Benefit of Intensive Statin Therapy in Women
Results From PROVE IT-TIMI 22

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Background—Despite the known benefit of intensive statin therapy for reducing future cardiovascular events, its effectiveness in women has been questioned by some.

Methods and Results—In the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial, 911 (21.9%) women and 3251 (78.1%) men were randomized to intensive statin (atorvastatin 80 mg) versus standard therapy (pravastatin 40 mg) therapy for a median duration of 2.1 years. The primary end point was death, myocardial infarction, unstable angina; revascularization (occurring after 30 days); or stroke. Safety end points included elevations in liver function tests, creatine kinase, and myalgias/myositis. Women had a reduction in low-density lipoprotein (LDL) of 42.8% from baseline at 30 days (to a median of 60 mg/dL) in the intensive therapy arm, with 88.8% reaching the LDL goal of $\leq 100$ mg/dL and 65.0% of $\leq 70$ mg/dL, compared with a 16.8% reduction in LDL (to a median of 88 mg/dL) in the standard therapy arm. Women receiving intensive statin therapy had a significant 25% relative reduction over standard dose (hazard ratio, 0.75; 95% CI, 0.57 to 0.99; $P=0.04$) for the primary composite end point compared with a 14% reduction for men (hazard ratio, 0.86; 95% CI, 0.75 to 0.99; $P=0.04$; $P$-interaction, 0.38). No differences were observed between sexes for safety (all $P$-interaction $\geq0.11$).

Conclusions—This trial provides evidence that both women and men derived benefit from intensive statin therapy after acute coronary syndrome, and thus, sex should not be a factor in determining who should be treated with intensive statin therapy.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00382460.

Key Words: hydroxymethylglutaryl-CoA reductase inhibitors ■ sex ■ acute coronary syndrome ■ prognosis ■ secondary prevention

Cardiovascular disease remains the foremost cause of mortality in women in the United States and throughout much of the world.1,2 The contemporary approach to prevention of cardiovascular disease in women includes lifestyle modification for all and medical therapy for those with cardiovascular disease risk factors or known disease.1 Several large, randomized controlled trials that included men and women have documented that lipid-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduces the risk of death or cardiovascular events across a wide range of cholesterol levels, with or without coronary artery disease.3–8 The benefit from intensive statin therapy has extended to the early time period after acute coronary syndrome (ACS).9–12

Editorial see p 266

The Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial showed that intensive lipid-lowering therapy (atorvastatin 80 mg) that achieved a median low-density lipoprotein (LDL) level of 62 mg/dL was superior to standard-dose lipid-lowering therapy (pravastatin 40 mg) that achieved a median LDL level of 95 mg/dL after ACS in reducing clinical events.10 Although the effects of statins on reducing future cardiovascular events are well established in men, the generalizability to women are less certain because of the relatively few number of women included in these large, randomized secondary prevention trials ($<20\%$ in each trial).4,5,13–15

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In addition, the observed risk reductions in women varied widely in these trials. Thus, the goal of the present analysis was to determine the efficacy and safety of intensive statin therapy in women in the PROVE IT-TIMI 22 trial.

WHAT IS KNOWN

- Intensive statin therapy with atorvastatin 80 mg is superior to standard-dose therapy with pravastatin 40 mg in reducing low-density lipoprotein and future cardiovascular events after acute coronary syndrome (ACS).
- Effects of statins on reducing future cardiovascular events are well established in men, but the generalizability to women is less certain because of the relatively few number of women included these large, randomized secondary prevention trials.

WHAT THE STUDY ADDS

- Intensive statin therapy after ACS leads to a significant reduction in cardiovascular events in women (as well as in men) with similar safety profiles when compared to standard-dose statin.
- To achieve a 1% reduction in events, the mean reduction in low-density lipoprotein level needed was 1.0 mg/dL in women and 2.4 mg/dL in men.
- With a 6.7% absolute reduction and 25% relative reduction of the primary end point with intensive-dose statin in women and a 3.2% absolute reduction and 14% relative reduction in men, both women and men should be treated with intensive regimens after ACS.

