Risk-treatment paradox in women with symptomatic coronary artery disease

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Abstract The implementation of evidence-based treatment including diagnostic and therapeutic invasive procedures has resulted in a reduction in the mortality attributable to coronary artery disease (CAD) despite the fact that patients at high risk are less likely to have access to it. Women in particular are up to 30 % less likely to receive percutaneous coronary intervention (PCI) following presentation with an acute coronary syndrome than men. This risk-treatment paradox for women is partially related to their older age, greater likelihood of comorbidities, and later presentation after symptom onset with more frequent atypical symptoms as well as to the higher proportion of symptomatic women having nonobstructive CAD. In addition, during the first decade of the PCI era, a poorer short-term survival after revascularization in women was reported while similar or better long-term outcomes than men was consistently observed. The subtly different spectrum of biological factors predisposing to high risk, frequent vascular complications, and high incidence of bleeding events, mostly related to the antithrombotic drugs over dosage, explain the early hazard seen in women. Newer antithrombotic regimens and the modern coronary stent platforms have contributed to drastic improvement of outcomes, particularly in high-risk subsets of patients including women. However, still more evidence from randomized trials with a representative proportion of women is required both to fully categorize CAD in women and to determine the most appropriate approach to therapy. Furthermore, physicians must continue to work to better identify high-risk patients

and to tailor the evidence-based therapy to individual risk independent of patient's sex.

Keywords Sex · Women · Coronary intervention · Myocardial infarction · Stent

Introduction

Although the burden of coronary artery disease (CAD) remains enormous, the mortality attributed to it has decreased considerably during the last two decades. This is mostly derived from the implementation of evidence-based medicine including revascularization procedures [36]. The risk of the population treated determines the amount of survival benefit attributable to percutaneous coronary intervention (PCI), with ST-segment elevation myocardial infarction (STEMI) patients deriving the greatest benefit from it [8, 43]. Paradoxical to the evidence-based research, an underuse of invasive diagnostic and therapeutic procedures has been observed in high-risk CAD patients. In particular, women, despite a frequent clinical presentation with acute coronary syndrome (ACS), are up to 30 % less likely to receive cardiac catheterization than men [8, 25, 43]. Several reasons have been proposed to explain these findings.

Poorer cardiovascular risk profile and frequently nonobstructive CAD in women

Women generally develop symptomatic CAD 6–10 years later than men [5, 7, 8, 26, 27, 36]. Because there is a significant association between age and unadjusted all-cause mortality, the oldest ACS patients derive the highest benefit from PCI compare to medical treatment alone. However, the use of

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PCI and the rate of prescription and adherence to evidence-based therapy decrease with increasing age in the CAD population [2]. The burden of comorbidity also increases with age, and this can disproportionately affect female patients. Women with CAD present more frequently with diabetes, renal insufficiency, cerebrovascular disease, and signs of congestive heart failure than men [1, 5, 7, 8, 26, 27]. Diabetes mellitus is a far more powerful coronary risk factor for women than men. It is associated with a twofold increased risk of reinfarction and a fourfold greater likelihood of developing heart failure in ACS women [19, 26, 32].

In contrast, the severity of CAD is less pronounced in women. One fifth of women presenting with ACS have angiographically documented nonobstructive CAD compared with only 10% of men [6, 14]. These women have a fourfold increased risk of adverse nonfatal and fatal events at long term compared with asymptomatic women [15, 33]. Impaired endothelial function of both epicardial and intramyocardial coronary arteries and differences in vascular structure may be an explanation for the presence of myocardial ischemia despite normally appearing coronary angiography in women [6].

Failure to efficiently recognize ischemic symptoms and lack of awareness in women

It is a common perception that CAD is a male disease. This is in part related to observed sex-based differences in symptoms and pain perception, with women presenting less frequently with chest pain and more often with the combination of throat, jaw, or neck discomfort and an inconclusive electrocardiogram (ECG) in comparison with men [11]. Consequently, at the time of an acute coronary event, women seek care at least 1.5 h later than men [12, 27]. Although the majority of studies did not report sex-specific differences in door-to-treatment time intervals [14, 27], the likelihood of getting primary reperfusion therapy is reduced in those with late presentation. Furthermore, sex-based differences in expression of cardiac biomarkers troponins and creatine kinase-MB, which is less likely elevated in women than in men [41], decrease the likelihood of women being assigned to an early PCI. Lack of awareness of warning signs may be one of the most important reasons for delayed presentation in women. Despite several national campaigns, only 8–20% of women above 35 years of age and one in five physicians were aware that cardiovascular disease was the leading cause of female deaths [34].

Higher likelihood of peri-interventional complications in women

Even after adjustment for body mass index, women have smaller coronary arteries than men [22, 26, 28, 35]. Consequent improvements in interventional techniques and devices have offset the previously observed sex-related differences in procedure-related mechanical complications [16]. However, women—mostly because of a higher occurrence of peripheral artery disease—experience peri-PCI vascular complication twice as often as men [23].

