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Closing the sex gap in cardiovascular mortality by achieving both horizontal and vertical equity

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ABSTRACT

Addressing sex differences and disparities in coronary heart disease (CHD) involves achieving both horizontal and vertical equity in healthcare. Horizontal equity in the context of CHD means that both men and women with comparable health statuses should have equal access to diagnosis, treatment, and management of CHD. To achieve this, it is crucial to promote awareness among the general public about the signs and symptoms of CHD in both sexes, so that both women and men may seek timely medical attention. Women often face inequity in the treatment of cardiovascular disease. Current guidelines do not differ based on sex, but their applications based on gender do differ. Vertical equity means tailoring healthcare to allow equitable care for all. Steps towards achieving this include developing treatment protocols and guidelines that consider the unique aspects of CHD in women. It also requires implementing guidelines equally, when there is not sex difference rather than inequities in application of guideline directed care.

1. Sex tailored healthcare strategies

Raffaele Bugiardini

1.1. Introduction

Historically, medical research and practice have often used men as the standard model for understanding and treating coronary heart disease (CHD), even if CHD affects both men and women. This practice can be traced back to ancient times and it has been a long-standing bias in the field of medicine. This attitude is still ongoing as very few trials have published results stratified by sex. To address this issue, the National Institutes of Health (NIH) has mandated the inclusion of women and underrepresented minorities in clinical research to ensure more diverse and representative study populations. The Sex and Gender Equity in Research (SAGER) guidelines gave specific recommendations on how to include the influence of sex in clinical research [1]. Additionally, other organizations such as the American Heart Association, the Canadian Institutes of Health Research, and the European Commission have called for more awareness and education about sex and gender differences in medicine and healthcare [2,3]. Despite these efforts, we still have limited understanding of the role of sex in CHD as studies often yield conflicting results. In this article, we discuss the current landscape of sex-specific research. It seems reasonable that if we want to learn more about atherosclerotic disease in women, we should identify what it is about women that make them so much different from men. Sex-specific research may contribute to the development and refinement of clinical guidelines.

1.2. Sex differences in cardiovascular risk factors and risk prediction models

Tailoring treatments and prevention strategies to individual needs can improve their effectiveness. What works best for one sex may not be the most effective approach for the other. There are sex differences in the prevalence and effect of traditional factors. There are nontraditional risk factors that are specific to women. Compared with men, obstructive coronary artery disease (CAD) risk in women is increased to a greater extent by current smoking and diabetes mellitus [4,5]. Women with obstructive CAD more often present with ST-segment elevation myocardial infarction (STEMI) and women with STEMI face a roughly 75% greater excess risk of 30-day mortality compared with men,

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especially at younger ages [6]. Moreover, pregnancy-related disorders such as gestational diabetes, preeclampsia, and gestational hypertension can be associated with an increased risk of cardiovascular disease [7]. As well, polycystic ovary syndrome (PCOS), premature menopause, multiparity and lactation can lead to insulin resistance, dyslipidemia, and obesity, all of which are risk factors for cardiovascular disease [8,9]. These findings emphasize the importance of sex-specific guidelines in cardiovascular primary prevention care. These findings also underscore a critical issue in cardiovascular care: the inadequacy of many commonly used cardiovascular risk prediction models in accounting for sex-specific features [10]. Healthcare providers might offer more tailored and effective preventive strategies by incorporating sex-specific features into the risk prediction models.

1.3. Do female patients with coronary heart disease die more than male patients?

There are sex differences in the clinical manifestations and outcomes of CHD. In 2022, the CHD age-adjusted death rates per 100,000 person-year in US were 236.8 for men and 115.4 for women [11]. While, on average, women appear to be at lower risk for CHD mortality due to the lower prevalence of disease, concurrent data highlight important sex differences in one manifestation of CHD: the outcomes following a myocardial infarction (MI). In the National Hospital Discharge Survey (NHDS) 1979–2005, women had a higher in-hospital case-fatality rate than men (14.9% *versus* 10.2%) [12]. In-hospital case fatality rates from 2015 to 2018 were higher in women in almost all districts of England at all ages up to 74 years [13]. The proportion of mortality from ischemic heart disease (IHD) in women is higher than in men in almost all Eastern European countries with a mean ratio of approximately 1.2 [14]. Women who survive the acute stage of MI also had a greater chance of death at 1-year compared with men [15]. There is, therefore, evidence suggesting that women may have higher mortality rates following MI compared with men. This disparity may be influenced by many factors including age, comorbidities, underuse of evidence-based therapies and delays in revascularization treatment.

