Research paper

Underrepresentation of women in implantable cardioverter defibrillator trials

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ABSTRACT

There are sex differences in the epidemiology and presentation of ventricular arrhythmias. Sudden cardiac death (SCD) is less common in women than in men. Women have been under-represented in implantable cardioverter defibrillator (ICD) trials evaluating the benefit of ICD therapy for primary and secondary prevention of SCD. Following ICD implantation, women are less likely to experience appropriate ICD therapy for ventricular arrhythmias, consistent with epidemiological findings of a lower rate of SCD in women. Sex differences in ICD implantation rates have also been noted for primary and secondary prevention of SCD in registries and large observational cohort studies. Reasons for these differences are unclear. Age and comorbidities at the time of presentation may be partially responsible, although sex bias, patient preference, or contribution of social determinants of health cannot be excluded. There are many unanswered questions regarding reasons for sex differences in ICD usage and under-representation of women in clinical device trials. Additional investigation is needed to better understand these differences to improve outcome of all patients who are at risk for sudden cardiac arrest.

1. Introduction

In the United States, sudden cardiac death (SCD) affects >350,000 people annually with an increased risk in those with left ventricular systolic dysfunction [1]. In general, the incidence of SCD is lower in women than in men for all age groups, lagging behind that occurring in men by greater than 10 years [2]. Women are less likely to present with ventricular tachycardia (VT) or ventricular fibrillation (VF) and are more likely to present with asystole or pulseless electrical activity as the initial rhythm documented at the time of sudden cardiac arrest (SCA) [3–6]. A meta-analysis of 23 studies (N = 897,805) evaluating the association between sex and survival after out-of-hospital cardiac arrest showed that women were older and more likely to have an unwitnessed SCA, less likely to experience an arrest in public places, less likely to have an initial shockable rhythm, and were less likely to receive bystander CPR than men [7]. However, pooled results showed that compared to age-matched men, women were significantly more likely to survive to hospital discharge or to 30 days [7].

Multiple randomized controlled trials have shown that implantable cardioverter-defibrillators (ICDs) significantly reduce mortality in specific patients at risk for sudden death or those who have already experienced a sustained ventricular arrhythmia, and both primary and secondary prevention ICDs are recommended for patients meeting guideline-directed criteria, regardless of sex [8,9]. However, it has been shown that sex disparities exist, with under-representation of women in many cardiovascular clinical trials, including arrhythmia and device trials [10]. In this review, we discuss sex profiles of patients enrolled in ICD clinical trials, sex-specific ICD outcomes, as well as sex disparities in ICD usage.

1.1. Secondary prevention

Limited data are available regarding sex differences in outcomes in secondary prevention trials. Secondary prevention trials that have informed guideline recommendations for ICD therapy are outlined in Table 1. A limited analysis of patients enrolled in the Antiarrhythmics Versus Implantable Defibrillator (AVID) trial demonstrated that women were younger, less often had coronary artery disease, more often had

Table 1
Secondary prevention ICD trials.

Study	Year	N =	Male (%)	Female (%)	Enrollment criteria	Results pre-specified by sex?	Follow-up, mean/median (months)
AVID	1997	1016	807 (79.4)	209 (20.6)	SCA survivors, documented sustained VT/VF	no	18
CIDS	2000	659	557 (84.5)	102 (15.4)	Resuscitated VT/VF or unmonitored syncope	no	36
CASH	2000	288	230 (79.9)	58 (20.1)	SCA survivors, documented sustained VT/VF	no	54
Total Secondary Prevention:		1963	1594 (81.2)	369 (18.8)			

Table 2
Primary prevention trials.

Study	Year	N =	Male (%)	Female (%)	Ischemic or Nonischemic	LVEF	NYHA Class	Other enrollment criteria	Results pre-specified by sex?	Follow-up, mean/median (months)	HR for Death (95% CI)
MADIT	1996	196	180 (91.8)	16 (8.2)	Ischemic	≤35%	I-III	prior MI, NSVT, I-VT (not suppressed)	no	27	NA
CABG-PATCH	1997	900	759 (84.3)	141 (15.7)	Ischemic	<36%	-	abnormal SAECG	no	32	NA
MUSTT	1999	704	1901 (86)	301 (14)	Ischemic	≤40%	I-III	NSVT, I-VT	no	39	Men vs. Women: 1.51 (0.86, 2.64)
CAT	2002	104	83 (79.8)	21 (20.2)	Non-ischemic	≤30%	II-III	DCM ≤9 mo	no	23	NA
MADIT II	2002	1232	1040 (84.4)	192 (15.6)	Ischemic	≤30%	I-III	prior MI ≥1 mo	yes	20	Men: 0.66 (0.48-0.91)
											Women: 0.57 (0.28–1.18)
AMIOVERT	2003	103	73 (70.9)	30 (29.1)	Non-ischemic	≤35%	I-III	NSVT	no	24	NA
DEFINITE	2004	458	326 (71.2)	132 (28.8)	Non-ischemic	<36%	I-III	NSVT/VEA	yes	29	Men: 0.49 (0.27-0.90)
											Women: 1.14 (0.50-2.64)
DINAMIT	2004	674	514 (76.3)	160 (23.7)	Ischemic	≤35%	I-III	post-MI 6-40 d, reduced HRV	yes	30	
SCD-HeFT	2005	2521	1963 (77.9)	588 (22.8)	Ischemic + nonischemic	≤35%	II-III		yes	45	Men: 0.71 (0.57, 0.88)
											Women: 0.90 (0.56, 1.43)
IRIS	2009	898	689 (76.7)	209 (23.2)	Ischemic	≤40%	I-III	post-MI 5-31 d	yes	37	
DANISH	2016	1116	809 (72.4)	307 (27.5)	Non-ischemic	≤35%	II-IV	includes CRT	yes	68	Men: 0.85 (0.64-1.12)
											Women: 1.03 (0.57-1.87)
Total Primary Prevention:		10,404	8337 (79.8%)	2097 (20.2%)							