Methods

Study Population

The PROVE IT-TIMI 22 was a multicenter, multinational trial consisting of 4162 patients who were hospitalized for ACS, which was defined as acute myocardial infarction (MI) or high-risk unstable angina (UA) within the previous 10 days. The study design, inclusion and exclusion criteria, and primary results have been reported previously.10,16 To be eligible, patients not previously on lipid-lowering therapy and exclusion criteria, and primary results have been reported previously.10,16 To be eligible, patients not previously on lipid-lowering therapy and exclusion criteria, and primary results have been reported previously.10,16 To be eligible, patients not previously on lipid-lowering therapy and exclusion criteria, and primary results have been reported previously.10,16 To be eligible, patients not previously on lipid-lowering therapy and exclusion criteria, and primary results have been reported previously.10,16 To be eligible, patients not previously on lipid-lowering therapy and exclusion criteria, and primary results have been reported previously.10,16 To be eligible, patients not previously on lipid-lowering therapy and exclusion criteria, and primary results have been reported previously.10,16 To be eligible, patients not previously on lipid-lowering therapy and exclusion criteria, and primary results have been reported previously.10,16

End Points

The primary end point was a composite end point defined as death, MI, and documented UA requiring hospitalization; revascularization (>30 days after randomization); or stroke. Secondary efficacy end points included hospitalization for heart failure; the components of the various end points individually and in combination; changes in LDL, high-density lipoprotein (HDL), high-sensitivity C-reactive protein (hs-CRP); and percentages of patients who achieved the target LDL of <70 mg/dL and <100 mg/dL, HDL >50 mg/dL, and hs-CRP <2 mg/L at 30 days and the final visit. Additionally, rates of increase in alanine aminotransferase or aspartate aminotransferase levels >3 times normal range, elevated creatine kinase >3 times the upper limit of normal, and myalgias/myositis were assessed for tolerability of therapy.

Statistical Analysis

Descriptive statistics were expressed as mean±SD or median with interquartile range (IQR) for continuous variables and as frequency and percentages for nominal variables. Differences in baseline characteristics between women and men were assessed by χ² test for categorical variables and Student t test or Wilcoxon rank sum test for continuous variables, as appropriate. When comparing the difference between treatment groups as stratified by sex, we used Wilcoxon rank sum test to compare the differences in lipid profile and χ² test to compare the proportions of patients who reached the target lipid goal and side-effect profiles. We used logistic regression to test the interaction between sex and side effects. Cumulative event rates stratified by intensive versus standard-dose lipid-lowering therapy were estimated using the product limit (Kaplan-Meier) methods and log-rank test for each sex separately. Cox proportional hazards models were used to evaluate the effect of treatment strategy for women and men separately. Cox regression was used to test for effect modification by evaluating the interaction terms for sex and treatment strategy for each outcome as well as the interaction for sex and gatifloxacin for the primary end point. In the subanalysis of women, we used Cox proportional hazards models to compare the effect of treatment strategy on the primary end point in each group as stratified by menopausal status and by estrogen replacement therapy (ERT). We also tested the interaction between treatment strategy and both menopausal status and ERT for the primary end point using Cox regression. We used Schoenfeld residuals to verify that the proportional hazards assumption was not violated. A 2-sided P<0.05 was considered to be statistically significant. All analyses were performed using STATA 10 (StataCorp LP; College Station, TX) statistical software.

