Impact of Female Sex on Lipid Lowering, Clinical Outcomes, and Adverse Effects in Atorvastatin Trials

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The aim of this study was to evaluate the effect of atorvastatin on lipid lowering, cardiovascular (CV) events, and adverse events in women compared with men in 6 clinical trials. In the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial (atorvastatin 80 mg vs simvastatin 20 to 40 mg), the Treating to New Targets (TNT) trial (atorvastatin 80 vs 10 mg), the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial (atorvastatin 80 mg vs placebo), and the Collaborative Atorvastatin Diabetes Study (CARDS), the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), and the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) (atorvastatin 10 mg vs placebo), lipid changes on treatment were compared between genders with studies grouped by dose. The association of on-study low-density lipoprotein (LDL) cholesterol and CV events by gender was evaluated in the combined studies and the impact of gender on adverse events in each study separately. Major CV events occurred in 3,083 of 30,000 men (10.3%) and 823 of 9,173 women (9.0%). Changes in lipids were similar in women and men. Major CV events were associated with gender-specific quintiles of on-treatment LDL cholesterol for women and men. In women, LDL cholesterol was a significant predictor of stroke, but not in men. Discontinuation rates due to adverse events were higher in women in 4 of 6 trials, but in only 1 trial was a significant treatment-gender interaction seen. Myalgia rates were slightly higher in women in both statin and placebo groups. In conclusion, the response of women to atorvastatin was similar to that of men, with slightly more discontinuations due to adverse events. Higher on-treatment LDL cholesterol was significantly associated with more CV events in both genders, but the association was stronger for stroke in women and for coronary heart disease death in men. **(Am J Cardiol 2015;115:447−453)**

Lipid-lowering therapy with statins decreases cardiovascular (CV) events and mortality in a variety of patient populations and clinical scenarios.[1,2] Fewer women than men have been enrolled in statin trials, and whether statins provide benefit to certain subsets of women has been controversial. For example, a meta-analysis of 6 trials including 11,435 women without CV disease published a decade ago showed no benefit for statins for any of the CV end points, although benefit was seen for secondary prevention.[3] In a meta-analysis of statins for primary prevention in women published 6 years later with larger numbers of subjects,[4] the relative risk for CV events for statin-treated women was 0.63 (95% confidence interval [CI] 0.49 to 0.82, p <0.001), with a trend toward a reduction in total mortality (relative risk 0.78, 95% CI 0.53 to 1.15). Two recent meta-analyses came to opposite conclusions. Gutierrez et al[5] concluded that statins for secondary prevention reduced total mortality and stroke in men but not women, while Kostis et al[6] showed similar benefits for men and women in primary and secondary prevention, including similar reductions in total mortality.

In most statin trials, adverse events have not been reported according to gender and have not included data on each individual patient. Some evidence suggests that statin discontinuation rates are higher in women,[7] and despite objective evidence, women are generally considered to be more likely than men to have side effects related to statins. Given these considerations, the purpose of this study was to evaluate the impact of female gender on lipid lowering, CV events, and adverse events (AE) in 6 large randomized clinical trials using patient-level data. These trials included atorvastatin at high and low doses in the settings of primary and secondary prevention: Treating to New Targets (TNT),[8] Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL),[9] Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL),[10] the Collaborative Atorvastatin Diabetes Study (CARDS),[11] Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN),[12] and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).[13]

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See page 452 for disclosure information.

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Table 1
Features of the trials

Variable	TNT	IDEAL	SPARCL	CARDS	ASPEN	ASCOT-LLA
Study Drug	A 80 mg	A 80 mg	A 80 mg	A 10 mg	A 10 mg	A 10 mg
Comparator	A 10 mg	S 20-40 mg	Placebo	Placebo	Placebo	Placebo
Patients	10,001	8,888	4,731	2,838	2,410	10,305
Women	1,902 (19.0%)	1,701 (19.1%)	1,908 (40.3%)	909 (32.3%)	811 (33.7%)	1,942 (18.8%)
Mean FU	4.9 years	4.8 years	4.9 years	3.9 years*	4 years	3.3 years*
Entry criteria	CHD, LDL 130-250 mg/dl	History of MI	Stroke or TIA 1-6 months	Diabetes + another RF, no CAD	Diabetes	Hypertension + 3 RFs, no CAD
Primary endpoint	CHD death, MI, stroke, cardiac arrest	CHD death, MI, cardiac arrest	Fatal or non-fatal stroke	CHD death, MI, UA, stroke cardiac arrest, PCI, CABG	CHD death, MI, UA, stroke cardiac arrest, PCI, CABG	CHD death, MI
Baseline LDL-C (mg/dl)	98	121	133	117	113	133
On-treatment LDL-C (mg/dl)	77 vs 101	81 vs 104	73 vs 129	75 vs 119	79 vs 113	87 vs 131
Event rates	8.7 vs 10.9%	9.3 vs 10.4%	11.2 vs 13.1%	5.8 vs 9.0%	13.7 vs 15.0%	1.9 vs 3.0%
HR (95% CI)	0.78 (0.69-0.89)	0.89 (0.78-1.01)	0.84 (0.71-0.99)	0.63 (0.48-0.83)	0.90 (0.73-1.12)	0.64 (0.50-0.83)