AMIOVIRT = Amiodarone Versus Implantable Cardioverter-Defibrillator: Randomized Trial; AVID = Antiarrhythmics Versus Implantable Defibrillator trial; CABG-Patch = Coronary Artery Bypass Graft (CABG) Patch Trial; CASH = Cardiac Arrest Study Hamburg; CAT = Cardiomyopathy Trial; CIDS = Canadian Implantable Defibrillator Study; DANISH = Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure; DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT = Defibrillator in Acute Myocardial Infarction Trial; IRIS = Immediate Risk-Stratification Improves Survival; MADIT = Multicenter Automatic Defibrillator Implantation Trial; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.

nonischemic cardiomyopathy, more often had VF rather than VT as the index sustained arrhythmia [11]. Despite differences in profile, there was no difference in ICD implantation rates and there was a similar 1-year mortality rate in men (15.5%) and women (14.4%).

In a single center study of survivors of SCA that included 1433 individuals (41% women) from 2002 to 2012, women were older, less likely white, less likely to have suffered an acute MI at the time of SCA and more likely to present with an initial rhythm other than VT or VF [6]. Following SCA, women were less likely to receive an ICD than men (22% vs 31%, P < 0.001). However, for patients with a shockable rhythm (VT or VF), women were equally likely as men to receive an ICD (41% vs 45%, P = 0.23). Over a median follow-up of 3.6 years, 674 (45%) patients died (53% women vs 43% men, P < 0.001). After adjusting for unbalanced baseline covariates and therapy, the sex difference in survival was no longer present. Differences in unadjusted mortality were felt to be mainly due to older age, different risk profiles at

the time of index event and differential treatment with an ICD.

In summary, women as well as men who present with sustained ventricular arrhythmias appear to have similar benefit from ICD therapy.

1.2. Primary prevention

While multiple randomized clinical trials have demonstrated the efficacy of ICDs for primary prevention of sudden cardiac death, women have been under-represented in these trials, representing only 8–29% of patients enrolled (Table 2). To date, there have been 11 randomized primary prevention trials that have helped inform the current guidelines for management of patients at risk for ventricular arrhythmias and SCD, enrolling a total of 10,404 subjects [12–22]. Overall, women comprised a total of 2097 (20.2%) participants. The Amiodarone Versus Implantable Defibrillator Randomized trial in Patients with Nonischemic
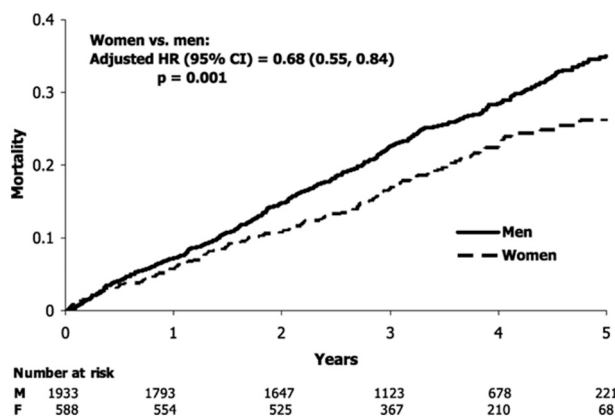
Fig. 1. Sex Differences in Mortality in SCD-HeFT. This figure includes subjects enrolled in all three arms of the trial, including placebo, amiodarone, and ICD therapy groups. Overall mortality was lower in women (20.9%) than in men (28.1%), HR 0.68 (CI 0.55,0.84, P = 0.001) in SCD-HeFT. Lower mortality was seen in women in the placebo group (21.4% vs. 31.0%, women vs. men, HR 0.67 (CI 0.46,0.98, P = 0.037) with a trend in the amiodarone group (22.3% vs. 30.6%, women vs. men, HR 0.71 (CI 0.50,1.01, P = 0.059). There was no difference in mortality between women and men in the ICD group (18.9% vs. 22.8%, women vs. men, HR 0.88 (CI 0.58,1.32, P = 0.52)). Hazard ratio for women vs. men from Cox proportional hazards model adjusted for randomized treatment, HF etiology, NYHA class, age, race, weight, pulmonary disease, lipids, AF, NSVT, syncope, BP, pulse, Na, and creatinine [26].

