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EDITORIAL COMMENT

Should Sex Matter When it Comes to High-Intensity Statins?*

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Historically, women have received less aggressive treatment with preventive therapies than men for acute myocardial infarction (AMI) (1), despite an increased mortality risk (2). Over the last 2 decades, substantial efforts have been made to heighten awareness of heart disease in women and reduce sex-related disparities in research and clinical care. The increased application of evidence-based preventive strategies is associated with a significant decline in cardiovascular disease (CVD) mortality in women, but there are worrisome trends of increasing mortality from CVD in men since 2009 and in women since 2014 (**Figure 1**) (3).

Statin therapy is a cornerstone of secondary prevention. The efficacy of statins for women with CVD is well established in randomized clinical trials (1). Statin use in the secondary prevention of CVD is endorsed by the American Heart Association in evidence-based guidelines exclusively focused on CVD prevention in women (4). In 2013, the American College of Cardiology/American Heart Association guidelines on the treatment of cholesterol to reduce CVD recommended the use of high-intensity statins in secondary prevention for both men and women (5).

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The study by Peters et al. (6) reported in this issue of the *Journal* suggests that there is a persistent sex-based gap in our application of guideline recommendations. Using 2 large cohorts of United States adults from commercial and government insurance databases, this retrospective study found that women were less likely than men to fill a prescription for high-intensity statins within 30 days after hospital discharge for AMI. The underutilization of preventive therapies for secondary prevention of CVD in women has been described previously (7). The study by Peters et al. specifically focused on persisting sex differences in statin intensity use, 1 year after guideline recommendations advocated for use of high-intensity statins. The results show surprisingly low percentages of patients filled a high-intensity statin: 56% of men and 47% of women. Obvious limitations include: 1) short time frame for adoption of the guidelines; and 2) the fact that the data are based on prescriptions filled and therefore do not account for the entire cohort of post-AMI patients. Regardless, this finding suggests an ongoing disparity in utilization of guideline-recommended therapy between women and men.

The authors (6) discuss the possibility that persistent provider bias may explain the disparity, with the erroneous ongoing perception of women with AMI being at lower risk for recurrent events. This theory would be disappointing considering the extensive efforts to educate providers and public to the contrary.

However, perhaps the provider bias can be explained by the pathophysiologic differences between women and men in ischemic heart disease (IHD). Women presenting with acute coronary syndrome are less likely than men to have flow-limiting coronary artery disease and more likely to present with nonobstructive IHD (8). Data have shown that other mechanisms exist among these women, such as coronary microvascular dysfunction, vasospasm, plaque erosion, and thrombus formation. Nonobstructive IHD is not benign. It is associated with recurrent angina as well as increased cardiac events compared with women with normal coronaries.

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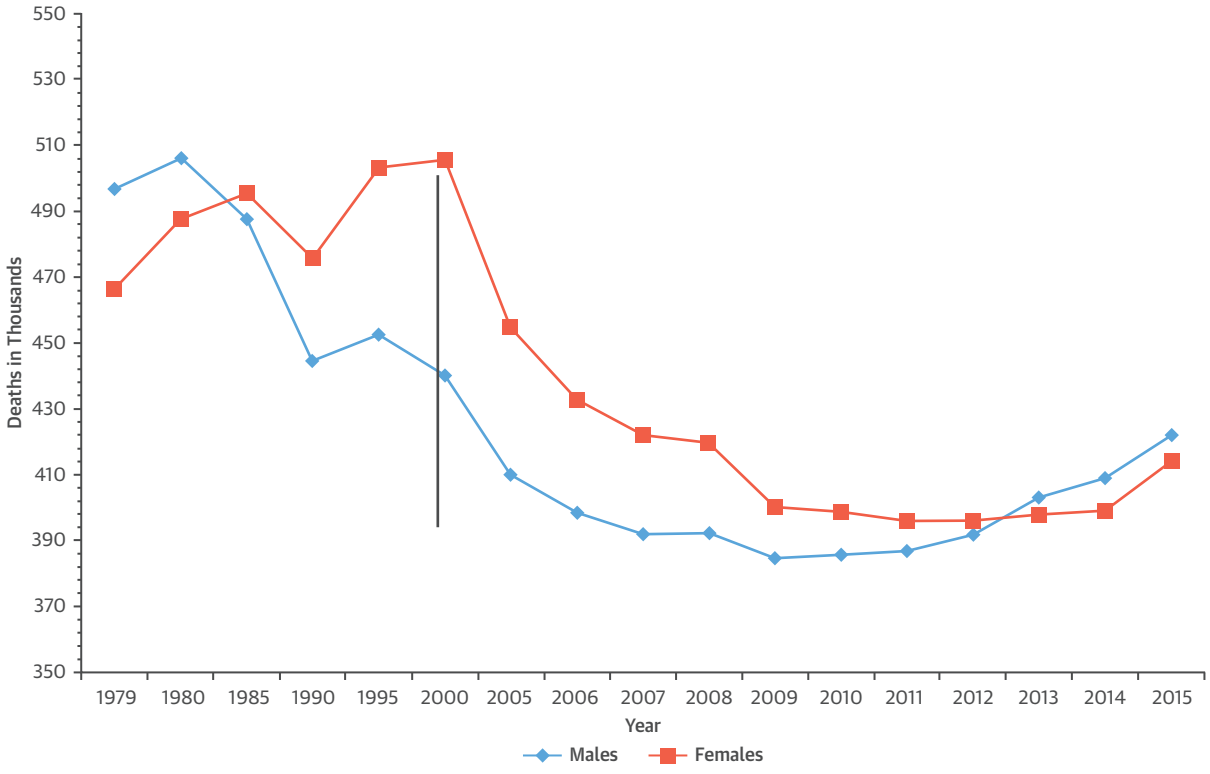
FIGURE 1 **Cardiovascular Disease Mortality Trends for Males and Females (United States: 1979 to 2015)**



