UCSF
UC San Francisco Previously Published Works

Title

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

Permalink

https://escholarship.org/uc/item/5kv602pt

Journal

The American Journal of Cardiology, 115(4)

ISSN

0002-9149

Authors

Hsue, Priscilla Y
Bittner, Vera A
Betteridge, John
et al.

Publication Date

2015-02-01

DOI

10.1016/j.amjcard.2014.11.026

Peer reviewed

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

Priscilla Y. Hsue, MD[a], Vera A. Bittner, MD, MSPH[b], John Betteridge, MD, PhD[c], Rana Fayyad, PhD[d], Rachel Laskey, PhD[d], Nanette K. Wenger, MD[e], and David D. Waters, MD[a,*]

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.   © 2015 Elsevier Inc. All rights reserved. (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]

[a]Division of Cardiology, San Francisco General Hospital, San Francisco, California; [b]Division of Cardiovascular Disease, University of Alabama at Birmingham, School of Medicine, Birmingham, Alabama; [c]University College London Hospital, London, United Kingdom; [d]Pfizer Inc., New York, New York; and [e]Emory University School of Medicine, Atlanta, Georgia. Manuscript received October 15, 2014; revised manuscript received and accepted November 12, 2014.

See page 452 for disclosure information.

*Corresponding author: Tel: (415) 420-6646; fax: (415) 206-5447.

E-mail address: dwaters@medsfgh.ucsf.edu (D.D. Waters).

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

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.

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,
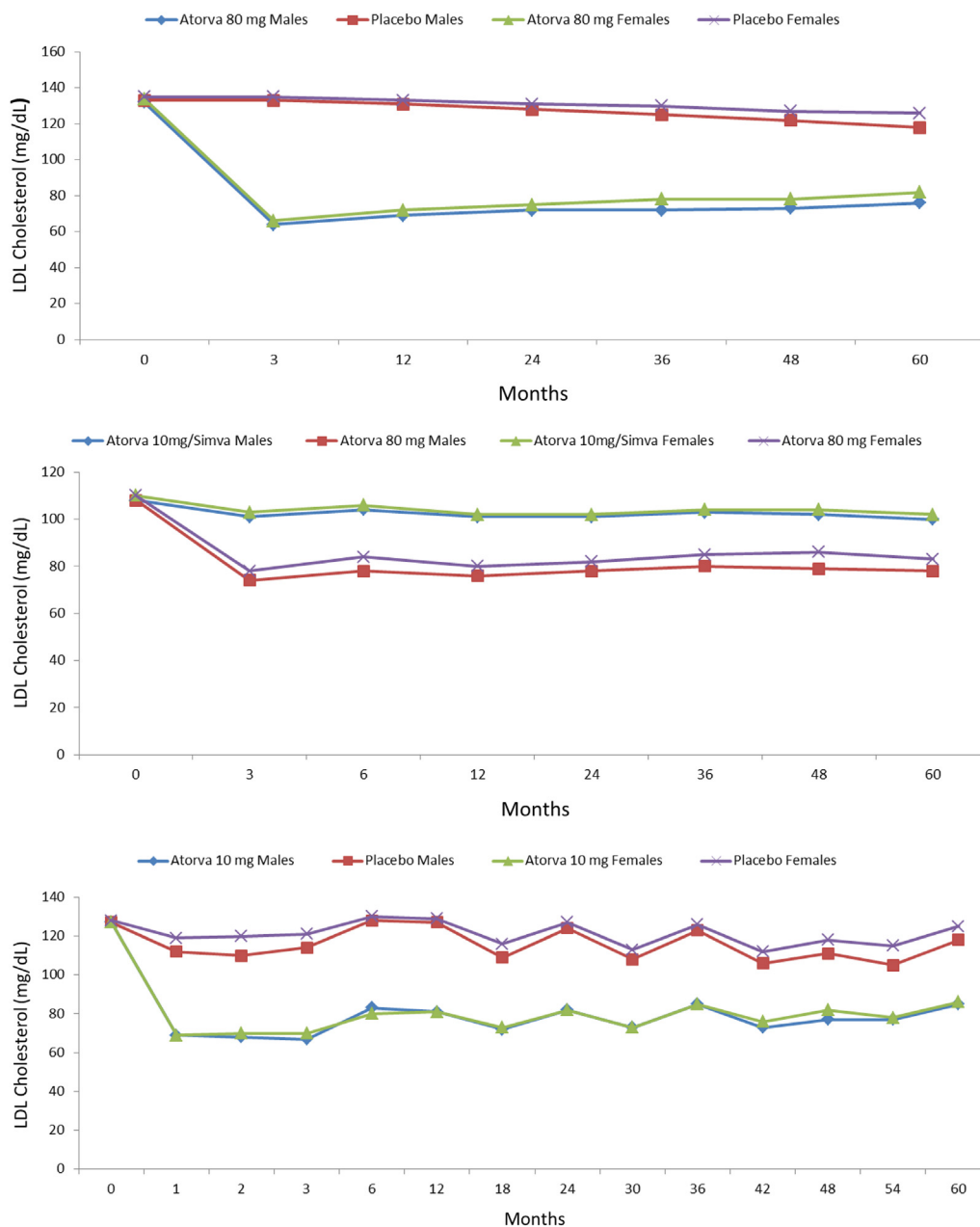
Figure 1. Changes in LDL cholesterol in men and women are shown for SPARCL study (*top*), TNT and IDEAL (*middle*), and ASPEN, CARDS, and ASCOT (*bottom*). Overall, the differences in LDL cholesterol lowering between women and men were small and not clinically significant.

