Abstract: Sex-specific differences in the epidemiology, pathophysiology, clinical presentation, clinical treatment, and clinical outcomes of atrial fibrillation (AF), sustained ventricular arrhythmias, and sudden cardiac death are recognized. Sex hormones cause differences in cardiac electrophysiological parameters between men and women that may affect the risk for arrhythmias. The incidence and prevalence of AF is lower in women than in men. However, because women live longer and AF prevalence increases with age, the absolute number of women with AF exceeds that of men. Women with AF are more symptomatic, present with more atypical symptoms, and report worse quality of life in comparison with men. Female sex is an independent risk factor for death or stroke attributable to AF. Oral anticoagulation therapy for stroke prevention has similar efficacy for men and women, but older women treated with warfarin have a higher residual risk of stroke in comparison with men. Women with AF are less likely to receive rhythm control antiarrhythmic drug therapy, electric cardioversion, or catheter ablation in comparison with men. The incidence and prevalence of sustained ventricular arrhythmias and sudden cardiac death are lower in women than in men. Women receiving implantable cardioverter defibrillators for primary prevention of sudden cardiac death are less likely to experience sustained ventricular arrhythmias in comparison with men. In contrast, women receiving a cardiac resynchronization therapy implantable cardioverter defibrillator for the treatment of heart failure are more likely to benefit than men. Women are less likely to be referred for implantable cardioverter defibrillator therapy despite current guideline recommendations. Women are more likely to experience a significant complication related to implantable cardioverter defibrillator implantation in comparison with men. Whether sex differences in treatment decisions reflect patient preferences or treatment biases requires further study.
Sex differences in cardiac electrophysiological properties, and differences in the epidemiology, pathophysiology, clinical presentation, and clinical outcomes of certain arrhythmias, as well, are well recognized. This review will focus on our current knowledge base of sex-related differences in atrial fibrillation (AF) and sustained ventricular arrhythmias/sudden cardiac death (SCD). Awareness of these differences may enhance arrhythmia detection and therapeutic decisions in women, thus improving their clinical outcomes.

**SEX DIFFERENCES IN CARDIAC ELECTROPHYSIOLOGY**

A number of differences in cardiac electrophysiological parameters have been described in women in comparison with men (Table 1). Women have a higher resting heart rate than men. Women also have shorter PR, AH, and HV intervals, shorter atrial and atrioventricular node refractory periods, and shorter QRS durations. The QT and HV intervals, shorter atrial and atrioventricular node heart rate than men. Women also have shorter PR, AH, and HV intervals, shorter atrial and atrioventricular node refractory periods, and shorter QRS durations. The QT and HV intervals, shorter atrial and atrioventricular node refractory periods, and shorter QRS durations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Females vs Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal heart rate</td>
<td>Higher</td>
</tr>
<tr>
<td>SNRT</td>
<td>Shorter</td>
</tr>
<tr>
<td>AERP</td>
<td>Shorter</td>
</tr>
<tr>
<td>AH interval</td>
<td>Shorter</td>
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<tr>
<td>AVN ERP</td>
<td>Shorter</td>
</tr>
<tr>
<td>HV interval</td>
<td>Shorter</td>
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<tr>
<td>QRS duration</td>
<td>Shorter</td>
</tr>
<tr>
<td>QTc</td>
<td>Longer</td>
</tr>
<tr>
<td>VERP</td>
<td>Longer</td>
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<tr>
<td>Ventricular APD</td>
<td>Longer</td>
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<tr>
<td>$I_{Ks}$</td>
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<tr>
<td>$I_{Kr}$</td>
<td>Decreased</td>
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<tr>
<td>$I_{f}$</td>
<td>Decreased</td>
</tr>
<tr>
<td>$I_{to}$</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

Sex hormones account for most of the differences in the cardiac electrophysiological properties observed between females and males. Much of these data have been derived from experimental studies in a variety of animal models and some limited human data. Sex hormones exert genomic effects on protein synthesis of some ion channels, ion pumps, and exchangers, and posttranslational influences, as well, on ion channel function mediated by signal transduction pathways. Human data demonstrate that the expression of a number of potassium channel subunits is reduced in female ventricles in comparison with male ventricles (Table 1) accounting for the prolongation of the ventricular action potential duration, the ventricular refractory period, and the QT interval in comparison with males. In addition, progesterone and testosterone acutely reduce the ventricular action potential duration by enhancing the slow delayed rectifier current ($I_{Kr}$) and reducing the L-type calcium current, whereas physiological concentrations of 17β-estradiol inhibit the rapid delayed rectifier current ($I_{Ks}$). Furthermore, some studies have reported that estrogen increases the L-type calcium current, the sodium calcium exchange current, and calcium release mediated by the ryanodine receptor, thus increasing the predisposition to triggered activity, whereas testosterone has opposing effects. Together, these sex-related differences in cardiac electrophysiological properties may explain some of the differences in arrhythmogenesis reported between the sexes (Figure 1). For example, the prolongation of ventricular repolarization and decreased repolarization reserve observed in women may explain the increased risk for torsade de pointes ventricular tachycardia (VT) in women with congenital long-QT type 2 or drug-induced long-QT syndrome. In contrast, an increase in the transient outward current ($I_{to}$) in right ventricular epicardial myocytes in men in comparison with women may explain the male predominant risk of ventricular fibrillation (VF) and SCD in Brugada syndrome.

