Sex differences in arrhythmic burden with the wearable cardioverter-defibrillator

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BACKGROUND Data on the arrhythmic burden of women at risk for sudden cardiac death are limited, especially in patients using the wearable cardioverter-defibrillator (WCD).

OBJECTIVE We aimed to characterize WCD compliance, atrial and ventricular arrhythmic burden, and WCD outcomes by sex in patients enrolled in the Prospective Registry of Patients Using the Wearable Cardioverter Defibrillator (WEARIT-II U.S. Registry).

METHODS In the WEARIT-II Registry, we stratified 2000 patients by sex into women (n = 598) and men (n = 1402). WCD wear time, ventricular and atrial arrhythmic events during WCD use, and implantable cardioverter-defibrillator (ICD) implantation rates at the end of WCD use were evaluated.

RESULTS The mean WCD wear time was similar in women and men (94 days vs 90 days; $P = .145$), with longer daily use in women (21.4 h/d vs 20.7 h/d; $P = .001$). Burden of ventricular tachycardia or ventricular fibrillation was higher in women, with 30 events per 100 patient-years compared with 18 events per 100 patient-years in men ($P = .017$), with similar findings for treated and non-treated ventricular tachycardia/ventricular fibrillation. Recurrent atrial arrhythmias/sustained ventricular tachycardia was also more frequent in women than in men (167 events per 100 patient-years vs 73 events per 100 patient-years; $P = .042$). However, ICD implantation rate at the end of WCD use was similar in both women and men (41% vs 39%; $P = .448$).

CONCLUSION In the WEARIT-II Registry, we have shown a higher burden of ventricular and atrial arrhythmic events in women than in men. ICD implantation rates at the end of WCD use were similar. Our findings warrant monitoring women at risk for sudden cardiac death who have a high burden of atrial and ventricular arrhythmias while using the WCD.

KEYWORDS ICD; Outcomes; Sex; Ventricular arrhythmias; Wearable cardioverter-defibrillator

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Introduction

It has been previously shown that sex influences the rate of death and ventricular arrhythmic events in at-risk cardiac patients. However, studies evaluating cardiac arrhythmias have been performed predominantly in male patients.[1] Specifically, women have been underrepresented in clinical trials evaluating primary prevention of sudden cardiac death (SCD) using the implantable cardioverter-defibrillator (ICD).[1–4]

While the ICD has been shown to be associated with improved survival, there are several patient subsets who are at-risk cardiac patients but are not candidates for an ICD according to the current guidelines.[5,6] These include patients with a transient risk for SCD, patients in whom a predefined waiting period after specific clinical events (eg, myocardial infarction [MI]) is indicated by guideline recommendation, patients who have had an ICD removed because of

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complications or malfunction, and patients with a suspected arrhythmic disorder who are still undergoing evaluation.[5,7] In these patients without an established ICD indication, the use of the wearable cardioverter-defibrillator (WCD) has been shown to be safe and effective during a time period of risk stratification.[8–10] However, there are no data available on sex differences in outcomes with the WCD.

Therefore, the objectives of this Prospective Registry of Patients Using the Wearable Cardioverter Defibrillator (WEARIT-II Registry) substudy were to assess sex differences in atrial and ventricular arrhythmias during WCD use, as well as in compliance with the WCD, and to evaluate improvement in cardiac function at the end of WCD use. On the basis of previous data in patients with implantable devices,[1–4] we hypothesized that women will have a lower rate of ventricular arrhythmic events during WCD use.

Methods

Study population

All patients who wore a medically prescribed WCD (LifeVest system, ZOLL Inc, Pittsburgh, PA) were offered participation in the registry through a letter included at the time of delivering the WCD. Current indication for use of the WCD has been outlined previously (patient group 1). Patients who agreed to participate were entered into the registry after providing a written informed consent. Patients were expected to receive guideline-directed care including medical therapy and management, and the registry physicians were not involved in any medical care of the subjects. The University of Rochester was the Coordination and Data Center for the WEARIT-II Registry, independent of the manufacturer of the WCD. The study protocol was approved by the Research Subjects Review Board at the University of Rochester, Rochester, NY. Patients were assigned to the following categories: (1) patients who had ischemic cardiomyopathy with previous MI, percutaneous coronary intervention, or coronary artery disease with a high risk for SCD; (2) patients who had nonischemic cardiomyopathy with no known coronary artery disease; and (3) patients who had an initial diagnosis of congenital/inherited heart disease and still undergoing evaluation.