and the most frequent AEs associated with discontinuation was generated. Statistical comparisons were performed for men and women using logistic regression comparing the difference in rates between treatments, and the treatment-by-gender interaction was computed for overall discontinuations due to AEs. Predictors of discontinuation were assessed for men and women separately.

An analysis to assess the effect of gender on CK elevations and AEs was performed for the 5 trials for which this information was available (CK levels were not measured in ASCOT). CK levels before treatment were categorized, and shifts in CK elevations were summarized at the maximum CK level during the study. Rates of discontinuations due to

AEs and treatment emergent myalgia were summarized for the baseline CK subgroups.

Results

Selected features of the 6 trials are listed in Table 1. Of the 39,173 patients enrolled in the 6 trials, 9,173 (23.4%) were women. As listed in Table 2, women were older (63.3 vs 61.6 years), were more likely to have hypertension and diabetes, weighed less, and had higher LDL and HDL cholesterol levels at baseline. Mean follow-up for 4 of the trials was 4-5 years but was shorter in CARDS and ASCOT−Lipid Lowering Arm (ASCOT-LLA) because

Table 3
Cardiovascular event rates in women and men according to quintiles of on-treatment LDL and HDL cholesterol levels

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P for trend
Women: LDL-C (mg/dl)	<65	65-83	84-103	104-128	>128	
Women: event rate	132/1727 (7.64%)	120/1702 (7.05%)	147/1685 (8.72%)	136/1694 (8.03%)	177/1715 (10.32%)	0.009
Men: LDL-C (mg/dl)	<66	66-81	82-99	100-123	>123	
Men: event rate	469/5430 (8.64%)	512/5807 (8.82%)	519/5574 (9.31%)	592/5598 (10.58%)	554/5603 (9.89%)	<0.0001
Women: HDL-C (mg/dl)	<43	43-50	51-57	58-65	>65	
Women: event rate	186/1792 (10.38%)	162/1613 (10.04%)	137/1809 (7.57%)	128/1658 (7.72%)	108/1760 (6.14%)	<0.0001
Men: HDL-C (mg/dl)	<38	38-42	43-47	48-54	>54	
Men: event rate	604/5549 (10.88%)	635/5905 (10.75%)	455/5667 (8.03%)	492/5674 (8.67%)	485/5734 (8.46%)	<0.0001

Table 4
On-treatment LDL cholesterol quintiles as predictors of cardiovascular events in women and men

	Women		Men		Gender*trend p-value
	HR (Quintile 5 vs 1)	Trend p-value	HR (Quintile 5 vs 1)	Trend p-value	
Major cardiovascular event	1.69 (1.25-2.27)	<0.001	1.34(1.14,1.57)	<0.001	0.920
Non-fatal myocardial infarction	2.14 (1.30-3.52)	0.004	1.43 (1.12-1.83)	0.007	0.864
Coronary heart disease death	1.16 (0.75-1.77)	0.893	1.74 (1.41-2.14)	<0.001	0.018*
Cardiovascular death	1.37 (0.80-2.35)	0.416	1.39 (1.05-1.84)	0.009	0.526
Stroke	1.63 (1.06-2.52)	0.022	1.08 (0.83-1.41)	0.533	0.184

Quintiles 5 versus 1 are presented to show the direction of effect; trend p values are shown to assess trend across the quintiles.