Women manifest cyclic variation in the QT interval during the ovarian cycle because of the large changes in estrogen and progesterone concentrations and their effects on potassium-repolarizing currents. During the follicular phase, associated with a higher ratio of estrogen to progesterone concentration, the ventricular action potential and QT interval are prolonged in comparison with the luteal phase. These differences may explain some of the changes in arrhythmia frequency that have been reported during the menstrual cycle, including an increased risk for torsade de pointes VT during the follicular phase of the ovarian cycle.

Delayed afterdepolarizations that occur under conditions of intracellular calcium overload are an important mechanism of ventricular arrhythmias in the setting of cardiac hypertrophy and heart failure. Sarcoplasmic reticulum calcium leak is lower in ventricular myocytes isolated from women with heart failure than from men. In association with this finding, a lower ratio of arrhythmic myocytes was observed in the female patients with heart failure. These sex differences may explain, in part, the lower incidence of spontaneous sustained ventricu-
Figure 1. Effect of sex hormones on gene expression and ion channel function and differences in ventricular electrophysiological parameters.

AP indicates action potential; $I_K$, delayed rectifier current; $I_{K1}$, inward rectifier current; $I_{to}$, transient outward current; VF, ventricular fibrillation. Reproduced from Tadros et al\textsuperscript{1} with permission of the publisher. Copyright © 2014, Elsevier.
lar arrhythmias observed in women with heart failure in comparison with men.

**ATRIAL FIBRILLATION**

AF is the most common sustained arrhythmia and is associated with a significant impairment in quality of life and a substantial increase in morbidity including increased risk of stroke and death.8,9 Because of the increasing epidemic of obesity and diabetes mellitus, and the aging of the population, as well, the global burden of AF is increasing, posing increased challenges to healthcare systems.10

**Incidence, Prevalence**

The risk of developing AF is 1.5 to 2.0 times higher in men than in women.8,9 However, because women live longer than men and AF increases in prevalence with age, the absolute number of women with AF exceeds that of men. On the basis of Framingham Heart Study data, after 40 years of age, the cumulative lifetime risk of developing AF is 1 in 4 for both men and women.11

Over the past several decades, the global burden of AF has increased in both men and women, particularly in the developed world.10 The age-adjusted incidence rates and period prevalence of AF over the 2 decades spanning 1988 to 2007 in the Framingham Heart Study are shown in Figure 2.12 The age-adjusted prevalence of AF reported between 1998 and 2007 was approximately half that for women in comparison with men. The lower prevalence of AF observed in women has also been confirmed in other recent studies. A retrospective analysis from a sample of Medicare recipients (≥65 years of age) reported that the prevalence of AF in 2007 was 74.1 per 1000 female Medicare beneficiaries and 103.4 per 1000 male beneficiaries.13 In a Swedish community-based randomized clinical trial of individuals between 75 and 76 years of age enrolled for screening of AF over a 28-month period between 2012 and 2014, the prevalence of AF was lower in women than in men (9.2% versus 15.0%).14

**Risk Factors**

Women with AF are older, have a higher prevalence of hypertension, valvular heart disease, and heart failure with a preserved ejection fraction and a lower prevalence of coronary heart disease in comparison with men.9,12,15,16 The prevalence of risk factors for AF has changed over time with increases in body mass index and diabetes mellitus, a reduction in valvular heart disease in high-income countries, and declines in mean systolic blood pressure.12,17 The latter observation is presumably attributable to improved detection, treatment, and control of hypertension. In women, moderate exercise has been reported to be associated with a reduced risk of AF.18 A recent meta-analysis reported that moderate-intensity exercise was associated with a 9% and 19% risk reduction of AF in women and men, respectively, in comparison with sedentary individuals.19 Men who performed intense exercise had a 3-fold increased risk of AF in comparison with sedentary individuals, whereas women performing vigorous exercise had a 28% reduction in incident AF. The reasons for the differential effect of sex on incident AF in association with vigorous exercise are uncertain. However, atrial volumes are significantly larger in endurance athletes, and atrial remodeling is significantly less marked in female athletes than in male athletes.20

Women (27.4%) undergoing isolated coronary artery bypass surgery are less likely to develop new-onset post-operative AF than men (30.2%). This difference remained significant after adjustment for recognized risk factors (odds ratio [OR], 0.75; 95% confidence interval [CI], 0.64–0.89; P<0.001).21 Furthermore, women who experienced this complication had shorter episodes of AF and a lower total burden of AF while in the hospital (median, 19 hours;
interquartile range, 18–21 hours versus median, 22 hours; interquartile range, 20–22 hours; \( P<0.001 \). The mechanisms for these differences are unknown.