Cardiovascular disease excludes congenital cardiovascular defects (International Classification of Diseases-10th Revision, codes I00 to I99). The overall comparability for cardiovascular disease between the International Classification of Diseases-9th Revision (1979 to 1998), and International Classification of Diseases, 10th Revision (1999 to 2015), is 0.9962. No comparability ratios were applied. Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute. Reprinted with permission from Benjamin et al. (3).

Without flow-limiting coronary lesions on angiography, providers may not recognize nonobstructive IHD as warranting a high-intensity statin prescription. Most patients with nonobstructive IHD exhibit coronary atherosclerosis on invasive imaging such as intravascular ultrasound. Furthermore, treatment with statins has been associated with a significant reduction in mortality for this group of patients (9). However, to date, no guideline-recommended therapy is available for nonobstructive IHD. Therefore, statin initiation and intensity of statin dose are left to the discretion of the provider.

In women of reproductive age, concerns about the potential teratogenicity of statin therapy may present a barrier to initiation of treatment. Statins continue to be considered teratogenic and are recommended to be discontinued before conception (10). The study by Peters et al. (6) reported that the subgroup of younger adults (<50 years of age) had a greater sex disparity in filling prescriptions for high-intensity statins, and it is the group of reproductive age women (35 to 44 years of age) that have been shown to have the slowest rate of decline in CVD rates in the United States (11). A better understanding of the risks of statins in reproductive age women may improve adherence to statin guidelines for this younger cohort.

It is also possible that the less-intense statin dose for women after AMI found in this study (6) was intentionally chosen based on clinical factors such as previous intolerance to drug, known drug interactions, unfavorable clinical characteristics of the patient, or refusal of the patient to take a higher dose. Studies have shown that, with regard to statin therapy, these factors tend to be more prevalent in women (12).

Previous statin intolerance may serve as another barrier to initiation of, or titration to, a high-intensity statin. Statin discontinuation rates have also been reported to be higher in women than in men, and

women are more likely than men to report nonadherence of statins due to muscle-related side effects. There is inadequate inclusion of sex-specific analyses in statin-related trials to further understand these reported findings (12).

Older women seem to be particularly vulnerable to statin-associated muscle symptoms (13). This outcome is especially true for those with multiple comorbidities and established polypharmacy. Myalgias seem to be dose dependent in aging individuals, and for this reason, many providers initiate statins at a low dose with subsequent titration as tolerated. The 2013 guideline emphasizes that the use of statin therapy should be individualized in patients >75 years of age, even in people with clinical CVD, taking into consideration life expectancy, functional status, goals of therapy, and comorbidities.

Although explanation for the underutilization of guideline-recommended high-intensity statins cannot be fully determined, the study by Peters et al. (6) supports the recognition of ongoing sex-specific treatment differences despite considerable efforts to reduce this gap. Differences in statin prescription and adherence between women and men may account for suboptimal outcomes in women post-AMI. We need to continue to expand our understanding of the difference in pathophysiology of IHD in women through sex-specific research. We also need to discover novel management strategies specific to women considering these differences. The unique barriers facing both women and men with regard to receiving evidence-based, guideline-recommended care should be characterized. We think sex should matter, as well as age, race, and ethnicities, when it comes to patient care and adherence to guidelines. Implementation of such sex-specific strategies will improve CVD outcomes for women and, by doing so, may also improve outcomes for men.

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