Despite receiving the same peri- and postinterventional antithrombotic treatment, women bleed more frequently than men [11, 18, 23, 24, 30]. Previously considered as an unavoidable and acceptable collateral damage, peri-PCI bleeding independently increases the 1-year mortality risk by a factor of three [1]. Although considerable controversy exists about the efficacy of glycoprotein IIb/IIIa inhibitors (GPI) regarding reduction of thrombotic events in women, a more pronounced relationship between GPI use and an increased incidence of bleedings among women has been consistently reported [1, 9, 30]. One of the reasons behind these findings is the 1.5-fold higher likelihood of excess dosing in women after accounting for age, body mass index, and renal function [1]. In the meantime, newer P2Y₁₂ receptor inhibitors have substantially reduced peri-interventional thrombotic events, making the use of GPI potentially redundant [20, 31, 42]. The P2Y₁₂ receptor is important for the potentiation of many platelet responses and for the formation of a stable hemostatic plug [13]. Different from glycoprotein IIb/IIIa receptor inhibitors—which mediate interplatelet bridging—P2Y₁₂ receptor inhibition is associated with reduction of thromboembolic events without thrombocytopenia. In the Bavarian Reperfusion Alternatives Evaluation (BRAVE) 3 trial, 800 patients with acute STEMI treated with 600 mg of P2Y₁₂ receptor inhibitor clopidogrel were randomly assigned to receive either GPI, abciximab, or placebo before primary PCI. Additional GPI was not associated with any additional benefit regarding infarct size and clinical events up to 1 year compared with clopidogrel alone [31, 37]. No thrombocytopenia and less bleeding were observed with clopidogrel alone [31].

Furthermore, replacing unfractionated heparin plus GPI with the direct thrombin inhibitor bivalirudin has been associated with a reduction of peri-interventional risk of bleeding of up to 50% in patients with ACS [20, 39]. Given that the reduction of bleeding with bivalirudin is independent of patient's sex and that women are at higher risk for bleeding independent of the drug combination used compared with men, bivalirudin could potentially be a preferred peri-interventional anticoagulant in female patients [24].

Lower restenosis risk despite pronounced aggregation of restenosis predictors in women

Following implantation of bare metal stents, women demonstrate more than 20% reduction of the adjusted risk for restenosis despite having a higher incidence of diabetes and smaller vessels, two major independent predictors of restenosis [28]. Use of drug-eluting stents (DES) compared with bare metal stents provides a decrease in restenosis of a similar magnitude among women and men [38]. Furthermore, the benefit derived from newer DES platforms, such as everolimus-eluting Xience stent, may be more pronounced in women than in men [35].

Higher short-term but not long-term unadjusted mortality after PCI in women

Large population-based studies have shown differences in the temporal pattern of mortality between women and men. The reported in-hospital and 30-day unadjusted mortality in women—particularly in those presenting with ACS—is up to twofold higher than in men, whereas during the course of the first year, this early excess risk gradually attenuates [7, 8, 10, 21, 26]. The early hazard in women seems to be less driven by sex-based differences in age and prevalence of comorbidities but mostly by the less frequent use of evidence-based diagnostic and therapeutic procedures and life-saving medical therapy in women [2, 4, 6–8, 25]. Although primary PCI has a guideline-recommended class I indication as the reperfusion strategy of choice in STEMI, it is estimated that in 2008, less than 70% of STEMI patients underwent PCI [44]. The life-saving role of primary PCI independent from symptom onset-to-treatment time interval is well established. Women present with an ACS up to 2 h later than their male counterparts and would be expected to derive more benefit from primary PCI. There is a large body of evidence showing that increasing the access to evidence-based care is associated with reduced mortality for both women and men with ACS, with women deriving the greatest benefit at long term (Fig. 1) [3–5, 14, 17, 24, 26, 27, 43].

Antithrombotic therapy is essential in coronary reperfusion. It diminishes not only the risk of thrombotic epicardial vessel occlusion but also the risk of peri-PCI myocardial infarction by preventing the blockage of coronary microvasculature [27, 29]. Consequently, given the biologic differences between female and male CAD patients, with women having a more pronounced vascular and microvascular dysfunction [6], the peri-PCI GPI therapy is associated with greater amount of jeopardized myocardium salvaged in women presenting with STEMI than in men [29]. This partially explains the observed 35% reduction of age-adjusted mortality in women compared with men

Fig. 1 One-year mortality in women and men presenting with acute coronary syndrome in relation to the proportion of patients treated with percutaneous coronary intervention (PCI)

1 year after primary PCI [27]. During the last decade, the use of GPI has been largely replaced by the newer and more potent P2Y₁₂ receptor inhibitors. Despite the nearly 30% increase major bleeding rates (according to Thrombolysis In Myocardial Infarction definition), prescription of prasugrel or ticagrelor for more than 1 year in patients with ACS is associated with net clinical benefit comparable to clopidogrel [40, 42]. Although female sex was the strongest independent predictor of serious bleeding associated with prasugrel in the first year following intervention in the TRITON-TIMI 38 trial, the anti-ischemic effect of newer P2Y₁₂ receptor inhibitors was similar in women and men [18, 40, 42]. Unfortunately, we cannot draw any definite conclusion about the performance of newer therapies in women because they still remain underrepresented in randomized clinical trials. In large population study cohorts, the proportion of women presenting with ACS is as high as 40%, in contrast to 25% in pivotal randomized trials [36, 39, 40, 42].

Prospective

Commonly, CAD in women is seen in the context of an additional risk factor, e.g., increased age, presence of diabetes, or comorbidities such as renal impairment and heart failure. Nevertheless, despite being at higher risk of death and demonstrating an even better response to evidenced-based therapy than men, women are underdiagnosed, undertreated, and underrepresented in randomized clinical trials. To rectify this situation, first, awareness in women of the symptoms of CAD must be increased. Second, the awareness of higher risk and poorer short-term outcomes in women must be increased among physicians and appropriate treatment tailored to the individual-specific risk must be offered. Early revascularization according to evidence-based principles, use of secondary prevention, and aggres-

sive risk-factor control in nonobstructive disease can reduce sex-based differences in short-term mortality following ACS. Third, patient inclusion in randomized controlled trials must reflect the composition of the presenting population in terms of sex, age, and overall risk profile more accurately. This will enable a greater understanding of the subtle differences of ACS in different high-risk groups and provide a representative evidence base to determine the most appropriate treatment strategies based on individual patient risk profile.

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