A Comparison of Statin Therapies in Hypercholesterolemia in Women: A Subgroup Analysis of the STELLAR Study

Francine K. Welty, MD,¹ Sandra J. Lewis, MD,² Karen E. Friday, MD,³ Valerie A. Cain, MS,⁴ and Deborah A. Anzalone, MD⁴

Abstract

Objective: Cardiovascular disease is the leading cause of mortality in women in the United States. Aggressive treatment of modifiable risk factors (e.g., hypercholesterolemia) is essential in reducing disease burden. Despite guidelines recommending the use of statin treatment in hypercholesterolemic women, this patient group is often undertreated. This subgroup analysis of the Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial examines the effects of statin therapy in hypercholesterolemic women.

Methods: As part of the STELLAR trial, 1,146 women with elevated low-density lipoprotein cholesterol (LDL-C ≥160 and <250 mg/dL) and triglycerides <400 mg/dL were randomized to rosuvastatin 10–40 mg, atorvastatin 10–80 mg, simvastatin 10–80 mg, or pravastatin 10–40 mg for 6 weeks.

Results: LDL-C reduction with rosuvastatin 10 mg, atorvastatin 10 mg, simvastatin 20 mg, and pravastatin 40 mg was 49%, 39%, 37%, and 30%, respectively, after 6 weeks. High-intensity statins (rosuvastatin 20–40 mg and atorvastatin 40–80 mg) reduced LDL-C to the greatest extent: 53% with rosuvastatin 20 mg, 57% with rosuvastatin 40 mg, 47% with atorvastatin 40 mg, and 51% with atorvastatin 80 mg. Similar results were observed for non-high-density lipoprotein cholesterol (non-HDL-C). Increases in HDL-C were greater with rosuvastatin across doses than with other statins. All treatments were well tolerated, with similar safety profiles across dose ranges.

Conclusions: Statin therapies in the STELLAR trial led to reductions in LDL-C, non-HDL-C, and triglycerides and increases in HDL-C among hypercholesterolemic women, with rosuvastatin providing the greatest reductions in LDL-C and non-HDL-C.

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality among women in the United States.¹ While coronary heart disease (CHD) rates in women increase markedly with age,²,³ of particular concern is the increasing number of CHD deaths among US women aged 35–54 years, believed to be due to the increasing prevalence of obesity.²⁴ Therefore, early identification and aggressive management of modifiable risk factors are essential to reduce the overall burden of CHD in women.⁵

Hypercholesterolemia is a major modifiable risk factor for CVD for both men and women.³ Low-density lipoprotein cholesterol (LDL-C) levels are typically lower in women than in men until menopause, when levels increase (from a mean of 117 mg/dL [3 mmol/L] to 145 mg/dL [3.7 mmol/L])⁶ and LDL particles tend to become more atherogenic.⁷ High-density lipoprotein cholesterol (HDL-C) levels are approximately 10 mg/dL (0.3 mmol/L) higher in women than in men,⁸ and low levels are more predictive of CHD in women compared with men, especially in women aged 65 years or older.³ Moreover, elevated triglycerides may be a more significant risk factor in women (especially older women) compared with men,⁴⁶ and, for both sexes, elevated non-HDL-C is recognized as a risk marker for CHD,¹¹ particularly in patients with hypertriglyceridemia, reflecting increased levels of atherogenic remnant very low-density lipoprotein (VLDL).

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Several guidelines recommend statins as first-line treatment for cholesterol reduction when diet and exercise are inadequate.\(^4,12\) A meta-analysis of 27 statin trials showed that a 39 mg/dL (1 mmol/L) reduction in LDL-C was associated with a 16% (rate ratio 0.84, 99% confidence interval [CI] 0.78–0.91) reduction in major vascular events in women, similar to the 22% (rate ratio 0.78, 99% CI 0.75–0.81) reduction observed in men.\(^13\) Further analysis of 5 studies comparing more versus less intensive statin therapy revealed that major vascular events were reduced by 25% (rate ratio 0.75, 99% CI 0.58–0.97) per 39 mg/dL (1 mmol/L) reduction in LDL-C in women receiving more versus less intensive statin therapy, compared with 29% (rate ratio 0.71, 99% CI 0.63–0.80) in men.\(^13\) Thus, although women derive a clear benefit from LDL-C reduction,\(^14–16\) available data indicate that major vascular events were reduced by 25% (rate ratio 0.75, 99% CI 0.58–0.97) per 39 mg/dL (1 mmol/L) reduction in LDL-C in women receiving more versus less intensive statin therapy, compared with 29% (rate ratio 0.71, 99% CI 0.63–0.80) in men.\(^13\) Thus, although women derive a clear benefit from LDL-C reduction,\(^14–16\) available data indicate that women are undertreated for hypercholesterolemia.\(^17,18\)

