Statins in the Primary and Secondary Prevention of Cardiovascular Disease in Women

Facts and Myths

Salim S. Virani, MD, PhD

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From: *Health Policy and Quality Program, Michael E. DeBakey VA Medical Center Health Services Research and Development Center of Excellence; Section of Cardiovascular Research, Department of Medicine, Baylor College of Medicine; and Center for Cardiovascular Disease Prevention, Methodist DeBakey Heart & Vascular Center; Houston, Texas 77030*

Address for reprints: *Salim S. Virani, MD, PhD, Health Services Research and Development (152), Michael E. DeBakey Veterans Affairs Medical Center, 2002 Holcombe Blvd., Houston, TX 77030*

E-mail: *virani@bcm.edu*

It has been suggested that statins do not lower the risk of cardiovascular disease (CVD), especially in primary prevention for women. In this article, we first describe CVD risk prediction associated with various lipid fractions in men and women, and then present a review of the literature on the efficacy of statins in primary and secondary prevention of CVD. Last, we describe sex disparities in cholesterol care in women with established CVD.

Cardiovascular Disease Risk Associated with Various Lipid Fractions in Men and Women

Multiple studies have shown that the increased risk of CVD associated with elevated levels of lipids and lipoproteins is comparable between men and women. In the Atherosclerosis Risk In Communities (ARIC) study,[1] risk ratios for coronary heart disease (CHD) associated with a 1 standard-deviation increase in low-density-lipoprotein cholesterol (LDL-C), total cholesterol, and high-density-lipoprotein cholesterol were comparable between men and women at 10 years of follow-up. Although women had very few events in the low-risk deciles for each lipid fraction, the fully adjusted models (including each lipid fraction, smoking, blood pressure, antihypertensive-medication use, and diabetes mellitus) showed much better CVD risk prediction in women than men. A meta-analysis of 29 studies showed a consistent association between triglyceride levels and future risk of CVD in both men and women.[2] In a recent 20-year follow-up of ARIC study participants,[3] lipoprotein(a) levels (known to be higher in women and in blacks of both sexes) were associated with increased CVD risk (CHD or ischemic stroke) across both sexes and both racial groups (blacks and whites).

Magnitude of Benefit Associated with Statin Use in Men and Women

The meta-analysis performed by the Cholesterol Treatment Trialists' (CTT) Collaboration of 170,000 participants in trials of statin therapy[4] showed that the 1-mmol/L (38.66-mg/dL) reduction in LDL-C associated with statin treatment (vs placebo) was associated with a 22% relative risk (RR) reduction in major vascular events. Similar results were obtained when intensive statin therapy versus less intensive therapy were compared. Statin therapy was also associated with a 14% reduction in risk of death from vascular causes and a 10% reduction in overall risk of death. Statin therapy in this large meta-analysis was not associated with any increase in the incidence of cancer or of death from any cancer. It is also important to note that the effects were comparable between men and women, and between those with no history of CHD (primary prevention) versus those with a history of CHD (secondary prevention).

In specific regard to primary prevention in association with statin use, a meta-analysis performed by Brugts and colleagues[5] in 2009 showed a 12% reduction in all-

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cause death, a 30% reduction in major coronary events, and a 19% reduction in major cerebrovascular events, with no increase in the incidence of cancer. It has been argued that this meta-analysis included some participants with a history of CVD, but when the researchers removed from their analyses 3 trials with 4,445 participants who had experienced previous cardiovascular events, the results did not change (13% reduction in all-cause mortality). No heterogeneity of effect was seen between men and women. In 2011, the Cochrane Research Group found, in another meta-analysis of statin therapy in primary prevention, a similar reduction in the all-cause mortality rate (16% relative reduction).[6] On the other hand, when Ray and colleagues[7] published a meta-analysis of the effect of statins on all-cause death among participants without CHD, it showed a nonsignificant reduction (risk ratio [RR]=0.91; 95% confidence interval [CI], 0.83–1.01). One should note that, in this meta-analysis, the 95% CI barely crossed 1.

In terms of the efficacy of statin therapy for primary prevention of CVD in women, a meta-analysis performed by Bukkapatnam and associates[8] showed a 22% reduction in CHD events in women who had no history of CHD (RR=0.78; 95% CI, 0.64–0.92). The risk ratio for all-cause death was reduced by 10%, although it was not statistically significant (RR=0.90; 95% CI, 0.60–1.35). Similarly, in the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER),[9] rosuvastatin therapy was associated with a similar RR reduction of CVD events in women (hazard ratio [HR]=0.54; 95% CI, 0.37–0.80) and men (HR=0.58; 95% CI, 0.45–0.73). All-cause death was not significantly reduced (HR=0.77; 95% CI, 0.55–1.06) in women. In that same study, an updated meta-analysis—exclusively of primary-prevention trials in women—showed that statin therapy was associated with a 37% reduction in total CVD events (RR=0.63; 95% CI, 0.49–0.82), although the total mortality (RR=0.78; 95% CI, 0.53–1.15) was not significantly reduced.

In summary, these data suggest that statin therapy reduces CVD events, including death, in secondary prevention for both men and women. For primary prevention, statin therapy reduces major CVD events in men and women, but we can debate whether it reduces all-cause death, especially in women.

Sex Disparities in Cholesterol Care and Statin Use in Women

There are still sex disparities in cholesterol care. A study from the Department of Veterans Affairs[10] showed that women veterans with CVD were less likely than male veterans to have LDL-C <100 mg/dL (odds ratio=0.56; 95% CI, 0.45–0.72). In addition, women veterans were less likely to receive treatment intensification (odds ratio=0.66; 95% CI, 0.43–1.00) for elevated cholesterol levels. In other settings, similar disparities in statin use have been described in women with obstructive coronary artery disease.[11]

In conclusion, disparities remain in the dyslipidemia management of women despite the similarity of CVD risk predictions for women and men and despite the proven benefit of statin therapy in women for the reduction of CVD events. This treatment gap is an area to target for future quality-improvement initiatives.

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