WCD

The commercially available market-released WCD devices were used in the WEARIT-II Registry. The WCD is composed of a garment containing defibrillation patch electrodes and nonadhesive electrocardiogram (ECG) electrodes connected to a monitoring unit. The WCD continuously monitors the patient's heart rhythm and can automatically deliver up to 5 posterior-anterior defibrillation shocks of 150 J with a biphasic shock waveform. Once an arrhythmia is detected, an alarm sequence starts with a silent vibration and is followed by escalating audible siren alarms. The device detection algorithm incorporates 3 inputs: heart rate, template matching, and persistence of the event. The default ventricular tachycardia (VT) and ventricular fibrillation (VF) detection rate thresholds are 150 and 200 beats/min, respectively. The algorithm also includes a pair of response buttons that allows a conscious patient to respond to the alarm, preventing an unnecessary WCD shock. In the absence of a patient response and the continuing detection of an arrhythmia through the responsiveness test, shocks are delivered. The WCD broadcasts an asystole alarm (including voice alerts to call for help and perform cardiopulmonary resuscitation) and starts ECG recording when there is a severe bradycardia detected (and also during other detected arrhythmic events).

Data collection and follow-up

After enrollment, a baseline questionnaire was completed collecting information on medical history, comorbidities, and other baseline clinical characteristics. Baseline data on medical history and comorbidities were collected from self-reports of the patients and from the medical order forms completed by the physicians at the participating centers. WCD device data were collected, providing daily compliance data by using the actual WCD monitoring data. *Compliance* was defined as hours per day of use. ECG data were transmitted on a weekly basis and recorded during arrhythmic and asystole alarms. Patients were sent follow-up questionnaires at 1, 3, and 12 months to evaluate interim clinical events. Physicians were sent follow-up questionnaires at the 3 and 12 months to assess the rate of ICD implantation and clinical events. At the end of WCD use, typically at 3 months of follow-up, we assessed whether the patients were implanted with an ICD or improved their ejection fraction (EF).

Arrhythmic events

An arrhythmic episode included an onset and a conversion to a slower and regular rhythm. Any arrhythmic episode that was separated by 5 minutes from the previous one was considered a separate episode. Each individual arrhythmic episode was reviewed and adjudicated in the registry and classified into 4 major categories: (1) sustained VT (lasting $\geq$30 seconds) or VF with WCD shock therapy, (2) sustained VT with no WCD shock delivered owing to the use of the response buttons, (3) nonsustained VT of $<$30 seconds of duration, or (4) atrial fibrillation or supraventricular tachycardia properly detected by the device. Inappropriate WCD therapy was classified as non-VT/VF episodes detected and treated by a WCD shock. Bradyarrhythmia and asystole events were detected and recorded by the WCD. The WCD broadcasts an asystole alarm (including voice alerts to call for help and perform cardiopulmonary resuscitation) and starts ECG recording when severe bradycardia is detected ($<$10 beats/min). An *asystole episode* was defined as bradycardia with heart rate $<$ 10 beats/min or having a pause lasting $\geq$10 seconds.