1.4. Women live longer than men. A key difference for mortality can be age, not sex

On average, women are older than men at the time of MI as they tend to develop cardiovascular disease later in life compared with men. Advanced age is a recognized risk factor for adverse outcomes after MI, which may place women at greater risk of short-term mortality [16]. However, studies that conduct stratified analyses by age provide a more nuanced understanding of the relationship between age and mortality patterns. The finding that younger women may have higher mortality rates after acute coronary syndrome (ACS) or MI compared with younger men emphasizes the importance of considering sex-specific factors rather than age in the determinant of outcomes after acute coronary events [6,14,17].

1.5. Are women with CHD receiving medications and access to invasive treatments less frequently than men?

Most studies consistently reported that women are less likely to receive CHD care [18,19]. The medical community may argue that women may be less likely to receive evidence-based therapies because they are presenting with less significant coronary disease. As such, gender biases and stereotypes can influence healthcare providers' decision-making. Yet, research in ACS [20] has demonstrated that both women with nonobstructive CAD and women with advanced disease were less likely to receive evidence-based medications at discharge as compared with men of similar disease severity. Nonetheless, the outcome of death at 6-month was similar among men and women after adjustment for age and number of diseased vessels (odds ratio [OR], 0.97; 95% CI, 0.81–1.15). This suggests that other factors or interventions may have played a role in mitigating the potential adverse effects of lower medication usage in women. This might also suggest that certain medications or treatment approaches may be more beneficial or effective for one sex over the other, or that sex-specific factors play a role in treatment responses. Although this observation raises concerns about sex disparities in cardiovascular care, it also introduces a major point of debate: the distinction between appropriately equal treatment of equals (horizontal equity), as compared with the appropriately differentiated response to individuals with unequal need (vertical equity). Vertical equity allows for targeted interventions to address sex differences; for example, understanding that women are more likely to have heart failure with preserved systolic function may require adapting diagnostic and treatment strategies accordingly [21].

1.6. Men and women respond differently to drugs

Women take more medications than men [22]. They also respond differently to medications because they differ from men in physiology, pharmacokinetics, and pharmacodynamics [23,24]. Women are more likely than men to have medication-related injuries [25]. Aspirin resistance was found to be 4 times more prevalent in women than men [26]. Similarly, women were more often found to be hyporesponsive to clopidogrel [27,28]. Glucagon-like peptide-1 receptor-agonists (GLP-1RAs) were associated with greater effectiveness in women than men in diabetes [29]. In a subgroup analysis of the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial, men, but not women had a lower cardiovascular event rate with the angiotensin receptor blockers, as compared with placebo [30]. As well, use of angiotensin converting enzyme (ACE) inhibitors in the Second Australian National Blood Pressure (ANBP-2) trial and Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was associated with reduction in major cardiovascular events among men, but not in women [31]. Digoxin therapy was associated with an increased risk of death from any cause among women, but not men, with heart failure and depressed left ventricular systolic function [18]. Prior beta-blocker therapy for hypertension may be an acute precipitant of acute heart failure among women, but not men with incident CHD, and acute heart failure is strongly related to 30-day mortality [32]. This finding is particularly important for practice, given that after three decades of beta-blocker therapy in hypertension, no study has shown that its use has reduced morbidity or mortality even when compared with the use of placebo [33,34]. Consideration of alternative treatments in women with hypertension would be, therefore, required as the medications in question, betablockers, have viable substitutes. In summary, all of these studies underscore the importance of investigations on sex-based variations in treatment efficacy. Nevertheless, few randomized, controlled trials are designed to test for sex-specific effects. Additionally, some of these trials may not be considered ethical, since they would be designed to confirm risk and not benefit, such as for the case of digoxin and betablockers. We believe, therefore, that the above reported data from observational studies may provide sufficient grounds for a reexamination of current guidelines and implementation of sex specific guidelines, especially when ethical concerns limit the feasibility of randomized controlled trials.

