpm median nighttime HR) among women and men is related to sustained VT/VF and appropriate WCD shock. Sex disparities in achieving guideline indicated HR control was evident. Compared to men, more women receiving WCD shocks had insufficiently controlled HR in the week preceding the VT/VF and a significant proportion of non-shocked women (43%) did not reach adequate HR control during WCD use in this study. In addition to treating sustained VT/VF, the WCD can be utilized as a remote monitoring tool to assess HR and ensure adequate up-titration of BB in at-risk women. Future research will be directed at understanding the clinical usefulness of these alerts.

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334 Table 1. Baseline clinical characteristics

	Full Sample N=38,768	Women N=21,440 (55%)	Men N=17,328 (45%)	P-value
Median WCD use, days	90 [58 116]	90 [59 116]	89 [57 115]	0.22
Median age, year	67 [58 75]	67 [58 75]	67 [58 75]	0.66
WCD indication, n (%)				<0.001
DCM/NICM/HF	25064 (65)	14391 (67)	10673 (62)	
Post-MI/PCI/CABG	11292 (29)	5896 (28)	5396 (31)	
Cardiac arrest/VT/VF	1919 (5)	916 (4)	1003 (6)	
Other/Unknown	414 (1)	176 (0.8)	238 (1)	
Familial/congenital condition	79 (0.2)	61 (0.3)	18 (0.1)	

335

336 CABG: coronary artery bypass graft, DCM: dilated cardiomyopathy; HF: heart failure, MI: myocardial
337 infarction, NCMI: nonischemic cardiomyopathy VT/VF: ventricular tachyarrhythmias/ventricular
338 fibrillation, WCD: wearable cardioverter defibrillator

339 Table 2. End of use outcomes by sex

End of Use Outcome	Full Sample N=38,768	Women N=21,440 (55%)	Men N=17,328 (45%)
LVEF Improved	14687 (37.88%)	8634 (40.27%)	6053 (34.93%)
Received ICD	11844 (30.55%)	6247 (29.14%)	5597 (32.30%)
Early Return by Patient's Choice	6141 (15.84%)	3142 (14.65%)	2999 (17.31%)
Planned Finish	3274 (8.45%)	1895 (8.84%)	1379 (7.96%)
Other	1996 (5.15%)	1088 (5.07%)	908 (5.24%)
Died	826 (2.13%)	434 (2.02%)	392 (2.26%)

340

341 LVEF: Left ventricular ejection fraction, ICD: implantable cardioverter defibrillator

Figures.

Figure 1. Percentage of non-shocked patients with resting HR below guideline recommended threshold (< 70 bpm) at BOU and EOU. Mean HR at BOU and EOU.

BOU: beginning of use, EOU: end of use, HR: heart rate, bpm: beats per minute

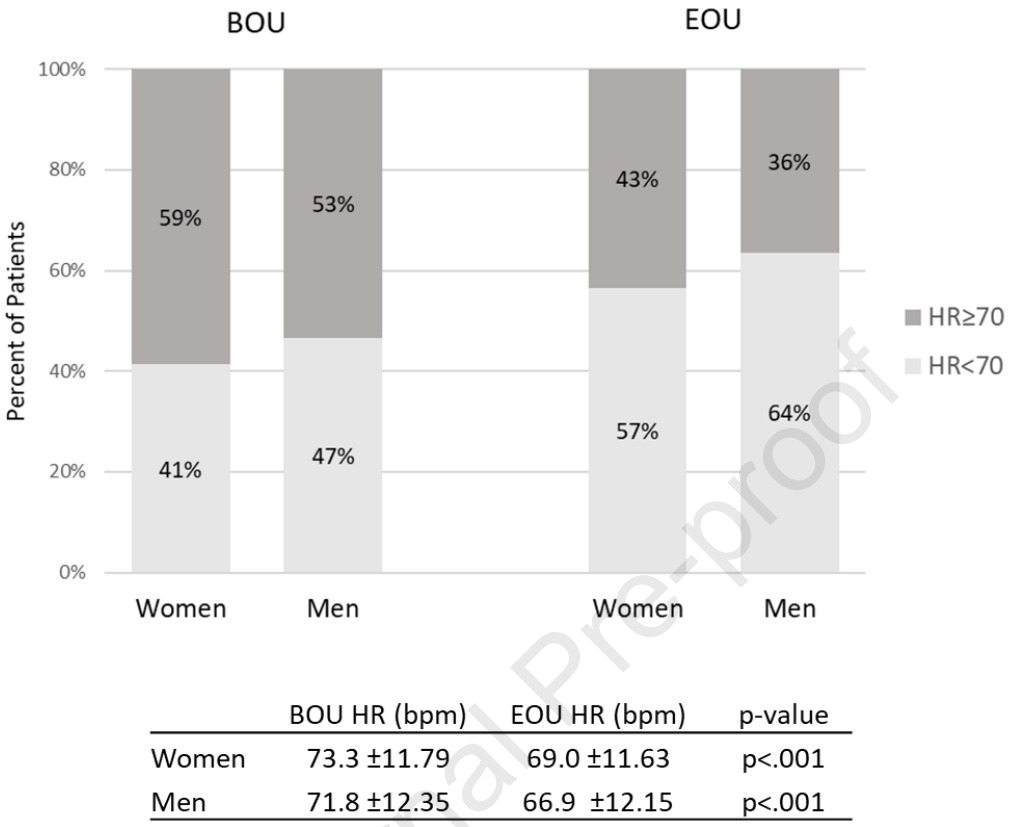
Figure 2. Percentage of patients who received a shock with resting HR below guideline recommended threshold (< 70 bpm) at BOU and during the week preceding the VT/VF. Mean HR at BOU and one week preceding the VT/VF.