Statistical analysis

Continuous variables are expressed as mean $\pm$ SD. Categorical data are summarized as frequencies and percentages. Baseline clinical characteristics were compared between

Table 1 Baseline clinical characteristics by sex

Characteristic	Women	Men	*P*
Demographics			
No. of patients	598	1402	
Etiology: ischemic cardiomyopathy	182 (30)	623 (44)	<.001
Nonischemic cardiomyopathy	337 (56)	590 (42)	<.001
Congenital/inherited condition	79 (13)	189 (13)	.871
Age (y)	58 ± 13	62 ± 12	<.001
White race	499 (83)	1192 (87)	.001
Ejection fraction (%)	35 ± 27	36 ± 28	.506
Hispanic	25 (4)	47 (5)	.422
Medical history			
Heart failure at baseline	346 (58)	694 (50)	.001
History of syncope	98 (16.4)	250 (17.8)	.436
Atrial fibrillation	135 (23)	422 (30)	.001
Hypertension	338 (57)	870 (62)	.021
Hyperlipidemia	294 (49)	701 (50)	.732
Diabetes	160 (27)	391 (28)	.604
Renal disease	40 (7)	122 (9)	.131
Myocardial infarction	128 (21)	428 (31)	<.001
Angioplasty	136 (23)	474 (34)	<.001
CABG	45 (8)	277 (20)	<.001
Cardiomyopathy	312 (52)	587 (42)	<.001
Medications			
Aldosterone antagonists	191 (32)	370 (26)	.011
ACE-I/ARB	431 (72)	1051 (75)	.177
β-Blockers	514 (86)	1216 (87)	.640
Amiodarone	59 (10)	200 (14)	.007

Values are presented as mean ± SD or n (%).

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting.

men and women by using the Kruskal-Wallis test for continuous variables and the χ^2 test or Fisher exact test for dichotomous variables, as appropriate. Differences in compliance with the WCD between men and women were assessed using *t* tests.

WCD-detected arrhythmic events were captured by calculating the number and percentage of patients with specific event types and event rates per 100 patient follow-up years to account for recurrent events. These different outcome measures were compared between men and women. The rates of arrhythmic events were analyzed using the total number of events and follow-up time and compared between women and men using bar graphs. Negative binomial regression models with log link were used to statistically compare the risk of arrhythmic events by sex, as appropriate. The offset variable in the model was the natural log of follow-up time in days. Models were further adjusted for baseline differences, including ischemic heart disease, congenital/inherited heart disease, baseline heart failure, baseline atrial fibrillation, and hypertension.

All statistical tests were 2-sided, and a nominal *P* value of <.05 was considered statistically significant. Analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

Results

Baseline clinical characteristics

The WEARIT-II Registry enrolled 598 women (30%) and 1402 men. Compared with men, women displayed important differences in baseline demographic and clinical variables, including a significantly younger age and a higher frequency of nonischemic cardiomyopathy and heart failure. In contrast, men displayed a significantly higher frequency of atrial fibrillation at baseline and they more frequently had ischemic heart disease (including a history of MI and coronary revascularization). Medical therapies with β-blockers and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker were administered at similar frequency in both men and women. However, women were less frequently amiodarone prescribed and they were more often treated with aldosterone antagonists than men (Table 1).

The mortality rate at 3 months was 0.04% in women and 1% in men. The mortality rate at 1 year was similar between women and men (3% and 4%, respectively; $P = .423$).

Compliance by sex

The mean number of days of WCD use was 94 days in women and 90 days in men, respectively ($P = .145$). The average hours of use per day were 20.7 in males and 21.4 in females, respectively ($P = .001$). The average daily hours use by biweekly time periods of the WCD use by sex is shown in Figure 1.

WCD-detected arrhythmic events by sex and by disease etiology

Overall an appropriate WCD shock occurred in 3% patients, with a similar frequency in women and men (1.9% and 1.1%, respectively). While the number of women and men with VT/VF events was similar, the overall event rate for recurrent VT/VF in women was significantly higher and yielded 30 events per 100 patient-years as compared with 18 events per 100 patient-years in men ($P = .017$) (Figure 2). It is noteworthy that ventricular arrhythmic events that were not treated by the WCD were sustained VTs (and not VF events), in which patients used the response button to delay therapy, and subsequently the VTs self-terminated. Nevertheless, the event rate of sustained VT without treatment was significantly higher in women (21 events per 100 patient-years) than in men (14 events per 100 patient-years) ($P = .039$). However, the event rate for a sustained VT event treated by WCD shock was similar in women (9 events per 100 patient-years) and men (4 events per 100 patient-years) ($P = .267$). Atrial fibrillation or supraventricular tachyarrhythmia events had similar incidence in men and women (~4%), but women had a much higher rate of recurrent events, with 167 events per 100 patient-years compared with 73 events per 100 patient-years in men ($P = .042$) (Figure 2). Similarly, data on supraventricular arrhythmias are interesting only as to how they may have triggered unnecessary therapy or required patient diversion. Inappropriate therapies were

