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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BACKGROUND Despite known clinical benefits, guideline-recommended heart rate (HR) control is not achieved for a significant proportion of patients with HF with reduced ejection fraction. The wearable cardioverter-defibrillator (WCD) provides continuous 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). The proportion of patients with adequate nighttime resting HR control at the beginning of use (BOU) and at the end of use (EOU) were compared by sex. Adequate HR control was defined as having a nighttime median HR <70 beats/min.

RESULTS A total of 21,440 women and a comparative sample of 17,328 men (median 90 [IQR 59–116] days of WCD wear) 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 beats/min improved by EOU, 43% of women and 36% of men did not achieve guideline-recommended HR control.

CONCLUSION A significant proportion of women and men did not achieve adequate HR control during a period of medical therapy optimization. Compared with men, a greater proportion of women receiving WCD shocks had insufficiently controlled HR in the week preceding ventricular tachyarrhythmia/ventricular fibrillation and 43% of nonshocked women, compared with 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 uptitration of beta-blockers, 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

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Introduction

Increased heart rate (HR) is associated with adverse clinical outcomes in patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF) ($\leq$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/min increase in HR in the general population.[5] A meta-analysis by McAlister and colleagues,[6] which included 19,209 patients with HF, found that the magnitude of HR reduction was significantly associated with the survival benefit of beta-blockers (BBs). 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

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KEY FINDINGS

- During a period of medical therapy optimization, 43% of women and 36% of men did not achieve guideline-recommended heart rate control.
- Compared with men, a greater percentage of women receiving wearable cardioverter-defibrillator shocks had insufficiently controlled heart rate in the week preceding the ventricular tachyarrhythmia/ventricular fibrillation.
- Results indicate that both women and men encounter challenges in achieving optimal heart rate control, with a more notable discrepancy observed among women.

escalating BB dosage to achieve a resting HR of <70 beats/min among patients in sinus rhythm.[7–10]

Jungbauer and colleagues[11] analyzed HR, recorded by a wearable cardioverter-defibrillator (WCD), during rest and activity in 1,353 patients with a recent HF-related hospitalization. Daytime and nighttime resting HR dropped significantly from the beginning to the end of WCD use (day: 72.5 beats/min vs 69.0 beats/min; $P < .001$; night: 68.1 beats/min vs 64.3 beats/min; $P < .001$). However, for 25% of patients, median nighttime HR remained ≥70 beats/min 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 with 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 (VTs)/ventricular fibrillation (VF),[10,13–19] also provides telemonitoring of several vital parameters including continuous HR measurement.[20,21] 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 to 2018. Because female patients typically represent only 30 percent of WCD users, a random sample of male patients (1 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) 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. De-identified 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 Department of Medicine at East Carolina University. 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 and last weeks of WCD use.

Wearable cardioverter-defibrillator

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 electrocardiography (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.[20] Continuous HR data are 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), and 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 uptitration 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 HR of 70 beats/min or higher as measured on 12-lead ECG, after at least 5 minutes of rest, performed on 2 consecutive visits.[1] Additionally, the target HR of 70 beats/min is based on evidence that a HR of 75 beats/min or lower is associated with a survival benefit in patients with HF with reduced ejection fraction (LVEF ≤35%).[22]

Table 1 Baseline clinical characteristics

	Full sample	Women	Men	*P* value
Patients	38,768 (100)	21,440 (55)	17,328 (45)	
WCD use, d	90 (58–116)	90 (59–116)	89 (57–115)	.22
Age, y	67 (58–75)	67 (58–75)	67 (58–75)	.66
WCD indication				<.001
DCM/NICM/HF	25,064 (65)	14,391 (67)	10,673 (62)	
Post-MI/PCI/CABG	11,292 (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)	

Values are n (%) or median (interquartile range).

