Statin Therapy in the Prevention of Recurrent Cardiovascular Events

A Sex-Based Meta-analysis

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Background: The effect of statins on the prevention of cardiovascular events is well demonstrated. Whether this protective effect is equal for women and men remains less well established. Our objective was to evaluate if statin therapy is equally effective in decreasing recurrent cardiovascular events in women and men.

Data Sources: Randomized clinical trials were searched in PubMed using as indexing terms *(statins OR cholesterol lowering medications)* AND *(cardiovascular events OR stroke OR myocardial infarction OR cardiovascular death)*.

Study Selection: We included randomized, double-blinded, placebo-controlled trials evaluating statins for secondary prevention of cardiovascular events. Studies with an open-label design and observational studies were excluded.

Data Extraction: The earliest citation was used to determine the characteristic of the studied population and the methodology. All subsequent citations corresponding to the trial were evaluated for outcome rates by sex.

Data Synthesis: Eleven trials representing 43 193 patients were included in the analysis. Overall, statin therapy was associated with a reduced risk of cardiovascular events in all outcomes for women (relative risk [RR], 0.81 [95% CI, 0.74-0.89]) and men (RR, 0.82 [95% CI, 0.78-0.85]). However, they did not reduce all-cause mortality in women vs men (RR, 0.92 [95% CI, 0.76-1.13] vs RR, 0.79 [95% CI, 0.720.87]) or stroke (RR, 0.92 [95% CI, 0.76-1.10] vs RR, 0.81 [95% CI, 0.72-0.92]).

Conclusions: Statin therapy is an effective intervention in the secondary prevention of cardiovascular events in both sexes, but there is no benefit on stroke and all-cause mortality in women.

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H YPERCHOLESTEROLEMIA IS a major contributor to the incidence of cardiovascular disease, and interventions aimed at curbing the effect that dyslipidemia has on cardiovascular morbidity and mortality are of great importance.[1-3] For the last 20 years, statins have been used to lower serum cholesterol levels. The statin trials have predominantly enrolled men, and although women

See Invited Commentary and Editor's Note at end of article

have been included at different proportions, there have been conflicting results on the benefits obtained in women with cardiovascular disease compared with men in secondary cardiovascular disease prevention. A recent guideline from the American Heart Association[4] recommended statin therapy to achieve the same low-density lipoprotein (LDL) goals in women as in men,

although determining if a differential statin benefit exists for men and women was not the focus of the report.

One previous attempt to determine the benefit of statins in women stratified by primary vs secondary prevention found a benefit on coronary heart disease (CHD) but not on total mortality for secondary prevention, while there was no benefit on CHD or total mortality for primary prevention.[5] This meta-analysis did not compare the statin benefit in men vs women, and stroke was not included as an outcome. Recently, another meta-analysis found an overall similar benefit of statin therapy for men and women in both primary and secondary prevention.[6] However, this meta-analysis included trials without placebo control and trials in predominantly diabetic populations; and the stroke outcome was derived mainly from primary prevention trials, excluding important statin trials such as the Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study (SPARCL)[7-12] and the

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Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering Study (MIRACL).[13-19]

Our goal in the present meta-analysis was to evaluate whether statin therapy is more effective than placebo in preventing the recurrence of cardiovascular events and all-cause mortality in men and women, and to determine the sex-specific effect of statins on the risk of recurrent cardiac and cerebrovascular events.

METHODS

ELIGIBILITY CRITERIA

Only trials focusing on secondary prevention were selected for detailed analysis. Previous cardiovascular disease was defined as prior myocardial infarction (MI), angina (stable or unstable), any cardiac intervention, any stroke or transient ischemic attack, peripheral arterial disease, or more than 3 cardiovascular risk factors. This last definition was thought to represent a very high risk of cardiovascular events similar to the risk seen in patients with cardiovascular events.

Only clinical trials were included and only if they met the following criteria: (1) random allocation to the groups (stratification and blocking were allowed); (2) double-blinding; (3) placebo-control; (4) follow-up of at least 16 weeks; (5) sample size of at least 100 total participants and (6) outcomes reported by sex in both active and control groups.

EXCLUSION CRITERIA

The following types of trials were excluded: (1) open-label trials; (2) observational trials; (3) trials conducted to evaluate secondary prevention in patients undergoing cardiac interventions; (4) trials designed to study secondary prevention in patients with kidney disease, congestive heart failure (ejection fraction below 30%), and/or aortic stenosis; (5) trials in which women were excluded; (6) trials without clinical events reported; and (7) trials to study primary prevention of cardiovascular events (including in patients with diabetes). The rationale underlying these exclusion criteria was to homogenize the included population as much as possible.