* The gender*trend p value of 0.018 changes to 0.56 after adjustment for diabetes, HDL cholesterol levels, hypertension, and smoking.

Table 5
Discontinuation rates due to AEs in women and men

Study	Men		Women		Treatment*gender interaction
	Study Drug	Comparator Drug	Study Drug	Comparator Drug	
TNT	9.6%	8.3%	13.9%	10.4%	0.620
IDEAL	8.3%	4.1%	15.1%	4.6%	0.010
SPARCL	1.8%	1.4%	3.2%	1.9%	0.396
CARDS	7.3%	7.8%	9.0%	8.8%	0.968
ASPEN	2.8%	3.1%	2.4%	3.0%	0.262
ASCOT	5.6%	5.4%	7.1%	7.7%	0.391

Study drug consisted of atorvastatin 80 mg in TNT, IDEAL, and SPARCL and atorvastatin 10 mg in CARDS, ASPEN, and ASCOT-LLA. Comparator drug was atorvastatin 10 mg in TNT, simvastatin 20 to 40 mg in IDEAL, and placebo in SPARCL, CARDS, ASPEN, and ASCOT-LLA.

they were stopped early for benefit. 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 generally similar in women and in men, as shown in Figure 1 for LDL cholesterol. High-dose atorvastatin lowered LDL and non-HDL cholesterol compared with the moderate dose slightly more in men than in women in the pooled TNT and IDEAL patients (p = 0.003 for treatment-by-gender interaction at 3 months for LDL cholesterol), but the absolute difference was small. No gender difference was seen with atorvastatin 80 mg in SPARCL. In contrast, atorvastatin 10 mg lowered LDL and non-HDL cholesterol compared with placebo slightly more in women than in men in the pooled CARDS, ASPEN, and

ASCOT-LLA patients (p = 0.02 for treatment-by-gender interaction at 6 months for LDL cholesterol), but this difference was also small and did not persist consistently at subsequent visits.

To consider the impact of discontinuation rates on lipid changes, the analysis was repeated after excluding all evaluations that occurred after the last treatment date. Overall, the decreases in LDL were slightly larger, and for IDEAL and TNT, the treatment-by-gender interactions from months 3 to 24 were no longer significant (data not shown).

In SPARCL, atorvastatin 80 mg slightly but significantly increased HDL cholesterol in men, but in women, the increase was smaller and not statistically significant, while no consistent gender differences in HDL cholesterol were seen

Table 6
Treatment-emergent myalgia rates by baseline CK level in women and men

CK (mg/dl)	Atorvastatin Number	Atorvastatin Myalgia	Placebo Number	Placebo Myalgia	Simvastatin Number	Simvastatin Myalgia
Women: total	4,481	505 (11.3%)	1,768	120 (6.8%)	841	91 (10.8%)
<ULN	4,226	479 (11.3%)	1,667	113 (6.8%)	765	83 (10.9%)
ULN-3xULN	233	24 (10.3%)	96	7 (7.3%)	74	8 (10.8%)
>3-<5xULN	8	2 (25%)	5	0	1	0
>5xULN	4	0	0	0	1	0
Men: total	14,602	1,373 (9.4%)	3,091	142 (4.6%)	3,556	274 (7.7%)
<ULN	12,563	1,169 (9.3%)	2,536	111 (4.4%)	2,982	231 (7.8%)
ULN-3xULN	1,948	191 (9.8%)	525	31 (5.9%)	553	42 (7.6%)
>3-<5xULN	73	10 (13.7%)	28	0	21	1 (3.7%)
>5xULN	18	3 (16.7%)	2	0	0	0

Atorvastatin 10- and 80-mg doses are combined; simvastatin 20 to 40 mg; ULN = upper limit of normal. Data are from 5 of the 6 trials; CK levels were not measured in ASCOT.

in TNT and IDEAL or CARDS, ASPEN, and ACOT-LLA. No consistent gender differences were seen for the triglyceride-lowering effect of either dose of atorvastatin.

For major CV events and nonfatal myocardial infarction, there was a significant trend across LDL and HDL cholesterol quintiles for men and women. The data for major CV events for LDL and HDL cholesterol quintiles are listed in Table 3. For HDL cholesterol quintiles, the trend-by-gender interaction was significant (p = 0.0089), indicating that HDL cholesterol was a stronger predictor of major CV events in women than in men. For CHD death, CV death, and all-cause mortality, there was a significant trend across LDL cholesterol quintiles for men but not women; in contrast, for stroke and non-CV death, we observed the opposite effect; namely, the observed trend was significant for women (for non-CV death, the trend was in favor of higher quintiles) and not men.