1.7. Doubts on statin primary prevention therapy in women

Despite widespread consensus about statin use for the secondary prevention of cardiovascular disease in both sexes, there has been substantial debate with regard to the use of statins for primary prevention among women. A large-scale meta-analysis of both primary and secondary statin prevention trials by Cholesterol Treatment Trialists' (CTT) Collaboration found no significant difference in major vascular events between statin therapy and control interventions for women when primary prevention trials were analyzed separately (OR, 0.85; 99% CI, 0.72–1.00) [35]. By contrast, another large-scale meta-analysis by Kostis W.J et al. [36] concluded that there was a statistically significant reduction in mortality rates with statin treatment in women (OR, 0.87; 95% CI, 0.78–0.97). These conflicting findings highlight the complexity of interpreting data from meta-analyses. There are only few primary prevention studies included in such metanalyses. Additionally, the lack of sufficient data to critically evaluate breakdowns by age [37] further complicates the interpretation of results, because women generally have a lower cardiovascular risk and lower annual mortality compared with men. As a result, the absolute benefit of statins may be less for women than for men. This situation presents a challenge in ensuring that treatment recommendations are both effective and equitable across sexes. Prospective studies should be complemented by retrospective studies designed with sufficient power to detect sex- and age-specific differences in outcomes.

1.8. Statins, sex differences, and severe disease manifestations

Mortality data from CHD has to be interpreted cautiously in statin primary prevention studies, as mortality from CHD can be related to multiple factors including age, type of MI, Killip class, time delay to revascularization treatment, renal failure, number of diseased coronary arteries, and left ventricular ejection fraction. To circumvent this issue, recent retrospective studies shifted from the traditional endpoint of reducing overall mortality to a more specific objective: reducing the number of individuals presenting with conditions that place them at high risk of mortality. As such, preventing the incidence of high-risk clinical presentations, such as severe forms of CHD like STEMI or acute heart failure on admission for ACS allows for a more detailed understanding of the potential statin benefits. On this background, a recent study demonstrated that primary prevention with statins can reduce the incidence of ischemic acute heart failure and the rate of 30-day all-cause mortality in patients presenting with acute heart failure. The effect of sex did not vary across treatment groups [38]. A further study carried out a statin prevention sex specific analysis in the elderly [39] and showed a substantially higher absolute risk reduction in the prevalence of STEMI in men compared with women. These studies may seem contradictory at first glance. However, these findings may coexist because acute heart failure and STEMI are distinct clinical manifestations of CHD and represent different pathological processes. Men have a higher baseline risk of STEMI. Statins might, therefore, lead to a more noticeable reduction in STEMI incidence among men without necessarily indicating a contradiction in their overall effectiveness in preventing ischemic acute heart failure across sexes. On the other hand, studies focusing on the overall ischemic population may, potentially, dilute sex-specific differences observed in studies specifically targeting the elderly. In summary, the real issue is not significance in mortality, but whether the beneficial effects of statins in women at high risk of mortality is materially different from similar effects in men at high risk of mortality, as well.

We may, therefore, conclude that primary prevention with statins work just as well in women as in men in the adult population. There are few pieces of evidence to sustain statin treatment for people above 75 years. As a result, current European and American guidelines do not make clear recommendations for statin use in older adults who do not have a history of pre-existing CHD. Perhaps the net benefit of using statins to prevent CHD may be less for elderly women, because post-menopausal hormonal changes revert some of the benefits obtained with statins [40]. Clearly, additional research is needed to confirm (or not) whether some of the observed sex differences reflect true biological effect.

1.9. Do women present to hospital later than men after they started having chest pain suggesting myocardial infarction?

Women tend to present to the hospital later than men after MI symptom onset [41–43]. This delay in presentation can have significant implications for timely revascularization with percutaneous coronary intervention (PCI), which is a critical component of improving outcomes in STEMI. Several factors may contribute to this delay, reflecting an intricate interplay of various elements including sex differences in clinical presentation as well as patient and professional bias. Women are more likely to have nonspecific chest pain symptoms than men [44–46]. Atypical symptoms may accompany or mask the primary symptoms [47]. It follows that both patients and healthcare providers may face difficulties in associating these symptoms with a heart-related issue. Women might downplay symptoms, attributing them to other causes, while healthcare providers might not immediately suspect the presence of MI [48]. Addressing these challenges involves public health campaigns and healthcare provider training.

