The Numbers Are In
Statins for the Primary Prevention of Cardiovascular Disease in Women

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In this issue of Circulation, Mora et al demonstrate for the first time that statins are effective for the primary prevention of cardiovascular events in women.\(^1\) Under a prespecified analysis, the authors examined sex-specific outcomes in JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), which enrolled 6801 women ≥60 years old and 11 001 men ≥50 years old without prior history of coronary heart disease, diabetes mellitus, or stroke who had low-density lipoprotein cholesterol (LDL-C) <130 mg/dL and high-sensitivity C-reactive protein (hsCRP) ≥2.0 mg/L.\(^2\)

Patients were randomized to receive rosuvastatin 20 mg daily versus placebo and were followed up for a median of only 2 years—a remarkably short period—because the trial was terminated early owing to the identification of significant benefit with treatment in the overall study population. The results from the subgroup analysis in the article by Mora et al indicate a statistically significant relative risk reduction in women for the primary end point of myocardial infarction, stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death, which was similar to the reduction seen in men (hazard ratio 0.54, P=0.002 versus 0.58, P<0.001, respectively).

To put their findings in appropriate context, the authors also included in their article a meta-analysis of 5 exclusively or predominately primary prevention trials of statins that reported sex-specific outcomes.\(^2\)–\(^7\) The total number of women in the 3 exclusively primary prevention trials (JUPITER, Primary Prevention of Acute Coronary Events With Lovastatin in Men and Women With Average Cholesterol Levels: Results of Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS], and Usefulness of Pravastatin in Primary Prevention of Cardiovascular Events in Women: Analysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese [MEGA]) was 13 154, and the summary relative risk reduction for the development of cardiovascular events in those 3 trials was 0.63 (95% confidence interval 0.49 to 0.82, P<0.001).

So why did results from JUPITER show statistically significant reductions for women in the development of cardiovascular events, in contrast to previous trials and pooled analyses? The most obvious reason lies in the number of patients enrolled; JUPITER enrolled >6800 women. By contrast, 997 women were enrolled in AFCAPS/TexCAPS and 5356 women in MEGA. Thus, for exclusively primary prevention trials, JUPITER essentially doubled the number of women who had been previously examined. Nonsignificant trends toward benefit, seen in MEGA and AFCAPS/TexCAPS, now were adequately powered to show significant benefit.

Additional numbers are just as important, however, and deserve further exploration. JUPITER limited enrollment to women over the age of 60 (median age of women in the trial was 68), in comparison with AFCAPS/TexCAPS, which enrolled women aged 55 to 73 years (mean age for women, 62 to 63 years), and MEGA, which enrolled men and women aged 40 to 70 years (mean age for women, 60 years). MEGA thus included fewer women at higher risk despite its large study population. This also likely led to less statistical power for MEGA to show significant benefit in comparison with JUPITER.

Another critically important number is the degree of LDL-C lowering achieved. In JUPITER, the median change in LDL-C was −51 mg/dL (47% reduction) for women with a mean LDL-C at 12 months of 55 mg/dL. By contrast, AFCAPS/TexCAPS achieved a 25% LDL-C reduction to a median value of 116 mg/dL.\(^3\) By use of a low dose of the less potent pravastatin at 10 to 20 mg daily, MEGA achieved only a 20% LDL-C reduction in women to 123 mg/dL.\(^4\) These results support the current hypothesis that the degree of LDL-C lowering is central to the benefits associated with statin therapy. Greater clinical impact in JUPITER may have resulted from the much greater differences in LDL-C reduction between treatment and control arms.

Although the broad implications of JUPITER have been widely discussed, several important questions are specifically raised for women by this subgroup analysis. For example, should all women be offered high-potency statins that are capable of lowering LDL-C by almost 50%? In JUPITER, the 5-year number needed to treat for the primary end point was 25 (95% confidence interval 18 to 40), and 20 (95% confidence interval 14 to 32) for the primary end point plus mortality, with corresponding values of 17 for men and 31 for women. The 5-year NNT values were 17 for men and 31 for women using the end point of MI, stroke, revascularization, or mortality.\(^5\) These numbers compare favorably to the numbers needed to treat for other cardiovascular treatments.

