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WOMEN AND ISCHEMIC HEART DISEASE (P. KOHLI, SECTION EDITOR)

Gender Differences in Residual Risk Factors for Major Adverse Cardiovascular Events Following ACS and How to Bridge the Gap

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Abstract

Purpose of Review The review aims to describe the differences between men and women in those factors that can influence a worse prognosis in women after an acute cardiovascular event.

Recent Findings Women adequately treated with current evidence-based medications for acute myocardial infarction and for conventional cardiovascular risk factors, such as hypertension, diabetes, smoking, and dyslipidemia, still have an extra risk of death compared with men. Additional factors that increase the risk of poor prognosis for the index event have been identified.

Summary The residual risk can be due to factors affecting the prognosis of the women from outside (they are external to the patient's body) and also to factors that, on the contrary, belong to the female body (female being/female sex). The review will give an update on those residual risk factors, including young age, vulnerability for de novo heart failure, time from symptom onset to treatment, heath care delivered during the weekend, and depression, which generally negatively influence the outcome of women with an acute myocardial infarction.

Keywords Women · Ischemic heart disease · Risk factors · Acute myocardial infarction · Gender differences

Introduction

In 1991, Bernardine Healy called attention to the discriminatory behavior of cardiologists towards women with underdiagnosed and undertreated ischemic heart disease in a publication in the New England Journal of Medicine entitled "Yentl syndrome." The term "Yentl Syndrome" has come to be used in medicine to define the possibility that diagnostic and therapeutic strategies are not offered in a similar manner to both men and women [1•]. "The Yentl Syndrome" also served as a call-to-action to increase knowledge regarding heart disease in women. The National Institutes of Health (NIH) established the Women's Health Initiative to address various chronic diseases that affect women. Concerns about sex disparity in research prompted two US regulation mandates. The first was the requirement that all NIH-funded clinical trials include women and be adequately powered to perform sex-specific analyses [2]. The second was the Food and Drug Administration requirement that all data analysis be sex specific in pharmaceutical trials [3]. Then, in June 2015, the NIH announced a new policy highlighting the expectation that sex as a biological variable be factored into research designs, analyses, and reporting of vertebrate animal and human studies [4]. Despite the international focus on heart disease in women, significant gaps still persist in sex-specific research and many questions of clinical importance remain unanswered.

This review article strongly supports the view that female sex is a biological variable and contributes to implement the Sex and Gender Equity in Research guidelines that were developed to assist researchers in reporting sex and gender information in publications [5]. The review also aims to give an update on differences between men and women in those factors that may influence sex-related outcomes after an acute cardiovascular event.

The Concept of Residual Risk

Residual cardiovascular risk can be defined as the residual risk of incident vascular event persisting in patients treated with current evidence-based medications for conventional risk

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factors, such as hypertension, diabetes, smoking, and dyslipidemia, and the risk connected to other factors often related to healthcare organizations, social and cultural behaviors, or sex. In this perspective, residual risk factors can be classified into two main categories: those affecting the prognosis of the women from outside (they are external to the patient's body) and those that, on the contrary, belong to the female body (female being/female sex). External and internal risk factors may have a multiplicative role, and many times they concurrently affect women (Fig. 1).

Extrinsic Factors

External residual risk factors do not affect women because of their female sex. They are mainly related to healthcare organizations and to social and cultural behaviors.