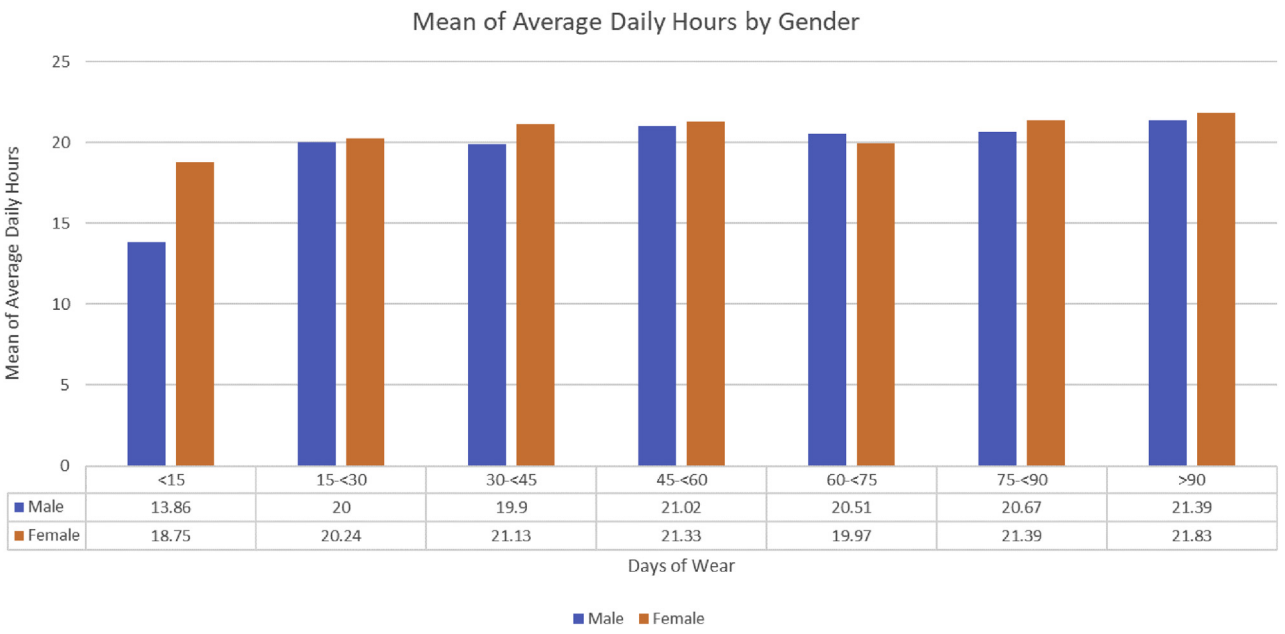

Figure 1 Wearable cardioverter-defibrillator compliance by sex in Prospective Registry of Patients Using the Wearable Cardioverter Defibrillator (WEARIT-II Registry).

