

## Sex and Outcomes After Percutaneous Coronary Intervention: A Cause for Concern for Young Women and Those With ST-Segment Elevation Myocardial Infarction?

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Since the first reports describing mortality differences in women and men with acute myocardial infarction nearly 25 years ago,<sup>1</sup> there has been a plethora of information regarding sex differences in the presentation, management, and outcomes of patients with coronary artery disease (CAD). The data are overwhelming and not uncommonly, the results are often discrepant. So, what do we *know* about CAD in women? We know that there are clear differences by sex in the presentation of patients with CAD. Women are typically about 5 to 10 years older than men and are significantly more likely to have a history of hypertension and diabetes mellitus and to be in heart failure on presentation to the hospital. Fewer women than men are smokers.<sup>1–18</sup> Women are less aggressively treated.<sup>2,17–20</sup> As such, women have a higher in-hospital, 30-day, and long-term mortality as compared with men. Yet, many of the differences in outcomes have been attributed to sex differences in the presentation and treatment of these patients. Although most studies have shown that after adjusting for the higher rate of comorbidities and therapies given, women and men have similar outcomes, some reports have suggested persistently higher adjusted odds for adverse events in women as compared with men.<sup>2,6–10,18–21</sup>

In this issue of *JAHA*,<sup>22</sup> the authors looked at sex differences in procedural events and hospital mortality among women and men referred for percutaneous coronary intervention (PCI) in 218 hospitals in Germany from 2007 to 2009. The advantage of

this analysis relates to the robustness of the data collected, providing detailed information regarding procedural characteristics and outcomes for 185 312 patients. Since the analysis is inclusive of all patients referred for PCI, it avoids some of the potential for treatment bias and permits a more uniform comparison of women and men with CAD undergoing revascularization for predefined clinical scenarios. Because of the extremely large sample size, the authors were able to compare sex differences in outcome among patients presenting with myriad disease conditions including stable ischemic heart disease, non ST-elevation acute coronary syndrome, and ST-segment elevation myocardial infarction (STEMI) as well as patients getting PCI for cardiogenic shock. In addition, the authors were able to examine difference in outcome for women and men in different age groups. The study demonstrated that PCI success rates were generally higher in women than men (although success of PCI was similar in women and men with STEMI). However, women were less likely to undergo a complex PCI procedure. Irrespective of the clinical scenario, vascular complications following PCI were higher in women. As compared to men, age-adjusted hospital mortality was significantly higher in women undergoing PCI for STEMI or cardiogenic shock, but mortality in women and men undergoing PCI for stable symptoms or non ST-elevation acute coronary syndrome was similar. When outcomes in women and men were compared for patients in discrete age groups, mortality was higher in younger women undergoing PCI as compared with younger men, while older women and men had similar mortality.

The findings in this study emphasize 3 very important and consistent themes noted in the literature regarding the sex differences in outcome of patients with CAD:

1. Women referred for PCI have more vascular complications than men.
2. Women with STEMI have a worse prognosis than men.
3. Younger women with CAD have a worse outcome than younger men.

This report lends further (and stronger) support to earlier studies demonstrating a worse prognosis for women as compared with men with STEMI,<sup>6–10,13,14,17,19,21</sup> and for younger women as

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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*J Am Heart Assoc.* 2017;6:e005739. DOI: 10.1161/JAHA.117.005739.

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compared with younger men.<sup>2,7,12–14,19,20</sup> Even among a select group of patients referred for primary PCI (the guideline recommended reperfusion therapy for STEMI), women have a higher in-hospital and 30-day mortality than men<sup>7,8,10,14,21</sup> and this is particularly notable among younger women as compared with younger men.<sup>14</sup> The big question is *Why?*

As stated earlier, women (particularly younger women) have more comorbidities than men, including more diabetes mellitus, hypertension, peripheral artery disease, and chronic kidney disease.<sup>2,19</sup> It has been suggested that traditional cardiovascular risk factors including diabetes mellitus, smoking, and the metabolic syndrome appear to have a greater influential risk for cardiovascular events in women.<sup>23–25</sup> Furthermore, studies have shown that women, especially younger women, are less likely than younger men to receive guideline-recommended care.<sup>2,17,19,20</sup> However, it appears that these differences by sex in presentation and treatment appear to account for only one third of the mortality risk difference noted in younger patients.<sup>2</sup> Even after adjusting for baseline presenting features and therapies administered, younger women with acute infarction are nearly twice as likely as younger men to die before hospital discharge.<sup>2</sup>