Time from Symptom Onset to Treatment

Time from symptom onset to treatment has a significant impact on patient outcome with acute myocardial infarction (AMI) [6, 7]. Unfortunately, time from symptom onset to hospital arrival did not improve significantly from 2001 through 2011 [8]. In fact, 45.8% of patients reached the hospital within 2 h of symptom onset in 2001 to 2003 compared with 48.9% of patients in 2009 to 2011 [9]. Also, it is well known that door-to-balloon time of ≤ 90 min is associated with lower risk of death (in-hospital, at 30 days, at 6 months, and also at 12 months) than door-to-balloon time of > 90 min [10]. Women experience longer time from symptom onset to hospital admission and longer door-to-balloon times than men [11, 12••]. The atypical presentation of AMI and the presence of undetermined mild symptoms are, at least in part, responsible for delayed hospital arrival diagnosis and treatment in women. The disadvantage of prolonged time of symptom onset to presentation is up to twofold for women: a greater percentage of women have delayed presentation, and women with delayed presentations have higher mortality than men with delayed presentation [13•]. The challenge of timely diagnosis and treatment of ST segment elevation myocardial infarction (STEMI) remains, and while the gender gap has improved, it persists and is costly in terms of survival for women [14]. Moreover, women still receive lower rates of guideline-directed medical therapy [6–8, 15••, 16]. Recently, a 4-step system-based approach to minimize STEMI care variability at the Cleveland Clinic resulted in reduced sex disparities and improved care and outcomes in women [11]. This successful approach consisted of (1) the implementation of cardiac catheterization lab activation criteria, (2) an early triage and management of STEMI patients, (3) a policy of immediate transfer to an immediately available cardiac catheterization lab at all times, and (4) increased use of transradial artery access for percutaneous coronary intervention in

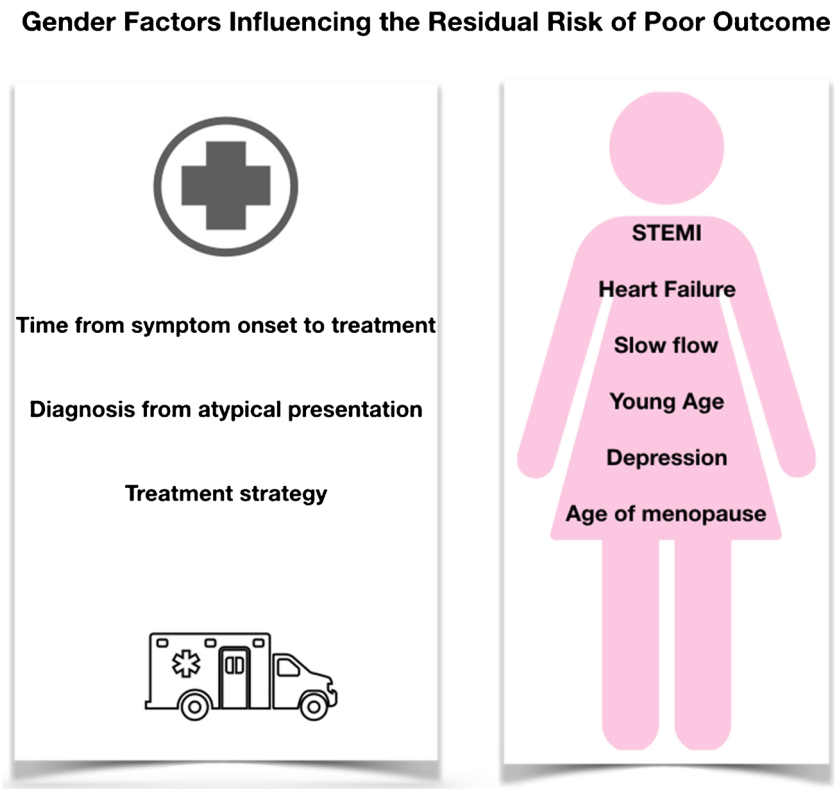

Fig. 1 Gender factors influencing the residual risk of poor outcome

patients without contraindications. Further efforts should be done so that women are equipped with the disease awareness to understand the importance of time to treatment when AMI is suspected and present to hospital as soon as possible to ensure the best outcomes [17, 18].