HR: heart rate, BOU: beginning of use, VT/VF: ventricular tachyarrhythmias/ventricular fibrillation, bpm: beats per minute

Figure 3. Change in HR over time by sex.

WCD: wearable cardioverter defibrillator

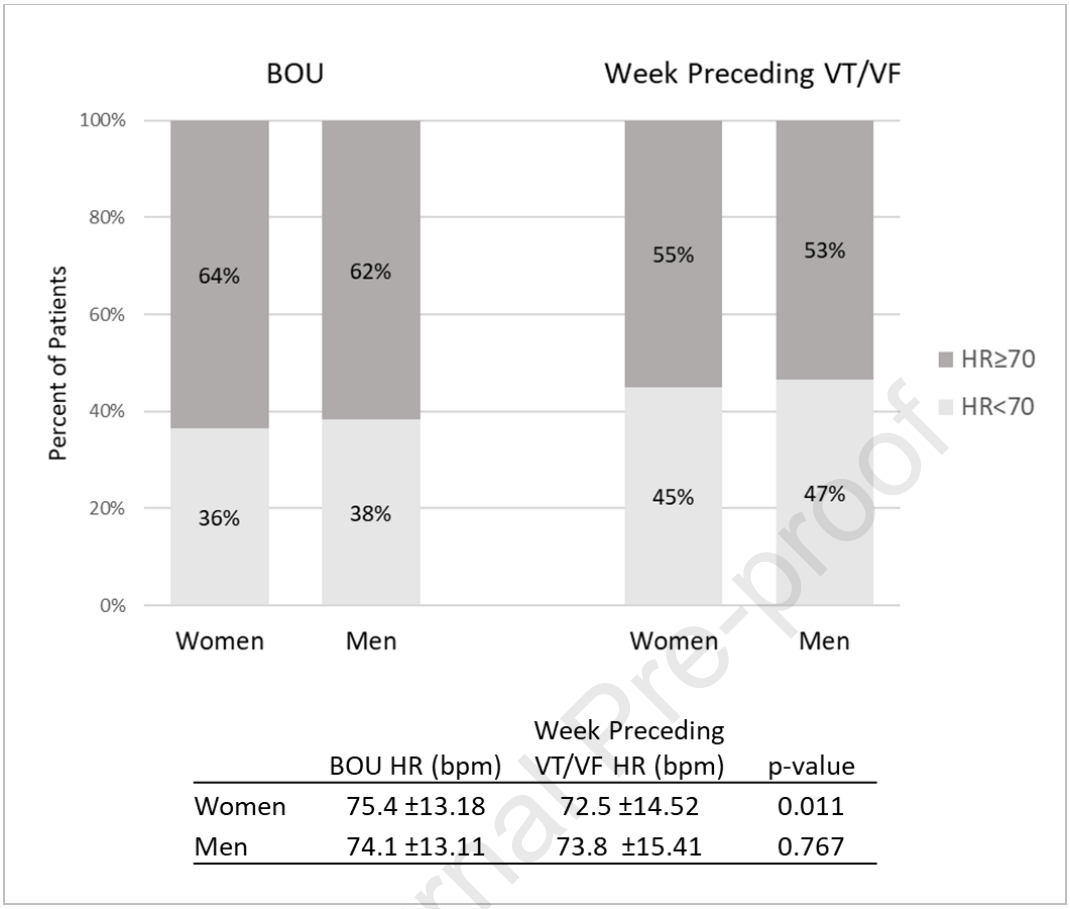
357 Figure 1.