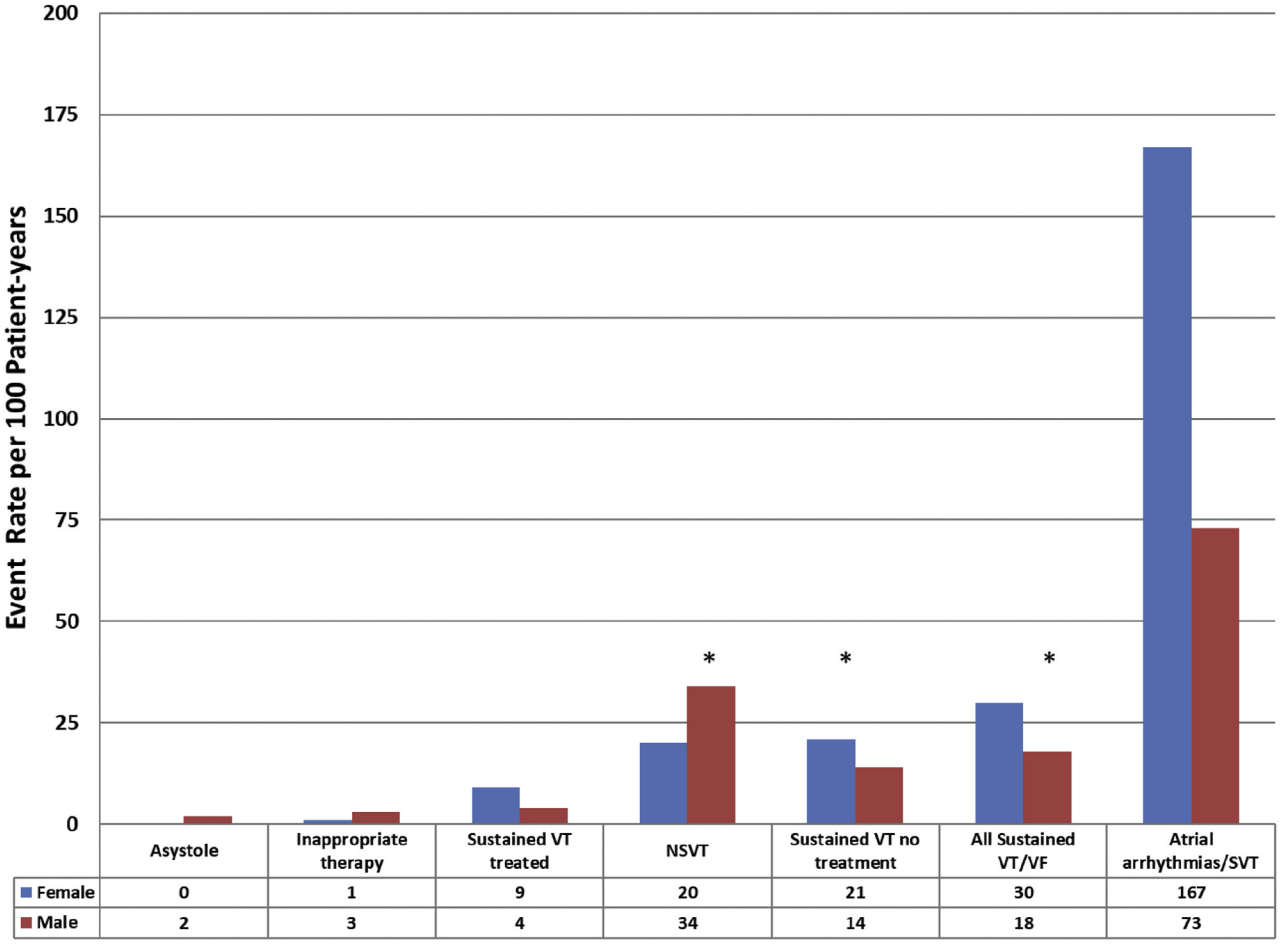

Figure 2 Wearable cardioverter-defibrillator–detected arrhythmic events by sex. NSVT = nonsustained ventricular tachycardia; SVT = sustained ventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 2 Arrhythmic events during wearable cardioverter-defibrillator use by sex