Delayed Diagnosis Due to Atypical Presentation

The NIH Red Dress and American Heart Association (AHA) Go Red for Women campaigns to increase awareness of heart disease in women were successful [19]. Awareness of heart disease as a leading cause of death among US women has almost doubled at 54% in 2012 in comparison with 30% in 1997 [20•], but it remains suboptimal. Awareness of atypical signs of a heart attack presentation has risen, with 18% in 2012 up from 10% in 1997 [21].

Acute coronary syndrome (ACS) without typical chest pain /discomfort is still one of the major causes of misdiagnosis of AMI and underuse of evidence base treatments [22•, 23]. ACS without typical chest pain/discomfort is more frequent in women (ranging from 6 to 65% of ACS) than in men (ranging from 8 to 48% of ACS), independently by the study population, the type of ACS (STEMI, non-STEMI [NSTEMI], and unstable angina), and the definition of typical chest pain used by investigators. Older age and comorbidities carry an increased probability of atypical symptoms. Patients with ACS who present without chest pain have higher in-hospital mortality rates than those with typical symptoms. Women are more likely than men to present without chest pain. Furthermore, women without chest pain had higher mortality than men who present without chest pain within the same age group. Sex differences in clinical presentation and in mortality were attenuated with increasing age [15••, 23]. As so, in the older age population, there is no difference between men and women in the rate of the atypical presentation [24].

Treatment Strategy

Management strategies for ACS appear to have different efficacies in women than in men. Some data seemed to indicate that an early invasive strategy is less beneficial in women versus in men with regard to outcomes such as death or recurrent non-ST-elevation myocardial infarction [16]. An invasive strategy did not appear to substantially benefit women without biomarker elevation, and it could potentially increase the risk of myocardial infarction [25]. As so, the ACC/AHA NSTEMI guidelines recommend an early invasive strategy (as a Class I, Level of Evidence A) only in women with high-risk features [26]. Women tend to have more complications than men also with regard to ST-elevation MI (STEMI), such as shock, heart failure bleeding, and stroke [27••, 28••]. Differences in clinical presentation may explain some of the sex disparities in ACS outcomes. As mentioned above, women are more likely to exceed in-hospital and transfer-time guidelines for percutaneous coronary intervention than men and more likely to exceed door-to-needle times, and women with delayed presentation are more likely to die than men with delayed presentation [13, 29]. On this background, it should not go unnoticed that about one in three patients did not receive any form of reperfusion [30, 31], and these patients are more often women [31]. Finally, another extrinsic factor that should be considered is the organization of health care during the weekend or holidays. In fact, during weekends, holidays, and national observance, patients with acute coronary syndrome (ACS) receive less coronary angiography (OR, 0.88; 95% CI, 0.89–0.90) and early invasive strategy (OR, 0.48; 95% CI, 0.47–0.48) and have higher in-hospital mortality than during weekdays [17, 18]. Since these days (and patients) are approximately 30% in a year, a lot of them are undergoing disparity in treatments. Many studies show that more women than men have an ACS during the weekend, but data are somewhat conflicting [17, 18, 32].

Intrinsic Factors

The idea that there are sex-based differences in early mortality after myocardial infarction is not new. One study investigated mortality trend sex differences from 1994 to 1998 using data on 691,995 patients from the National Registry of Myocardial Infarction (NRMI) [33]. The overall in-hospital mortality rate was significantly higher for women compared with that for men (16.7% versus 11.5%). After accounting for clinical variables, women still had a higher mortality risk. In younger patients (less than 50 years old), the in-hospital mortality rate was more than twofold as high among women. This difference decreased with increasing age and was no longer significant after the age of 74 years. The study also showed that approximately one-third of the sex-based disparities in in-hospital mortality was explained by differences in risk factors, comorbidity, and clinical profile on hospital presentation leaving unanswered the higher mortality risk of young women relative to men. More recently, the ISACS-TC investigators have reported that women continue to be at increased risk of 30-day mortality after STEMI even in the contemporary era of reperfusion therapies [34, 35••]. Among 2657 women (mean age, 66.1 years) and 6177 men (mean age, 59.9 years) [35••], women had a significantly higher 30-day mortality risk than men (11.6% versus 6%). After restricting the analysis to patients undergoing primary PCI, the difference in sex-specific mortality dropped to 7.1% for women and 3.3% for men. On this background, it seems odd to suggest that sex differences in outcomes after AMI in women constitute a “hot topic” given that the first major report of this finding dates back over 15 years and the most recent study dates back 2 years. Why is such interest still persisting? A huge storm of papers by excellent scientists has generated a turbulence of dissenting voices on the reasons, not on the presence, of such a sex

