



Editorial

Sex Differences in Acute Myocardial Infarction: Good News and Bad News

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See article by Madan et al., pages 1651–1660 of this issue

Although mortality caused by cardiovascular disease has declined over the past few decades,¹ the incidence of hospitalization for acute myocardial infarction (AMI) is showing a concerning increase among young women < 55 years of age.² Higher mortality in young women compared with young men hospitalized with AMI has been documented in numerous studies. In addition, lower rates of coronary angiography and the use of evidence-based medication in female patients with AMI have persisted for decades.^{1–3}

Madan et al.⁴ evaluated 38,071 young patients, aged 18 to 55 years, admitted to hospitals for AMI in Ontario between 2009 and 2019. The study aimed to determine whether sex disparities continue to exist in contemporary care, especially in younger patients with AMI. They used population-linked clinical and administrative data to assess comorbidities, angiographic findings, revascularization rates, and 1-year all-cause mortality or readmission for unstable angina, AMI, heart failure, or stroke. One-year mortality did not differ by sex after adjustment for baseline differences; however, cardiovascular and all-cause readmission rates were significantly higher in female patients: 25.8% vs 21.1%. Almost all patients underwent coronary angiography (96%), but revascularization rates were lower in female patients, probably reflecting the lower prevalence of obstructive disease. The prevalence of comorbidities was worryingly higher in female patients: particularly diabetes, hypertension, chronic obstructive pulmonary disease, and renal failure. Of particular concern is the sharp increase in the prevalence of diabetes in female patients: from 25% in 2009 to 34.9% in 2018. Smoking rates were high in both

sexes—46.9% overall—which is in stark contrast to the overall population rate of 15.8%.⁵ Although the authors concluded that some sex-based care gaps are closing, they thought that the high levels of comorbid conditions—especially among female patients—underscored the need for intensive primary prevention.

Although Madan et al.⁴ have demonstrated that the adjusted 1-year mortality rate did not differ by sex—2.9% and 2.8% in women and men, respectively—it is important to note that the crude rates—3.6% and 2.5%—demonstrate a significantly higher rate in female patients ($P < 0.001$). By adjusting for baseline differences, the sex difference is significantly attenuated. In other words, if women and men share the same burden of comorbid conditions, age, rural residence, and socioeconomic status, the mortality rate at 1 year no longer differs by sex. So, although this is good news, it is important to recognize that young women hospitalized for AMI do not look like their male counterparts. Indeed, they have a much higher burden of comorbid conditions, and these comorbid conditions are driving the higher crude mortality rate in female patients. It is important to note that, on average, the population incidence rate of AMI in men is 2.1 to 2.5 times higher than in women⁶; thus, the absolute number of men who die of AMI in this young cohort will be greater, even though the mortality rate is higher in women (Fig. 1).

In similar studies conducted in young adults (aged ≤ 50 years) presenting with a first MI in the United States and Canada, higher rates of comorbid conditions were also noted in women compared with men.^{3,7} In a US study of 2097 patients (19% female), there was no sex difference observed for in-hospital mortality, but at a median follow-up of 11.2 years, the all-cause mortality rate was significantly higher in female patients, even after adjustment (hazard ratio, 1.63; $P = 0.01$).³ However, in the **Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond—Premature Acute Coronary Syndrome (GENESIS-PRAXY)** study from Canada,

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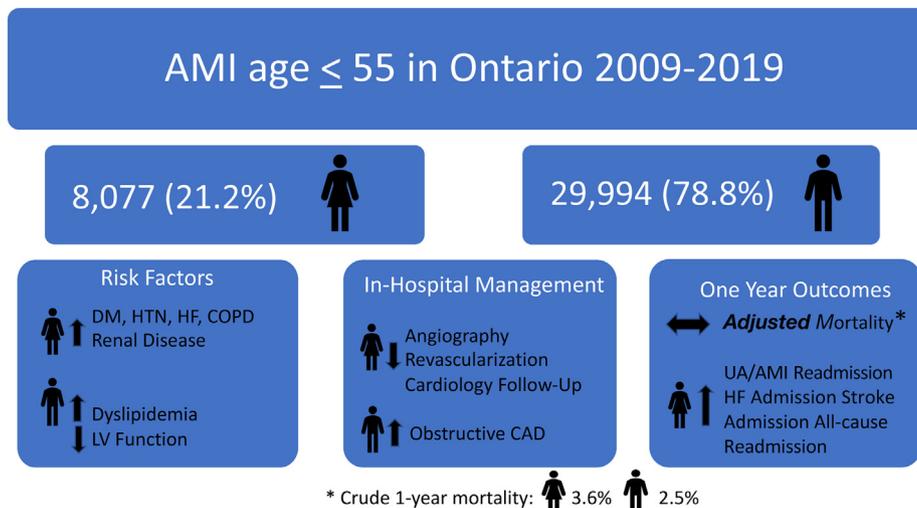