**Pathophysiology**

There are limited data on sex differences in atrial electrophysiology and mechanisms of AF. In experimental studies, sex differences in the electrophysiology of the left atrium and pulmonary veins have been described that might explain an increased risk of arrhythmogenesis in men. A higher spontaneous beating rate, increased burst firing, and isoproterenol-induced triggering of delayed afterdepolarizations were observed in male pulmonary veins in comparison with female pulmonary veins. Furthermore, delayed afterdepolarizations were more frequently observed in male left atrial myocytes than in female atrial myocytes, and this was associated with an increase in the late sodium current, calcium transients, and sarcoplasmic reticulum calcium content. Women undergoing ablation for atrioventricular nodal reentrant supraventricular tachycardia have shorter atrial effective refractory periods than men. However, in a smaller cohort of 93 patients, differences in left atrial refractoriness or pulmonary vein refractoriness were not observed between male and female patients undergoing ablation procedures for supraventricular tachycardia or AF. These parameters were not adjusted for age, menopausal status, or the use of hormone replacement therapy and may explain some of the difference in observations observed between the 2 studies. Although 1 study reported that women have a higher incidence of nonpulmonary vein triggers for AF in comparison with men (16% in women versus 8.4% in men, \( P<0.001 \)), there were significant imbalances between the 2 comparator groups. Women were older and had more associated comorbidities and larger left atrial diameters than men. Whether differences in atrial electric and structural remodeling between the sexes influenced these observations is uncertain.

Acute administration of 17\( \beta \)-estradiol in postmenopausal women has been reported to prolong right atrial conduction time and the right atrial refractory period. However, whether estrogens play an important role in the decreased incidence of AF observed in women in comparison with men is uncertain, because most women develop AF at an older age, usually after menopause. In the Women's Health Initiative Study, a modest but statistically significant increased risk of AF was observed in postmenopausal women assigned to estrogen replacement alone in comparison with the placebo group or the group assigned to estrogen and progesterone therapy. However, this difference was attenuated after adjustment for incident coronary heart disease or heart failure. Recently, a retrospective data analysis from the Taiwan National Health Insurance Research Dataset (1998–2008) reported that the incident rate of AF was 9.2 and 22.3 per 1000 person-years in postmenopausal women treated with estradiol and conjugated equine estrogens, respectively. The adjusted hazard score for risk of AF associated with conjugated equine estrogens was 1.96 (95% CI, 1.03–3.73; \( P=0.042 \)). In a large cohort of Danish women discharged from the hospital following myocardial infarction between 1997 and 2007, hormone replacement therapy was associated with a decreased risk of AF (HR, 0.82; 95% CI, 0.68–1.00). The lowest risk of AF (37% decrease) was observed in women ≥80 years. The potential mechanisms of this effect are unknown but might include the anti-inflammatory effects of estrogens, estrogen effects on infarct size and subsequent myocardial remodeling, or protective effects on endothelial function. Lower testosterone levels in men have been reported to be associated with a higher risk of incident AF. The mechanisms of this effect are likely multifactorial.

**Symptoms and Quality of Life**

Women with AF experience more symptoms, more functional impairment, and worse quality of life in comparison with men. The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), a multicenter prospective registry of 10135 outpatients with AF, reported that women had higher AF symptom scores than men. Women reported a higher frequency of palpitations, exertional dyspnea, effort intolerance, lightheadedness, dyspnea at rest, fatigue, and chest discomfort (Figure 3). In a quality-of-life substudy, women...
reported lower quality-of-life scores, including more limitations in their daily life activities, and they expressed more concern about their treatment in comparison with men. The differences in symptoms reported between women and men in the ORBIT-AF Registry occurred despite the fact that women were more frequently in sinus rhythm at the time of evaluation.

Similar results were reported in the Euro Observational Research Program on Atrial Fibrillation (EORP-AF) Pilot survey of 3119 individuals with AF. Women were more symptomatic than men, experiencing more palpitations (80.2% versus 68.5%, \( P < 0.0001 \)) and expressing more fear and anxiety (14.6% versus 10.5%, \( P = 0.0007 \)). Women tended to experience more dyspnea and general non-well-being than men, although these differences were not statistically significant. Health status scores were significantly lower for women overall, specifically for the psychological and physical domains.

Women seeking medical attention in the emergency department are more likely to present with atypical symptoms such as weakness and fatigue. Women are also more likely to have experienced symptoms for >48 hours and are more likely to be hospitalized for the management of AF.

**Mortality**

The Framingham Heart Study initially reported that AF was associated with a 1.5-fold increased risk of death in men and a 1.9-fold increased risk of death in women.\(^{34} \) A meta-analysis of 30 studies including >4 million participants, reported that AF is a significantly greater risk factor for all-cause mortality (relative risk, 1.12; 95% CI, 1.07–1.17) and cardiovascular death (relative risk, 1.93; 95% CI, 1.44–2.60) in women than in men.\(^{35} \) The reasons for the differences in mortality between the sexes are unclear. There are some reports that women with AF are undertreated in comparison with men both in terms of anticoagulant therapy for stroke prevention and rhythm control therapies. However, this meta-analysis included studies spanning almost 2 decades. More recent Framingham Heart Study analysis reports that, despite the increased event rates of AF over 50 years of observation, survival has improved for both men and women.\(^{12} \) Furthermore, the more contemporary registry data from ORBIT-AF reports that women experience lower all-cause death (HR, 0.57; 95% CI, 0.49–0.67; \( P < 0.001 \)) and cardiovascular death (HR, 0.56; 95% CI, 0.44–0.72) in comparison with men.\(^{15} \) In addition, a post hoc analysis of the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulant Therapy) reported that male sex was an independent predictor of overall cardiovascular mortality (HR, 1.40; 95% CI, 1.12–1.71; \( P = 0.0036 \)).\(^{36} \) Thus, there currently remains controversy about the magnitude of sex-related differences and associated risk of death in the AF population.

