



Women, Coronary Artery Disease and Percutaneous Coronary Intervention: Still the Same after All These Years?

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Despite major advances in the diagnosis and treatment of heart disease, coronary artery disease remains the leading cause of morbidity and mortality in developed countries and in Israel, in both men and women. However, after more than a decade of research, controversy still exists as to whether the short and long-term outcomes after percutaneous coronary intervention in women are comparable to those in men.

The controversy goes beyond gender differences and outcome. Recent studies have demonstrated lower utilization of revascularization procedures, including percutaneous transluminal angioplasty and coronary artery bypass graft surgery, in women than in men [1]. Women are referred for revascularization procedures at an older age, and perhaps at a later stage of the disease, possibly related to expectations of a worse procedural outcome and less symptomatic improvement. However, the reason for referral at a later age may well be due to coronary artery disease presenting at a later stage in women. The Framingham Heart Study provided 30 years of observational data that emphasized striking gender-based differences in the clinical presentation and prognosis of coronary heart disease [2]. CAD occurred at a later age among women than men. The mean age of clinical presentation was 10 years older for women than for men and, equally, for the occurrence of myocardial infarction was 20 years later. While it is clear that the reasons for this occurrence are multifactorial, they remain largely unexplained. Nonetheless, the prognosis for women who had angina in the Framingham study was more favorable than for men. Only 24% of women with angina had myocardial infarction within a 5 year follow-up compared to 75% of men. These data promoted the widespread notion that angina pectoris is associated with a more benign course in women. In spite of that, the prognosis for women with myocardial infarction in the Framingham study, both in terms of survival and morbidity, were significantly worse when compared to their male counterparts. Although myocardial infarction was less often the initial presentation in women, it was more likely to be fatal, with a 45% 1 year mortality rate as compared to 10% in men [3].

Added to the problem of misinterpretation of the prognostic value of angina in women, are reports alluding to the lesser predictive accuracy of exercise testing and myocardial perfusion studies in diagnosing CAD in women. Even with abnormal exercise tests, women with chest pain are less likely than men to be referred for coronary angiography. Women are more likely to be considered by their physicians as having a non-cardiac cause for their chest pain, probably contributing to the unfavorable outcome in these patients. Several studies have shown that women referred for either surgical or percutaneous coronary revascularization are usually older and smaller in body size. Although angiographically they may have less severe disease, mortality remains higher when compared to male patients.

Several studies have examined gender differences in procedural morbidity and mortality after percutaneous balloon angioplasty, with conflicting results. Two registries from the National Heart, Lung, and Blood Institute Coronary Angioplasty Registry Study showed lower success rates and significantly higher in-hospital angioplasty-related mortality rates in women [Figure 1] [4]. Studies that compared the outcome of women after plain balloon angioplasty also showed that women are usually older and present at a later age than men; however, after adjustment for the older age of women, the hospital mortality rate was no longer significantly different. A study performed by Welty et al. [5] from Boston in the late 1980s showed that the procedural outcome and long-term follow-up of 301 men and 139 women with post-myocardial infarction ischemia who underwent balloon angioplasty was similar [Figure 1]. There was no difference in the need for repeat angioplasty and bypass surgery, or in re-infarction or death during the follow-up period. Recurrent angina occurred significantly more often in women (54%) than in men (42%) ($P < 0.01$), despite a similar incidence of single-vessel or multivessel disease. A large study from Emory [6], which compared the in-hospital and long-term outcomes after angioplasty in 2,845 women and 7,940 men, showed marked differences in CAD in women compared to men. Women were older, had more co-morbid conditions, differed in body habitus, yet had less multivessel disease and slightly better left ventricular function [6]. Essentially there was no difference in

CAD = coronary artery disease

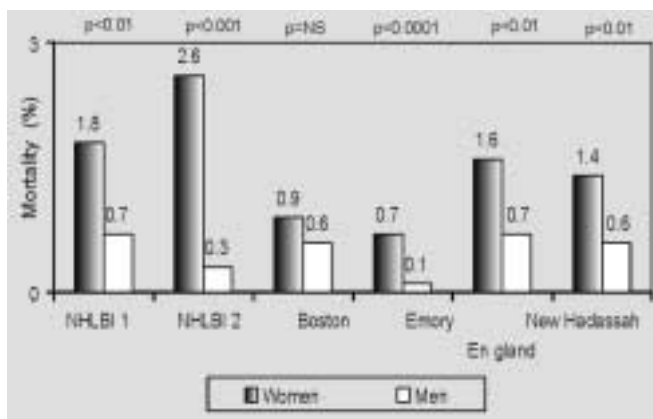


Figure 1. Differences in in-hospital mortality rates by gender after percutaneous transluminal coronary angioplasty. Data abstracted from references 4–8.

angiographic outcome. Nevertheless, the in-hospital and long-term mortality rates were significantly higher in women [Figure 1], but when age and body habitus (shorter stature) were taken into account, long-term survival rates were similar, despite higher in-hospital mortality rates [6]. Another large study from the New England Cardiovascular Disease Study Group analyzed the data of 13,061 procedures in 12,232 patients who underwent balloon angioplasty. Despite similar success rates for both sexes, in-hospital mortality was significantly higher for women (1.64% vs. 0.7%, $P < 0.01$) [Figure 1]. Non-fatal events, such as myocardial infarction and the need for coronary bypass surgery, were also higher in women, although attributable to a higher incidence of co-morbid conditions [7]. Data from 2,067 consecutive patients who underwent balloon angioplasty at the Hadassah University Hospital in Jerusalem showed the same pattern [8]. Mortality among women was significantly higher (1.4% vs. 0.6%, $P < 0.001$) with similar rates of myocardial infarction and bypass surgery [Figure 1] [8].