One reason for undertreatment may be underestimation of CVD risk in women. Standard risk stratification tools, such as the Framingham risk score, are limited in that they focus on short-term (i.e., 10-year) risk of myocardial infarction and CHD death only, exclude family history, and overestimate or underestimate risk in non-white populations. This, together with the fact that subclinical CVD can have relatively high prevalence among women, means that many women under the age of 75 years may never exceed a predicted 10-year risk for CHD of ≥10% and subsequently may not be considered for dyslipidemia treatment.\(^4\)

Mindful of these limitations, the 2011 American Heart Association (AHA) evidence-based guidelines for CVD prevention in women recommend defining high risk in women as a 10-year risk of ≥10% for all CVD, not just CHD alone.\(^4\) The guidelines also recommend that all women should be encouraged to reach ideal levels of four critical lipid parameters (Table 1) through lifestyle approaches.\(^4\) For high-risk women (i.e., those with CHD, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, end-stage or chronic kidney disease, diabetes mellitus, or a predicted 10-year CVD risk ≥10%), the addition of lipid-lowering pharmacotherapy is recommended if lifestyle changes alone are insufficient at reducing lipids to the ideal levels.\(^4\)

More recently the AHA, in collaboration with the American College of Cardiology (ACC), published guidelines on the treatment of cholesterol to reduce atherosclerotic cardiovascular risk in adults (men and women).\(^12\) These guidelines identify patients and provide treatment recommendations according to four statin-benefit groups (Tables 2, 3).

The Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial (clinicaltrials.gov identifier: NCT00654537) compared rosuvastatin treatment with three other widely used statins (atorvastatin, simvastatin, and pravastatin) in a hypercholesterolemic patient population.\(^19\) This subgroup analysis examines the effects of statin therapy in improving lipid profiles in the hypercholesterolemic women who participated in the STELLAR trial. Because of its large number of female participants (51%, n = 1,146), the STELLAR trial is particularly appropriate for this analysis.

### Materials and Methods

The STELLAR trial was a randomized, parallel-group, open-label, comparator-controlled multicenter trial in 2,431 hypercholesterolemic patients. A detailed description of the methods of the trial is provided elsewhere.\(^19\) Briefly, after a 6-week dietary lead-in period, men and women aged 18 years

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**Table 1. American Heart Association’s Recommended Lipid Parameters for Women**

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Recommended level</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>&lt;100 mg/dL (&lt;2.6 mmol/L)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&gt;50 mg/dL (&gt;1.3 mmol/L)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt;150 mg/dL (&lt;1.7 mmol/L)</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>&lt;130 mg/dL (&lt;3.4 mmol/L)</td>
</tr>
</tbody>
</table>

Source: Mosca et al., 2011.\(^4\)

**Table 2. American College of Cardiology/American Heart Association Statin-Benefit Groups**

<table>
<thead>
<tr>
<th>Statin-benefit group</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical ASCVD</td>
<td>Age ≤75 years: high-intensity statin Age &gt;75 years or not candidate for high-intensity statin: moderate-intensity statin</td>
</tr>
<tr>
<td>Primary elevations</td>
<td>High-intensity statin (moderate-intensity statin if not candidate for high-intensity statin)</td>
</tr>
<tr>
<td>LDL-C ≥190 mg/dL</td>
<td>Estimated 10-year ASCVD risk ≥7.5%: high-intensity statin</td>
</tr>
<tr>
<td>Diabetes aged 40–75</td>
<td>Moderate-intensity statin</td>
</tr>
<tr>
<td>years and LDL-C 70–189 mg/dL (1.8–4.1 mmol/L), but without clinical ASCVD</td>
<td></td>
</tr>
<tr>
<td>Without clinical ASCVD or diabetes with LDL-C 70–189 mg/dL (1.8–4.1 mmol/L) and estimated 10-year ASCVD risk ≥7.5%</td>
<td>Moderate- to high-intensity statin</td>
</tr>
</tbody>
</table>

Source: Stone et al., 2014.\(^12\)

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.
or older with fasting LDL-C ≥160 mg/dL and <250 mg/dL (≥4.1 mmol/L and <6.5 mmol/L) and triglycerides <400 mg/dL (<4.5 mmol/L), discontinued from all cholesterol-lowering drugs and dietary supplements, were randomized to 6 weeks of treatment with one of four statins.