Dilated Cardiomyopathy and Asymptomatic Non-sustained Ventricular Tachycardia (AMIOVERT) trial enrolled the highest proportion of women with a total of 103 participants and 30 (29.1%) women, while the Sudden Cardiac Death in Heart failure Trial (SCD-HeFT) enrolled the highest total number of women with a total of 2521 participants and 588 (22.1%) women [17,20]. Several of these trials published results stratified by sex [16,18,20–23].

Enrollment criteria may be at least partially responsible for under-representation of women in primary prevention ICD trials. As women develop coronary artery disease at a later age than men, trials that restricted enrollment to patients with ischemic heart disease might be expected to enroll a smaller number of women, as elderly patients may have multiple comorbidities and may not be considered ideal candidates for ICD therapy. In addition, women may be underrepresented in trials that required inducibility of sustained ventricular arrhythmias as a criterium for enrollment, including the Multi-center UnSustained Tachycardia Trial (MUSTT) and MADIT, as women are less likely than men to have inducible sustained ventricular arrhythmias in the setting of coronary disease and prior myocardial infarction (MI) [23,24].

No randomized trial to date evaluating the efficacy of ICD therapy for primary prevention of sudden cardiac death has been adequately powered to specifically examine sex differences in mortality. Most data regarding sex differences in ICD outcomes have been derived from various subgroup and post-hoc analyses of randomized primary prevention ICD clinical trials, meta-analyses using data from these same randomized trials, and observational cohort studies using large ICD databases and registries.
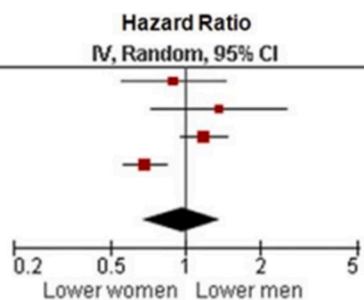
1.2.1. Sex differences in baseline characteristics

Post-hoc analyses of randomized trials demonstrated sex differences in baseline characteristics at the time of enrollment. For example, in the Multicenter Unsustained Tachycardia Trial (MUSTT), women were older and more likely to have a history of heart failure, recent angina or suffered a myocardial infarction within 6 months compared with men [23]. In MADIT II, women were more likely to have hypertension, diabetes mellitus or LBBB, and were less likely to have undergone prior CABG surgery [25]. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HEFT), women were more likely to have class III heart failure and nonischemic heart disease and worse baseline 6 min walk test than men [26,27]. Similarly, in a Medicare cohort, women were older and had more comorbidities when they presented for ICD implantation [27].
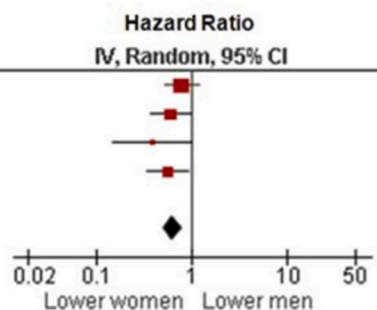

Fig. 2. Meta-analysis of primary prevention trials with outcomes of women versus men. The hazard ratios of overall morality (A) and appropriate ICD interventions (B) are shown. While overall mortality did not differ in men versus women in the meta-analysis, women were less likely to receive appropriate ICD therapy for ventricular arrhythmias than men [29].

1.2.2. Outcomes – mortality and sudden death

The benefit of primary prevention ICD therapy in reducing mortality in women has been questioned. Table 2 outlines enrollment criteria and outcomes in these randomized trials. In a post-hoc analysis of MUSTT, there were no sex differences in risk of arrhythmic death or cardiac arrest (9% vs 12%, adjusted HR 0.88, P = 0.78) or overall mortality (32% vs 21%, adjusted HR 1.51, P = 0.15) in those randomized to EP-guided therapy. However, due to the very small number of women in this trial, especially women implanted with ICDs (18 total), firm conclusions could not be drawn [23]. In MADIT II, there was no significant interaction between sex, mortality and ICD therapy, suggesting similar effectiveness of ICD therapy in men and women [25]. A sex subgroup analysis of DEFINITE, which enrolled patients with nonischemic cardiomyopathy, found no sex difference in the effectiveness of primary prevention ICDs in reducing mortality either in univariate or multivariate analyses. There was no statistically significant difference in arrhythmic mortality between sexes, but women in the ICD arm had significantly higher noncardiac death when compared to women without ICDs (P = 0.02) [28].

In SCD-HeFT, which randomized therapy to ICD vs. amiodarone vs. placebo in a 1:1:1 ratio in patients with ischemic and nonischemic heart disease, overall mortality risk was lower in women than in men after adjusting for differences in baseline characteristics [26] (Fig. 1). When examining each of the randomized groups, a sex difference in overall mortality was seen in the placebo group, while there was no sex difference in overall mortality in the ICD group. While this suggests that women may have a smaller ICD benefit than men, the test for an interaction between sex and therapy was not significant. The lower overall mortality risk of women in the placebo group and the small number of women enrolled in the trial may make treatment differences in women more difficult to detect. If women were to have a similar ICD benefit as men (HR 0.71), with 90% power and α = 0.05, a study larger than SCD-HeFT would be required (1585 women in each treatment arm, 3170 total) [26].

