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Gender differences in cardiac interventions

Based on a presentation to the IG-WIC, an interest group of female Swiss cardiologists

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Differences in pathophysiology, clinical presentation, and outcomes of cardiovascular disease in men and women have been known for decades, but are not fully understood; women are underrepresented in most cardiovascular trials. Furthermore, women remain a minority in interventional cardiology and clinical cardiac electrophysiology.

Introduction

This short review is based on a presentation given at a workshop organised by Women in Cardiology at the Swiss Society of Cardiology / Swiss Society of Cardiac Surgery (SSC/SSCS) Joint Annual Meeting 2018. Women in Cardiology (IG-WIC) is an interest group of female Swiss cardiologists acknowledged by the SSC. The objectives of IG-WIC are development of networking possibilities for female cardiologists in Switzerland, improvement of career opportunities for women in cardiology and coordination of collaboration with international Women in Cardiology sections [1]. Having found my own interest in cardiology at medical school after a clinical course given by a female consultant cardiologist who later became my first mentor, and, as a clinical electrophysiologist, performing ablation procedures and device implantations in female and male patients in everyday practice, I realised the different aspects of the gender issue in cardiology only when I considered the task ahead.

On the one hand, differences in pathophysiology, clinical presentation, and outcomes of cardiovascular disease in men and women have been known for decades. The effectiveness and safety of medical products and procedures can differ between women and men as a result of several intrinsic and extrinsic factors. But reasons for these differences are inadequately understood. Gender has a profound influence on epidemiology, pathophysiology and clinical presentation, which may influence clinical outcome. In the context of medical research, gender is a complex construct that captures behavioural, cultural, and psychological traits linked to biologically human males and females through social context, whereas sex is identified as a biological variable, according to reproductive organs and chromosomal complement [2]. In clinical research, the gender rather than the sex of the participants is typically reported. Women are underrepresented in many cardiovascular trials, and gender bias exists in the way we actually perform clinical cardiology.

On the other hand, there is a huge disparity at the providing end, too: female physicians are largely underrepresented in clinical cardiology. This is even more pronounced in the subspecialties of interventional cardiology and clinical cardiac electrophysiology.

Female physicians in interventional cardiology and electrophysiology

In the US, the number of female applicants for cardiology fellowships has been stagnant at 22% since 2007 [3]. In contrast, other (noninvasive) subspecialties in internal medicine had a marked increase in female fellows.

Among ≈2.5 million percutaneous coronary interventions (PCIs) performed at 1431 hospitals in the US between 2009 and 2013, only 4.5% of operators were women and they performed 3% of procedures. Individual female operators performed a lower median number of PCIs per year than male operators [4].

A recent survey on structure and training in electrophysiology in Germany showed an increase of female fellows between 2010 and 2015 [5]. The percentage of women as primary operators for ablation also increased. However, only 18% of electrophysiological procedures were performed by female operators. In contrast to the 49% female physicians in training for electrophysiology, only 2% of department heads and 21% of consultants were women [5].

The website of the Swiss Working Group for Pacing and Electrophysiology lists nearly 300 ordinary members, of whom less than 10% are female [6].

A variety of reasons have been identified that help to explain the small numbers of women who seek careers in interventional cardiology or electrophysiology. Role models for both personal and professional life seem to play an important role. Duration of training and radiation exposure during child-bearing age in interventional cardiology and electrophysiology may contribute to the fact that women are more likely than men to interrupt their train-

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ing or practice for longer periods [7]. However, gender discrimination, discrimination based on parenting responsibilities, and disparities in compensation, promotion and career advancement have also been identified as contributing factors that affect the careers of women in cardiology and may decrease their interest in the field of interventional cardiology and electrophysiology [7].