The current subgroup analysis involves 1,146 women who began study treatment with rosuvastatin 10, 20, or 40 mg; atorvastatin 10, 20, 40, or 80 mg; simvastatin 10, 20, 40, or 80 mg; or pravastatin 10, 20, or 40 mg. To be included, all women had to have a baseline and at least one post-baseline assessment of clinical adverse events and laboratory values. Changes in LDL-C, non-HDL-C, triglycerides, and HDL-C from baseline to 6 weeks were assessed by statin dose group. To compare changes in lipid levels among treatments, least-squares mean changes from baseline to 6 weeks for 22 pairwise comparisons of rosuvastatin 10, 20, or 40 mg with milligram-equivalent or higher doses of comparator statins (Fig. 1) were obtained using a Bonferroni adjustment with a significance level of 0.002 to obtain an experiment-wise error rate of 0.05. This is an adjustment for the 22 multiple comparisons (0.05/22 = 0.002). For efficacy variables, the last observation was carried forward for those women not completing 6 weeks of treatment.

Safety evaluations are described in Jones et al. and involved assessment of clinical adverse events and laboratory values.

Results

Patients

Of the 1,146 women in this subgroup analysis from the STELLAR trial, 249 received rosuvastatin 10–40 mg, 320 received atorvastatin 10–80 mg, 333 received simvastatin 10–80 mg, and 244 received pravastatin 10–40 mg. Baseline characteristics are shown in Table 4. Mean ages, 58–60 years, were similar across the statin groups. Most of these women were taking at least one concomitant medication. At baseline, mean LDL-C was 190 mg/dL (4.9 mmol/L), indicating that the women had substantial hypercholesterolemia.

Efficacy

Statin treatment produced dose-related decreases in LDL-C levels ranging from 21% to 57% at 6 weeks, depending on the statin and dose used (Fig. 2A). At the lowest statin dose, 10 mg, LDL-C was reduced by 49% with rosuvastatin, 39% with atorvastatin, 30% with simvastatin, and 21% with pravastatin (p < 0.002 rosuvastatin vs. all comparators). A similar pattern was observed for the high-intensity doses of statins defined by the ACC/AHA guideline and recommended for those at risk of atherosclerotic cardiovascular disease:12 LDL-C reductions were 53% with rosuvastatin 20 mg, 57% with rosuvastatin 40 mg, 47% with atorvastatin 40 mg, and 51% with atorvastatin 80 mg. Rosuvastatin 20 mg produced statistically greater reductions in LDL-C compared with atorvastatin 20 mg and 40 mg (p < 0.002 for both comparisons). In addition, rosuvastatin 40 mg produced statistically greater reductions in LDL-C compared with atorvastatin 40 mg (p < 0.002).

Reductions in non-HDL-C levels ranged from 45% to 53% with rosuvastatin, 37% to 48% with atorvastatin, 27% to 44% with simvastatin, and 19% to 28% with pravastatin (Fig. 2B). Reductions in non-HDL-C with rosuvastatin 10 mg were significantly greater when compared with atorvastatin 10 mg; simvastatin 10, 20, or 40 mg; and pravastatin 10, 20, or 40 mg (p < 0.002 for all comparisons). Rosuvastatin 20 mg reduced non-HDL-C significantly more than milligram-equivalent doses of atorvastatin, simvastatin, and pravastatin (p < 0.002 for all comparisons).

The increases in HDL-C were numerically greater with rosuvastatin than with the other statins, but the differences were not statistically significant, except that rosuvastatin 20 and 40 mg increased HDL-C significantly more than milligram-equivalent or higher doses of atorvastatin (Fig. 2C).