Variable	Women			Men		
	Patients, n (%)	Events (mean events per patient)	Event rate per 100 patient-years	Patients, n (%)	Events (mean events per patient)	Event rate per 100 patient-years
1. Total population						
All sustained VT/VF	12 (2%)	51 (4.3)	30	29 (2.1%)	69 (2.4)	18
Sustained VT no treatment	7 (1.2%)	36 (5.1)	21	15 (1.1%)	54 (3.6)	14
Sustained VT treated	8 (1.4%)	15 (1.9)	9	14 (1%)	15 (1.1)	4
NSVT	8 (1.4%)	33 (4.1)	20	20 (1.4%)	131 (6.6)	34
Atrial arrhythmias/SVT	22 (3.7%)	281 (12.8)	167	50 (3.6%)	280 (5.6)	73
Asystole	0	0	0	6 (0.4%)	9 (1.5)	2
Inappropriate therapy	1 (0.2%)	1 (1)	1	9 (0.6%)	10 (1.1)	3
2. Patients with ischemic cardiomyopathy						
All sustained VT/VF	4	14 (3.5)	29	20	39 (2.0)	23
Sustained VT no treatment	3	11 (3.7)	23	8	26 (3.3)	16
Sustained VT treated	3	3 (1)	6	12	13 (1.1)	8
NSVT	1	9 (9)	19	7	42 (6)	25
Atrial arrhythmias/SVT	7	16 (2.3)	33	18	116 (6.4)	69
Asystole/bradycardia	0	0	0	4	7 (1.8)	4
Inappropriate therapy	0	0	0	1	1 (1)	1
3. Patients with nonischemic cardiomyopathy						
All sustained VT/VF	4	9 (2.3)	9	6	27 (4.5)	16
Sustained VT no treatment	1	6 (6)	6	5	26 (5.2)	15
Sustained VT treated	3	3 (1)	3	1	1 (1)	1
NSVT	2	6 (3)	6	10	85 (8.5)	50
Atrial arrhythmias/SVT	11	179 (16.3)	184	29	158 (5.4)	93
Asystole/bradycardia	0	0	0	2	2 (1)	1
Inappropriate therapy	0	0	0	5	5 (1)	3
4. Patients with congenital/inherited heart disease						
All sustained VT/VF	4	28 (7)	127	3	3 (1)	6
Sustained VT no treatment	3	19 (6.3)	86	2	2 (1)	4
Sustained VT treated	2	9 (4.5)	41	1	1 (1)	2
NSVT	5	18 (3.6)	82	3	4 (1.3)	8
Atrial arrhythmias/SVT	4	86 (21.5)	391	3	6 (2)	12
Asystole	0	0	0	0	0	0
Inappropriate therapy	1	1 (1)	5	3	4 (1.3)	8

The Fisher exact test revealed no differences in the number of patients with events by sex for any of the arrhythmic end points.
NSVT = nonsustained ventricular tachycardia; SVT = sustained ventricular tachycardia; VT/VF = ventricular tachycardia/ventricular fibrillation.

infrequent and similar in both men and women with <1% incidence in both groups (Table 2, section 1).

We additionally analyzed WCD-detected arrhythmic event rates by sex and by disease etiology including ischemic cardiomyopathy, nonischemic cardiomyopathy, and congenital/inherited heart disease (Table 2, sections 2, 3, and 4, respectively). Notably, the event rate of any sustained VT/VF in women with congenital/inherited heart disease was higher, 127 events per 100 patient-years, whereas the event rate in men with the same etiology was 6 events per 100 patient-years. Subgroup analysis showed that the higher event rate observed in women vs men was consistent in patients with both congenital heart disease and inherited arrhythmic disorders. There was a consistently higher rate of sustained VT/VF events in women vs men in the ischemic cardiomyopathy subgroup, with 29 events per 100 patient-years vs 23 events per 100 patient-years. In contrast, this pattern was not seen in the nonischemic cardiomyopathy subgroup as the event rate for sustained VT/VF in women was 9 events per 100 patient-years as compared with 16 events per 100 patient-years in men (Table 2).

End of WCD use outcomes by sex

At the end of WCD use, the ICD implantation rate was similar in both men and women (39% of men and 41% of women; $P = .448$). Consistently, an EF improvement at the end of WCD use was similar (41% of men and 42% of women; $P = .770$) (Figure 3). Interestingly, however, our analysis revealed that 93% men who experienced ventricular tachyarrhythmic events with WCD shock received an ICD while only 75% of women who experienced a ventricular tachyarrhythmic event with WCD shock received an ICD at the end of the study. This appropriately highlights potential