difference in death. Women continue to have poorer cardiovascular outcomes than men due to a multitude of factors including underuse of evidence-based medical therapies; delays in presentation, diagnosis, and treatment; and lack of sex-specific data regarding the appropriate treatment of coronary heart disease in women. In turn, sex-specific differences may include differences in coronary anatomy (women compared with men have smaller vessel size, less collateral flow, and more vascular stiffness [36•, 37. 38••]), myocardial vulnerability to ischemia [13, 28••, 38••], and different rates and responses to conventional cardiovascular risk profile (diabetes and hypertension are prevalent in women [15, 35••, 39, 40]). Furthermore, depression is common in women and may be associated with ischemic heart disease [41]. We need to clarify the unique pathophysiology of coronary heart disease in women, with the goal of creating specific guidelines for treatment and improving outcomes in women. For these reasons, sex-based differences in early mortality after AMI are still a topic worthy of consideration [13•, 15••, 20•, 42–44]. The main issue remains: what is the pathophysiologic evidence that female sex is a biological variable?

Transmural Versus Subendocardial Infarction

Some researchers and scientists pointed out that the major flaw encountered in early research studies on sex and myocardial infarction was the failure to estimate outcomes without differentiating patients with and without STEMI. This holds true. STEMI is a unique clinical entity with epidemiology, incidence, and outcomes distinct from those of non-STEMI (NSTEMI). STEMI and NSTEMI differ remarkably in the management strategies. Treatment of NSTEMI patients is more complex and challenging than treatment of patients with STEMI. In STEMI, total ischemic time is the main factor influencing prognosis. In NSTEMI, the acuity level of the clinical presentation is the key factor affecting outcomes. Risk stratification should be assessed at admission and may largely impact clinical decision-making.

Women with STEMI have worse short-term mortality than men with STEMI, but multiple factors contribute to this sex difference, including older age at presentation, increased cardiovascular risk profile, differences in reperfusion time and therapy, and differences in STEMI pathophysiology in women [35••, 45]. The sex-specific mortality gap narrows if the analysis is limited to men and women undergoing primary PCI [35••], but even for patients treated with primary PCI, there is a sex difference in the outcome [27••]. In 2014, Pancholy et al. [27••] conducted a meta-analysis of observational studies that examined differences in mortality by sex in patients with STEMI treated with primary PCI. Twenty-two studies reported unadjusted in-hospital all-cause mortality comparing women with men and involved a total of 41,766 patients. In the unadjusted analysis, women had a significantly higher risk of in-hospital all-cause mortality compared with men (RR, 1.93; 95% CI, 1.75–2.14). Importantly, all of these studies except 4 showed statistically significant differences, and the remaining 4 studies showed a trend towards significance. In other terms, all studies found that women with STEMI die over 30 days more than men (crude mortality rate). However, using adjusted RRs from 12 studies, the strength of association for all-cause mortality in women compared with men, though remaining significant, was significantly attenuated (RR, 1.48; 95% CI, 1.07–2.05). In sum, even in STEMI patients treated with primary PCI, women are a vulnerable population [27]. On the opposite, the most recent investigation on NSTEMI and unstable angina patients ($n = 68{,}730$) from the Thrombolysis In Myocardial Infarction (TIMI) clinical trial database [46] revealed that the adjusted 30-day mortality risk was similar among women and men (hazard ratio 0.91, 95% CI 0.76–1.08).