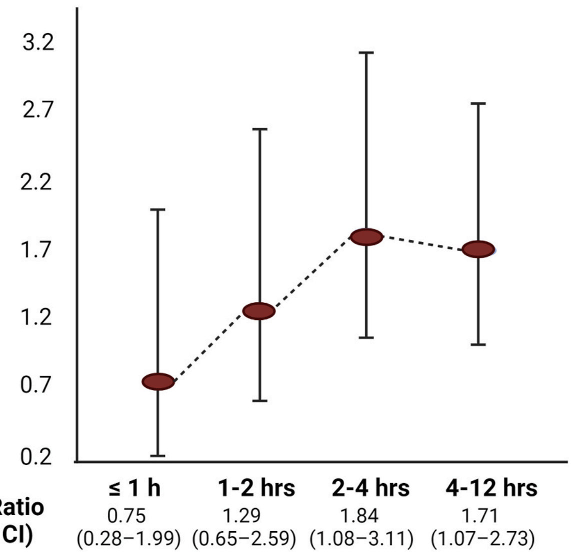

Fig. 1. Impact of various treatment delays on the odds of 30-day mortality in women compared with men receiving primary PCI for STEMI.
Estimates of mortality in women compared with men in various time-delay cohorts; time from symptoms onset to hospital presentation: ≤1 hour, >1 to ≤2 hours, >2 to ≤4 hours, >4 to ≤12 hours. CI: confidence interval; STEMI: ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention.

1.10. Sex differences in response to delay to hospital presentation

Sex-specific differences in time to hospital presentation in STEMI provides an example of both horizontal and vertical inequity in healthcare. The horizontal treatment principle would imply that both men and women, presenting with similar clinical indications, should receive comparable and timely interventions. In clinical practice, however, there are sex-specific differences in time to hospital presentation being female sex an independent predictor of pre-hospital delay, which translates to horizontal inequity and poor outcomes for women [41,49,50]. Vertical equity recognizes that individuals with different needs may require different levels of interventions. Recent data of the International Survey of Acute Coronary Syndromes (ISACS) investigators [41] align with the concept of vertical equity and acknowledge that the optimal approach may vary for men and women. This study delves deeper into the implications of delay in presentation among women and men. In the group of patients with the shortest delay in presentation (<1 hour), there was no apparent sex difference in mortality rates. By contrast, as the delay in presentation increased, there was a notable sex difference in mortality rates, with women showing higher rates compared with men. This difference became more pronounced as the delay extended, ranging from 1.29 times higher within 2 hours to 1.84 times higher within 4 hours (Fig. 1). This observation underscores the need of a sex-centered approach for advancing health equity in cardiovascular care. In summary, the disadvantage of prolonged time of symptom-onset to hospital presentation is two-fold for women: a greater percentage of women had delayed presentation, and women with delayed presentations had higher mortality than men with similar delayed presentation. The higher mortality rate in women than men even with comparable delays in receiving primary PCI, suggests the need for more research into why these differences exist.

1.11. Biologic factors specific to women and sex-specific considerations on guidelines

The implications of sex-based differences in vulnerability to delay to hospital presentation in STEMI are numerous. Biological differences between men and women may play a role. Women may be more prone to microvascular dysfunction, which may result in increased sensitivity to ischemia, especially if coronary perfusion is compromised for extended periods. Women may have a higher burden of comorbid conditions, such as diabetes, and these comorbidities can exacerbate the impact of prolonged ischemia. Addressing this issue involves other advances in furthering our understanding of the mechanisms of vulnerability in women with STEMI, but also involves reconsideration of guidelines. Although there is great appeal in identifying a sole door-to-needle or door-to-balloon time as the optimal goal of STEMI reperfusion care, applying identical time to treatment approaches to men and women without considering the potential sex-specific differences in the impact of delays could result in suboptimal outcomes for women.