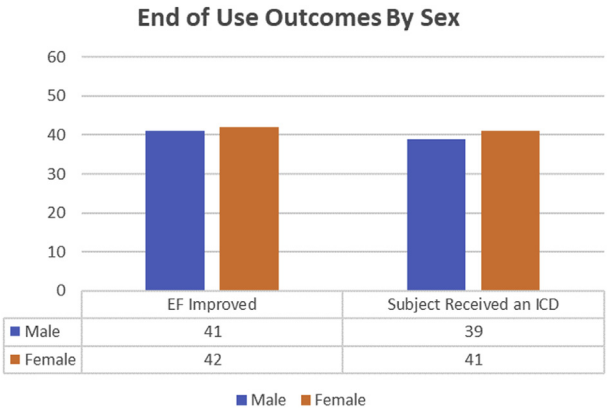

Figure 3 Clinical outcomes at the end of wearable cardioverter-defibrillator use by sex. EF = ejection fraction; ICD = implantable cardioverter-defibrillator.

sex bias in ICD implantation after WCD use, even in the face of life-threatening arrhythmias.

Discussion

To our knowledge, this is the first study to assess sex differences and outcomes with the WCD in patients at risk for SCD. Our results show that in a real-life cohort of patients prescribed the WCD, (1) women demonstrated a longer daily use of the WCD than did men, (2) women have a higher burden of ventricular arrhythmias while wearing the WCD, (3) women with ischemic cardiomyopathy and congenital/inherited heart disease had the highest burden for ventricular arrhythmias than did men, (4) women had a significantly higher burden of supraventricular arrhythmic events during WCD use, and (5) ICD implantation rates at the end of WCD use were similar in both men and women in patients enrolled in the WEARIT-II Registry.

To date, guidelines on WCD use mainly rely on registry studies and on the recently published Prevention of Early Sudden Death Trial (VEST) randomized clinical trial. Nevertheless, the patient population who may benefit the most from a WCD remains to be characterized.[11] The cohort in our study consists of patients at high risk for SCD because of a variety of etiologies but do not meet the current indications for receiving an ICD device. Our results suggest that women using the WCD have a greater burden of ventricular tachyarrhythmias during this period of risk stratification. It is important to note that most patients who are prescribed a WCD are patients with a low EF resulting from potentially reversible conditions such as a newly diagnosed dilated cardiomyopathy (that could be due to transient myocarditis) or an ischemic cardiomyopathy in the early period after revascularization or early period after MI.[11] Therefore, patients who are prescribed the WCD are distinct from patients who are prescribed an ICD, the former are at risk for SCD early in the course of the disease while the latter are at risk at a later period during the course of their disease. Therefore, we hypothesize that the sex difference in the risk for life-threatening ventricular tachyarhythmias may be dependent on the time from the diagnosis and temporal changes in patients at risk for SCD. As our study suggests, it is possible that women are more susceptible to ventricular tachyarrhythmias early in the disease process while later their arrhythmia risk is lower than that in men, as shown by multiple ICD studies in the past.[12] It is also possible that differences in baseline clinical characteristics between men and women contributed to the observed differences in arrhythmic events. However, in this study, women presented with clinical characteristics that are generally considered to be associated with a lower rate of ventricular arrhythmias, including a younger age and a higher frequency of nonischemic etiology.

Previous studies tried to elucidate the differential role of sex in arrhythmogenesis. The fact that female sex has been associated with a longer QT interval on the ECG has been known since Bazett described it in 1920.[13] In addition, women have a greater response to drugs that prolong the QT interval and a greater propensity to drug-induced torsades de pointes.[14] The reason for this phenomenon was attributed to the effects of estrogen on prolonging ventricular repolarization and reducing repolarization reserve.[15] In the Oregon Sudden Unexpected Death Study, higher testosterone levels were associated with a lower risk of cardiac arrest in men whereas higher estradiol levels were associated with an increased risk of cardiac arrest in both men and women.[15,16] We hypothesize that sex hormones may have a potential role in the increased burden of ventricular tachyarrhythmias in women during the early period of risk for SCD; however, we did not have data on sex hormones in our study, including hormone-replacing therapies in the older age group. Further studies are warranted to elucidate the role of sex hormones in arrhythmogenesis in women.