With no information on the type of myocardial infarction, sex differences in early outcomes are not predictable.

The "Young Woman's Paradox"

The rate of female death for AMI is higher than that of male either before or after 65 years [15••, 35••]. However, at young ages, ACS is a relatively uncommon disease. In fact, only from 2 to 10% of STEMI occurs in subjects younger than 45 years. Moreover, these patients are mostly men (3 to 5 men for 1 woman) and have a lower risk of 30-day death than older patients (1.3% vs 6.9%) [20•, 43]. AMI has never been considered a risky disease for young women, according to the well-established notion that female hormones are protective against the development of ischemic heart disease. Nevertheless, observational studies explored the outcome of young patients with ACS showing unexpected results [20•, 43, 47]. The most known of these studies is based on the Get With the Guidelines-Coronary Artery Disease registry data [43]. The study examined 31,544 patients presenting with STEMI and evaluated two cohorts of patients: those aged 45 years or less and those aged more than 45 years. Young women were more likely to have lower quality of care and, consequently, experienced more unfavorable short-term prognosis than young men. According to some observers, this finding indicates that sex may not play a role for young patients with STEMI. However, in such study, it was unclear whether there was a similar sex–age interplay among patients presenting with non-ST segment–elevation ACS and whether there was a role for severity and extent of coronary artery disease. A study by the Acute Coronary Syndrome Israeli Surveys (ACSIS) added to ambiguity on the role of sex and age in ACS [47]. In 3949 young adult patients (< 55 years) with ACS enrolled from 2000 to 2013, women had a higher mortality rate during hospitalization than men (2.7% versus 1.0%), regardless of the ACS subtype. Still, after accounting

for history of prior myocardial infarction, higher GRACE score, diabetes mellitus, hypertension, year of enrollment, PCI, and cholesterol levels, mortality remained about fourfold greater in women than in men. It should not go unnoticed that of the 3949 patients that were analyzed in the survey, only 103 presented with STEMI. Thus, it remained unclear whether sex disparities in mortality remained in young patients throughout the full spectrum of ACS or only in STEMI and which factors may influence this gap in mortality, if any. A more recent study shed light on these uncertainties [20•]. The ISACS-TC investigators showed, in a large contemporary cohort of young (≤ 45 years old) patients with ACS, that female sex is an independent prognosticator of 30-day mortality [20•]. Young women had more diabetes and hypertension than young men. The young women cohort was managed as well as its male counterparts. Young women and young men had the same rates (68%) of STEMI as index event. They had fairly use of evidence-based treatments, and a comparable proportion of young women and young men experienced delays to hospital presentation over 12 h. However, young age was an independent predictor of lower 30-day mortality in men, but not in women [20•]. Compared with older women, young women had a considerably lower ischemic risk, but they were more likely to undergo PCI. Delays to hospital presentation over 12 h were more frequent with older age. These results, therefore, suggested convincing evidence that the young women's paradox of higher short-term mortality compared with men among patients with ACS cannot be supported only by a lower quality of care, as evaluated by previous studies. These results indicate an interactive role of age and sex in ACS. The mean caveat of the abovementioned research was instead the definition of younger or older ages. The findings of subgroup analyses by age can result in either consistent or insignificant results, differing on the definition of age used in the analysis. No subgroup analysis will accomplish effectiveness when undertaken without any explanatory background, no matter how considerable the findings may be. Yet, after 15 years of research and debate, there is still a considerable extent of uncertainty on the definition and application of the definition of young adults with myocardial infarction. In another study, the aim of the ISACS-TC investigators was to analyze 3 subgroups of patients based on age subgroups (< 60 years, 60 to 74 years, and 75 years) that were predetermined on a rational basis [35••]. They suggested 60 years according to the World Health Organization (WHO) Minimum Data Set Project on Aging and Health [48] and the United Nations "Population Aging Report" [49]. They found that treatment disparities may account for a portion of the adverse outcomes. However, even when women and men were balanced in terms of baseline characteristics, medication treatment, and time to presentation and revascularization, young women continued to have higher mortality than young men (OR 1.49, 95% CI 1.15–1.92).