**Stroke and Systemic Thromboembolism**

It is well recognized that women with AF are at increased risk for stroke or systemic thromboembolism in comparison with men even after adjustment for risk factors and the use of vitamin K antagonists.\(^{37–40} \) On the basis of these data, current AF guidelines recommend the use of the CHA₂DS₂-VASc score, which includes female sex in the risk assessment, for the prediction of stroke risk and guidance of anticoagulation therapy in individuals with AF.\(^{41–43} \) In a Swedish study of >100,000 patients with nonvalvular AF who were not receiving warfarin treatment, the incidence of thromboembolic stroke was 47% higher in women than in men (Figure 4).\(^{38} \) Although women had more risk factors for stroke than men, including older age, after adjustment for these differences, women still had an 18% higher risk of stroke than men. The sex difference in stroke risk has also been observed in patients with AF and no comorbidities at ≥65 years of age.\(^{40} \) In a Canadian population cohort study of >80,000 patients hospitalized for recently diagnosed AF, women, par-
particularly those >75 years of age, had a higher risk of stroke in comparison with men, even after adjustment for stroke risk factors and the use of warfarin. A Swedish national health registry study reported that the annual risk of stroke for women with a CHA2DS2-VASc score of 1 (i.e., <65 years) was 0.1% to 0.2%. Together, these data suggest that female sex is a substantial risk factor for stroke, predominantly for those >75 years of age.

It remains unknown why women with AF are more susceptible to stroke. Some studies report that women with AF are less likely to be treated with oral anticoagulants despite their higher risk for stroke. However, more contemporary registry data report no differences in anticoagulant use between men and women. Some biological factors that might contribute to the sex differences in stroke risk include sex differences in hemodynamics and cardiovascular remodeling, systemic inflammation, and prothrombotic state, in particular, following menopause. Women with AF are older and have larger left atrial volumes and lower left atrial mechanics in comparison with men. Older women have higher blood pressures and elevated pulse pressure in comparison with men. They are also more likely to have diastolic dysfunction and heart failure with preserved ejection fraction. These hemodynamic changes may lead to alterations in blood flow, endothelial dysfunction, atrial strain, and remodeling. Some markers of systemic inflammation and procoagulant state have been reported to be elevated in women in comparison with men.

**SEX DIFFERENCES IN AF TREATMENT**

**Arrhythmia Management**

Despite experiencing more symptoms, women are less likely to receive rhythm control treatment than men. In ORBIT-AF the use of antiarrhythmic drug therapy was similar in men (28.6%) and women (28.9%). However, women were less likely to undergo an electric cardioversion (26.7% versus 32.4%, P<0.001) and they were less likely to be referred for AF ablation (4.9% versus 5.9%, P=0.04). In contrast, women were more likely to undergo atroventricular node ablation for rate control of AF (2.9% versus 1.7%, P<0.001). Women were less likely to be receiving β-blocker therapy (62.0% versus 65.5%, P<0.001) and were more likely to be on digoxin (24.6% versus 22.6%, P=0.02). Similar differences in treatment patterns for men and women are reported by the EORP-AF registry. Women with symptomatic AF were more likely to receive rate control therapy alone (33.1%) in comparison with men (26.0%, P=0.002). Women were also less likely to receive electric cardioversion (18.9% versus 25.5%, P=0.0001). Although β-blocker therapy was similar in men and women (72.5% and 70.0%), women were more likely to be taking digoxin (25.0% versus 19.8%, P=0.0056). The greater use of digoxin in women is of concern given its association with increased mortality in the AF population.

Although AF ablation has increased over the past decade, several large administrative registries from Canada and the United States have reported that, in comparison with men, women are substantially less likely to undergo catheter ablation for AF. Women are older at the time of AF ablation and are referred for the procedure later following presentation than men.

Outcomes from the German Ablation Registry report that women were older at the time of the procedure, had a higher prevalence of paroxysmal AF, and were less likely to have cardiovascular disease. Women experienced more complications related to the procedure predominantly related to major bleeding. Furthermore, at 1 year of follow-up women experienced a higher recurrence of AF (OR, 1.19; 95% CI, 1.03–1.38; P=0.017) and reported more severe limitations in functional capacity and angina. Although the risk of cardiac tamponade complicating AF ablation is low, on the basis of a worldwide survey of almost 35,000 AF ablation procedures, women have a 2-fold increased risk for developing this complication.