Gender differences in cardiovascular trials and clinical practice

Cardiovascular disease is the leading cause of death in women in all European countries except Denmark [8]. In many countries mortality from cardiovascular disease for women is even higher than for men. Despite this fact, women have been largely underrepresented in randomised trials of cardiovascular disease prevention [9]. A recent analysis of 36 trials used to support drug approval showed adequate representation of women in some forms of cardiovascular disease (arterial hypertension, atrial fibrillation, pulmonary hypertension) relative to their overall representation in disease populations. However, representation was below the prevalence estimate for trials in heart failure, coronary artery disease and acute coronary syndromes (ACS) (fig 1) [10]. Especially in the key trials of cardiac interventions and device therapy have women been underrepresented.

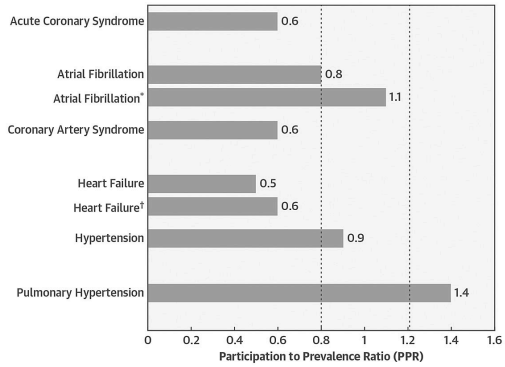
Catheter ablation for atrial fibrillation

Female patients with atrial fibrillation are more symptomatic than their male counterparts and have lower health status scores [11]. They report more palpitations, and a higher degree of fear and anxiety. A higher proportion of patients in European Heart Rhythm Association (EHRA) class III or IV are women. Although the aforementioned analysis showed adequate enrolment of female patients with atrial fibrillation into drug trials, women are less likely to receive rhythm control than men [11]. They are less likely to undergo electrical cardioversion and catheter ablation for atrial fibrillation, but more likely to undergo atrioventricular node ablation and pacemaker implantation after antiarrhythmic drug therapy has failed [12, 13]. In general, women are referred for atrial fibrillation ablation later, with more advanced symptomatic disease states, and show more advanced left atrial remodelling than men [14, 15]. In two recent landmark trials on catheter ablation of atrial fibrillation, 39 and 37% of enrolled patients were female [16, 17].

There seem to be significant sex disparities in referral patterns. In one study, women were referred three times less often than men for atrial fibrillation ablation [18]. This bias persisted even when a cardiologist was caring for the patient before referral. After patients were referred to an electrophysiologist, there appeared to be no sex-based differences in subsequent treatment decisions.

But gender also seems to have an impact on outcome of atrial fibrillation ablation. In the FIRE AND ICE trial, female sex was associated with a ≈40% higher risk of primary efficacy failure and cardiovascular rehospitalisation after atrial fibrillation ablation [19]. Women have a higher incidence of femoral vascular complications and pericardial tamponade [20]. Some of the sex differences may be explained by different baseline characteristics. However, data suggest that sex-dependent physiological and pathophysiological mechanisms influence clinical outcome after atrial fibrillation ablation and may predispose women to higher rates of atrial fibrillation recurrence after ablation.

Figure 1: Participation of Women in cardiovascular disease clinical trials: prevalence-corrected estimate (modified after [10], reprinted with permission). Ratio of women among trial participants to the percentage of women in the disease population (PPR) for the targeted disease categories for cardiovascular drugs approved between 2005 and 2015. A PPR of 1 indicates that the gender composition of the trial was equal to that of the disease population. A PPR between 0.8 and 1.2 (dashed lines) indicates that the proportion of women in the trial was similar to the proportion of women in the disease population. * PPR was calculated with two references: one based on age-adjusted prevalence from published population-based studies and the other based on a cohort of atrial fibrillation patients within Kaiser Permanente of Northern California. † PPR was calculated with two references: one based on the prevalence of all heart failure patients in the US and the other based on the Framingham cohort with heart failure with reduced ejection fraction.



Implantable cardioverter defibrillator and cardiac resynchronisation therapy

There is no obvious difference between women and men in the rates of implantation of permanent pacemakers. However, females are underrepresented in the device trials for prevention of sudden cardiac death (SCD) and heart failure.