1.12. Do more women than men get fatal complications after a clinical manifestation of CHD?

Most studies on the association of sex and MI prognosis focused on mortality. The data on complications are scarce and often conflicting [51–53]. The development of heart failure post-ACS is a serious concern, as it is linked to a substantially higher risk of mortality. Recent studies conducted by the ISACS investigators [54,55] provide important insights into sex differences in the risk of acute heart failure following different types of ACS. Women are at a higher relative risk of developing acute heart failure on hospital admission for STEMI than men (33.7% *versus* 29.0%). By contrast, the similarity in the risk for acute heart failure between women (25.6%) and men (25.1%) in non-ST-segment elevation (NSTE)-ACS patients indicates that the sex-related risk difference is less pronounced in this type of ACS. Further studies [56,57] appear to build upon and confirm the findings observed by the ISACS investigators. These studies raise questions about the underlying causes of these sex differences and, especially, how they can be addressed in clinical practice.

1.13. Sex specific heart failure treatment post-myocardial infarction

The Prospective ARNI *versus* ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction (PARADISE-MI) trial was designed to determine whether the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan provides superior benefits compared to an ACE inhibitor in reducing heart failure events following MI in patients with a reduced ejection fraction ($\leq$40%) followed for a mean duration of about 19 months [58]. A post hoc analysis specifically examined the impact of sex on the treatment effects of sacubitril/valsartan [57]. Its results indicating no significant modification of treatment effects by sex might lead to further research exploring the best individualized post-MI treatments for heart failure for both women and men. Additionally, such findings contribute to reinforce the growing clamor for enrollment of more women in clinical research trials, and to power such studies to allow for appropriate sex-specific analysis for questions such as response to drug or interventional therapies, rather than to rely only on post-hoc subgroup analyses.

1.14. Other mechanisms for sex differences in outcomes

Other mechanisms for differences in outcomes have been explored. Studies have shown that there is excess bleeding risk in women; however, there are no data showing that reducing bleeding events improves outcomes [59]. Women are also at higher risk of complications after coronary revascularization. In an angiographic analysis [60], suboptimal Thrombolysis In Myocardial Infarction (TIMI) blood flow 0 to 2, despite minimum residual percent diameter stenosis<25% in women with STEMI, was higher than in men, even after adjustment for baseline differences including symptom-to-hospital presentation time. These findings highlight the ongoing need to accurately account for biologic factors specific to women with acute ischemia. The ultimate goal is to ensure that both men and women receive equitable, effective care for heart disease, tailored to their specific needs and risks.

1.15. Policy implications

Healthcare guidelines and policies play a crucial role in addressing equity issues. Developing guidelines that consider sex-specific differences in cardiovascular health is one way to balance horizontal and vertical equity. And while we have seen progress in the past two decades in improving horizontal equity, much work remains in achieving vertical equity. The challenge of timely diagnosis and treatment of STEMI remains, and while the gender gap has improved, it persists, and is costly in terms of survival for women. Raising awareness and educating healthcare providers that biological features may predispose women to a higher burden of cardiovascular mortality and complications, even when they experience similar delays in hospital admission as men can contribute to a more equitable healthcare system. Finally, only ensuring equal representation in clinical trials will lead to findings that may be fully applicable to women.

2. Differences in cardiovascular outcomes are due to the unequal application of guidelines in women

Martha Gulati

Cardiovascular disease remains the leading killer of women globally [61], and when women experience a cardiovascular event, often outcomes are worse compared with men [62]. Certainly it is well-established that women remain underrecognized, underdiagnosed, undertreated, and understudied when experiencing a cardiovascular event [63]. Ultimately, all these issues contribute to the increased morbidity and mortality of women.

Certainly, there are established sex differences in cardiovascular disease, as described above by Dr. Bugiardini. Additionally, there are sex-differences in the pharmacokinetics and pharmacodynamics of medications, related to potential sex differences in the absorption, distribution, metabolism, and elimination of cardiovascular drugs [64]. Surprisingly, randomized clinical trials in cardiology of drug therapies, devices, and other interventions continue to under enroll female participants, limiting our complete understanding of sex-differences in our therapies and interventions [65]. As a result, cardiovascular guidelines to date do not have any sex-specific difference in recommendations.

Nonetheless, cardiovascular guidelines are unequally applied in women, when compared with men. Numerous examples exist, particularly in IHD and ACS, where there are a number of national registries where differences have been demonstrated globally [62]. These inequities in cardiovascular care, likely due to implicit bias, lack of recognition of the risk to women, and misconceptions, contribute significantly to the poorer outcomes seen in women compared with men with cardiovascular disease globally. Disparities in the application of guidelines based on sex will be reviewed below based on cardiovascular conditions.