Coronary artery stenting has become the mainstay of catheter-based percutaneous coronary intervention in patients with coronary artery disease, and its use has surpassed plain balloon angioplasty in almost all subsets of patients. There are limited published data regarding gender differences in morbidity and mortality following PCI with stents. A recently published study by Mehilli et al. from Germany [9] in 1,001 consecutive women and 3,263 consecutive men who underwent stenting between 1992 and 1998 has shown once again that women were significantly older and more likely to have co-morbid conditions such as diabetes, hypertension and hyperlipidemia. Women had less extensive CAD, were less likely to have a prior myocardial infarction and had better left ventricular function. Compared with men, 30 day mortality and the risk of non-fatal myocardial infarction were significantly higher in women (1.7 vs. 0.8%, $P = 0.02$) [Figure 2]. At 1 year follow-up, however, both men and women had comparable outcomes [9]. A study by Watanabe and colleagues [10] from the United States Nationwide Inpatient Sample, which included more than 1,000 hospitals in 22 states, showed that in-hospital mortality was roughly twofold higher in

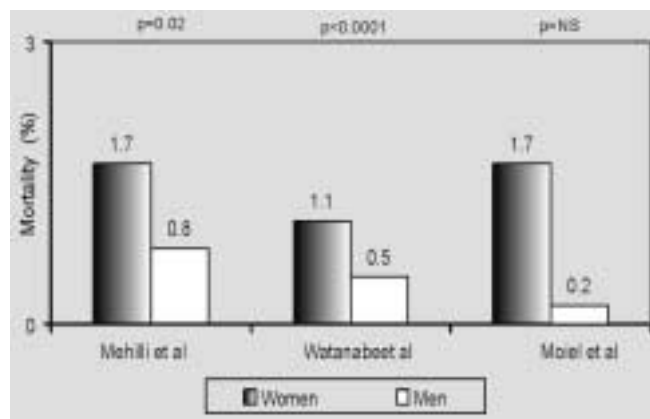


Figure 2. Differences in short-term mortality rates by gender after percutaneous coronary intervention with stents. Data abstracted from references 9–11.

women compared to men, regardless of whether they underwent stenting during acute myocardial infarction or not (4.0 vs. 2.0%, $P < 0.001$ and 1.1 vs. 0.5%, $P < 0.0001$, respectively) [Figure 2] [10].

In this issue of *IMAJ*, Moriel et al. [11] report the results of a retrospective study of 560 consecutive patients, 119 women and 441 men, who underwent PCI with stents between 1994 and 1996. Not surprisingly, female patients were older and had a higher incidence of co-morbid conditions such as diabetes, hypertension and hypercholesterolemia. The incidence of prior myocardial infarction or bypass surgery and angiographic characteristics were similar in both groups. Data were not provided regarding left ventricular function, history of congestive heart failure or body habitus. Procedural success and in-hospital outcomes were similar in both groups, although mortality was higher for female patients [Figure 2]. Vascular and bleeding complications occurred in a small number of patients in both groups. At long-term follow-up, mortality was threefold higher in women compared to men, although it did not achieve statistical significance (3.3% vs. 0.9%, $P = NS$). By multivariate analysis, gender was not an independent predictor of worse outcome [11]. The authors indicated that the main limitation of the study was the small number of patients, especially women, and concluded that women with CAD suitable for percutaneous intervention with stents achieve similar benefit as do their male counterparts.

Given the results of the study by Moriel et al. [11], what have we learned? First, the Israeli female population that undergoes PCI presents substantial differences in baseline clinical characteristics, in the temporal pattern of outcome and in the prognostic factors, concurring with previous studies in other countries. Second, the outcomes from this and all previous studies were strikingly similar, as shown in Figures 1 and 2, and no objective evidence has emerged that would suggest that women with CAD suitable for percutaneous intervention would benefit less than men presenting with comparable clinical and angiographic findings. Third, there are still conflicting results among the different trials regarding the outcome of women after PCI compared to those of their male counterparts. During the early phase after PCI, women usually experience more adverse events than men. In particular, the risk of death or

PCI = percutaneous coronary intervention

myocardial infarction is higher, and the differences in baseline clinical characteristics may not sufficiently explain this increase. The excess risk that women experience during the short-term follow-up gradually diminishes and, over the long-term follow-up, both men and women have essentially the same outcomes. The introduction of stents has not produced a significant change in the large-scale outcome. Lest we forget, stenting relieves angina in many patients and its impact on survival is similar to that of balloon angioplasty.

It is our feeling that we are only at the beginning of understanding the impact of gender differences on the short and long-term outcomes after percutaneous coronary intervention in patients with coronary artery disease. The minor gender differences are not sufficient to dilute the clear clinical benefit of PCI in both genders in spite of a higher procedural risk for women. The long-term success of the procedure is extremely favorable. Future studies should aim to improve the benefits of interventions for both genders, using specific drugs and devices to adjust the optimal treatment for the specific patient.

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