Figure 1. Study outline with key sex differences.

neither the crude nor the adjusted mortality rates at 1 year differed by sex, but the crude rates were very low—0.6% in men and 1.3% in women; $P = 0.31^7$ —thus limiting the power of the study.

Although the use of coronary angiography in this study was high (95.9% overall), there was still a significant—albeit it small—difference favouring the use of coronary angiography in men: 96.6% vs 93.5%, $P < 0.001$. Of note, the use of angiography was also high in GENESIS-PRAXY (98.5%) and the US Mass General Brigham YOUNG-MI registry (94%), but although there was no sex difference in GENESIS-PRAXY, a small and significant underuse of angiography was also seen in the US study: 93.5% of female patients and 96.7% of male patients ($P = 0.003$). In both the Madan et al. study and the US study, coronary revascularization remained significantly lower in women: 66.0% vs 84.8% ($P < 0.001$) and 82.1% vs 92.6% ($P < 0.001$), respectively. However, this is likely a reflection of less obstructive coronary artery disease (CAD) in women, which was seen in both studies. Indeed, numerous studies have reported a higher prevalence of non-obstructive CAD in women and a higher occurrence of microvascular disease, which would not be evident on angiography.⁸

Given the ages of the Ontario cohort—aged 18 to 55 years—the authors were unable to determine if there were any sex differences in postdischarge medication use. The underuse of evidence-based medications in women post-AMI has been well documented, and the sex gap has proved to be stubbornly persistent.⁹

In contrast to the low mortality rate in this young AMI population, more than one-quarter of patients were readmitted within 1 year post-AMI. Indeed, 27.9% of women and 20% of men were readmitted within 1 year. Importantly, cardiac readmissions, unstable angina or AMI, heart failure, and stroke were all significantly higher in women, although the overall higher readmission rate was driven by noncardiac causes. The impact of readmission in this young population cannot be overlooked given that most are still in the workforce. Even after adjustment for baseline differences, readmission rates remained significantly higher in women. One

possible explanation for the higher readmission rates in women may be the longer delay to catheterization that has been observed in female patients presenting with ST-elevation MI.¹⁰ It has also been noted that women have higher complication rates from both acute coronary syndromes (ACS) and its subsequent treatment. Some of the factors contributing to this risk include delayed presentation, delayed diagnosis, and less guidelines-based therapy both before and after ACS.¹¹

Depression was not measured in the study by Madan et al., but its role in cardiovascular events, especially in women, has been well documented.^{12,13} In the seminal work by GENESIS-PRAXY,¹⁴ depression was found to be much higher in young women than young men, and, in the Mass General Brigham YOUNG-MI study, twice as many women as men had depression. Depression also affects adherence to medications and lifestyle changes.¹⁵

This important analysis by Madan et al. presents us with both good news and bad news. Although coronary angiography is now routinely offered to almost 96% of patients with AMI, small but significantly lower rates were observed in women. And, although adjusted mortality rates at 1 year do not differ by sex, crude mortality rates continue to demonstrate higher rates in women, apparently driven by higher levels of comorbid conditions. Readmission rates—both cardiovascular and noncardiovascular—remain significantly higher in women; adjustment for baseline differences did not alter this finding, suggesting that factors other than comorbid conditions are driving these readmissions.

Although the results of this study provide evidence that the sex differences in AMI are diminishing, the high rates of cardiovascular risk factors, especially in this younger cohort of women, requires attention. Particularly concerning is the increase in diabetes: 0.99% per year in women compared with 0.45% per year in men. There is also an urgent need to understand what is driving the higher readmission rates in females. Is this caused by unrecognized depression, less use of evidence-based medication post-AMI, or delays in access to care? Gender roles were not addressed in this study, but their importance needs to be considered, given the impact of gender

on the likelihood of follow-up, economic challenges with filling prescriptions, and stress associated with work and family responsibilities, particularly in this young age group. More focus on these areas of investigation is clearly needed.

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