Controversy and Consensus About Statin Use

It Is Not About the Sex*

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If statistics is a science of probability then Sir William Osler expressed the limitations of its applications when he articulated “Medicine is a science of uncertainty and an art of probability” (1). Despite widespread consensus about statin use for the secondary prevention of cardiovascular disease (CVD) in both sexes, there has been substantial debate with regard to the use of statins for primary prevention among women. Much of the discourse has centered on the fact that women have not participated in primary prevention trials to that extent that men have; therefore, less-definitive conclusions can be drawn about the likelihood of benefits and risks among women. The short-term absolute risk of a future cardiovascular event among women is substantially lower than men in a primary prevention population, further amplifying the challenge of under-representation of women in primary prevention trials. The potential for pooling individual studies to provide a more precise single estimate of a treatment effect was recognized over 100 years ago by the statistician Karl Pearson as a method to reduce error in drawing conclusions based on small group sizes (2).

The current meta-analysis by Kostis et al. (3) in this issue of the Journal, which included trials with 141,235 participants, adds unique information to the existing body of evidence aimed to examine a possible interaction between sex and the effects of statins on the prevention of CVD. The authors conducted a systematic published data search to identify relevant randomized controlled clinical trials reporting sex-specific outcome data. Of the more than 2,300 potential studies identified, 18 met all the inclusion criteria for the meta-analysis (8 primary prevention trials), 2 included sex-specific data on adverse effects, and all but 1 were funded by the pharmaceutical industry. Pooled weighted treatment effects were calculated overall and by sex with random effects models, and then pre-specified analyses were conducted according to the category of prevention trial (primary, secondary, or mixed), the classification of endpoint (coronary or stroke), the type of control (low-dose statin or usual care/placebo), and the annual mortality risk of the study population (high, medium, or low).

The authors concluded that the benefit of statins were significant for both sexes for primary and secondary prevention; the benefits of treatment were observed, regardless of the type of endpoint studied, the type of control used, or the mortality risk of the population. Additionally, the mortality benefit with statins did not differ significantly by sex (approximately 4,000 deaths had sex-specific mortality data), and all-cause mortality statin benefits were significant in women when primary prevention trials were analyzed separately. The reduction in CVD event rates with treatment versus control was not different in women compared with men (19% and 23%, respectively). The CVD benefit for secondary prevention was greater than for primary prevention but both were significant among women (odds ratio: 0.78 vs. 0.85, respectively). The benefits of statins were robust across different populations of risk and unexpectedly showed greater benefit in studies with lower mortality risk populations, a possible artifact of international trial variations and differences in study design.

The finding of no interaction by sex in this contemporary meta-analysis is concordant with prior meta-analyses that were limited by smaller numbers of women and suggests statin therapy has similar proportional benefits for men and women, regardless of the type of endpoint studied or the level of population risk (4,5). Although pooling studies might solve problems related to small sample sizes with limited power, it is important to recognize that by increasing the numbers of women in meta-analyses the precision of a point estimate might increase but the accuracy or validity of the treatment effect might not necessarily be improved. Meta-analyses have well-recognized limitations, and the biases of individual studies might be magnified rather than mitigated when pooled together. Remember the mantra “garbage in, garbage out”? In the case of Kostis et al. (3), the authors did due diligence by using selective inclusion criteria to analyze the highest quality evidence with highly sophisticated statistical techniques; they conducted sensitivity analysis, systematically examined publication bias, and tested for interaction by several important parameters.

Interestingly, the problem the study faced remained one of small numbers. There were only a handful of primary prevention studies, and only 4 were classified as low-risk populations that could inform the controversy around statin use in women. One of the largest contributors to the analysis was the MEGA (Primary prevention of cardiovas-
cular disease with pravastatin in Japan) trial, which investigated the effects of open label pravastatin in a Japanese population with hypercholesterolemia (6). Older women had a more pronounced benefit than younger women—although effects were similar to men—suggesting that even within a primary prevention population a benefit gradient is observed (7). The meta-analysis also included the JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin), which individually documented a similar relative risk reduction for men and women with elevated levels of inflammation without clinical CVD who were randomized to rosuvastatin compared with placebo (8). Some have interpreted the data as not supporting the use of statins for the primary prevention in women—despite the JUPITER trial enrolling nearly 7,000 women—because the trial was “flawed,” had a short follow-up, and might not readily generalize to other primary prevention populations (9). Concerns have also been raised about the potential long-term safety of statins for primary prevention in both men and women, due to a potential increased risk of incident diabetes that might not be fully realized in short-term trials (10).

Can one conclude that this well-conducted meta-analysis came to the right conclusion? Beyond the inherent limitations of meta-analytic approaches and intrinsic biases within the individual studies, there are other issues to consider in drawing conclusions about statin use on the basis of the data. The focus of the analyses was relative risk reduction, and there was limited assessment of risk or costs of therapy. The authors came to the statistical conclusion that sex does not matter when it comes to the benefits of statins, all other things being considered equal. Agreed, but if sex doesn’t matter, what does? A recent Cochrane review of the evidence for statins in primary prevention suggests that the annual mortality risk of the patient should drive the decision about use of statins in primary prevention (11). Women without CVD have a lower annual mortality risk and lower CVD risk than men without CVD. Therefore, the absolute benefit of statins will typically be less for women than men, suggesting it might be appropriate that women receive statins less frequently than men in the setting of primary prevention. The current meta-analysis provides information about sex-specific relative risk benefit and not absolute benefit. Both the absolute risk of CVD and the proportionate risk reduction associated with statin therapy are needed to make informed clinical choices with regard to the use of statins for primary prevention. Although the latter might be similar for the sexes, the former might be quite different.

Did the authors come to the correct clinical conclusion about the data? Perhaps, but no data about individual baseline risk level were evaluated for potential sex differences in statin effectiveness; within each primary prevention population there might be substantial heterogeneity of risk. Moreover, the authors did not have enough data to critically evaluate adverse side effects, because only 2 studies provided sex-specific data. Adverse outcomes are important to study in pooled analyses, because despite their low frequency, they are clinically important. But scientists cannot do pooled analyses of adverse effects according to sex if individual studies do not provide the data.

The Institute of Medicine has called for more uniform reporting of sex-specific data with respect to both efficacy and safety (12). Sex-specific results in cardiovascular prevention trials should be provided for relative and absolute benefits, adverse outcomes, and cost-effectiveness. Only then will we know with less uncertainty whether what is good for the gander is also good for the goose. Medicine is still an art.

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REFERENCES


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