8th Annual Women's Heart & Vascular Symposium

Lipid-Lowering Therapies: Risks in Women and Evidence-Based Options

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Cardiovascular disease is the chief cause of death in women in the United States. Therefore, sex-based (biological) and gender-based (sociocultural) variations in the pathophysiology, symptoms, and response to pharmacologic interventions should be considered between men and women during primary and secondary prevention of coronary artery disease. In the evaluation of patients who have signs and symptoms of myocardial ischemia, women typically exhibit more symptoms and functional disability than do men. They also have a higher prevalence of nonobstructive coronary artery disease[1] and worse cardiovascular outcomes. Therefore, it is important to recognize the prevalence of traditional atherosclerotic cardiovascular disease (ASCVD) risk factors (dyslipidemia, hypertension, smoking, obesity, physical inactivity, and diabetes mellitus [DM]), their differential impact, and emerging, nontraditional risk factors unique to or more often identified in women (such as pregnancy-related disorders, psychological depression, and autoimmune diseases).

Statin Use in Women

Abnormally low levels of high-density-lipoprotein cholesterol and elevated low-density-lipoprotein cholesterol (LDL-C) are well established as modifiable risk factors for cardiovascular disease. Greater ASCVD risk is typically not observed in women before menopause. As in men, pharmacologic therapy for hyperlipidemia in women as secondary prevention has clearly reduced recurrent cardiovascular events and ASCVD mortality rates. However, data on the benefits of primary prevention in women are lacking; most primary prevention trials included few women and provided no sex-specific results. Statins are the cornerstone of LDL-C–lowering therapy and ASCVD prevention. Investigators who performed a meta-analysis of 27 statin therapy trials concluded that the proportional reduction in major vascular events per 1.0 mmol/L reduction in LDL-C was similar for men and women—risk ratio for women, 0.84 (99% CI, 0.78–0.91); versus men, 0.78 (99% CI, 0.75–0.81)—regardless of the baseline level of ASCVD risk or subtype of ASCVD outcome.[2] Despite the known benefits of lipid-lowering medications, investigators[3] have identified sex-specific differences in consistent treatment and adherence to lipid-lowering regimens: women are less likely to be prescribed statin therapy and adhere less to it. These concerns underscore the importance of improving the awareness of patients and clinicians about the benefits of lipid-lowering therapies, and further analyzing reasons for the disparities.

Side Effects of Statins in Women

No compelling evidence supports the claim that statins are less safe for women than for men. In the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study, which enrolled more women than had any other statin trial, rates of myopathy between men and women did not differ.[4] The results, however, revealed that women taking rosuvastatin had a greater increase in HbA_{1c} level and more risk of developing new DM than did women who took a placebo. The precise mechanism behind statin-induced DM remains unclear, although most patients who develop DM have prediabetes or baseline features of metabolic syndrome that indicate a high risk of DM. It is hypothesized that statins have detrimental effects on insulin sensitivity and β-cell secretion. Various statins and various doses of statins also appear to have differential metabolic effects that need

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to be considered when developing treatment plans for patients at high risk for DM.

New-onset DM consequent to statin therapy has not yet been associated with an increase in adverse cardiovascular events. In addition, data suggest that the clinical benefits of statin therapy outweigh the increased risk of DM. Investigators[5] who performed a meta-analysis estimated that treating 255 patients with standard-dose statin therapy for 4 years would avoid 9 vascular events and lead to one case of new-onset DM (9:1 benefit-risk ratio). Despite few long-term studies, the benefits of statins outweigh the risks in women, as well. It is therefore recommended that statins be first-line therapy for male and female patients at risk of ASCVD. Patients taking statins and who are at high risk for DM should undergo regular blood glucose monitoring. It is also recommended that these patients be counseled about regular physical activity and dietary interventions that would reduce their risk of developing DM.

Nonstatin Therapies

Nonstatin therapies like ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may also reduce the risk of ASCVD. Results of the IMPROVE-IT trial showed the benefit of adding ezetimibe to statins among men and women with recent acute coronary syndrome, thus supporting the use of intensive lipid-lowering therapy in combination to optimize cardiovascular outcomes.[6] In the FOURIER trial, adding evolocumab to high-intensity statin therapy in patients with stable ASCVD reduced the risk of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, and coronary revascularization when compared with placebo; the benefits were largely consistent across major subgroups, including age, sex, and type of atherosclerotic vascular disease.[7]

Conclusion

The substantial differences in epidemiology, pathology, and therapeutic response between men and women should be considered when treating women who have or might have ischemic heart disease. For evaluation of sex-related differences in the efficacy of statins prescribed to manage ASCVD, women need to be better represented in prospective randomized clinical trials.

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