A = atorvastatin; CABG = coronary artery bypass grafting; CHD = coronary heart disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; RF = risk factor; S = simvastatin; TIA = transient ischemic attack; UA = unstable angina.
* Stopped early because of benefit.

Methods

The main results of the 6 trials included in this analysis have been published previously and are summarized in Table 1.[8–13] All trials were randomized, double-blinded, and had placebo or active treatment comparators. Follow-up was open label, with blinded end point evaluation in IDEAL and blinded in the other 5 trials. The primary end points differed among the 6 trials, and for this study, major CV events were defined as CV death, myocardial infarction, resuscitated cardiac arrest, and stroke. The analysis plan for this study was designed prospectively to answer questions related to gender differences with statins in low-density lipoprotein (LDL) cholesterol lowering, CV events, and discontinuation rates due to AEs and creatine kinase (CK) elevations.

To assess the impact of gender on lipid lowering, changes from baseline in LDL-C, high-density lipoprotein (HDL) cholesterol, triglycerides, and non-HDL cholesterol over time by treatment were analyzed. Within each gender, treatment comparisons were performed using an analysis-of-covariance model containing baseline and treatment. Treatment-by-gender interactions were computed to assess consistency of treatment effect by gender. IDEAL and TNT were pooled and presented by treatment (atorvastatin 80 mg, simvastatin 20 to 40 mg/atorvastatin 10 mg). SPARCL was summarized separately, and CARDS, ASCOT, and ASPEN were pooled (atorvastatin 10 mg vs placebo for all 3 trials). To assess the association of LDL and HDL cholesterol on CV events by gender, the 6 studies were pooled. We evaluated major CV events, coronary heart disease (CHD) death, nonfatal myocardial infarction, stroke, and CV mortality. Analysis was performed by month 3 LDL cholesterol gender-specific quintiles for all studies except ASCOT, in which month 6 LDL cholesterol was used because month 3 lipids were not collected. Subjects with events occurring before month 3 LDL cholesterol or month 6 LDL cholesterol in ASCOT were excluded from the analysis. Cox proportional-hazards models adjusting for study and treatment were used and hazard ratios (HRs) were computed comparing each quintile with the lowest LDL cholesterol quintile. The p value for trend across the 5 quintiles was computed. The analysis was performed for men and women separately. To examine the consistency of LDL cholesterol effect on events by gender, the interaction between gender and LDL cholesterol quintiles was computed. This analysis was repeated using month 3 HDL cholesterol quintiles.

The impact of gender on discontinuation rates was examined separately for each of the 6 studies. A summary of discontinuation by treatment, reasons for discontinuations,

Table 2
Clinical features of women and men in the trials

Variable	Women (n=9,173)	Men (n=30,000)	P value
Age (years)	63.3±9.4	61.6±9.1	<0.0001
Diabetes mellitus	3,269 (35.6%)	7,870 (26.2%)	<0.0001
Hypertension	6,467 (70.5%)	18,686 (62.3%)	<0.0001
Current smoker	1,939 (21.1%)	6,450 (21.5%)	0.75
Body mass index (Kg/m^2)	28.6±5.2	28.1±4.1	<0.0001
Body weight (Kg)	74.6±14.5	86.1±14.0	<0.0001
Systolic BP (mmHg)	143.7±22.4	142.8±22.5	0.0015
Diastolic BP (mmHg)	82.1±11.6	84.4±12.2	<0.0001
Total cholesterol (mg/dl)	207.5±34.5	194.4±34.2	<0.0001
LDL-C (mg/dl)	122.0±31.1	117.7±30.1	<0.0001
HDL-C (mg/dl)	55.0±14.5	46.8±11.8	<0.0001
Triglycerides (mg/dl)	153.3±78.3	150.2±82.3	0.0017
ApoA1 (mg/dl)	124.0±73.1	95.0±69.0	<0.0001
ApoB (mg/dl)	93.8±55.8	78.3±57.7	<0.0001

Data are expressed as mean ± SD or as number (percentage). At baseline, TNT patients had been taking atorvastatin 10 mg for 8 weeks.