CABG = coronary artery bypass grafting; DCM = dilated cardiomyopathy; HF = heart failure, MI = myocardial infarction, NICM = nonischemic cardiomyopathy; PCI = percutaneous coronary intervention; VF = ventricular fibrillation; VT = ventricular tachyarrhythmia; WCD = wearable cardioverter-defibrillator.

The WCD provides continuous HR monitoring. Investigators defined resting HR as median nighttime HR (midnight to 7:00 AM), 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 use (BOU) and at the end of use (EOU). For patients who received a WCD shock, median resting nighttime HR was analyzed from the 7 days prior to VT/VF.

Data analysis

Descriptive statistics were used to summarize the datasets. Categorical variables were reported as frequency and percentage and continuous variables as mean ± SD or median (interquartile range [IQR]). Baseline clinical characteristics were compared between women and men using the *t* test for continuous variables and the chi-square test for categorial variables. Paired *t* tests were performed to determine differences in HR at BOU and EOU for nonshocked 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, and a *P* value of <.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 (IQR 58-75) years. Patients wore the WCD for a median duration of 90 (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 nonischemic heart disease (65%), which was significantly more common in women ($P < .001$). An indication of ischemic heart disease with new-onset HF, including interventional or surgical revascularization (29%), was more common in men ($P < .001$). 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

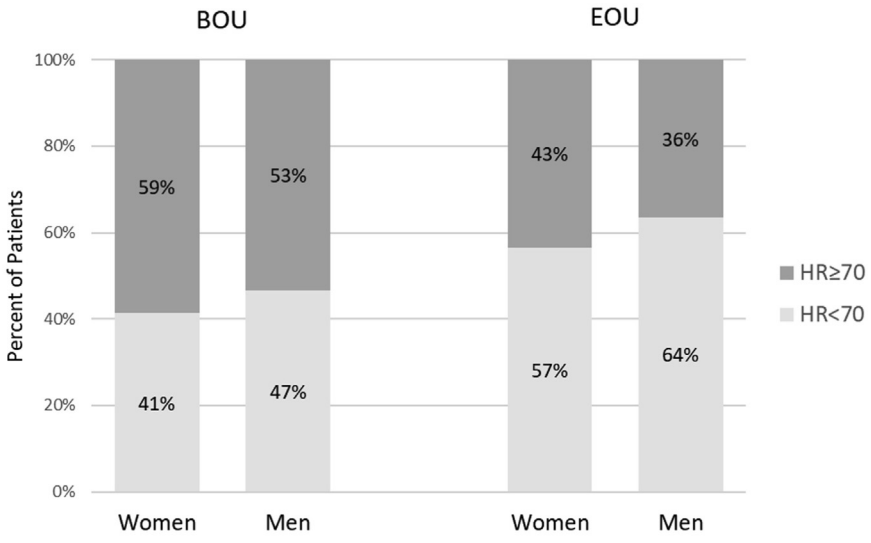
Among patients who did not receive a shock, a higher proportion of women had a median nighttime HR ≥70 beats/min, compared with men at BOU (women 59%, men 53%) (Figure 1). By EOU, the proportion of patients with insufficient HR control decreased among both women and men. The median nighttime HR in women was 73.3 ±11.79 beats/min at BOU and decreased to 69.0 ±11.63 beats/min at EOU, suggesting therapy optimization ($P < .001$). Similarly, nighttime HR among men decreased from 71.8 ±12.35 beats/min at BOU to 66.9 ±12.15 beats/min at EOU ($P < .001$). 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%).

HR profiles 1 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 with patients who did not receive a shock, regardless of sex, though it reached statistical significance only for men (shocked women: 75.4 ± 13.18 beats/min; nonshocked women: 73.3 ± 11.79 beats/min; $P = .089$; shocked men: 74.1 ± 13.11 beats/min; nonshocked men: 71.8 ± 12.35 beats/min; $P = .042$). In the week preceding VT/VF, 55% of women had inadequate HR control compared with 53% of men.