**Treatment for Stroke Prevention**

Recent registry data report that the use of anticoagulant therapy for stroke prevention is similar for men and women. The GARFIELD-AF registry (Global Anticoagulant Registry in the Field-Atrial Fibrillation) enrolled 17,184 patients with newly diagnosed nonvalvular AF and ≥1 risk factor for stroke. The use of anticoagulants was similar in men (60.9%) and women (60.8%). Underuse of anticoagulation therapy in high-risk patients was reported for both sexes. Overuse of anticoagulation was also reported in 41% of individuals at low risk of stroke. In EORP-AF, oral anticoagulants were prescribed in 79.8% of women and 81.5% of men overall and in 95.3% of women and 76.2% of men with a CHA2DS2-VASc score ≥2. In ORBIT-AF, warfarin therapy was similar in men (79.6%) and women (80.5%) with a CHADS2 score ≥1. However, of concern in the PINNACLE registry (Practice Innovation and Clinical Excellence), women with moderate to high risk of stroke were more likely to receive aspirin therapy rather than oral anticoagulants in comparison with men. Furthermore, in a survey of general practitioners in the United Kingdom, women with AF and at moderate to high risk of stroke identified were significantly less likely to receive oral anticoagulant therapy than men (47% versus 52%, P=0.006).

A population-based cohort study of patients from the province of Quebec reported that women with AF, despite a higher stroke risk profile, were more likely to be treated with a lower dose of dabigatran in comparison with men (OR, 1.35; 95% CI, 1.24–1.48). Moreover, women treated with the higher dose of dabigatran tend-
ed to have a lower risk of stroke (HR, 0.79; 95% CI, 0.56–1.04). Thus, although recent AF guidelines have likely influenced the appropriate use of anticoagulant therapy in those at moderate to high risk for stroke, underuse of this therapy in women remains a concern, and elevating awareness of the risk for stroke in women with AF remains a priority.

In a meta-analysis of 5 randomized clinical trials, women treated with warfarin therapy had a greater risk of stroke or systemic thromboembolism than men (OR, 1.279; 95% CI, 1.111–1.473; P=0.001). In contrast, an analysis of data from 4 randomized trials evaluating the novel oral anticoagulants (apixaban, dabigatran, and rivaroxaban) reported that stroke and systemic thromboembolism were similar in men and women (OR, 1.146; 95% CI, 0.97–1.354; P=0.109). Women treated with warfarin spend more time outside the therapeutic treatment range than men, which may explain the greater residual risk of stroke observed in women treated with warfarin in comparison with men.

Major bleeding rates for men and women with AF treated with warfarin reported in 4 randomized trials were similar (OR, 0.926; 95% CI, 0.81–1.059; P=0.26). However, the novel oral anticoagulants were associated with significantly less major bleeding in women than in men (OR, 0.844; 95% CI, 0.745–0.955; P=0.007). In a separate meta-analysis including patients enrolled in the ENGAGE AF-TIMI 48 trial (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction study 48), differences in bleeding rates between women and men were not significant.

VENTRICULAR ARRHYTHMIAS/SUDDEN CARDIAC DEATH

Epidemiology

SCD is a leading cause of premature death in North America with an estimated incidence between 200,000 and 450,000 per year. The lifetime risk of SCD for women is at least half that of men. Recent data from the Framingham Heart Study reported lifetime risk estimates for SCD at index age of 45 years to be 2.8% (95% CI, 2.1–3.5) for women and 10.9% (95% CI, 9.4–12.5) for men. These lifetime risks remained similar at index ages 55 and 65 years. These lifetime risk estimates increase on the basis of the presence and severity of established risk factors: hypertension, diabetes mellitus, elevated cholesterol, and smoking history.

In the Oregon Sudden Unexpected Death Study, women were older than men, and they were more likely to present with asystole and pulseless electric activity, whereas men were more likely to present with sustained VT or VF. Women were more likely to have return of spontaneous circulation. Men experiencing SCD are more likely to have underlying coronary heart disease, whereas women are more likely to have a dilated cardiomyopathy or valvular heart disease. Depressed left ventricular ejection fraction (LVEF) is a major risk factor for SCD. Similar differences in presentation have been described in the Ontario Prehospital Advanced Life Support study. Commtio cordis, VF triggered by a blunt chest blow, is observed predominantly in young boys in the setting of sport. The disproportionate number of males experiencing this cause of SCD (95%) may reflect their higher rate of participation in the implicated sports including baseball, cricket, hockey, and lacrosse.

Sex Hormones and SCD

Female sex hormones are considered to be protective in reducing the incidence of cardiac disease, in particular, coronary artery disease. Hormone replacement therapy has not been linked to an increased risk of SCD in postmenopausal women. In the Oregon Sudden Unexpected Death Study, higher testosterone levels were associated with a lower risk of cardiac arrest in males (OR, 0.75; 95% CI, 0.58–0.96; P=0.02), whereas higher estradiol levels were associated with an increased risk of cardiac arrest in both males (OR, 2.0; 95% CI, 1.5–2.6; P<0.001) and females (OR, 3.5; 95% CI, 1.9–6.4; P<0.001). Estradiol has been reported to trigger ventricular arrhythmias in an experimental model of long-QT type 2. Female sex increases the risk for torsade de pointes VT in congenital and acquired long-QT syndrome because of the effects of estrogen on prolonging ventricular repolarization and reducing repolarization reserve.