Results

Patient Characteristics

There were 911 (21.9%) women and 3251 (78.1%) men. The number of women randomized to high-dose atorvastatin was 465, whereas 446 received standard-dose pravastatin. Table 1 depicts the baseline characteristics of the PROVE IT-TIMI 22 cohort as stratified by sex. On average, women were 2.6 years older and more often had diabetes, hypertension, and a history of heart failure, whereas more men smoked and had a history of MI, and coronary artery bypass graft. With respect to ACS type, more women had UA, whereas more men had ST-segment elevation MI, with no difference found in the percentage of non-ST-segment elevation MI. Importantly, there was no difference in the percentage of prior statin use between women and men (26.3% versus 24.9%, P=0.37). At the time of randomization, the proportions of men and women taking β-blockers and aspirin were similar. There were no major differences in baseline characteristics by randomization group in the subgroup of men and the subgroup of women.
Sex Differences in Lipid Profile and Biomarkers

The baseline median LDL levels were similar in men (106 mg/dL; IQR, 88 to 127 mg/dL) and women (106 mg/dL; IQR, 88 to 129 mg/dL; P=0.65). The baseline median triglyceride levels also were similar in women (157 mg/dL; IQR, 121 to 218 mg/dL) and men (155 mg/dL; IQR, 116 to 209 mg/dL; P=0.13). Not surprisingly, the baseline HDL was higher in women (median, 44 mg/dL; IQR, 37 to 53 mg/dL) than in men (median, 37 mg/dL; IQR, 32 to 43 mg/dL; P<0.0001). The baseline median hs-CRP level in women was 13.5 mg/L (IQR, 5.7 to 29.3 mg/L) and 11.9 mg/L (IQR, 4.7 to 28.9 mg/L) in men (P=0.02).

Figure 1 shows the changes in median LDL and hs-CRP levels by treatment group when stratified by sex. At 30 days, women had a reduction in LDL levels by 42.8% (to 60 mg/dL) in the atorvastatin 80 mg arm at 30 days compared with 16.8% (to 88 mg/dL) in the pravastatin 40 mg arm. The difference was statistically significant (P<0.0001). Comparably, men had a reduction of 47.5% (from 106 to 56 mg/dL) in LDL at 30 days in the atorvastatin 80 mg arm compared with 18.1% (from 106 to 89 mg/dL) in the pravastatin 40 mg arm (P<0.0001). This reduction in LDL with atorvastatin was greater in men than in women (P<0.0001), whereas the LDL reduction with pravastatin did not differ between sexes (P=0.32). For both women and men, the hs-CRP levels drastically fell from baseline and were persistently lower when treated with high-dose atorvastatin than with standard-dose pravastatin (all P≤0.003).

Figure 2 shows that at 30 days, 88.8% of women reached the target LDL level of <100 mg/dL in the atorvastatin 80 mg arm compared to 67.5% in the pravastatin 40 mg arm, with the target LDL level of <70 mg/dL reached in 65.0% compared to 24.5%, respectively. Similarly, in men at 30 days, the target LDL of <100 mg/dL was achieved in 95.5% of the atorvastatin arm compared to 66.1% in the pravastatin arm, with the target of <70 mg/dL reached in 74.4% compared to 20.9%, respectively. When comparing the achievement of goals between men and women, fewer women than men achieved these 2 target levels of LDL when treated with high-dose atorvastatin (all P<0.001), whereas there were no differences between the sexes in reaching target LDL levels when treated with standard-dose pravastatin (all P=0.13). Moreover, for both men and women, a greater proportion of patients achieved an hs-CRP level <2 mg/L and a dual goal of hs-CRP <2 mg/L and LDL <70 mg/dL with high-dose atorvastatin than with standard-dose pravastatin (all P≤0.015). However, within both the high-dose atorvastatin and the standard-dose pravastatin groups, more men reached the dual goal than did women at 30 days (P<0.001).

The increase in HDL levels at 30 days was slightly higher in the standard-dose pravastatin group than in the high-dose atorvastatin group in both sexes (women, 5.3% increase in HDL levels with pravastatin versus 0% with atorvastatin; men, 2.9% increase with pravastatin versus 0% with atorvastatin; both P<0.0001). When comparing the effects of statin therapy to achieve the HDL target levels of >50 mg/dL at 30 days, both women and men who received pravastatin reached the target HDL levels more frequently than those receiving atorvastatin (women, 39.9% with pravastatin versus 27.0% with atorvastatin; men, 13.7% with pravastatin versus 9.3% with atorvastatin; both P<0.001). These differences persisted throughout the study (all P<0.001).