2.1. Cardiovascular risk factor management

2.1.1. Hypertension

Hypertension is the most prevalent cardiovascular risk factor and is also the most preventable cause of cardiovascular disease, but remains poorly treated globally, in both women and men. Drugs used for the treatment of hypertension have been demonstrated to be equally beneficial in men and women in terms of cardiovascular outcomes, despite the fact that early clinical trials of hypertension enrolled few women [66,67]. Population-based studies have demonstrated that women have higher rates of treatment and blood pressure control [68], but this contrasts with primary care data, which has shown better blood pressure control in men [67,69]. Certainly women are more likely to seek out healthcare than men, and as a result women compose more than half (52–58%) of the treated hypertensive population in most primary care data [69–71]. Additionally, influencing the primary care data, is the fact what women live longer and for elderly women often the presumed fall risk often will limit blood pressure control in the elderly [72]. In real life clinical practice, the blood pressure of women is treated less well, compared with men, despite the fact that the blood pressure targets are the same for both sexes [73–76].

2.1.2. Hyperlipidemia

Hyperlipidemia is equally common in women and men [61], and is an essential component of primary prevention of cardiovascular disease [77]. Similar to hypertension, our current guideline for initiation of statin therapy does not differ in women compared with men [78], and yet clinical practice data and registries continue to demonstrate that women eligible for statin therapy for primary or secondary cardiovascular disease prevention are less likely to receive any statin therapy compared with men, and are also less likely to receive high intensity statin therapy when indicated [79–83]. Certainly, women are more likely to have side effects to statins, and poorer adherence to such therapies as a result, contributing to these findings [84,85]. Nonetheless, there remains an underutilization of prescribing appropriate statin therapies in women compared with men, when prescription patterns are examined in post myocardial infarction patients [82,86,87].

2.1.3. Diabetes

Diabetes is more common worldwide in men compared with women, but when women are diagnosed with diabetes, they have far more comorbidities than men [88]. Additionally, there are sex differences in the prescription and adherence to pharmacologic treatment, with women being less aggressively treated compared with men [89,90]. Hence, women with diabetes have a much greater risk of developing cardiovascular disease, having more cardiovascular complications and a higher mortality compared with men [90,91]. Despite this, there are no sex specific considerations for preventive strategies or the management of diabetes.

2.1.4. Smoking

Smoking is more common in men than women worldwide, with variations in prevalence [92,93]. In the US, an analysis of the Medical Expenditure Panel Survey demonstrated that smoking cessation was prescribed more often in women [94]. In the US Veteran population, women are actually more likely to smoke compared with men, and although women were more likely to be counselled to quit, prescriptions in the Veteran hospitals was relatively equal by sex [95]. Other evidence has demonstrated women were more likely to use recommended resources for smoking cessation than men [96]. Nonetheless, most guidelines recommend nicotine replacement therapy as the first line pharmacotherapy without any sex specific consideration for the fact that women are less responsive to nicotine replacement and are more likely to quit with varenicline [97]. Guidelines need to reflect any sex differences in response to therapies, in order to ensure the best outcomes for women and men.