Primary and Secondary Prevention of SCD

Clinical trials have demonstrated the clinical benefit of implantable cardioverter defibrillators (ICDs) for secondary prevention in survivors of life-threatening arrhythmias and for primary prevention in patients at high risk for SCD. LVEF ≤0.30 to 0.35 has been the major risk marker used for the selection of patients with prior myocardial infarction or systolic heart failure enrolled in the primary prevention ICD trials. Women have generally been underrepresented in these clinical trials with enrollment ranging from 8% to 30% of the study populations.

A detailed analysis of sex differences in outcomes of ICD therapy has not been reported for the secondary prevention randomized clinical trials. Analysis of a Medicare sample reported that women were less likely to receive ICD therapy for a secondary prevention indication in comparison with men. However, for those treated with ICD therapy, the mortality benefit was significant for both men (HR, 0.62; 95% CI, 0.55–0.69) and women (HR, 0.68; 95% CI, 0.60–0.78).
Summary data of primary prevention clinical trials evaluating ICDs and cardiac resynchronization therapy (CRT-ICDs) by sex are shown in Table 2. In the Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II), 16% of the population enrolled were women. Although women had more comorbidities, survival rates at 2 years were similar for men and women. However, the risk of receiving appropriate ICD therapy was lower in women (HR, 0.66; 95% CI, 0.37–0.9; P=0.039). In the SCD-HeFT trial (Sudden Cardiac Death in Heart Failure Trial), 23% of the study population were women. Overall, women had a significantly lower mortality risk than men (HR, 0.68; 95% CI, 0.55–0.84; P=0.001). A survival benefit of ICD therapy was not observed in women. Women tended to be less likely to experience appropriate ICD shocks in comparison with men. In SCD-HeFT, women were more likely to have nonischemic heart disease than men, which may explain some of the observed differences in arrhythmia event rates. In the sex substudy of the DEFINITE trial (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation), a significant reduction in all-cause mortality was observed in men but not in women. However, this difference was not significant when adjusted for multiple covariates. Women tended to have a lower rate of appropriate shocks. None of these trials were powered to compare survival differences between the sexes.

In a meta-analysis of 5 major randomized primary prevention trials comparing medical therapy with ICD therapy, Ghanbari et al reported that ICD did not confer a survival benefit for women (HR, 1.01; 95% CI, 0.76–1.33; P=0.95). In contrast, a 22% reduction in mortality was observed for men receiving ICD therapy (HR, 0.78; 95% CI, 0.70–0.87; P<0.001). A second meta-analysis that also included 1 CRT-ICD trial concluded that the overall mortality rate was similar for men and women. The benefit of ICD on mortality was significantly higher in men (HR, 0.67; 95% CI, 0.58–0.78; P<0.001) but did not reach statistical significance in women (HR, 0.78; 95% CI, 0.57–1.05; P=0.1). In this analysis, women also

Table 2. Characteristics and Outcomes of Some Primary Prevention and CRT Randomized Trials

<table>
<thead>
<tr>
<th>Study/Design</th>
<th>No. of Subjects (%)</th>
<th>Enrollment Criteria</th>
<th>Randomization</th>
<th>HR (95% CI)</th>
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<tr>
<td><strong>Primary prevention trials</strong></td>
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<tr>
<td>MADIT-II</td>
<td>Males: 1040 (84)</td>
<td>ICM LVEF ≤30%</td>
<td>OMT vs OMT+ICD</td>
<td>HR for death</td>
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<td></td>
<td>Females: 192 (16)</td>
<td>NYHA class I–III</td>
<td>Males: 0.71 (0.52–0.92)</td>
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<td></td>
<td></td>
<td></td>
<td>Females: 0.56 (0.32–1.14)</td>
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<tr>
<td>DEFINITE</td>
<td>Males: 326 (71)</td>
<td>NICM LVEF ≤35%</td>
<td>OMT vs OMT+ICD</td>
<td>HR for death</td>
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<tr>
<td></td>
<td>Females: 132 (29)</td>
<td>Holter: PVC/NSVT</td>
<td>Males: 0.49 (0.27–0.98; 0.018)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>NYHA class I–III</td>
<td>Females: 1.13 (0.5–2.65; 0.76)</td>
<td></td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td>Males: 1294 (77)</td>
<td>LVEF ≤35%</td>
<td>OMT+placebo</td>
<td>HR for death ICD vs placebo</td>
</tr>
<tr>
<td></td>
<td>Females: 382 (23)</td>
<td>NYHA class II–III</td>
<td>Males: 0.73 (0.57–0.93)</td>
<td>(97.5% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vs OMT+amio</td>
<td>Females: 0.96 (0.58–1.61)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>vs OMT+ICD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CRT trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REVERSE</td>
<td>Males: 479 (78)</td>
<td>LVEF &lt;40%</td>
<td>CRT-ON vs CRT-OFF</td>
<td>HF composite end point</td>
</tr>
<tr>
<td></td>
<td>Females: 131 (22)</td>
<td>NYHA class I–II</td>
<td>CRT</td>
<td>Males: 0.69 (0.43–1.11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>QRS ≥120 ms</td>
<td></td>
<td>Females: 0.75 (0.26–0.97)</td>
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<tr>
<td></td>
<td></td>
<td>LVEDD ≥30 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADIT-CRT</td>
<td>Males: 1367 (75)</td>
<td>LVEF ≤30%</td>
<td>ICD vs CRT-D</td>
<td>HR for HF event or death</td>
</tr>
<tr>
<td></td>
<td>Females: 453 (25)</td>
<td>NYHA class I–II</td>
<td>Males: 0.76 (0.59–0.97)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>QRS ≥130 ms</td>
<td>Females: 0.37 (0.22–2.19)</td>
<td></td>
</tr>
<tr>
<td>RAFT</td>
<td>Males: 1490 (83)</td>
<td>LVEF ≤30%</td>
<td>ICD vs CRT-D</td>
<td>HR death or HF admission</td>
</tr>
<tr>
<td></td>
<td>Females: 308 (17)</td>
<td>NYHA class II–III</td>
<td>Males: 0.82 (0.7–0.95)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>QRS ≥120 ms</td>
<td>Females: 0.52 (0.35–0.85)</td>
<td></td>
</tr>
</tbody>
</table>