We have also shown that women had a higher rate of recurrent atrial arrhythmias than did men. These data may have implications regarding the need for more careful WCD programming and follow-up in women to avoid inappropriate WCD therapies.

Interestingly, we have also shown that women have better compliance with the WCD than do men (21.4 hours vs 20.7 hours; $P = .001$); however, the difference was not clinically meaningful. This is important since it is easy to surmise that there would be less comfort or greater difficulties with using the WCD in women on the basis of physiological differences. However, our study suggests excellent compliance in both men and women.

Subgroup analysis also revealed that ventricular arrhythmic burden in women with ischemic cardiomyopathy is greater than in men. Ischemic heart disease is more common in men than in women, but sex differences in the incidence of ventricular arrhythmias in patients with ischemic heart disease has been previously limited by a paucity of data from female cohorts.[1,17] In 1 study, however, women had a lower risk of appropriate ICD therapy for VT/VF than did men but only 20% of the subjects were women.[6] In contrast, our results suggest that women may be more susceptible to VT/VF early after MI or revascularization. We hypothesize that this difference is due to the fact that

patients who were prescribed a WCD in our study are closer in time to the ischemic events than patients who have an ICD, suggesting that during this early time period women may be more vulnerable and develop more frequent arrhythmic events. It is also possible that there was a sex bias in the management of heart disease for secondary prevention in women (eg, lipid-lowering medications, diet modification, use of anticoagulants, or referral to cardiac rehabilitation).[18,19] This stresses the importance of monitoring women with ischemic cardiomyopathy early in the course of the disease, as they have a burden of life-threatening ventricular tachyarrhythmias.

Our study has also shown that women with congenital heart disease experience more ventricular tachyarrhythmic events than do men. This patient group included a variety of different etiologies including long QT syndrome, arrhythmogenic right ventricular dysplasia, Brugada syndrome, and hypertrophic cardiomyopathy. Of these etiologies, it is established that female patients with long QT syndrome have more cardiac events than do male patients.[5] In contrast, in a large study of patients with hypertrophic cardiomyopathy, SCD and mortality were similar in men and women. Additionally, in arrhythmogenic right ventricular dysplasia, male sex was shown to be a risk factor for ventricular tachyarrhythmias during a follow-up period of 5.8 years. Regardless of the etiology, however, our results suggest that women are at a higher risk of ventricular tachyarrhythmic events and need to be monitored during risk stratification for an ICD.

Study limitations

Our study has a number of limitations. First, enrollment in the WEARIT-II Registry was on a voluntary basis, and thus, more compliant patients might have been preselected for participation in the study. We did not have data on the number of eligible patients per site who were not prescribed a WCD. Thus, it is also possible that there was a sex bias in the selection for use of the WCD that was not accounted for in the present study. Further studies are warranted to investigate sex bias in WCD prescription patterns. Second, while we have information on WCD-detected arrhythmic events in the study, we do not have data on subsequent ICD-treated events after ICD implantation. Thus, a comparison of sex differences in the risk of long-term arrhythmic events was not possible. Third, we are limited by the relatively low event rates in the study; only 2.1% of patients had WCD-detected ventricular arrhythmic events, limiting power for subgroup analysis by sex in the study that should be considered exploratory. Nevertheless, this is still one of the largest studies on patients using the WCD in a real-life setting and provides valuable information for the management of women and men with low EF and a temporary high risk for SCD. Fourth, it should also be noted that there were important baseline differences between women and men that may have contributed to the observed difference in the risk of arrhythmic event despite multivariate adjustment.

Conclusion

The results of our WEARIT-II substudy suggest that women have a higher daily use of the WCD than do men. Women prescribed with the WCD were younger, they more often had nonischemic cardiomyopathy, but they had a lower rate of previous atrial fibrillation. In a real-life cohort of patients prescribed the WCD, women were shown to have a greater burden of both ventricular and supraventricular arrhythmic events during WCD use. These results suggest that the WCD is a useful tool to monitor arrhythmic burden in women because of their higher likelihood of developing recurrent events.

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