The unadjusted HRs comparing quintile 5 with quintile 1 in women and men for different end points are listed in Table 4. Adjusting for diabetes, HDL cholesterol levels, hypertension and smoking increased the HR for major CV events for women from 1.69 to 2.10 (95% CI 1.49 to 2.94) and for men from 1.34 to 1.48 (95% CI 1.22 to 1.79). After adjustment, the trend-by-gender interaction for CHD death was no longer statistically significant (p = 0.56).

As listed in Table 5, discontinuation rates due to AEs were slightly higher in women than in men in 4 of the 6 trials; however, a treatment-by-gender interaction was present only in IDEAL. The most common AE causing discontinuation in women was myalgia in IDEAL and ASPEN and elevated hepatic enzymes in TNT and SPARCL. Increasing age, higher atorvastatin dose, and number of concomitant medications were predictive of treatment discontinuation in women and men (all p values <0.0001) by multivariate analysis. The presence of diabetes was also predictive in women but not men (HR 1.33, 95% CI 1.09 to 1.63, p = 0.005, gender-by-factor interaction p = 0.036).

As listed in Table 6, most subjects did not have significant CK elevations and remained in their baseline CK categories. Rates of myalgia were slightly higher in women than in men in each of the 3 treatment groups: 11.3% versus 9.4% with atorvastatin, 10.8% versus 7.7% with simvastatin, and 6.8% versus 4.6% with placebo.

Discussion

The results of this study show that the effects of atorvastatin 10 and 80 mg in 6 large randomized trials did not differ markedly overall in women compared with men. The 10-mg dose lowered LDL cholesterol levels slightly more in women than in men, but the 80-mg dose lowered LDL cholesterol levels slightly more in men. On-treatment LDL, non-HDL, and HDL cholesterol levels were correlated with major CV events for women and men, with a marginally significant treatment-by-gender interaction for HDL cholesterol. Differences were seen for components of the composite end point, perhaps abetted by the smaller number of women than men: for CHD death, CV death, and all-cause mortality, there was a significant trend across on-treatment LDL cholesterol quintiles for men but not for women. For stroke, the trend across LDL cholesterol quintiles was statistically significant for women but not men. For non-CV deaths, LDL cholesterol levels were significantly correlated in women, with benefit at higher LDL cholesterol levels.

Differences between women and men in the amount of LDL cholesterol lowering for the same statin dose have not been highlighted in previous studies. In a network meta-analysis of 256,827 patients from 181 trials,[14] the investigators concluded that the proportion of women in a trial did not influence the degree of LDL cholesterol lowering with different statins; however, they did not have access to patient-level data. The difference in LDL cholesterol lowering between genders seen in this study is much smaller than the variation between individuals.

The Cholesterol Treatment Trialists' Collaboration meta-analysis of 170,000 patients included 45,495 women.[1] Each 1 mmol/L reduction in LDL cholesterol was associated with a 17% reduction in CV events for women and a 23% reduction for men (p for heterogeneity = 0.04). This meta-analysis did not detail other differences between genders, and meta-analyses that did focus on gender did not have access to patient level data.[4–6] We found no heterogeneity between genders in the relationship between on-treatment LDL cholesterol and CV events, but we did for the relation between on-treatment HDL cholesterol and CV events.

More women than men die from stroke every year, and fatal plus nonfatal stroke constitutes a higher proportion of

CV events in women compared with men.[15] In our study, the association between on-treatment LDL cholesterol and stroke was stronger in women than men. In patients with recent stroke or transient ischemic attacks included in SPARCL, women were older, had higher systolic and lower diastolic blood pressure, were more likely to have diagnosed hypertension, and were less likely to smoke cigarettes.[16] They also had higher levels of total cholesterol, LDL cholesterol, HDL cholesterol, and apolipoprotein A1 levels than men. Despite these differences, a gender-by-treatment interaction for stroke was not seen, and event reduction was similar for both genders.