For effects on triglycerides, the baseline median levels were not different between treatment groups in women (159 mg/dL with atorvastatin versus 156 mg/dL with pravastatin,
whereas they were slightly higher in men receiving intensive-dose statin than those receiving standard-dose statin (157 mg/dL versus 153 mg/dL, \(P=0.05\)). There was a greater decrease at 30 days in the intensive-dose versus the standard-dose statin for both sexes (women, 114 mg/dL versus 138 mg/dL; men, 107 mg/dL versus 139 mg/dL; both \(P<0.0001\)). The median triglyceride levels remained lower in the intensive-dose group than the standard-dose group at study termination (women, 131 mg/dL versus 153 mg/dL; men, 122 mg/dL versus 149 mg/dL; both \(P<0.0001\)).

Sex Differences in Side Effects of High-Dose Versus Standard-Dose Statin

Table 2 depicts the difference in rates of discontinuation of statin and side effects observed during the study using the safety cohort of patients who received at least 1 dose of study drug. There were no differences in the rate of statin discontinuation between men and women or between atorvastatin and pravastatin \(P\)-interaction, 0.77). Although more women and men had an increase in alanine aminotransferase or aspartate aminotransferase levels >3 times normal in the high-dose atorvastatin arm than in the pravastatin arm (both \(P=0.001\), no sex differences were detected with either alanine aminotransferase or aspartate aminotransferase elevations for either drug \(P\)-interaction, 0.11). Both women and men had similar rates of elevated creatine kinase >3 times the upper limit of normal and myalgias/myositis (all \(P\)≥0.20), with no sex differences between statin groups and the increase in creatine kinase level \(P\)-interaction, 0.62) and the presence of myalgias/myositis \(P\)-interaction, 0.63).

Sex Differences in Outcomes With High-Dose Versus Standard-Dose Statin

Figure 3 illustrates the Kaplan-Meier curves for the primary end point when stratified by treatment group for women and men separately, with fewer events shown in the high-dose statin arm than in the standard-dose statin arm for both sexes. As shown in Figure 4, the event rates at 2 years for the primary end points were lower both in women (20.3% with atorvastatin versus 27.0% with pravastatin, log-rank \(P=0.04\)) and in men (23.0% with atorvastatin versus 26.2% with pravastatin, log-rank \(P=0.04\)) when treated with high-dose...
versus standard-dose statin. Although there was no sex difference between treatment group and the primary end point ($P$-interaction, 0.38), women benefited from intensive statin therapy with a 6.7% absolute reduction in events and a 25% relative risk reduction (RRR) in hazard over standard statin therapy ($P$-interaction, 0.04), whereas men had a 3.2% absolute reduction in events and a 14% RRR in hazard ($P=0.04$). Results of the interaction test are consistent when adjusting for differences in baseline characteristics between men and women ($P$-interaction, 0.34). Based on a mean LDL δ between treatment groups at 30 days of 25.6 mg/dL in women and 32.1 mg/dL in men and a RRR of 24.5% (95% CI, 0.95 to 42.5%) in women and a RRR of 13.6% (95% CI, 0.7 to 24.9%) in men for the primary end point event, a mean change of 1.0 mg/dL (95% CI, 0.6 to 27.0 mg/dL) would produce a 1% reduction in events in women, whereas in men, a mean change of 2.4 mg/dL (95% CI, 1.3 to 45.9 mg/dL) would produce the same 1% reduction in events.

