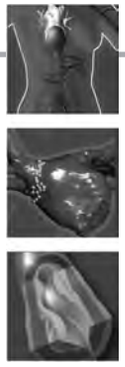

Inferior outcomes in percutaneous coronary interventions: narrowing the gap between men and women

"...bleeding has itself now been identified as a predictor of other major adverse events after PCI, and the interactions of gender, bleeding and mortality after PCI is currently a major 'hot topic' in the interventional community."

KEYWORDS: coronary artery disease ■ female ■ gender ■ outcome ■ percutaneous coronary interventions

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Heart disease is the number one cause of mortality among women in Western society. Among the Framingham cohort, at the age of 50 years healthy female participants had a lifetime risk for developing CVD of 39.2%, with a median survival of 36 years [1]. For those free of disease at 40 years of age, the lifetime risk of developing CVD is two in three for men and one in two for women. However, this gender gap narrows with advancing age, so that by the age of 70 years both males and females have a 50% chance of developing CVD [2]. Futher supporting these data, in the USA in 2007 the leading causes of death in women ≥65 years of age were (in descending order) diseases of the heart (number 1), cancer (number 2) and stroke (number 3) [2]. Inevitably, a large number of these women will present to the catheterization laboratory. As a major area of concern that has troubled the interventional and cardiovascular communities for several decades, female gender has emerged as a risk factor for unfavorable outcomes following percutaneous coronary interventions (PCI).

Gender-based inequalities for coronary revascularization were first noted in the 1970s, when early studies of coronary artery bypass graft surgery identified that women suffered from higher operative mortality and lower graft patency rates [3–4]. With the advent of coronary angioplasty, even in the earliest of studies published in the mid 1980s it was apparent that women, at least in unadjusted analyses, have lower procedural success and higher long-term mortality rates after PCI than males [5]. In the ensuing 25 years, the interventional community has struggled with this disparity, as a steady stream of publications continued to reinforce the fact that women 'do worse' after PCI than males [6–9]. As recently as 2009, Lansky *et al.* reported in a *post-hoc* analysis of 1,002 patients receiving drug eluting stents that the 1-year rates of death and all adverse cardiovascular events were significantly higher in women compared with men [8].

Many factors have been blamed for these gender differences after PCI. For example, factors associated with the coronary anatomy that might directly contribute to poorer procedural PCI results were proposed, such as smaller arterial diameter [10], abnormal coronary artery vasoreactivity ('endothelial dysfunction') [11], microvascular dysfunction [12] and differences in plaque morphology [13]. It was hoped that with improvements and evolution of PCI techniques and drug-eluting stents these coronary anatomical factors would be overcome. However, while perhaps minor inroads were made to narrow the gap, after more than two decades of technical advances, the negative reports regarding women's outcomes after PCI continued to appear [6,8,14].

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In further attempts to explain these outcome differences, other factors have been evoked, including hormonal differences [10], decreased sensitivity and specificity of non-invasive stress testing [15], and the suboptimal use of adjunctive medical therapies [16,17]. However, even with all these factors considered, there was still an uneasy feeling about the plight of women after PCI. Simply put, it just seemed that angioplasty and stenting did not 'work' as well in females. In addition, other data emerged to demonstrate that the

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poorer outcomes of women after PCI extended to include an increased risk for major bleeding [18]. Importantly, bleeding has itself now been identified as a predictor of other major adverse events after PCI, and the interactions of gender, bleeding and mortality after PCI is currently a major 'hot topic' in the interventional community. While these relationships are still being defined, the finding that women are at increased risk for bleeding serves to reinforce the concept that coronary anatomy alone is unlikely to account for the PCI outcome gap between males and females.

> "*Numerous studies have demonstrated that, compared with males, a plethora of adverse cardiovascular risk factors are more common in females at the time of PCI.*"

At the same time as interventionalists grappled with these issues, we have become increasingly aware that clinical characteristics are likely to have been significantly under-recognized as critical factors for accurately predicting outcomes after PCI. This has been verified in numerous 'risk scores' which have demonstrated that rather than just coronary anatomy, outcomes after PCI may be accurately predicted by features, such as age, ejection fraction, renal function, diabetes and the presence of peripheral vascular disease. If this is the case, what then are the clinical characteristics of females undergoing PCI? The short answer is highly unfavorable. Numerous studies have demonstrated that, compared with males, a plethora of adverse cardiovascular risk factors are more common in females at the time of PCI. In addition to the features already mentioned, compared with males, women undergoing PCI are generally 4–5 years older, with a higher incidence of hypertension and diabetes [19], and they more frequently present with unstable symptoms and/or heart failure [7,20,21]. As a whole, these data indicate that women presenting for PCI are significantly 'sicker' than their male counterparts. Therefore, the poorer outcomes of women undergoing PCI may have less to do with the technical challenges of their coronary anatomy, but more with age and comorbidities.

Consistent with our growing appreciation of these multiple adverse factors in women as well as improved statistical modeling techniques, several contemporary studies have now suggested that being female, while remaining a marker for adverse outcomes, is unlikely to be an independent risk factor for morbidity and mortality following PCI [20–22]. Collectively, these converging lines of evidence appear to indicate that females generally have poorer outcomes after PCI because they have more comorbidities.

As a marker of risk, several concerning issues are uncovered if we honestly engage the question of why women fare worse after PCI and how we might bridge this outcome gap. First, we must dispel the long-held hope that newer guidewires, next-generation stents and other procedural PCI advances will solve the outcome disparity between males and females following PCI. While technical advances may help, if PCI is not to blame then PCI is unlikely to hold the answer. A far broader outlook will be required to bridge this outcome gap. Second, we require more data. Which risk factors or comorbidities are most important in females following PCI? Are these modifiable? Are the interventional and medical therapies we use adequately tailored to women? Should we intervene earlier in the disease process? The need for more data that is specific to women speaks to a long-standing problem with cardiovascular clinical trials: women are under-represented. While in the past this was perhaps tolerated due to the fact that more men die of cardiovascular disease, the time has come to move beyond this overly simplistic outlook. Third, the overwhelmingly disproportionate burden of cardiovascular comorbidities and risk factors in females is of major concern. Indeed, this preponderance of cardiovascular risk may have at least partially arisen due to our neglect to target females in clinical studies. Clearly, the collective data presented here points to the fact that further efforts must be directed towards risk factor reduction in women. Finally, new initiatives toward bridging the gap between males and females should be broad and permeate widely through the community. Gender-specific studies need to be coupled with a grass-roots interest in improving the outcome of women following PCI and from a wider cardiovascular health perspective. In the day-to-day management of patients, it is important that physicians focus on areas, such as hypertension and diabetes, where women are known to be doing poorly.

Where does all this leave the practicing interventionalist? As an important conclusion that has taken almost three decades to reach, it seems as if revascularization by PCI may have been exonerated from the charge of 'not working as well' in women. However, this is only a small part of a much larger story. The interventional community remains confronted by numerous

gender disparities in both our clinical trial data and in the comorbidity profiles of the patients we treat. While we have clarified that female gender is unlikely to be an independent risk factor, it remains an important marker of morbidity and mortality after PCI. Rather than breathing a sigh of relief, it is time to step up our game.

Future perspective

Females have been under-represented in clinical cardiovascular trials for decades. The coming years will see a steadily increasing number of studies that are conceived and conducted with the aim of better understanding clinical outcomes in women. Attention must now be directed towards defining of how this can be best achieved: women-only trials? 50–50 male–female trials? Having taken several decades to begin to understand the problem, it will assuredly take a significant length of time to effectively address the cause.

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