Meta-analyses of primary prevention trials also revealed no statistically significant decrease in all-cause mortality in women who received ICDs, in contrast to men [29,30] (Fig. 2). These findings suggest a smaller benefit of ICD therapy on survival in women compared with men who have ischemic or nonischemic cardiomyopathy.

As ICD trials enrolled a limited number of women, clinical practice data have been examined to compare survival rates among women with heart failure with or without a primary prevention ICD. Propensity score matching was performed using data from the GWTG-HF registry and the Centers for Medicare and Medicaid Services (CMS), with a resulting cohort of 430 women with heart failure who received a primary prevention ICD and 430 women who did not receive an ICD, as well as 859 men who received an ICD and 859 men who did not receive an ICD [31]. Mortality was significantly lower in women with an ICD than without (HR 0.78; 95% CI, 0.66–0.92; P = 0.003). This was also true comparing men with and without an ICD (HR 0.76; 95% CI, 0.067–0.087; P < 0.001). There was no interaction between sex and presence of an ICD with respect to survival (p = 0.79) [31]. In this analysis, a primary prevention ICD was associated with a significant survival advantage among women as well as among men, supporting guideline-directed use of primary prevention ICDs in both sexes.

Using data from 5 trials or registries, sex differences in mode of death among a large cohort of patients with heart failure who met criteria for a primary prevention ICD were evaluated using the Seattle Heart Failure Model to estimate total mortality [32]. Women had a 20% lower all-cause mortality (HR 0.80; 95% CI, 0.71–0.89; P < 0.001) and 30% fewer deaths that were sudden (HR, 0.70; CI, 0.59–0.82; P < 0.0001) compared with men. As women are less likely to die suddenly, they may have less opportunity to benefit from primary prevention ICDs, which may help explain previously reported sex-differences in ICD benefit [32].

In summary, while men had a significant mortality benefit from ICD therapy in primary prevention trials, the same benefit was not seen in women. However, caution is needed when interpreting post-hoc analyses, as trials enrolled small numbers of women and were not adequately powered to detect sex differences in outcomes. It is possible meta-analyses may still be underpowered to demonstrate a similar benefit of ICD therapy in women, based on calculations performed in the post-hoc analysis of SCD-HeFT. Alternatively, it is possible that women may derive less benefit from ICD therapy than men, consistent with epidemiological findings of a lower risk of SCD in women. Presentation of women at an older age, with more competing comorbidities, more severe heart failure, or presence of unmeasured confounders, might also impact on outcome and benefit of ICD therapy.

1.2.3. ICD therapies during follow-up

Sex differences in appropriate ICD therapy for ventricular arrhythmias have been examined in primary prevention trials. Conflicting results have been noted in analysis of individual primary prevention studies and registries, including a tendency for women to have lower rates [25,28,33–37] or similar rates [26,38] of appropriate ICD therapies during follow-up. In SCD-HeFT, a large randomized primary prevention trial, there was no significant difference in the risk of appropriate shock therapy for women versus men [27]. Meta-analyses suggested that women were less likely to receive appropriate ICD therapies for ventricular arrhythmias than men [29,39] (Fig. 2). In contrast, no differences in inappropriate shock therapies were seen in men versus women [36,39].

A sex difference in the epidemiology of sudden cardiac death and risk of subsequent sustained ventricular arrhythmias would support findings of a reduced risk of appropriate ICD therapies during follow-up, and thus potentially lower benefit of primary prevention ICDs in women as sudden cardiac death may have a smaller impact on total mortality in women than in men. However, it should again be emphasized that sex differences in baseline characteristics and comorbidities were seen in individual trials that were not powered to examine differences in outcomes based on sex, and unknown confounders may also influence results.

1.2.4. ICD complications

While some individual studies, such as SCD-HeFT, demonstrated no difference in ICD implantation complication rates in men versus women [26], the rate of significant adverse events is relatively low with contemporary ICD implantation. Data from the National Cardiovascular Data Registry (NCDR) in 28,912 initial implants (25% women) demonstrate that women who receive transvenous ICDs for primary prevention experience higher rates of device-related complications, even after adjusting for differences in baseline characteristics and device type. This includes a higher risk of pneumothorax, cardiac tamponade, and mechanical complications requiring revision [27]. Potential explanations for the higher risk of complications in women include smaller caliber vasculature and a thinner walled right ventricle, which may increase risk for pneumothorax or perforation.