Changes in HR over time by sex

Repeated-measures analysis confirmed a significant decreasing trend in HR over the initial 12 weeks of guideline-recommended therapy ($F = 1554.34$, $P < .001$, dfs = 11) (Figure 3). The decrease in HR over the 12-week period was present for women and men. However, a significant interaction between sex and week suggests that the improvement in HR control over time was greater for men compared with women ($F = 11.81$, $P < .001$, dfs = 11).

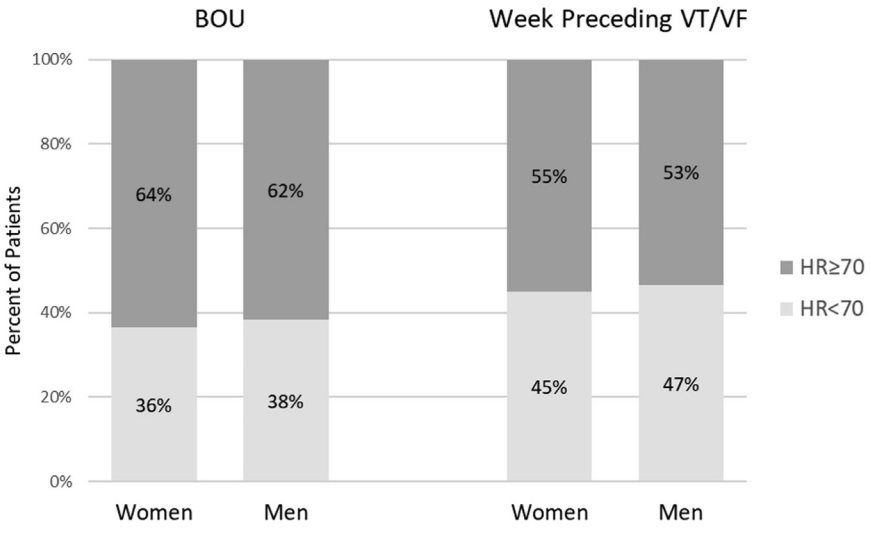


	BOU HR (bpm)	EOU HR (bpm)	p-value
Women	73.3 ±11.79	69.0 ±11.63	p<.001
Men	71.8 ±12.35	66.9 ±12.15	p<.001

Figure 1 Percentage of nonshocked patients with resting heart rate (HR) below guideline recommended threshold (<70 beats/min) at beginning of use (BOU) and end of use (EOU). Mean HR at BOU and EOU.

End-of-use outcomes in the study

For the full sample, the most common WCD EOU reason was that LVEF improved (n = 14,687 [37.88%]), followed by received an implantable cardioverter-defibrillator (n = 11,844 [30.55%]), early return of the WCD by patient's choice (n = 6141 [15.84%]), planned WCD finish (n = 3274 [8.45%]), other (n = 1996 [5.15%]), and patient died (n = 826 [2.13%]) (Table 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

Figure 2 Percentage of patients who received a shock with resting heart rate (HR) below guideline recommended threshold (<70 beats/min) at beginning of use (BOU) and during the week preceding the ventricular tachyarrhythmia (VT)/ventricular fibrillation (VF). Mean HR at BOU and 1 week preceding the VT/VF.