Amio indicates amiodarone; CI, confidence interval; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter defibrillator; ICM, ischemic cardiomyopathy; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; NICM, nonischemic cardiomyopathy; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; OMT, optimal medical therapy; and PVC, premature ventricular contraction.

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received fewer appropriate ICD therapies than men (HR, 0.63; 95% CI, 0.49–0.82; P<0.001).

A large prospective provincial ICD registry in Ontario of >6000 patients referred to an electrophysiologist for consideration of ICD therapy between 2007 and 2010 reported that ICD implantation rates were similar for men and women.74 Furthermore, survival was similar between men and women. However, women were 31% less likely to receive an appropriate shock than men and 27% less likely to receive any appropriate ICD therapy than men. A recent meta-analysis of 20 contemporary studies in primary prevention cohorts, confirmed that women are significantly less likely to receive appropriate ICD shocks than men (HR, 0.62; 95% CI, 0.44–0.88; P=0.0175) and this study also reported that their risk of death was lower than men (HR, 0.78; 95% CI, 0.68–0.89; P=0.001).75

Together these data highlight the underrepresentation of women in ICD trials. These studies were not powered to detect a significant survival benefit of ICD therapy in women. Although women with left ventricular systolic dysfunction are at lower risk of SCD in comparison with men, the current consensus is that ICD therapy is beneficial for the prevention of SCD in women at risk.

**Cardiac Resynchronization Therapy**

CRT has been shown to improve functional capacity, quality of life, and survival and to reduce hospitalizations for heart failure. Study design and outcomes from several major randomized clinical trials are summarized in Table 2.68 Women were underrepresented in these heart failure trials, ranging from 17% to 25% of enrolled participants.

In MADIT-CRT, women experienced a significant 69% reduction in death or heart failure, a significant 70% reduction in heart failure alone, and a significant 72% reduction in overall mortality.76 These benefits exceeded those observed in men. Over longer-term follow-up in MADIT-CRT, women with underlying left bundle-branch block (LBBB) continued to derive a greater clinical benefit from CRT therapy on the outcomes of heart failure and death or heart failure alone in comparison with men.77 Similar benefits of CRT therapy on death or heart failure admission for women in comparison with men were also observed in the RAFT study (Resynchronization for Ambulatory Heart Failure Trial).78

Analysis of outcomes in Medicare records from 144642 CRT-ICD recipients reported that LBBB was associated with greater survival in women than in men. After adjustment for differences in comorbidities, women experienced a 26% reduction in death (HR, 0.74; 95% CI, 0.71–0.77) in comparison with a 15% reduction in death in men (HR, 0.85; 95% CI, 0.83–0.87).79

A pooled analysis of patient data from MADIT-CRT, RAFT, and REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) included 4076 patients, 22% women.80 Women receiving CRT-ICD experienced a 60% relative reduction in heart failure or death and a 55% relative reduction in death alone in comparison with 26% and 15% relative reductions in heart failure or death alone in men. The greatest magnitude of benefit was observed in those with LBBB and QRS durations of 130 to 149 ms. In this subset, women experienced a 76% reduction in heart failure or death (HR, 0.24; 95% CI, 0.11–0.53; P<0.001). In contrast, in this subset, there was no significant benefit in men for the end point of heart failure or death (HR, 0.85; 95% CI, 0.60–1.21; P=0.38). On the basis of data from >75000 patients enrolled in the National Cardiovascular Data Registry, the mortality benefit of CRT-ICD was greater in women (HR, 0.74; 95% CI, 0.68–0.81) than in men (HR, 0.84; 95% CI, 0.79–0.89). A significant survival benefit of CRT therapy was not observed in those without LBBB (Figure 5).81

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**Figure 5. Survival by sex in CRT-D and ICD recipients on the basis of the presence of LBBB or non-LBBB.**

Solid lines represent survival in CRT-D recipients and dashed lines represent survival in ICD recipients for women (red) and men (black). CRT-D indicates cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter defibrillator; and LBBB, left bundle-branch block. Reproduced from Zusterzeel et al81 with permission of the publisher. Copyright © 2015, American Heart Association.
The reasons why women are more likely to benefit from CRT therapy in comparison with men may include the higher prevalence of LBBB and nonischemic cardiomyopathy, and shorter QRS durations, as well, in women in comparison with men.\textsuperscript{81,82}