In contrast to the higher risk of procedural complications seen in women with transvenous ICD systems, the totally subcutaneous ICD (S-ICD) is not associated with sex differences in procedural complications [40]. This can be explained by the type of complications seen more often in women with transvenous systems, specifically complications such as cardiac perforation or pneumothorax, which are avoided with the S-ICD as central venous access and placement of leads in the heart are not required. With the S-ICD, there were no significant differences in inappropriate shock rates or survival between men and women in the IDE study or EFFORTLESS registry.

1.2.5. Potential reasons for sex differences in primary prevention ICD benefit

Multiple reasons have been cited to explain the findings of a possible lower benefit of primary prevention ICD therapy in women compared

with men. It has been well established that the incidence of SCD is considerably lower in women than in men at any given age group, with a 10 to 20 year lag in women, which parallels the incidence of ischemic heart disease [2,41]. Women appear to have a lower predilection for ventricular arrhythmias even with coronary disease, with less ventricular arrhythmia inducibility, lower spontaneous ventricular arrhythmias and lower occurrence of ICD detected ventricular arrhythmias [23,25,33]. The reasons for sex differences in the epidemiology of SCD and differences in ventricular arrhythmia occurrence in patients with ICDs are poorly understood. Animal models show that sex and sex hormones may influence electrophysiological properties [42,43]. This includes differences in calcium and potassium sensitivity and handling, repolarization currents, and autonomic function, leading to a lower arrhythmia susceptibility in women [30].

Significant differences in sex hormones have been identified in patients who suffered SCA compared with controls [44]. Specifically, higher testosterone levels were associated with lower odds of SCA in males while higher estradiol levels were associated with higher odds of SCA in both males and females. Myocardial scar burden has been shown to predict life-threatening ventricular arrhythmias and appropriate ICD therapy in ischemic or nonischemic cardiomyopathy [45]. Women may have a smaller overall scar burden on cardiac MRI, primarily driven by prevalence of nonischemic CM [46]. Sex differences in cardiac MRI scar patterns may help to explain lower risk of life-threatening ventricular arrhythmias, as well as better CRT response, in women. Women with heart failure and those enrolled in ICD trials have also been shown to have worse baseline clinical status than men, and may have competing causes of death that may obscure their overall mortality benefit from primary prevention ICDs. Importantly, it must again be noted that all pooled analyses showed wide confidence intervals for ICD benefit in women, as women were under-represented and trials were all under-powered to detect significant sex-differences in outcomes [29,30,47]. As such, the conclusions from pooled analyses should only be taken as hypothesis generating and not to deny guideline-directed therapy.

1.2.6. Disparities in ICD usage

Large cohort studies using databases and registries have shown that sex differences exist in the utilization of ICDs in women.

A study of sex differences in the use and outcomes of primary and secondary ICDs in 236,084 Medicare beneficiaries aged 65 and older between 1999 and 2005 showed that women were less likely than men to receive ICDs. Men were 3.2 times more likely to receive a primary prevention ICD and 2.4 times more likely to receive a secondary prevention ICD than women [48]. This sex-disparity held true across all ages and races and White men were the most likely to receive an ICD [48].

An analysis of the Get With The Guidelines Heart Failure (GWTG-HF) database was performed to examine the sex and racial differences in use of ICDs in hospitalized HF patients [49]. In the cohort of 13,034 patients eligible for ICD therapy, only 27.2% of women who were eligible for an ICD received one. White women (OR 0.62; 95% CI, 0.56–0.68; P < 0.001) and even more so, Black women (OR 0.56; 95% CI, 0.44–0.71; P < 0.001), were significantly less likely to receive an ICD than White men [49]. In a subsequent analysis of 11,880 GWTG-HF patients with a history of HF and left ventricular ejection fraction ≤35%, ICD usage significantly increased across all race and sex groups with an 8% absolute increase for White women and 23.3% increase for Black women [50]. However when comparing women to men overall, there was no significant sex difference in trend over time (P = 0.510), with women remaining just as unlikely to receive an ICD during the 1st GWTG-HF analysis as in the subsequent analysis [50].

In contrast, a prospective analysis of 5213 patients in the Ontario ICD Database who received primary or secondary prevention ICDs between February 2007 and July 2010, found no sex-differences in the rates of ICD implantation in Canada (RR 0.99, 95% CI 0.97–1.02; P = 0.60) [35].

In summary, there are some inconsistent results between clinical trials and real-world data. While randomized clinical trials and a meta-analysis of trials evaluating the benefit of ICD therapy for the primary prevention of SCD show that women benefit less from ICD implantation compared with men, these findings were not demonstrated in registry publications. As observational data suffers from selection bias, it must also be noted that women have been under-represented in ICD trials and these trials were not powered to determine sex differences in ICD benefit. Caution is needed with interpretation of post-hoc analyses. Women have more procedure-related complications then men with transvenous ICDs, which does not appear to be the case for the totally subcutaneous ICD. Data suggest that women may not have the same benefit from ICD therapy as men, and women appear to be less prone to