Women had a 37% relative reduction in hazard in death, MI, and UA ($P=0.01$); a 43% reduction in UA ($P=0.05$); a 47% reduction in hospitalization for heart failure ($P=0.04$); and a 30% reduction in the combination of primary end point or heart failure ($P=0.007$) when treated with high-dose atorvastatin. Figure 4 depicts the results of the 5 individual components that comprise the prespecified primary end point. No significant difference in all-cause mortality was seen in women with intensive versus standard statin therapy (2.8% versus 3.0%; hazard ratio [HR] 0.93; 95% CI, 0.43 to 2.00;
P = 0.85), whereas there was a trend toward reduced mortality in men (2.1% versus 3.3%; HR, 0.67; 95% CI, 0.44 to 1.01; P = 0.06), although the power for these comparisons was low given the low rates of death in both groups. Similarly, there was no difference in revascularizations in women (15.6% with intensive statin therapy versus 17.3% with standard statin therapy; HR, 0.88; 95% CI, 0.64 to 1.22; P = 0.45), with a trend toward fewer revascularizations in men (16.5% versus 19.2%; HR, 0.85; 95% CI, 0.72 to 1.01; P = 0.06). However, there were no sex differences between high- versus standard-dose statin therapy for 2-year outcomes evaluated individually or in various combinations (all P-interaction, ≥0.18). No interaction was seen between sex and treatment with gatifloxacin (P-interaction, 0.22).

Subgroup Analysis of Women

Figure 5 depicts the RRR of the primary end point when treated with intensive- versus standard-dose statin in women only, when stratified based on premenopausal and postmenopausal status, and when stratified by ERT. No differences in primary end point between women receiving intensive- and standard-dose lipid therapy were seen based on menopausal status (P-interaction, 0.27) or ERT (P-interaction, 0.75), although women not receiving ERT did achieve a 26% reduction in hazard (P = 0.04). The nonsignificant 22% reduction in primary end point for the postmenopausal group remained unchanged after adjustment for ERT (adjusted HR, 0.78; 95% CI, 0.58 to 1.02; P = 0.08).

Discussion

In this subgroup analysis of PROVE IT-TIMI 22, use of intensive statin therapy with high-dose atorvastatin after ACS led to a significant reduction in cardiovascular events in women (as well as in men) and with similar safety profiles compared to standard-dose pravastatin. For a 1% reduction in events, the mean reduction in LDL level needed in women was 1.0 mg/dL, whereas in men, a reduction of 2.4 mg/dL was needed to achieve the same benefit. With a 6.7% absolute reduction and 25% relative reduction of the primary end point with intensive-dose atorvastatin in women compared to a 3.2% absolute reduction and 14% relative reduction seen in men, the clinical impact of intensive statin therapy is quite robust in women and reinforces the value of treating women with intensive statin therapy after ACS to reduce cardiovascular events.

The benefit of statin therapy for women remains controversial with some authors who question the effectiveness of statins in the primary prevention of coronary artery disease in this subgroup of patients, claiming insufficient data, whereas advocates recommend their use in women even in primary prevention. Despite equally high 30-day mortality rates after ACS in men and women, gender bias has been observed in the management of women, with fewer treated with statin therapy after such events than men. Our study examines the efficacy and safety of intensive statin therapy for secondary prevention and provides further evidence to support its use in women. In addition to the 25% reduction in
the prespecified primary end point of the PROVE IT-TIMI 22 trial in women, we found consistent beneficial effects of high-dose atorvastatin on cardiovascular events in women, with 30% to 47% relative reductions in the risks for death, MI, and UA; UA; heart failure, and the combination of primary end point with heart failure.

When analyzing the 5 individual components of the primary end point separately, we did not observe a significant difference in all-cause mortality between the statin groups in women (or men), which reinforces the findings of a meta-analysis of 4 trials of intensive versus standard dose statin therapy. Although not powered to analyze the individual end points separately, the present subanalysis provides some insight on the driving forces behind the favorable response of intensive statin therapy over standard-dose statin therapy in the reduction of the primary end point. Reassuring is that neither softer end point of revascularization or stroke was the driving force and that UA and MI were the predominant factors leading to our primary results. Although we lacked power for the analysis, the benefit of intensive statin therapy appeared to be similar in premenopausal and postmenopausal women, with suggestion toward greater reduction in the primary end point in the premenopausal group.