	BOU HR (bpm)	EOU HR (bpm)	p-value
Women	73.3 ±11.79	69.0 ±11.63	p<.001
Men	71.8 ±12.35	66.9 ±12.15	p<.001

358

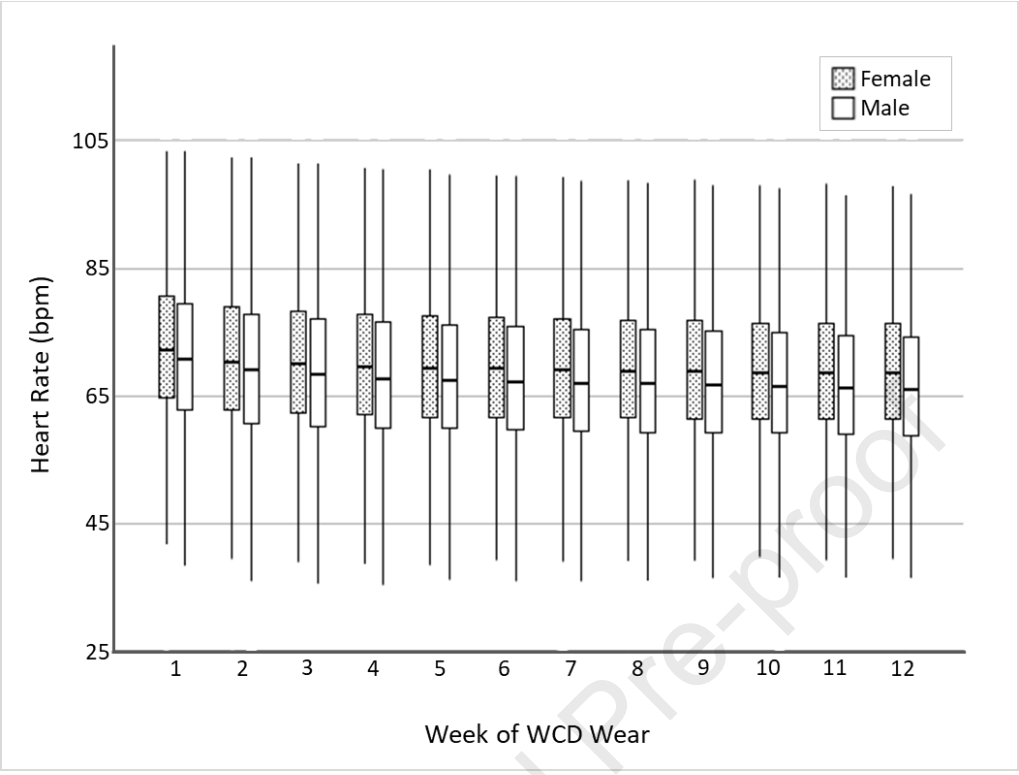
359 Figure 2.



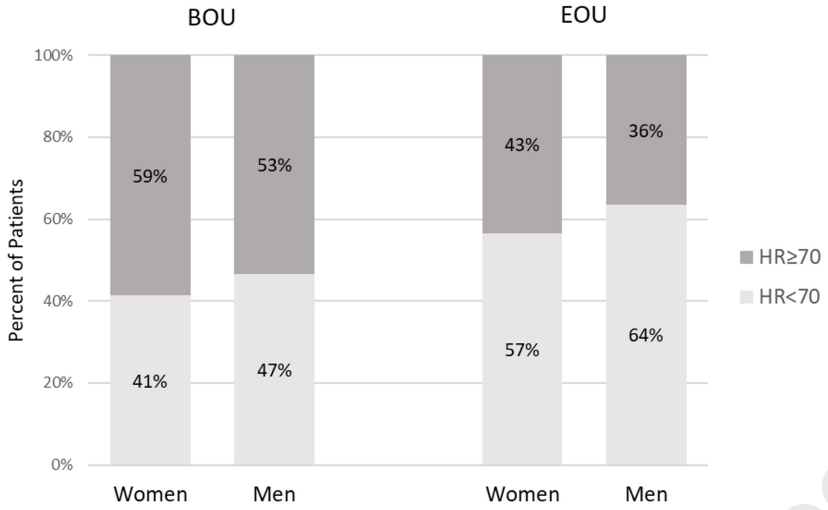
	BOU HR (bpm)	Week Preceding VT/VF HR (bpm)	p-value
Women	75.4 ±13.18	72.5 ±14.52	0.011
Men	74.1 ±13.11	73.8 ±15.41	0.767