Women with acute coronary syndromes (ACS) are more likely than men to have no chest pain or to have atypical symptoms,<sup>2,4,18,20</sup> and this is particularly prominent in younger women.<sup>2,4,20</sup> Women, especially younger women, take longer to arrive after symptom onset.<sup>2,3,6,20</sup> This is likely because of a combination of factors including the lack of recognition that symptoms are related to a heart event, and the tendency to call a doctor, before calling 911. This will inevitably lead to a delay in hospital diagnosis and subsequent treatment. Unlike patients with stable ischemic heart disease, or non ST-elevation acute coronary syndrome, total ischemic time in STEMI is an important determinant of outcomes, and therefore these delays will have a stronger adverse impact on outcome for patients presenting with STEMI as compared with other forms of ischemic heart disease. Although delays to hospital presentation, as well as use of emergency medical services in STEMI have improved over time, there remains a gap in presentation times for women.<sup>26</sup> This highlights the importance of continuing efforts toward raising awareness of heart disease and related symptoms. While there has been a great improvement in heart disease awareness in women over the past 15 years, awareness of heart disease, symptoms related to heart disease, and cardiovascular risk factors remains suboptimal in minority women and younger women.<sup>27</sup>

Bleeding<sup>2,6,8,9,12,16,28</sup> and vascular complications<sup>12,16,28,29</sup> are higher in women and are independent of baseline variables. Bleeding (and vascular complications) are associated with advanced age, lower body weight, and overdosing of anticoagulant medications, all of which are more common in women than men. A prespecified subgroup analysis of the Radial Vs

femorAL access for coronary intervention (RIVAL) Trial<sup>29</sup> demonstrated a similar proportional reduction in vascular complications with radial artery access as compared to femoral artery access in women and men. In the Study of Access Site for Enhancement of PCI for Women (SAFE-PCI) Trial, which randomized women undergoing PCI to radial or femoral artery access, radial artery access resulted in a significantly lower rate of vascular complications and bleeding.<sup>30</sup> Unfortunately, women are more likely than men to have failed radial artery access, with higher rates of radial artery vasospasm and arterial tortuosity, leading to difficulties with catheter advancement.<sup>29</sup> Although the introduction of bleeding avoidance strategies including the use of bivalirudin in lieu of alternative anticoagulant/antiplatelet regimens, “safe-zone arteriotomy,” and radial artery access has resulted in decreased bleeding events over time, bleeding and vascular complications remain higher in women compared with men, and this is particularly notable in young women and women undergoing emergency PCI such as in STEMI or for cardiogenic shock.<sup>13</sup> It is important to note that the use of radial artery access in the current study by Heer et al<sup>22</sup> was estimated to be very low.

Women, especially younger women, with ACS (including STEMI) are less likely than men to have extensive CAD and a larger proportion of younger women have nonobstructive CAD as compared with younger men.<sup>5,7,9,10,12,18</sup> This implies that there may be alternative mechanisms leading to the manifestation of CAD in some women, extending beyond atherosclerosis. While the overwhelming majority of women with ACS or stable ischemic heart disease have coronary atherosclerosis, one needs to consider alternative nonatherosclerotic causes of CAD in some of the younger women or in a select group of women with STEMI. Vasospasm, vasculitis, fibromuscular dysplasia, and spontaneous coronary artery dissection are all reportedly more common in women. In addition, plaque erosion leading to an ACS is more commonly seen in women than men. It is important to always have a wide differential for other causes of CAD, especially in young women without cardiac risk factors who present with severe stenosis, or in women with ACS who do not have obstructive CAD. These conditions sometimes respond differently to the standard therapies used to treat atherosclerotic heart disease. The use of optical coherence tomography or intravascular ultrasound imaging can aid in diagnosing some of these conditions, thereby supporting the use of additional therapies to treat the underlying disease process, including vasodilating agents or anti-inflammatory drugs.

The overarching point we must remember is that young women and women with STEMI have a worse outcome, and this is likely a combination of factors. When evaluating women presenting with symptoms suggestive of ACS (or even atypical symptoms), we need to maintain a high index of suspicion so that we can make an early diagnosis and begin treatment as soon as possible. Furthermore, we need to be aggressive about

administering guideline-recommended therapies to women with CAD, while employing maneuvers to minimize bleeding and vascular complications. Finally, we must always maintain a solid clinical acumen, especially in the younger cohort of women, to help identify the rare case (or maybe not so rare) in which there is an unusual etiology of CAD.

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**Key Words:** Editorials • complication • mortality • percutaneous coronary intervention • ST-segment elevation myocardial infarction • women