Left Ventricular Dysfunction and Slow Flow

Some recent findings represent another progress in our understanding of the mechanisms of ischemic vulnerability in women with STEMI and emphasize the continuing need to account for biologic aspects specific to women. Left ventricular function should be always carefully pondered in women in order to activate every possible intervention against acute heart failure, since modest to severe impaired left ventricular function up to cardiogenic shock is more frequent in women than in men [50]. Left ventricular dysfunction is the strongest predictor of in-hospital mortality in patients with AMI and determines up to sixfold increase risk of 30-day mortality. Many factors can contribute to excess acute heart failure in women, including higher rates of underlying hypertension and diabetes mellitus time from symptom onset to reperfusion AMI, the extension of the necrotic area, and slow or no flow after reperfusion [12••, 51–53]. Besides, delay to hospital presentation and suboptimal post-PCI flow are independently associated with excess mortality in women, suggesting complementary mechanisms of reduced survival [12••]. Recently, it has been shown that de novo heart failure is a key feature to explain mortality gap after STEMI among women and men [28••]. The ISACS investigators reported a gender-based outcomes analysis for "de novo heart failure" presentation in 10,443 STEMI patients of whom 29.8% were women [41]. The study had two main objectives: address sex differences in the incidence of de novo heart failure at admission in STEMI patients and address sex differences in 30-day mortality in patients presenting with STEMI complicated by de novo heart failure. The study revealed that the disadvantage caused by heart failure was twofold for women: women are more likely than men to have de novo heart failure complicating STEMI on admission (25.1% vs. 20.0%) and women with heart failure have worse survival than do their male counterparts (OR 1.29, 95% CI 1.05–1.58) even when women and men were balanced in terms of baseline characteristics, comorbidities, angiographic disease severity, delay to hospital presentation, and treatment by early reperfusion therapy [28]. Among several factors that may cause the excess of left ventricular impaired in women with STEMI, the investigators hypothesized that myocardial tissue in women could be more vulnerable to prolonged ischemia and postulate microvascular dysfunction as a potential pathologic mechanism for future research focus. The study represents an advance in furthering our understanding of the mechanisms of vulnerability in women with STEMI and highlights the ongoing need to accurately account for biologic factors specific to women. In this regard, a recent analysis showed that female sex is associated with post-procedural slow or no flow (TIMI flow 0 to 2) [12••]. The study investigated 2016 patients with complete clinical and coronary hemodynamic data who underwent primary PCI for STEMI of whom 26% were women [12••]. The study

showed a significant sex difference in the incidence of post-PCI TIMI blood flow grades 0 to 2 (8.8% versus 5.0% in women and men, respectively, adjusted OR 1.83, 95% CI 1.31–2.56). Sex difference in post-PCI coronary blood flow grade was consistent regardless of time to hospital presentation. There was also a nearly threefold increase in 30-day mortality rates in women compared with men with TIMI blood flow grades 0 to 2 (OR, 2.00; 95% CI 1.27–3.15), but sex gap in mortality was no longer significant for patients having hospital presentation of ≤ 120 min (OR, 1.28; 95% CI 0.35–4.69). These findings indicate that delayed hospital presentation and suboptimal post-procedural TIMI blood flow grade are variables associated with higher death rates in women. These data support growing evidence of coronary microvascular disease and endothelial dysfunction in women, which may be linked with unfavorable outcomes [38••].