Implantable cardioverter defibrillators (ICDs) are recommended for secondary and primary prevention of SCD [21].

Out-of-hospital cardiac arrest (OHCA) has a poor prognosis. Reports on sex differences in outcome after OHCA are controversial. However, some studies found higher mortality rates for women than for men [22]. In contrast, in the three landmark trials of ICD therapy vs medical treatment for the prevention of SCD in survivors of OHCA, only about 20% of the patients were female [23]. A more recent analysis describing the implantation of ICDs after OHCA associated with acute myocardial infarction in Denmark between 2001 and 2012 found that only about 10% of ICD recipients were women. The authors detected a trend towards higher odds of ICD implantation in men [24].

A study on a nationally representative sample of Medicare beneficiaries found that men were 3.2 times more likely than women to receive an ICD for primary prevention and 2.4 times more likely to receive an ICD for secondary prevention of SCD [25]. For those treated with ICD therapy, the mortality benefit was significant for both men (hazard ratio 0.62) and women (hazard ratio 0.68) [25]. However,

a detailed analysis of sex differences in outcomes of ICD therapy has not been reported for the secondary prevention randomised clinical trials.

There are also gender differences in ICD therapy for primary prevention of SCD. In a recently analysed primary prevention ICD population from 11 European countries with ICDs implanted between 2002 and 2014, only 19% of ICD recipients were female [26]. No gender-related temporal trends were observed during the observation period. Importantly, women had a lower mortality than men (hazard ratio 0.65), and experienced fewer appropriate shocks. However, the rate of inappropriate shocks was identical and the overall complication rate was higher than in men [26].

A large prospective provincial ICD registry in Ontario including >6000 patients referred to an electrophysiologist for consideration of ICD therapy between 2007 and 2010 reported that after referral ICD implantation rates were similar for men and women [27].

Three meta-analyses of primary prevention trials came to the conclusion that women had a smaller benefit than men or no benefit from prophylactic ICD implantation [28–30]. However, these were not powered to detect a significant survival benefit of ICD therapy in women. In contrast, mechanical adverse events (pneumothorax, pericardial tamponade, mechanical complications requiring revision) affect women disproportionately [31].

In conclusion, the use of ICDs in women is disproportionately low in clinical practice. Older age at manifestation of coronary artery disease and sudden cardiac death in women with greater comorbidity and more advanced heart failure at the time of ICD implantation, the lower prevalence of systolic heart failure, the lower risk of SCD and incidence of spontaneous sustained ventricular tachyarrhythmias, and the underrepresentation of female participants in the key trials may explain this disparity.

Cardiac resynchronisation therapy (CRT) has been shown to improve functional capacity, quality of life and survival, and to reduce hospitalisations for heart failure [32]. Although the number of women and men with heart failure is nearly the same, women constituted less than one third of the study population in CRT trials. In the COMPANION and CARE-HF trials, which evaluated the benefits of CRT in patients with moderate to severe heart failure, the hazard ratios for the primary endpoints were very similar [33, 34]. Some studies, however, have shown greater benefit for women. A meta-analysis of three CRT trials in patients with mild heart failure showed a greater benefit for women [35]. The main difference occurred in patients with left bundle branch block (LBBB) and a QRS of 130 to 149 milliseconds: women had a significant reduction in heart failure or death and in overall mortality, whereas there was no significant benefit in men. This is an important finding, since guideline recommendations use the same LBBB criteria for patient selection for CRT for women and men. New sex-specific ECG criteria for LBBB have been proposed [36]. Several confounding factors may explain the better response of female patients: there was a higher proportion of men with ischaemic cardiomyopathy and atrial fibrillation, as well as a smaller percentage of "true" LBBB cases, all factors known to decrease the response to CRT.