Most studies that evaluated the safety of statins did not focus specifically on women[17]; however, it has been suggested that women may be at a higher risk for statin-induced myopathy.[18] Among the 6 trials included in this report (Table 5), discontinuation rates due to AEs were higher in women than men in 4, but a significant treatment-by-gender interaction was present only in IDEAL, the only trial in which treatment allocation during follow-up was not blinded. In the trials that included atorvastatin 10 mg, myalgia was the most common reason for drug discontinuation, while in the atorvastatin 80 mg treatment groups, elevated hepatic enzymes were the most common cause. The rates of treatment-related myalgia were slightly higher in women than in men in the statin and placebo groups. We examined whether baseline CK elevations could predict on-treatment myalgia, but CK levels were almost always normal at baseline, limiting the utility of this approach.

We have not reported gender differences in new-onset diabetes in these trials, because those data have already been published. Of the 6 trials, 2 were restricted to subjects with diabetes at baseline (CARDS and ASPEN). In TNT, IDEAL, and SPARCL, we have previously reported that the incidence of new-onset diabetes did not differ between women and men.[19] Gender was also not a factor predictive of new-onset diabetes in ASCOT.[20]

The results of this study are relevant to the types of patients enrolled in the 6 trials. Approximately 40% of the women across the trials had documented coronary disease (TNT and IDEAL), about 20% were enrolled for diabetes (CARDS and ASPEN), 20% for cerebrovascular disease (SPARCL), and 20% for hypertension and other risk factors (ASCOT-LLA). Women with hyperlipidemia in the absence of CV disease, diabetes, or hypertension are not represented, and the results therefore may not apply to them. Atorvastatin was used in each trial, and the profile of AEs might be different with other statins.

Disclosures

1. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 2010;376:1670−1681.
2. Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;380:581−590.
3. Walsh JM, Pignone M. Drug treatment of hyperlipidemia in women. *JAMA* 2004;291:2243−2252.
4. Mora S, Glynn RJ, Hsia J, MacFadyen JG, Genest J, Ridker PM. Statins for primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women in primary prevention trials. *Circulation* 2010;121:1069−1077.
5. Gutierrez J, Ramirez G, Rundek T, Sacco RL. Statin therapy in the prevention of recurrent cardiovascular events: a sex-based meta-analysis. *Arch Intern Med* 2012;172:909−919.
6. Kostis WJ, Cheng JQ, Dobrzynski JM, Cabrera J, Kostis JB. Meta-analysis of statin effects in women versus men. *J Am Coll Cardiol* 2012;59:572−582.
7. Caspard H, Chan AK, Walker AM. Compliance with a statin treatment in a usual-care setting: retrospective database analysis over 3 years after treatment initiation in health maintenance organization enrollees with dyslipidemia. *Clin Ther* 2005;127:1639−1646.
8. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK; Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425−1435.
9. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendiksen FS, Lindahl C, Szarek M, Tsai J; Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA* 2005;294:2437−2445.
10. Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, Zivin JA; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;355:549−559.
11. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH; CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685−696.
12. Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN). *Diabetes Care* 2006;29:1478−1485.
13. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J; ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149−1158.
14. Naci H, Brugts JJ, Fleurence R, Ades AE. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. *Eur J Prev Cardiol* 2013;20:658−670.

15. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Piña IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC Jr, Sopko G, Chandra-Strobos N, Urbina EM, Vaccarino V, Wenger NK. Effectiveness-based guidelines for the prevention of cardiovascular disease in women - 2011 update: a guideline from the American Heart Association. *Circulation* 2011;123:1243−1262.

16. Goldstein LB, Amarenco P, Lamonte M, Gilbert S, Messig M, Callahan A, Hennerici M, Sillesen H, Welch KM; SPARCL Investigators. Relative effects of statin therapy on stroke and cardiovascular events in men and women: secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Study. *Stroke* 2008;39:2444−2448.

17. Armitage J. The safety of statins in clinical practice. *Lancet* 2007;370: 1781−1790.

18. Tomlinson SS, Mangione KK. Potential adverse effects of statins on muscle. *Phys Ther* 2005;85:459−465.

19. Waters DD, Ho JE, DeMicco DA, Breazna A, Arsenault BJ, Chuan-Chuan W, Kastelein JJ, Colhoun H, Barter P. Predictors of new-onset diabetes in patients treated with atorvastatin. Results from 3 large randomized clinical trials. *J Am Coll Cardiol* 2011;57: 1535−1545.

20. Gupta AK, Dahlof B, Dobson J, Sever PS, Wedel H, Poulter NR; Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Determinants of new-onset diabetes among 19,257 hypertensive patients randomized in the Anglo-Scandinavian Cardiac Outcomes Trial − Blood Pressure Lowering Arm and the relative influence of antihypertensive medication. *Diabetes Care* 2008;31:982−988.