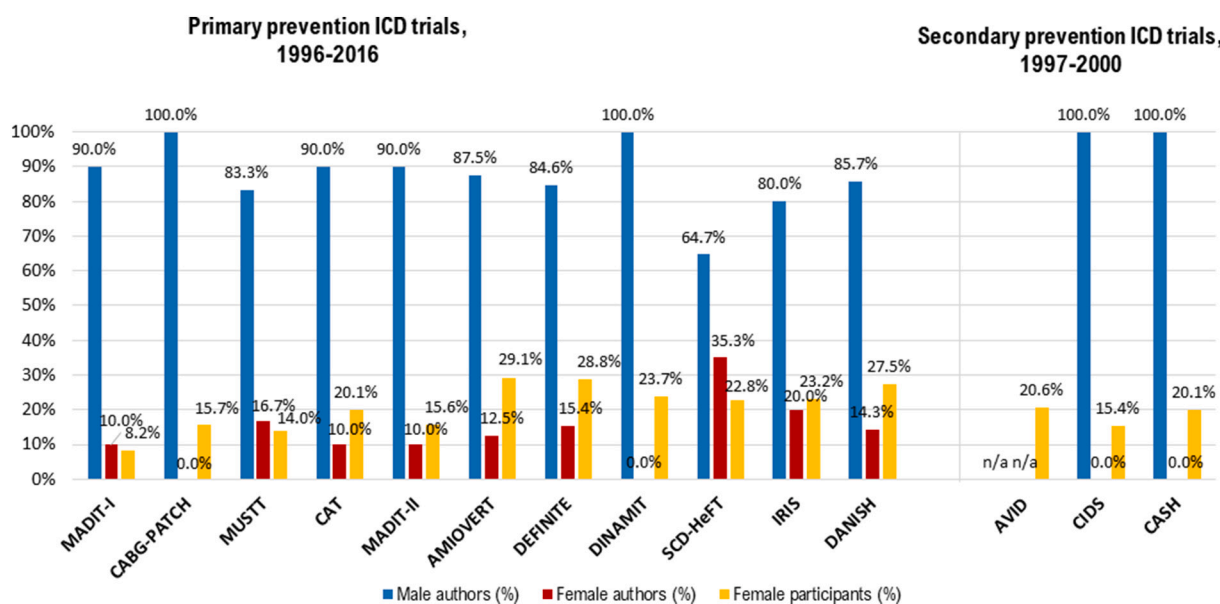**Fig. 3.** Author sex and representation of female participants in primary and secondary prevention ICD trials, 1996–2016. Proportion of male (blue) authors, female (red) authors and female participants (yellow) per trial is show in percent of total authors and total participants per trial. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
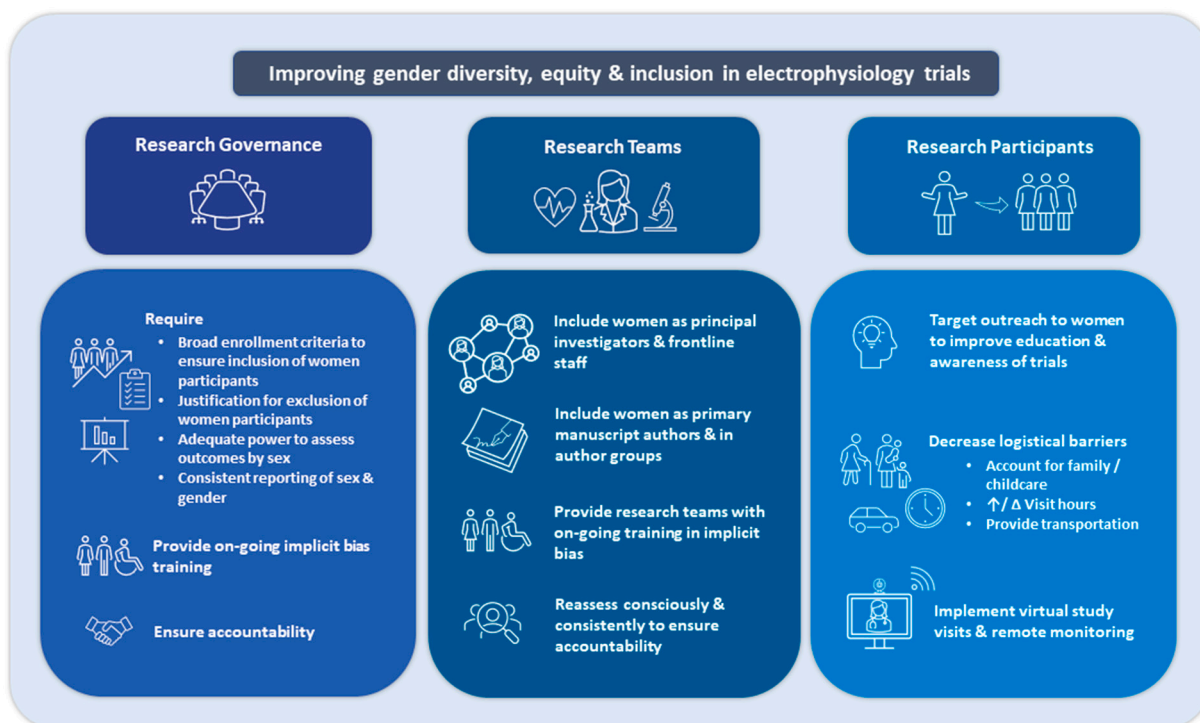
Fig. 4. Identification of gaps and potential ways to improve diversity, equity and inclusion in electrophysiology trials.

recurrent ventricular arrhythmias, consistent with epidemiological findings of a lower risk of SCD in women. When indicated, women are less likely to receive ICDs than men, and reasons for these disparities are unclear. It is possible that the perceived lower benefit of ICD therapy in women could be a driver for lower implantation rates of ICDs in women, although studies are currently lacking to identify reasons for these differences.