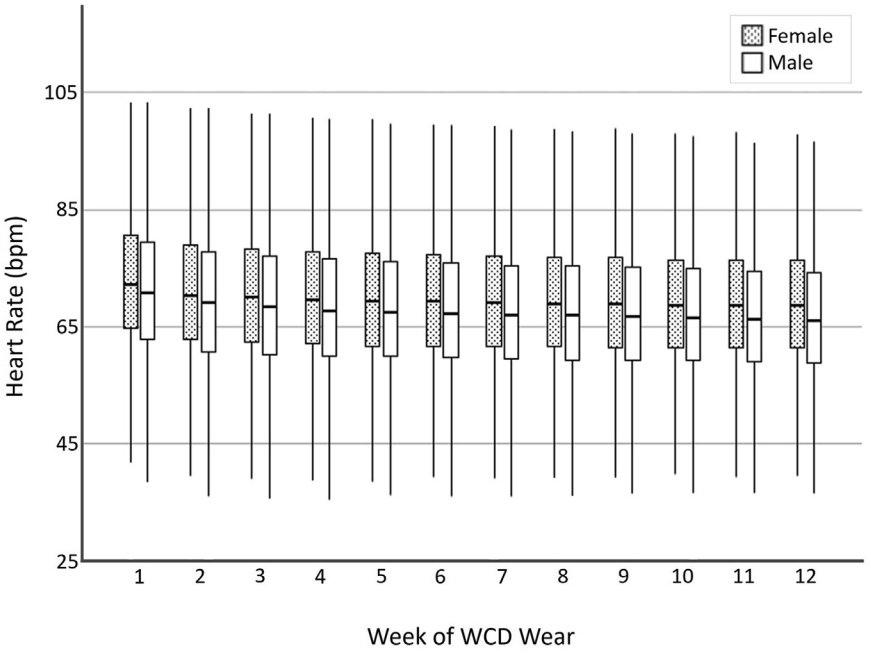


Figure 3 Change in heart rate over time by sex. WCD = wearable cardioverter defibrillator.

Discussion

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

Table 2 End-of-use outcomes by sex

Outcome	Full sample (N = 38,768)	Women (n = 21,440)	Men (n = 17,328)
LVEF improved	14,687 (37.88)	8634 (40.27)	6053 (34.93)
Received ICD	11,844 (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)

Values are n (%).

ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction.

WCD and HR monitoring

The WCD is an established therapy for safe and effective treatment of patients at-risk for sudden cardiac death.[13–19] Recently, a number of studies have reported on the diagnostic utility of HR monitoring in patients with HF or myocardial infarction fitted with the newest generation WCD.[11,12,19] Jungbauer and colleagues[11] found that 40% of 1353 patients fitted with a WCD had a median nighttime HR ≥70 beats/min at BOU, and by EOU, HR control remained inadequate for 28% of patients. However, their sample consisted primarily of male patients (80%) and they did not report differences in HR due to sex or shock status. Another retrospective study of patients fitted with a WCD investigated the relationship between HR and HF-related mortality in the early posthospitalization period.[12] Of the 4,590 patients included in the study, 88 (2%) died during the study period. In comparison with 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 beats/min 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 with men, a greater proportion of women lacked adequate HR control 3 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] We previously investigated safety and efficacy of the WCD in women at risk for SCD[18,19,21] and reported that the majority of women receiving shocks had newly diagnosed HF or nonischemic heart disease.[18] In a post hoc analysis of the U.S. WEARIT-II registry comprising 2000 patients (598 [30%] women), the burden of ventricular tachycardia or VF was even higher in women, with 30 events per 100 patient-years compared with 18 events per 100 patient-years in men ($P = .02$), with similar findings for treated and nontreated ventricular tachycardia/VF. 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; $P = .04$).[19]

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 uptitration to achieve significant HR reduction (<70 beats/min)[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 Food and Drug Administration approval of cardiovascular drugs.[25] For example, in the PARADIGM-HF (angiotensin-neprilysin inhibition versus enalapril in heart failure) trial, evaluating sacrubitril/valsartan vs 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 United States 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 (eg, a 50% male/50% female recruitment goal). We aim 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 OPT-BB (Women Optimizing Beta-Blocker Dosage in Women using the Wearable Cardioverter-Defibrillator) trial 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 BB 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 beats/min 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 were evident. Compared with men, more women receiving WCD shocks had insufficiently controlled HR in the week preceding the VT/VF, and a significant proportion of nonshocked 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 uptitration of BB in at-risk women. Future research will be directed at understanding the clinical usefulness of these alerts.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: All patients consented to data collection for quality monitoring and research.

Ethics Statement: This secondary analysis of deidentified data was approved by the Institutional Committee on Human Research at East Carolina University.

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