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\(^{4}\) Article see p 1069

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Of course, treatment may be even further targeted. For those with and without a family history of premature atherosclerosis, for example, the numbers needed to treat were 9 and 26, respectively. Family history of premature heart disease may be a particularly important risk factor for women in JUPITER, as others have noted in the past.9

Another factor related to JUPITER that remains controversial but deserves mention is the use of hsCRP as an inclusion criterion. To participate in JUPITER, patients needed to have hsCRP levels of $\geq 2.0$ mg/L. In fact, women had higher concentrations than men at baseline (4.6 mg/L versus 4.1 mg/L). Ridker et al have previously identified elevated hsCRP level as a strong predictor of cardiovascular events in women, even among those with LDL-C levels $<130$ mg/dL (not coincidentally, the upper cutoff for inclusion into JUPITER).10 It also appears that the degree of reduction achieved in hsCRP levels may be important; in an analysis of the JUPITER results, the magnitude of hsCRP lowering correlated directly to the magnitude of clinical benefit (as did the magnitude of LDL-C lowering).12

The importance of hsCRP as an independent predictor for cardiovascular events continues to be hotly debated, but there is a consensus that elevated hsCRP is a marker, if not a causal factor, for cardiovascular events.12 In JUPITER, elevated hsCRP perhaps served as a surrogate for insulin resistance, glucose intolerance, or obesity (an inflammatory state), although the authors noted a trend for greater reduction in the primary end point in women without the metabolic syndrome than in those with it.1

Of course, many important questions remain unanswered by this analysis. For example, what should the age cutoff for therapy recommendations be in women? This study included women over the age of 60, but the authors acknowledged few events in the women between the ages of 60 and 65. Should women with average cholesterol levels and no diabetes be treated with statins as of age 65?

What is the role of inflammatory marker screening? Should all women who don’t already qualify for statins and have a Framingham risk estimate of at least 5% for a cardiovascular event over the next decade be screened with hs-CRP levels? We tend to believe that this assay should be reserved for those in whom therapeutic intensity would clearly be altered by the result, but exactly whom that population consists of remains open for debate.

So how should these results change the way we approach primary prevention of cardiovascular disease using statins in women? Many cardiologists would assert that they already aggressively treat in women at least one other traditional risk factor, and the findings of Mora et al would not materially affect their clinical algorithms. However, the Adult Treatment Panel III guidelines and the 2004 update would not call for statin therapy in nearly all of the women enrolled in JUPITER (and many of the men), because the baseline LDL-C values were $<130$ mg/dL.13,14 In addition, the mean Framingham risk estimate for a hard event was low in this trial: about 5% in the women. Some practitioners have argued against treating women who do not have diabetes mellitus or known coronary heart disease with statin therapy regardless of their cholesterol level.15 The data presented in this issue of Circulation challenges that line of thinking.

We would favor earlier consideration of statin therapy in postmenopausal women who have at least one traditional risk factor, especially if it includes a family history of premature cardiovascular disease. We also believe that evidence supporting the hypothesis that statins slow the progression of atherosclerosis and stabilize potentially vulnerable atherosclerotic plaques favors the use of these agents in adults who meet the age criteria of JUPITER and have at least one other risk factor.

In summary, this study indicates that statin therapy among middle-aged and older women with low LDL-C but above average hsCRP achieves better outcomes than those previously observed in primary prevention trials that were conducted with less potent statins in individuals with overt hyperlipidemia. Clearly, the evidence base for statin therapy in asymptomatic middle-aged and older women with other risk factors is now much more compelling, thanks to the work of Mora and colleagues. We await publication of the formal cost-effectiveness analyses from the landmark JUPITER data set, as well as data on the long-term safety of high-potency statin therapy. In the meantime, clinicians will undoubtedly use the data by Mora et al to prescribe statin therapy much earlier for women who meet the entry criteria of the JUPITER study, and this change will improve cardiovascular outcomes in women.

Disclosures

None.

References


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