Although women tend to receive equal or even more benefit form CRT than men, as with ICD therapy they seem to be underrepresented. The higher prevalence of systolic heart failure in men and older age at the time of manifestation of heart disease with more comorbidities in women may, in part, explain the lower usage of CRT in women. The roles of patient preference and potential referral bias also need to be examined.

Interventional cardiology in acute coronary syndromes

In older reports, female gender has been linked to adverse outcomes following ACS or after PCI. The 2016 AHA Heart and Stroke Statistics update reported a higher 1-year mortality for women compared with men [37]. Women <55 years of age had longer in-hospital stays and greater in-hospital mortality than young men. In-hospital mortality declined significantly for women from 2001 to 2010 [38]. However, especially young women still have worse long-term outcomes after ACS compared with men [39]. There is also evidence that female patients have higher complication rates with PCI, especially bleeding complications [40]. There are controversies regarding the reasons for these differences in outcome. Women with ACS are mostly older, have a different cardiovascular risk profile and often present with "atypical" symptoms [41]. If outcome and complications are adjusted for age, health status and psychosocial factors, many of these differences are attenuated. Bias has long been described for women presenting with ACS, resulting in delayed diagnosis, undertreatment and worse outcomes. Women have lower rates of referral for angiography and PCI, and receive guideline-directed treatments less often [42].

More recent reports on PCI demonstrated similar or better outcomes in female patients with ACS. A recent analyses of 2168 patients prospectively enrolled in the Swiss ACS Cohort (2009–2012) investigated gender-related outcomes in ACS patients [43]. In patients >75 years, 1-year rates of major adverse cardiovascular and cerebrovascular events (MACCE) were 15 and 23% in women and men, respectively. Women >75 years had a lower cardiovascular mortality (6 vs 12%, adjusted odds ratio 0.31, 95% confidence interval 0.12–0.81; $p = 0.02$). In patients aged ≤75 years, 1-year MACCE rates did not differ between women and men. There was also no significant difference in rates of major bleeding. These results suggest that with guideline-directed treatment and current interventional strategies the gender gap in ACS management can be attenuated.

Conclusions

- Although the number of female fellows and cardiologists has increased in recent years, women remain a minority in interventional cardiology and clinical cardiac electrophysiology. Among the many reasons for this are lack of mentorship and the challenge of balancing career and family. But discrimination based on gender and parenting is still prevalent [7].
- There is an underrepresentation of women in most cardiovascular trials. This is especially true for trials in interventional cardiology, or ablation and device trials. Hypothesised obstacles to participation of women include clinical presentation, difficulty accessing study sites, familial responsibilities, cultural barriers, socioe-

conomic barriers and concerns about risk. The prevalence of cardiovascular disease is higher in older women, and previous studies have suggested that focus on recruitment of younger patients decreases overall enrolment of women. Inclusion criteria that would tend to select men and exclusion criteria more common in women have also been proposed as contributors. Nevertheless, the erroneous perception, from both patients and healthcare providers, that women are protected against cardiovascular disease is still widespread, which leads to underestimation of the disease and, possibly, may be one of the reasons for the underrepresentation of women in clinical trials [44].

– Several studies show that lower representation of women reflects the lower number of women referred to a specialist for invasive diagnostic or therapeutic procedures.

– To better understand the differences in pathophysiology, clinical presentation, and outcome of cardiovascular disease in men and women, gender-sensitive study strategies are required. It is important that future research has adequate participation of women to enable studies to be appropriately powered to allow examination of possible gender differences in treatment response and to address the applicability of the results to the female population [45].

– Another key to reduce the knowledge gap in cardiovascular disease in women is to encourage more women to enter the field of cardiology and advocate for research in women by becoming an investigator or encouraging female patients to participate in trials [3].

– In this light, initiatives like the one by IG-WCI may help to bring more women into the field of cardiology and assist in overcoming the barriers to the appropriate cardiovascular care in women. Hopefully, our whole cardiology community will embrace and support the activities of the IG-WIC for the benefit of cardiologists and patients.

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