The on-going "AnaLysIs of Both sex and device specific factoRs on outcomes in pAtients with non-ischemic cardiomyopathy (BIO-LIBRA)" multicenter prospective study has been designed and specifically powered to examine sex-specific ICD outcomes. Having already enrolled nearly 50% women, with end-points including all-cause mortality, treated VT/VF, cardiac death and sudden cardiac death, this study will hopefully better elucidate sex-differences in ICD benefit [51].

2. Future directions

Participation of women ranged from 26.9%–76.3% in completed cardiovascular clinical trials between 2010 and 2017, with the lowest rates of participation in device and procedure trials (p < 0.0009). The proportion of women in arrhythmia trials remained low even after correcting for the prevalence of arrhythmias in women [10]. As shown, women have been underrepresented in landmark ICD trials. Reasons for under-enrollment are likely multifactorial. Women tend to have heart failure with preserved systolic ejection fraction and might not have met eligibility criteria for primary prevention ICD trials which enrolled heart failure patients with reduced ejection fraction. With the previously described lower implantation rates of ICDs in women, referral bias as a contributor to low enrollment cannot be excluded. Women have also been found to be less willing to participate in research trials in general, due to higher perceived health risks [52]. One study found that women were 60% more likely than men to believe that women are more likely than men to be taken advantage of when they participate in research trials [53]. In particular, Black women were 4 times, and Hispanic women 3.5 times more likely to feel this way than White women. Sex-differences in the rates of refusal to participate have not been

adequately captured in ICD trials to understand if this could have contributed to the under-representation of women [23,28]. Some trials have cited lack or transportation and the dependence on caregivers or family members to provide transportation as a barrier to the recruitment of older women [54].

Inclusion of women as trial leaders and authors can also affect the enrollment of women participants [55]. In a recent publication evaluating the sex representation of authors in heart failure guidelines and clinical trials, a higher number of women authors was associated with higher enrollment of women in heart failure trials [56]. The proportion of women authors per trial was a significant independent predictor of female participant enrollment (P < 0.001). Notably, there were very few women authors in the original primary and secondary ICD trials which might have affected enrollment of women (Fig. 3). Other potential barriers to women's cardiovascular trial participation include lack of research awareness, caregiver responsibilities, need for more flexible visit schedules, financial responsibilities and reproductive exclusion criteria [57,58].