Figure 4. Hazard ratios between intensive-dose atorvastatin and standard-dose pravastatin therapy in women and men. All P-interactions were nonsignificant.

Figure 5. Hazard ratios of the primary end point in women treated with intensive lipid-lowering therapy (atorvastatin 80 mg) compared to standard lipid-lowering therapy (pravastatin 40 mg) therapy. P-interaction was 0.27 for menopausal status and lipid therapy and 0.75 for ERT and lipid therapy. ERT indicates estrogen replacement therapy.
Interestingly, these clinical benefits of intensive statin therapy were seen in women despite less favorable achieved LDL levels. Fewer women on intensive statin therapy reached targeted LDL levels of <100 mg/dL and <70 mg/dL as recommended by the National Cholesterol Education Program Adult Treatment Panel III\(^28\) compared to men. With regard to the effect of the 2 statin treatment strategies on HDL levels, more women reached their HDL target level of >50 mg/dL than did men. This small advantage for women in reaching HDL targets might have contributed to the modestly greater risk reduction in the primary end point in women. We also observe a reduction in triglyceride levels for both women and men on intensive therapy over standard-dose therapy. Furthermore, for both women and men, the LDL and hs-CRP levels achieved were lower in the high-dose atorvastatin-treated group than in the standard-dose pravastatin-treated group. This improvement in both lipid and inflammatory profiles in conjunction with lower event rates confirm prior reports that reduction in both LDL and hs-CRP levels are predictors of therapy response and outcomes.\(^29–33\)

The dramatic benefit of intensive statin therapy in women in the present study of a 25% relative reduction in the primary end point; 37% reduction in death, MI, and UA; and 43% reduction in UA is supported by other trials.\(^34\) In the Treating to New Targets study, 1902 women with stable coronary heart disease with median follow-up of 4.9 years had a relative reduction of 27% in cardiovascular events when treated with atorvastatin 80 mg compared to atorvastatin 10 mg (HR, 0.73; \(P=0.049\)), whereas men had a relative reduction of 21% (HR, 0.79; \(P=0.001\)), a pattern similar to our study.\(^15\) Multiple trials have demonstrated efficacy of statins in both primary and secondary prevention of coronary events and death in women with both elevated and normal levels of cholesterol.\(^7,8,15\) It seems appropriate to continue to apply to women preventive strategies shown to be successful in men while recognizing that optimal classification and management of women with dyslipidemia and encouraging the enrollment of more women in lipid-lowering trials.

Heart failure is common in women.\(^2\) An additional finding in the present analysis was a benefit in reducing the risk of hospitalization for heart failure in women (and men). We found a striking benefit of intensive statin therapy for reducing not only the primary end point of cardiovascular events, but also of heart failure, and the greatest relative risk reduction in women for any outcome was for heart failure, with a 47% reduction.

**Limitations**

Several limitations are noteworthy of the present analysis. Despite the lack of interaction found in our analysis, each subgroup was significant on its own, thus demonstrating the benefit of intensive statin therapy in both sexes. Although we cannot conclude that women benefit more than men, our results may be constrained by power because it is uncertain what constitutes a meaningful power for subgroup analysis of interaction term with survival analytic data. The seemingly paradoxical effect of less LDL lowering in women versus men with high-dose atorvastatin, yet with a trend to greater absolute reduction in cardiovascular events in women over men, is intriguing. However, the LDL reductions with intensive statin therapy were large in both women and men. Our analysis is underpowered for the comparison between premenopausal and postmenopausal women, although trends were seen for the reduction of cardiovascular events in premenopausal women. Future randomized trials should include more women, both premenopausal and postmenopausal, and in numbers robust enough to assess the effects of interventions on clinical outcomes, including not only primary and secondary prevention, but also all levels of risk along the cardiovascular continuum.

**Conclusions**

Despite having less significant LDL lowering with intensive compared to standard lipid-lowering therapy than men, women had dramatic and significant reductions in clinical events. Both women and men benefit from high-dose statin therapy after ACS, and they should be treated with intensive regimens.

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