Statin Therapy in Women

Released April 1, 2014

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Background

Statins reduce coronary events and stroke in high-risk women by approximately 20%, but more than half of cardiovascular events occur in low-risk women. Few studies have evaluated statin use for primary prevention in women. This Practice Pearl reviews statin use in both primary and secondary prevention trials in women, safety concerns, and the latest guidelines on treatment of cholesterol.

Statin Use for Secondary Prevention

Although women are generally underrepresented (<20% of participants) in secondary prevention trials, clear evidence has emerged to support the use of statins in both men and women with known cardiovascular disease (CVD). A meta-analysis by Gutierrez and colleagues provided sex-based analysis of 11 secondary prevention trials that included approximately 11,000 women and 32,000 men. This study concluded that statin therapy reduced risk of CVD similarly in women (relative risk [RR] = 0.81; 95% confidence interval [CI], 0.74-0.89) and men (RR = 0.82; 95% CI, 0.78-0.85). Although statins significantly reduced stroke and all-cause mortality in men only, this finding may be attributable to limited statistical power in women.

In another meta-analysis, women had a clear benefit from statin therapy for secondary prevention of CVD (odds ratio [OR], 0.78; 95% CI, 0.70-0.88); however, benefits for primary prevention were less robust (OR, 0.85; 95% CI, 0.75-0.98). In contrast to the Gutierrez analysis, a significant stroke benefit was found for women (OR, 0.74; 95% CI, 0.55-0.99), but all-cause mortality was reduced only in men.
In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 trial, results of aggressive lipid lowering after acute coronary syndrome using standard (pravastatin 40 mg) versus intensive (atorvastatin 80 mg) therapy for 2 years were evaluated. Women randomized to intensive therapy had a large reduction in death, myocardial infarction (MI), unstable angina, revascularization, or stroke (hazard ratio [HR], 0.75; 95% CI, 0.57-0.99); the corresponding HR for men was 0.86 (95% CI, 0.75-0.99).\(^3\) Statins benefit both sexes in secondary prevention settings. Despite these findings, women hospitalized with acute coronary syndrome are less likely to be discharged with a statin than men.

**Statin Use for Primary Prevention**

The role of statins in primary prevention in women is less clear. The Justification for Use of Statins in Prevention, an Intervention Trial Evaluating Rosuvastatin (JUPITER) tested statin therapy for primary prevention of CVD in men and women with low levels of low-density lipoprotein cholesterol (LDL-C; <130 mg/dL or <3.36 mmol/L) but elevated high-sensitivity C-reactive protein (>2 mg/dL or >0.05 mmol/L).\(^4\) In this trial, 38% of participants were women. Rosuvastatin was found to lower global CVD event risk in men and in women; however, the absolute benefit in women was small, and the 5-year number needed to treat to prevent a major CVD event was almost twice as high in women as in men.\(^4\)

A sex-specific meta-analysis by Bukkapatnam and associates\(^5\) of 6 primary prevention trials with the mean age of women studied 62.5 years and baseline LDL of 144 mg/dL (or 3.72 mmol/L) found a significant reduction in coronary heart disease in women (RR, 0.78; 95% CI, 0.64-0.96) but not all-cause mortality (RR, 0.90; 95% CI, 0.60-1.35). In another meta-analysis of 18 primary and secondary trials, data were analyzed by baseline level of risk: low, medium, or high. For primary events, statin use benefited women at all levels of risk but had the most significant benefit in the lowest risk category (OR, 0.59; 95% CI, 0.41-0.87 for low risk; OR, 0.75; 95% CI, 0.64-0.89 for medium risk; and OR, 0.88; 95% CI, 0.81-0.95 for high risk).\(^6\)

In the Cholesterol Treatment Trialists’ Collaboration meta-analysis, the use of statins in low-risk participants was evaluated. The greatest benefit was found in the lowest-risk group, with a 38% risk reduction of major vascular events.\(^7\) Overall, the HRs for major vascular events with statins in primary prevention were 0.84 (95% CI, 0.79-0.89) in women and 0.78 (95% CI, 0.76-0.80) in men. Although the CVD risk reductions were robust in both sexes (both \(P\) values <.0001), the difference in effect between sexes was significant (\(P=0.02\)).

**Safety of Statin Use**

Statin therapy is classified as a category X drug during pregnancy and should be avoided in women with the intent of childbearing. Myalgias have also been reported in 1% to 5% of participants in clinical trials; however, this is as high as 20% in observational studies.\(^8\) FDA recently reduced liver function monitoring, which now should occur just once after starting or changing to a new statin. It is unknown whether adverse hepatic effects differ by sex. Statin use may cause increased blood glucose and risk of diabetes. In meta-analyses, a 12% increased risk of diabetes was found.\(^9\) The American Heart Association (AHA) and American Diabetes Association have stated, however, that the cardiac benefits of statin use outweigh the risk of developing diabetes. Available research does not provide consistent evidence for an increase or a
decrease in cancer risk with statin use. Finally, there are rare reports of nonserious memory/cognitive impairment. Available studies, however, do not suggest that the cognitive changes are common or lead to a persistent decline in memory.

2013 ACC/AHA Guidance Regarding Statin Use

The 2013 American College of Cardiology (ACC)/AHA guidelines on the treatment of cholesterol have made considerable changes to previous recommendations. The guidelines continue to emphasize diet, exercise, and weight loss for lipid management. However, the new guidelines move away from targeting a specific cholesterol goal and instead recommend moderate- or high-intensity statin therapy for 4 specific patient types: 1) those with CVD; 2) those with LDL-C of 190 mg/dL or higher*; 3) patients aged 40 to 75 years with type 1 or 2 diabetes mellitus and LDL-C between 70 mg/dL and 189 mg/dL**; and 4) patients aged 40 to 75 years with LDL-C between 70 mg/dL and 189 mg/dL** and 10-year risk of CVD (using their new risk calculator) of ≥7.5%. This risk calculator (available as a mobile app called “ASCVD Risk Estimator”) takes into account age, sex, race, cholesterol, blood pressure, diabetes, and smoking status and estimates the future risk of MI and stroke. If a clinician remains uncertain about statin use on the basis of these calculations, additional parameters such as family history of premature CVD, high-sensitivity C-reactive protein, coronary artery calcium score, and/or ankle-brachial index may be considered. Although controversial, this new risk calculator represents an improvement over previous risk-prediction models, especially for women.

*4.9 mmol/L or higher
**1.8 mmol/L and 4.9 mmol/L, respectively

Summary

- In secondary prevention in women, statin therapy reduces the incidence of coronary events and stroke by approximately 20%.
- Statin therapy may increase serum glucose levels, but cardiovascular benefits outweigh potential risks in populations at higher baseline risk of CVD.
- The 2013 ACC/AHA guidelines on the treatment of cholesterol recommend statin therapy for 4 specific patient groups and use a novel risk calculator for MI and stroke to determine whether statin therapy should be used in primary prevention.
- In view of safety concerns, which may have particular relevance to women, statins should be avoided in low-risk groups and targeted to women at elevated risk of CVD.
- Future research on treatment should focus on sex-specific differences in benefits and risks for patients at different levels of CVD risk.

References


**Disclosures**

Drs. Shufelt and Manson report no relevant financial relationships.

This *Practice Pearl*, developed by the author(s), provides practical information on current controversial topics of clinical interest. It is not an official position of The North American Menopause Society (NAMS). Clinicians must always take into consideration the individual patient along with any new data published since the publication of this statement on April 1, 2014.

Made possible by donations to the NAMS Education & Research Fund.

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