**Arrhythmic Events in ICD Recipients**

Individual studies and data from some meta-analyses of ICD trials have reported that women are less likely to experience treated ventricular arrhythmias following device implant. A detailed analysis of sex differences in VT/VF events was reported by the MADIT-CRT investigators.\textsuperscript{68} A lower proportion of women (21%) in comparison with men (35%) experienced VT/VF or death ($P<0.001$) over 3 years of follow-up. The mean number of VT and VF episodes was significantly greater in men in comparison with women (VT 1.97±12.2 versus 0.60±3.0, $P<0.0001$; VF 0.24±3.0 versus 0.12±0.83, $P=0.033$). Overall, women were 38% less likely to experience VT/VF or death than men. Figure 6 illustrates the cumulative incidence of VT/VF or death on the basis of sex and etiology of heart disease. In those with ischemic heart disease, the probability of these combined events was significantly lower in women than in men. The cumulative incidence of VT/VF or death was not significantly different between men and women with nonischemic heart disease. The cumulative incidence of VT/VF (Figure 6B and 6D) was significantly lower in women than in men independent of the underlying etiology of heart disease.

Thus, data from multiple clinical trials, observational studies, and meta-analyses demonstrate that women experience fewer sustained ventricular arrhythmias in comparison with men. The reasons for the sex differences are unknown but may include differences in arrhythmia substrate because men are more likely to have ischemic heart disease and scar-related VT. Sex differences in ion channel expression/function, autonomic regulation, and intracellular calcium handling may also influence the substrate and triggers for ventricular arrhythmias.\textsuperscript{1,7}

**Figure 6.** Probability of VT/VF or death (A and C) and cumulative incidence of VT/VF (B and C) on the basis of sex and the etiology of heart disease.

ICD indicates implantable cardioverter defibrillators; VF, ventricular fibrillation; and VT, ventricular tachycardia. Reproduced from Tompkins et al\textsuperscript{68} with permission of the publisher. Copyright © 2015, John Wiley and Sons.
Sex Disparities in ICD and CRT Therapy

Women are less likely to receive ICD or CRT therapy than men. An analysis of a subset of the Medicare population in 2005 reported that, of potentially eligible ICD candidates, men were 3 times more likely to receive ICD therapy than women. A more recent analysis of a cohort of 11,880 patients with heart failure and LVEF ≤0.35 enrolled in the Get With the Guidelines Trends program reported that ICD use has increased over time, but that the sex differences still persist. Although women experience lower rates of SCD in comparison with men, the body of evidence supports a survival benefit of ICD therapy for eligible women.

Trends in CRT-ICD use was examined in the Nationwide Inpatient Sample database in the time frame 2002 to 2010. Significant sex and racial barriers were noted over the time period on the basis of the total CRT implants and the number of hospital admissions for heart failure. The differences for disparities in CRT-ICD use are unclear. Age and associated comorbidities may be important factors because women are older and have more comorbidities when they present with heart failure. The roles of patient preference and potential referral bias also need to be examined.

Sex Differences in Device-Related Complications

Data from the National Cardiovascular Data Registry ICD registry report that women receiving an ICD for a primary prevention indication were more likely to have heart failure, a lower LVEF, and a nonischemic cardiomyopathy in comparison with men. Women were more likely to experience a device-related complication in comparison with men (7.2% versus 4.8%, P<0.001). These included pneumothorax or hematoma requiring intervention, cardiac tamponade, and mechanical complications requiring revision. After adjustment for differences in baseline characteristics, device-related complications remained significantly higher in women than in men (OR, 1.39; 95% CI, 1.26–1.53; P<0.001). Additional studies have confirmed the higher risk of device-related complications in women receiving ICDs or CRT therapy in comparison with men.

VT Ablation

The International VT Ablation Center Collaborative Group reported on sex differences in patients with structural heart disease undergoing catheter ablation for VT. Of 2062 patients who underwent VT ablation, 12.9% were women. Women were younger, had fewer comorbidities, had higher LVEF, and were significantly less likely to have ischemic cardiomyopathy. Following ablation, women were more likely to have recurrent VT in comparison with men (30.5% versus 25.3%, P=0.03). The survival free from VT was lower for women with ischemic heart disease in comparison with men, whereas event rates were similar for men and women with nonischemic cardiomyopathy.

CONCLUSIONS

Sex hormones contribute to differences in cardiac electrophysiological parameters and influence the risk for some inherited arrhythmias. Female sex hormones contribute to the delay in onset of cardiovascular disease in women which contribute to differences in the incidence and prevalence of AF and SCD between men and women. The mechanisms of sex differences in the epidemiology, pathophysiology, and treatment responses for AF and sustained ventricular arrhythmias are complex. Factors influencing sex differences in the use of therapies and treatment outcomes for these arrhythmias include associated comorbidities and patient preferences, and disparities and biases in healthcare use, as well.

DISCLOSURES

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FOOTNOTES

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Anne M. Gillis

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