All statins reduced triglyceride levels, with similar effects across the dose range for rosuvastatin and atorvastatin, and a trend for dose-related reductions for simvastatin and pravastatin. No significant differences in effect on triglycerides were observed between rosuvastatin and atorvastatin. However, rosuvastatin 10 mg decreased triglycerides significantly more than simvastatin 10 mg, and pravastatin 10 mg and 20 mg; rosuvastatin 20 mg decreased triglycerides significantly more than 20 mg of simvastatin and pravastatin (Fig. 2D) (p < 0.002 for all comparisons).

Safety

All treatments were generally well tolerated, with similar safety profiles across treatments and dose ranges (Table 5). Study withdrawal due to drug-related treatment-emergent adverse events occurred in 5 rosuvastatin-treated women (2.0%), 13 atorvastatin-treated women (4.1%), 7 simvastatin-treated women (2.1%), and 7 pravastatin-treated women (2.9%). The most common adverse events were pain (6.4%), pharyngitis (5.4%), headache (4.4%), and myalgia (4.0%). There were no cases of rhabdomyolysis, myopathy, or clinically significant elevations (>3 times the upper limit of normal) in serum creatine kinase in these women. Clinically significant elevations (>3 times the upper limit of normal on two consecutive occasions) in alanine aminotransferase were infrequent, occurring in 1 patient receiving atorvastatin 20 mg (1.3%), 2 patients receiving atorvastatin 80 mg (2.4%), and 1 patient receiving simvastatin 80 mg (1.2%). No patients in this analysis had creatinine levels that increased >100% from baseline, and no women had creatinine levels that were above the upper limit of normal.
To our knowledge, this is the first large-scale comparative subgroup analysis of the lipid-lowering effects of statins across their dose ranges in hypercholesterolemic women in a clinical trial population. As in the total STELLAR population,19,20 rosuvastatin 10–40 mg reduced LDL-C and non-HDL-C more than milligram-equivalent doses of atorvastatin, and milligram-equivalent and higher doses of simvastatin and pravastatin. In our analysis, mean baseline LDL-C was 190 mg/dL (4.9 mmol/L), indicating that the women had substantial hypercholesterolemia, with many of them fulfilling the ACC/AHA 2013 guideline criteria for high-intensity statin therapy according to their baseline LDL-C levels alone, irrespective of other risk factors.

Although the 2011 AHA and 2013 ACC/AHA lipid guidelines represent important directives in preventive cardiovascular care for women4,12 and awareness of CVD among women has increased over the last couple of decades, significant gaps in the understanding and management of the disease remain, particularly among black and Hispanic women4,9,18,21 Indeed, the majority of women (approximately 85%) in the STELLAR trial were white, and so results from this and other statin studies need to be interpreted with caution in women of ethnic minorities.

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Some of this undertreatment may be due to the misconception that risk factors in premenopausal women do not need to be managed aggressively and to the earlier belief, now disproved22–24 that hormone replacement therapy reduced cardiovascular risk in postmenopausal women. Some undertreatment may be due to lack of awareness of overall
cardiovascular risk in women and to differences in presentation and diagnosis of CVD in women compared with men.

Our 6-week treatment period was not long enough to assess the effect on clinical events; therefore, our data cannot suggest a preferential advantage of one statin versus another in preventing cardiovascular events. However, based on the Cholesterol Treatment Trialists' meta-analysis of >170,000 patients in 26 prospective, randomized statin trials, which showed that every 39 mg/dL reduction in LDL-C led to a 22% (95% CI: 0.76–0.80, \( p < 0.0001 \)) reduction in major vascular

### Table 5. Adverse Events of Women in the STELLAR Trial (Randomized Population)

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin 10–40 mg (n = 250)</th>
<th>Atorvastatin 10–80 mg (n = 320)</th>
<th>Simvastatin 10–80 mg (n = 331)</th>
<th>Pravastatin 10–40 mg (n = 244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs</td>
<td>110 (44.0)</td>
<td>181 (56.6)</td>
<td>168 (50.8)</td>
<td>130 (53.3)</td>
</tr>
<tr>
<td>AEs leading to death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AEs leading to withdrawal</td>
<td>7 (2.8)</td>
<td>14 (4.4)</td>
<td>10 (3.0)</td>
<td>8 (3.3)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>2 (0.8)</td>
<td>4 (1.3)</td>
<td>4 (1.2)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Drug-related AEs</td>
<td>28 (11.2)</td>
<td>53 (16.6)</td>
<td>36 (10.9)</td>
<td>25 (10.2)</td>
</tr>
<tr>
<td>Drug-related AEs leading to death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Drug-related AEs leading to withdrawal</td>
<td>5 (2.0)</td>
<td>13 (4.1)</td>
<td>7 (2.1)</td>
<td>7 (2.9)</td>
</tr>
<tr>
<td>Drug-related serious AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

AEs, adverse events.