2.2. Acute coronary syndrome

National registries have made assessment of the clinical care of acute MI/ACS available for analysis. This has ultimately contributed to improved outcomes, with a focus on measurement of implementation of guidelines directed medical therapies and interventions. Such registries have also allowed the cardiovascular community to understand where disparities occur. From these national registries and databases, sex-differences in the management of acute myocardial infarction have been identified, with women being undertreated, in terms of guideline recommended medications and intervention, both in-hospital and upon discharge, on a global scale [62]. The ISACS registry demonstrated that for those who presented with STEMI, women were less likely than men to undergo PCI. Women had a higher unadjusted mortality in this cohort, but after adjusting for differences in risk factors and clinical management, mortality remained higher only in the younger women (<60 years) when compared with men of the same age (OR, 1.88; 95% CI, 1.04–3.26, p-value = 0.02) [6]. Data from 30 hospitals in Australia demonstrated that even when women experience an in-hospital STEMI, the time from onset of symptoms to PCI was 10 min longer in women (104.6 *versus* 94.3 min, p-value<0.001), although there was no sex difference in 12-month mortality in this analysis [98]. The Variation in Recovery: Role of Gender on Outcomes of Young MI Patients (VIRGO) study of young adults with STEMI demonstrated longer door-to-balloon times in women compared with men (114.6 vs 97.8 min, p-value = 0.004) and it was more likely in women to exceed the reperfusion time guidelines, compared with men (42% *versus* 32%, p-value<0.01) [99]. In a large study of over 82,000 patients with ACS in China, women were less likely to receive guidelines directed therapy compared with men, including less early dual antiplatelet therapy, heparin, and acute reperfusion therapy for STEMI [100]. Secondary prevention strategies were also less likely prescribed for women on discharge, including less ACE-inhibitors/angiotensin receptor blockers, statins, smoking cessation, or referral to cardiac rehabilitation. In hospital mortality was significantly higher in women compared with men (2.6% *versus* 1.5%, p-value<0.001) [100]. In a study from Switzerland that included over 224,000 patients with ACS, women were less likely than men to undergo any diagnostic procedure, revascularization, and had a poorer prognosis than men, particularly the women who were younger than 50 years of age [101]. Despite clear guidelines that do not differ based on sex or gender, the inequitable application of guidelines continues to affect the outcomes of women.

2.3. Heart failure

There are a number of sex differences identified in heart failure that may affect outcomes [64]. Although women with heart failure do not have a higher mortality than men, they do have worse quality of life. The applications of guideline directed medical therapy for heart failure lags in women, compared with men [102]. In young US Veterans with heart failure with reduced ejection fraction (HFrEF), women had half the odds of being on at least one guideline directed medical therapy compared with men at one year (OR, 0.54; 95% CI, 0.37–0.79) [103]. Other studies confirm the suboptimal treatment of women with HFrEF, with an underuse of guideline directed medical therapies and devices [104,105]. The under prescribing of diuretics, anticoagulants, ARNI and device therapy in women compared with men has been demonstrated in a number of recent heart failure with preserved ejection fraction (HFpEF) trials and registries [104,106]. Even though women derive greater benefit at lower doses of some guideline directed medical therapies [64], currently guidelines do not differ by sex, even though implementation of guidelines clearly do [107].

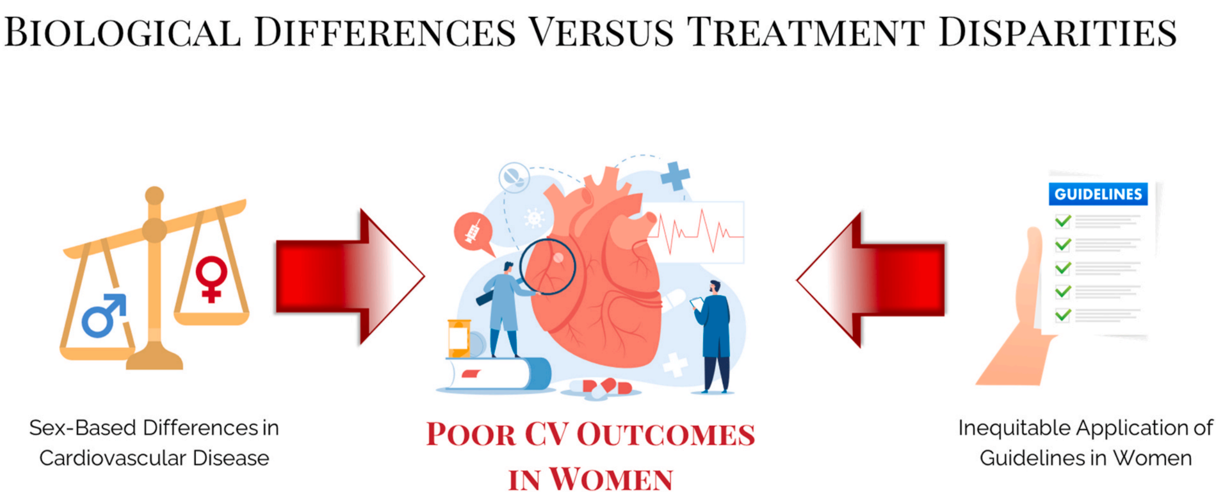

Fig. 2. Biological differences *versus* treatment disparities.