Age of Menopause and Sex Hormones

Ischemic heart disease in women is less frequent in pre- than post-menopausal age. The age of menopause is an important factor in the risk stratification of cardiovascular disease for women as recently definitively proved by Zhu D et al. [54]. Authors published a large study on the association between ages at menopause and incident cardiovascular disease. Of 301,438 women, 4.3% had a first cardiovascular disease event after menopause. The study shows that, compared with women who had menopause at age 50–51 years, women with premature (< 40 years) and early menopause (from 40 to 44 years) had a substantially increased risk of first nonfatal cardiovascular disease event before the age of 60 years, but not after age 70 years. Early or premature menopause might be considered an important factor in risk stratification of cardiovascular disease for women [54].

Finally, it should be mentioned that, among post-menopausal women, a higher testosterone/estradiol ratio was associated with an elevated risk for incident cardiovascular disease, coronary heart disease, and heart failure [55]. Preventive measures should consider all these associations as part of active management of cardiovascular disease risk factors for women.

Depression

Among women, depression is approximately twice as prevalent as in men and has shown few strong associations with ischemic heart disease [56••]. Women with ischemic heart disease similarly have twice the rates of depression as men with ischemic heart disease [57–59]. The condition is especially common in young women who have survived an AMI [57, 58, 60]. Approximately half of women younger than 60 years with a previous myocardial infarction have a history of major depression [58–60]. Of note, young women are more likely to die of AMI than men [35••]. The patient burden of comorbid ischemic heart disease and depression would seem to warrant targeted intervention.

Traditional Cardiovascular Risk Factors

Risk factor reduction may have contributed to the overall decline in rates of CHD in women. In a report from the Nurses' Health Study of 85,941 women who were followed for 14 years, incident CHD was 31% lower in the 2 years from 1992 to 1994 than it was in the 2 years from 1980 to 1982 [61]. Nevertheless, traditional cardiovascular risk factors still are into play. The prevalence of hypertension reaches 70 to 80% in women above 60 years of age. Hypertension in women, including premenopausal women, is a stronger predictor of coronary risk compared with men [62]. Dyslipidemia is somewhat different in women compared with that in men. Low HDL, rather than high LDL cholesterol, is more predictive of coronary risk in women than in men [63]. The total cholesterol concentration appears to be associated with CHD only in premenopausal women or at very high levels (> 265 mg/dL [6.9 mmol/L]) [64]. The increase in CHD risk in patients with diabetes is greater in women than in men [65]. Smoking has been associated with one-half of all coronary events in women [66]. Some studies have suggested that smoking has a much larger relative detrimental impact on CHD in women [67]. Other studies have shown that smoking has a similar effect on increasing the risk of CHD in both men and women [68]. Conflicting results between studies may be related to many factors including definition of smokers, age with consequent prevalence of oral contraceptive use, and synergistical action of smoking with other conventional risk factors. In summary, adverse trends in traditional CVD risk factors among women are an ongoing concern.

How to Bridge the Gap?

The blame for the sex-lag in improved CHD mortality and complications in women compared with men is complex; it includes older age, longer pre-hospital delays, lower rates of revascularization, socioeconomic and cultural factors, and biological aspects specific to women, such as greater vulnerability of myocardial function to prolonged ischemia. Lifestyle modifications at a population level (such as positive changes in conventional cardiovascular risk factors) as well as expanded use of evidence-based medical therapies had influenced the decline in the incidence of AMI between 1995 and 2012 and improved its survival [8, 69]. However, this is not enough [70]. Mortality rates for AMI are still high with relevant sex differences [8]. Although public campaigns on women continue their efforts so that women are equipped with disease awareness to recognize the importance of hospital

presentation when AMI is suspected to optimize treatment, sex-based differences in vulnerability to ischemia exist. The underlying basis for these findings largely remains elusive. Only when the effects of sex and gender are studied will we be able to fill the gaps in the knowledge base and discover new opportunities for a better women health.

Compliance with Ethical Standards

Conflict of Interest Dr. Olivia Manfrini has nothing to disclose. Dr. Edina Cenko has nothing to disclose. Dr. Raffaele Bugiardini has nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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