**FIG. 2.** (A) LS mean % change from baseline in LDL-C at week 6 (LOCF). (B) LS mean % change from baseline in non-HDL-C at week 6 (LOCF). (C) LS mean % change from baseline in HDL-C at week 6 (LOCF). (D) LS mean % change from baseline in TG at week 6 (LOCF). The dashed line refers to the least-squares mean percentage change for rosuvastatin 10 mg. LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LOCF, last observation carried forward; LS, least-squares; TG, triglycerides.
events and a 10% (95% CI: 0.87–0.93, \(p<0.0001\)) reduction in all-cause mortality.\(^{15}\) It would be predicted that greater LDL-C reductions would confer greater benefit in reducing cardiovascular events. Although women have been underrepresented in clinical end-point trials of statins, analyses of subgroups of women from these trials indicate that LDL-C reduction decreased cardiovascular event rates to a similar degree in women compared with that documented in men.\(^{14,16,25}\)

A meta-analysis of 18 randomized controlled trials of statins in primary prevention found that statin intervention was associated with a lower cardiovascular event rate versus control and was similar in women and men (odds ratio [OR] 0.81, 95% CI: 0.75–0.89; \(p<0.0001\) vs. OR 0.77, 95% CI: 0.71–0.83; \(p<0.0001\), respectively).\(^{14}\) In addition, a sex-specific analysis of data from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study assessed the efficacy and safety of rosuvastatin in apparently healthy individuals with raised high-sensitivity C-reactive protein.\(^{25}\) Overall, the absolute CVD rates in women for rosuvastatin and placebo (0.57 and 1.04, respectively) were lower than those in men (0.88 and 1.54, respectively), although the relative risk reduction associated with rosuvastatin was similar in women and men (hazard ratio [HR] 0.54, 95% CI: 0.37–0.80; \(p=0.002\) vs. HR 0.58, 95% CI: 0.45–0.73; \(p<0.001\)).\(^{25}\)

Another meta-analysis compared the effect of statins in secondary prevention of CVD in men and women in 11 trials.\(^{16}\) Statin therapy (atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin) was shown to be associated with a reduced risk of cardiovascular events in all outcomes for women (risk ratio [RR] 0.81, 95% CI 0.74–0.89) and men (RR 0.82, 95% CI 0.78–0.85). However, there was no benefit with regard to stroke and all-cause mortality in women, although there was in men.\(^{16}\)

Data on the impact of statin treatment on carotid intima-media thickness are equally limited. A small study of 51 postmenopausal women aged ≥55 years with dyslipidemia showed that women who received rosuvastatin 2.5 mg per day for 12 months had significantly lower carotid intima-media thickness values when compared with the women who received no statin therapy.\(^{26}\) These changes were in conjunction with significant decreases in LDL-C and high-sensitivity C-reactive protein.

Overall, statins have proved to be generally well tolerated in most patients.\(^{27,28}\) Safety data from a number of large-scale statin trials, when analyzed by gender, indicate that statins are generally well tolerated in women.\(^{14,16}\) Taken together, the available efficacy and safety data indicate that dyslipidemic women should receive appropriate statin therapy to reduce LDL-C levels and thereby reduce risk of CVD.

### Conclusion

Our subanalysis of the STELLAR study confirms that women can achieve effective LDL-C reduction with statin therapy. Mean reductions in LDL-C were ≥49% with rosuvastatin doses of 10 mg or higher, ≥39% with atorvastatin 10 mg or higher, ≥30% with simvastatin 10 mg or higher, and ≥21% with pravastatin 10 mg or higher. Moreover, statin therapy was generally well tolerated in the women included in this study. These results suggest that substantial improvements in lipid levels are achievable with moderate- to high-intensity statin therapy.

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Each author has participated in the research and/or article preparation. All authors have approved the final article.

### Author Disclosure Statement

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[314 citations not visible]
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