Implantable cardioverter defibrillator (ICD) Therapy: Women account for a minority of ICD implanted and are less likely to be referred for ICD implantation. Data from the US Centers for Medicare & Medicaid Services estimated that for ICD eligible persons in the first year of eligibility only 8.6/1000 women received an ICD, compared with 32.3/1000 men for a primary prevention indication [108]. Similar sex disparities for ICD-eligible patients was seen for secondary prevention, where 38.4/1000 women received an ICD compared with 102.2/1000 men. The US Get With The Guidelines-Heart Failure registry examined 13, 034 patients with heart failure who were eligible for an ICD based on established guidelines and while only 44% of eligible men received an ICD, for women this was even lower at 28% [109].

2.4. Atrial fibrillation

Women are less likely to develop atrial fibrillation than men, but are more likely to experience adverse sequela of atrial fibrillation, such as stroke, heart failure or death [110]. Guideline recommendations for the treatment of atrial fibrillation do not differ by sex. Nonetheless, women are less likely to be adequately anticoagulated or receive rhythm control treatment [111]. Although women and men benefit equally from ablation therapy for atrial fibrillation [112,113], women are less likely to undergo catheter ablation as part of their management of atrial fibrillation [114–116].

2.5. Valvular heart disease

2.5.1. Transcatheter Aortic Valve Implantation

Transcatheter Aortic Valve Implantation (TAVI) has a Class 1 recommendation for the treatment of patients with symptomatic severe aortic stenosis, who are at high risk for surgical intervention [117]. Additionally, TAVI has a Class 1 recommendation for those aged 65–80 years with characteristics suitable for the transfemoral approach. None of the guideline recommendations for TAVI are sex specific, but most of the trials related to TAVI enrolled almost equal numbers of women and men, and procedural success did not differ by sex or even demonstrated better survival in women [118–120]. Women had been shown to have greater vascular complications and major bleeding with TAVI [118,119,121]. Women had historically had worse outcomes with surgical valve replacement and the outcomes with TAVI should have made this a preferential approach for women. Nonetheless, women with aortic stenosis are referred less often for any aortic valve replacement [122,123].

2.5.2. Mitral valve repair with transcatheter edge-to-edge repair (TEER)

Current guidelines for TEER give it a Class IIA recommendation in symptomatic patients with primary mitral regurgitation at higher or prohibitive surgical risk or in secondary mitral regurgitation who are severely symptomatic despite guideline directed medical therapy, if anatomically appropriate [117]. One Italian registry showed that although short term outcomes with TEER did not differ by sex, long-term outcomes were worse in women [124]. This conflicts with the European Registry of Transcatheter Repair for Secondary Mitral Regurgitation (EuroSMR) registry and a large German registry, both of which confirmed similar efficacy of TEER in secondary mitral regurgitation by sex [125,126]. Women have a higher prevalence of mitral valve prolapse than men, yet are less often referred for surgery or TEER [127,128]. As a result of lower referral rates of women for intervention of mitral regurgitation, the measurements and guidelines for TEER are primarily based on male data. The values used to determine intervention are not indexed or sex-based, due to limited data. Ultimately this can affect the outcomes of women, if there are delays in referral and further progression of the disease [129].

3. Conclusion

Although sex differences in cardiovascular disease do exist, we are just at the beginning of understanding how they impact cardiovascular outcomes and how we might tailor therapies based on sex. At this point in time, cardiovascular guidelines do not differ by sex, but the application of guidelines do. The persistent inequities in cardiovascular care have affected the health of women globally. Research must focus on closing these gaps in care. The potential implications of our electronic health records and artificial intelligence may be potential solutions. Additionally, education in medical schools will empower a new generation of physicians to ensure equity in cardiovascular care in both women and men. Future emphasis must focus on application of guideline directed therapies to all patients, in order to ensure improved health outcomes for the hearts of women everywhere (Fig. 2).

Declaration of competing interest

Raffaele Bugiardini has no conflict of interest to declare. Martha Gulati declares: Consultant Fees/Honoraria: Esperion, Novartis, and Boehringer Ingelheim Research/Research Grants: Congressionally Directed Medical Research Program-Department of Defense (WARRIOR study).

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