360

361 Figure 3.



362



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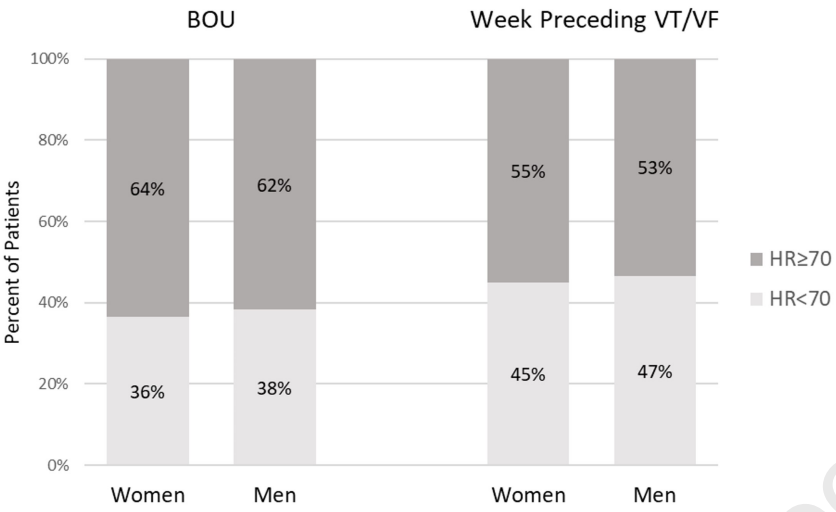

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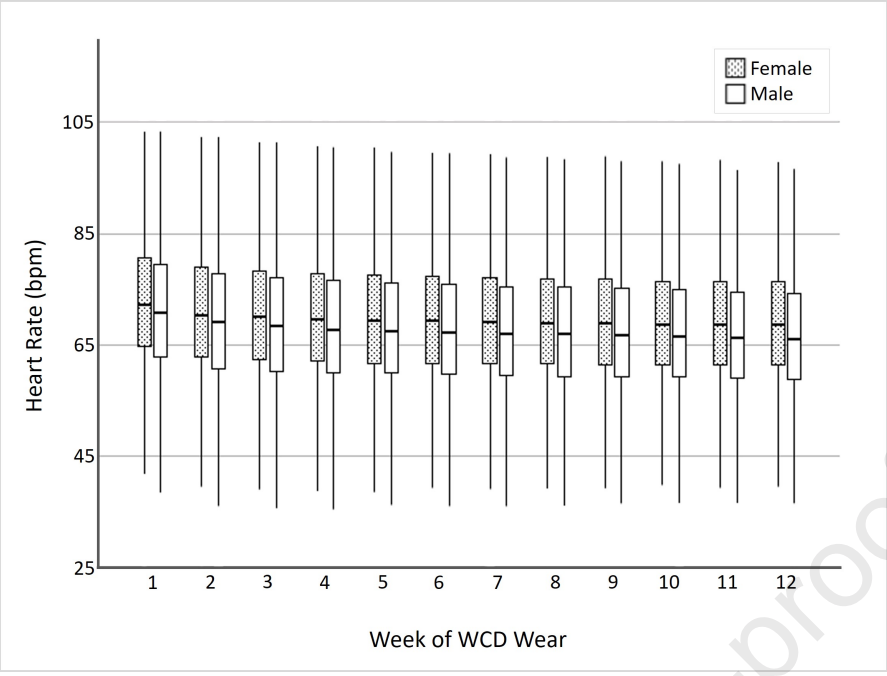

Key Findings

1) During a period of medical therapy optimization 43% of women and 36% of men did not achieve guideline-recommended HR control.
2) Compared to men, a greater percentage of women receiving WCD shocks had insufficiently controlled HR in the week preceding the VT/VF.
3) Results indicate that both women and men encounter challenges in achieving optimal heart rate control, with a more notable discrepancy observed among women.