INFORMATION SOURCES

A systematic search of publications was carried out in PubMed. No other sources of information were sought. The search terms used for the Boolean search were

(statins OR cholesterol lowering medications) AND *(cardiovascular events OR stroke OR myocardial infarction OR cardiovascular death)*, with results limited to humans, male, female, clinical trials, English language, and all adults older than 19 years from date of inception until September 15, 2010.

STUDY SELECTION

The first screening was carried out by looking at the title and the abstract. If doubt existed, the citation was kept for further detailed screening. The second screening consisted of retrieving the full text or extended abstract from the remaining citations. One of us (J.G.) independently classified the studies as appropriate for further review or not and extracted the data from each trial.

DATA COLLECTION PROCESS

The evaluated outcomes were any cardiovascular event (MI, coronary death, and/or stroke), all-cause mortality, coronary mortality, MI, cardiac interventions (coronary artery bypass graft and/or percutaneous coronary intervention), and/or stroke (fatal or nonfatal). For trials with no disclosure of event rates by sex but otherwise qualified for inclusion, the contact author was contacted for sex data if an e-mail address was provided in the article.

RISK OF BIAS IN INDIVIDUAL STUDIES

A good-quality study must have equal cardiovascular risk factor prevalence between sexes or no more than 1 unbalanced characteristic. In addition, no imbalance in antiplatelet agent use was allowed in good-quality trials. If 2 or more cardiovascular risk factors or antiplatelet agent use were significantly more common in men or women at baseline or at follow up, the study quality was rated as *fair*.

SYNTHESIS OF RESULTS

Fixed effects were used for all outcomes. Random effects were used secondarily to test robustness of results.[20,21] Risk ratios were obtained comparing active vs control group rate of events. Risk ratios were obtained using the Mantel-Haenzel statistical method provided by the Review Manager (RevMan) computer program, version 5.0. (The Nordic Cochrane Center, the Cochrane Collaboration, 2008). Subgroup analysis was performed, stratifying only by sex. Interactions between sex and treatment arm were obtained for the

outcomes where the stratified analysis did not show benefit for women. The Stata metaregression command was used for this analysis (StataCorp LP). Heterogeneity was tested only in sex subgroups, and it was quantified with Q test and I^2. A 2-tailed α value of 0.05 was used to determine statistical significance.

RISK OF BIAS ACROSS STUDIES

Funnel-plot visualization was used to assess publication bias in pooled outcomes with a minimum of 10 trials.[20] The adverse effects associated with statin therapy are probably less well characterized, but an effort was made to collect these data as well.

Sensitivity analysis was conducted by temporarily eliminating a trial, 1 by 1, and altogether if 2 or more trials were identified in the categories specified a priori. We considered a combined outcome to be sensitive to the trial(s) if (1) the risk ratio changed by 10% in either direction by subtracting the trial or trials and/or (2) if the statistical significance changed.

Sensitivity analyses were performed for trial subgroups based on the shortest follow-up, less similar qualifying events, greater confidence intervals, lowest LDL levels at baseline, highest LDL levels at baseline, older participants, lowest proportion of women, and solubility of statins.[22]

RESULTS

STUDY SELECTION

From the original 878 citations retrieved from PubMed, we excluded 609 citations. The most common reasons for exclusion were the lack of event rates by sex, open-label design, absence of placebo control, and primary prophylaxis (**Figure 1**). Eleven authors and/or sponsors listed as contacts in the trial publication who disclosed e-mails were contacted for the trials that did not report sex rates in their publications, but only 1 (Fluvastatin on Risk Diminishment After Acute Myocardial Infarction [FLORIDA] trial[23]) answered the request with the rates information (unpublished data, 2002).

STUDY CHARACTERISTICS AND RISK OF BIAS

Eleven trials were included in the final analysis (see eAppendix for a detailed description of each trial; http:

//www.archinternmed.com). Most of the trials evaluated patients with a recent qualifying cardiovascular event (8 with only coronary disease as the qualifying event, 2 with cerebrovascular disease as an inclusion criterion). However, 1 trial, the Anglo-Scandinavian Cardiac Outcomes Trial–lipid-lowering arm (ASCOT-LLA),[24-27] included patients with more than 3 risk factors for any of these outcomes. We included ASCOT-LLA trial in the analyses because of the expected very high risk of cardiovascular events in this predominantly nondiabetic population.