Both the FDA and National Institutes of Health have published guidance documents and policies regarding the inclusion of women and persons from diverse racial and ethnic backgrounds in research [59–62]. Documents have also emerged from multiple cardiovascular societies and councils, as well as individual leaders in cardiovascular research. All provide concrete actions that can be taken to increase diversity and inclusivity in cardiovascular research in general, that should also be applied to arrhythmia and CIED trials [57,58,63–65]. Implementation of and adherence to these guidance documents must be a global and consistent effort at all levels – from studies conducted at a local level to multi-national studies, and from federally-funded to industry-funded trials. Fig. 4 outlines potential ways to improve diversity, equity and inclusion in electrophysiology trials. Patient-level recommendations can include targeting outreach and education to raise awareness of clinical trials. As women are often caregivers for dependent children, grand-children, or aging parents, expanding on-site visitation hours, and/or providing caregiver relief during needed follow-up research visits may beneficial [66]. In-person visits could be limited in favor of remote
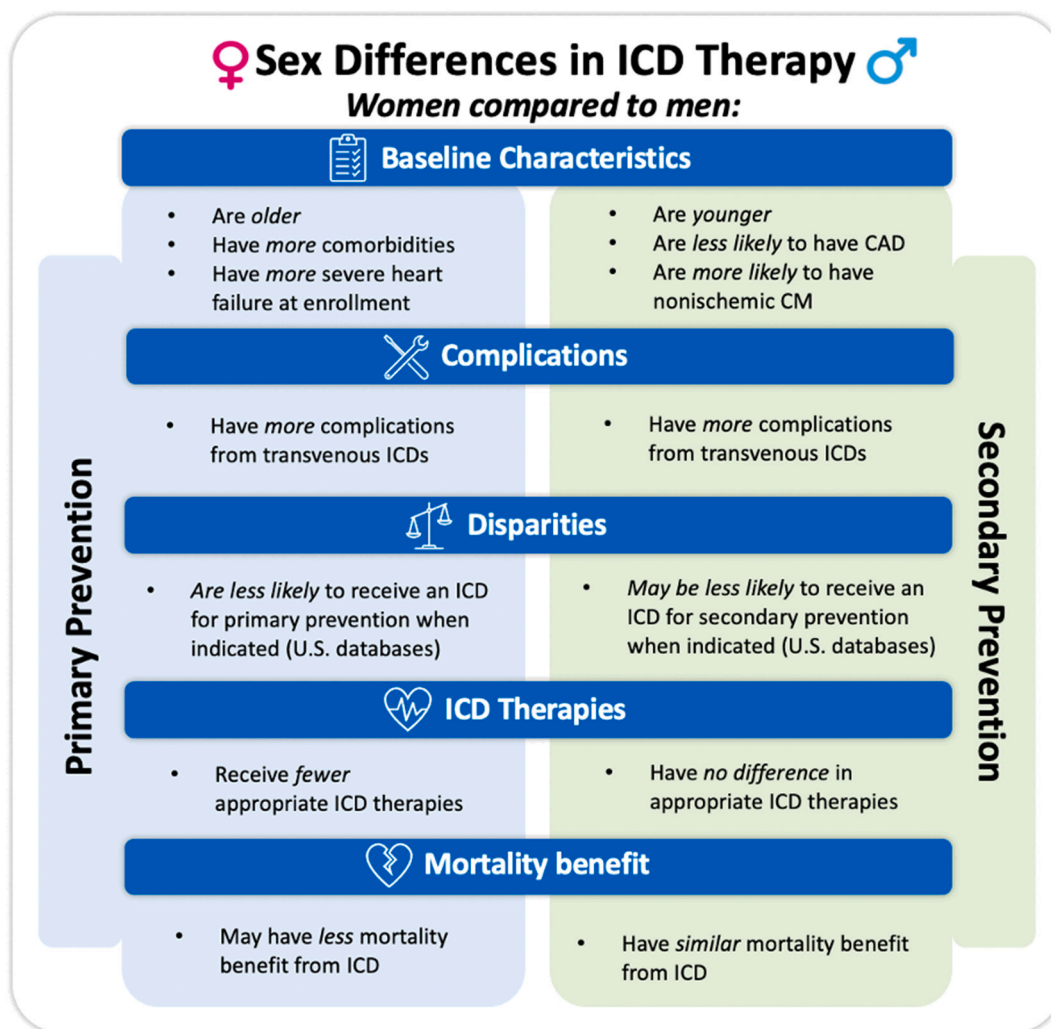
Fig. 5. Summary of sex differences in ICD therapy.

follow-ups. Electrophysiologists have been early adopters of digital modalities for arrhythmia care that would facilitate virtual visits for research. These include not only the use of smartwatch and handheld ECG devices as well as telehealth, but also remote monitoring of CIEDs [67]. Remote follow-up should be strongly considered especially for trials involving ICDs, as it is not only the standard of care for CIED patients, but a Class I recommendation for routine care in the 2015 Heart Rhythm Society Expert Consensus Statement on Remote Interrogation and Monitoring for Cardiovascular Electronic Implantable Devices [68].

Recommendations for changes at the research team, trial design and institutional levels have also been made [57,58,63,64]. Research staff should be diversified at all levels, from frontline research staff to trial leadership, steering committees and manuscript author groups. Ongoing training in cultural awareness and implicit bias should be provided. Trial designs should require processes for enrolling diverse populations, with institution of broadened enrollment criteria to be more inclusive of women participants. Sex and gender should be consistently and systematically reported and studies should aim to be adequately powered to assess outcomes by sex. A conscious and consistent effort should be made to apply these same recommendations to future arrhythmia and ICD trials.

3. Conclusion

Fig. 5 provides a summary of sex differences in ICD therapy. With respect to primary prevention of sudden cardiac death, women

experience less appropriate ICD therapy for ventricular arrhythmias and appear to have a smaller survival benefit from ICD therapy than men in randomized trials. Sex differences in ICD implantation rates have been noted for primary and secondary prevention of SCD in registries and large observational cohort studies. Women who meet criteria for ICD implantation appear to be less likely to receive ICDs than men. The reasons for these sex differences in outcomes and disparities in ICD usage have not been fully elucidated and are likely multifactorial, including potential provider bias, patient preference, and/or social determinants of health. Could women be refusing ICD implantation more often than men? Are they more likely to accept ICD implantation when presented in a different manner or with incorporation of certain shared decision-making tools that are sex-concordant? Will emphasis on ease of follow-up with remote CIED monitoring assist in the decision-making process, increasing ICD implantation rates in eligible women?

We currently have an incomplete understanding of sex differences in the epidemiology of sudden cardiac death. There are many unanswered questions regarding reasons for sex differences in ICD usage and underrepresentation of women in clinical device trials. Additional investigation is needed to better understand sex differences in presentation, therapy and outcome of ventricular arrhythmias and differences in ICD therapy between men and women to improve outcomes for all patients.

Declaration of competing interest

The authors declare the following financial interests/personal

relationships which may be considered as potential competing interests.

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