The follow-up ranged from 16 weeks (MIRACL[13-19]) to 6.1 years (Long-Term Intervention with Pravastatin in Ischaemic Disease [LIPID[28-36]]) and was at least 2 years in 8 of the studied populations. The statins evaluated were lovastatin (Canadian Coronary Atherosclerosis Intervention Trial [CCAIT]),[37,38] simvastatin (Scandinavian Simvastatin Survival Study [4S]),[28,39-47] pravastatin (LIPID,[28-36] Prospective Study of Pravastatin in the Elderly at Risk [PROSPER],[48,49] Cholesterol and Recurrent Events trial [CARE],[50] and Pravastatin Limitation of Atherosclerosis in the Coronary Arteries trial [PLAC-I][51]), fluvastatin (FLORIDA[23] and Fluvastatin on Cardiac Events[52]), and atorvastatin (SPARCL,[7-12] MIRACL,[13-19] and ASCOT-LLA[24-27]). Five studies evaluated middle-dose statins; 1, low-dose; 3, high-dose; 2, escalated low-dose to middle-dose if LDL level was not at goal; and 1 escalated middle-dose to high dose if LDL level was not at goal (**Table 1** and **Table 2**).

RESULTS FROM INDIVIDUAL STUDIES

All studies showed efficacy of statins in reducing the rate of any cardiovascular events. Stratifying by sex, the results were less consistent for women than for men (**Figure 2**). None of the individual trials reporting all-cause mortality reported statistically significant risk reduction in women taking statins (4S,[28,39-47] LIPID,[28-36] and SPARCL[7-12]), while for men, 2 of 5 trials showed statistically significant rate reduction (LIPID[28-36] and 4S[28,39-47]) (**Figure 3**).
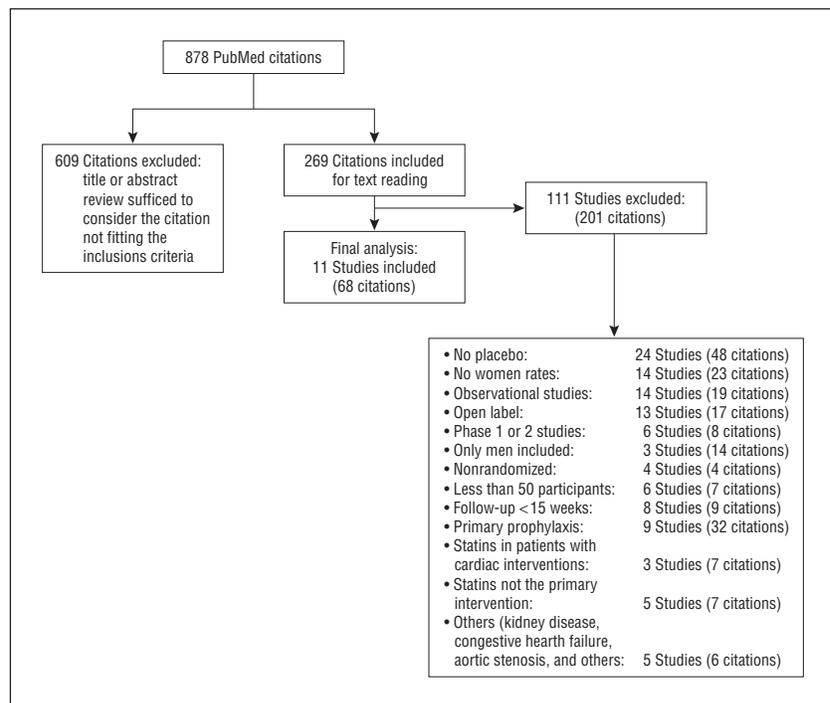
Figure 1. Study flowchart. Please note, there is no conflict between the 68 citations noted in the figure to be included in the analysis and the fewer citations present in this article. All pertinent information from the relevant trials was obtained from the articles cited herein.

Of the 3 studies reporting coronary mortality (4S,[28,39-47] CARE,[50] and LIPID[28-36]), only CARE showed a significant risk reduction for women taking statins, while all 3 showed benefit in men (eFigure 1). In the prevention of any MI, the LIPID[28-36] trial provided most of the cases to both subgroups, and it showed a benefit for men but not for women treated with statins compared with placebo (eFigure 2). Only 1 of 6 trials showed a beneficial effect of statins for women in the prevention of recurrent stroke (MIRACL[13-19]; follow-up, 16 weeks), and 2 point estimates were above 1 (LIPID[28-36] and PROSPER[48,49]) (**Figure 4**).

SYNTHESIS OF RESULTS

The pooled sample size from the 11 trials was 43 191 participants; 20.6% were women (**Table 3**). Statins were effective in the prevention of any cardiovascular event compared with placebo (relative risk [RR], 0.81 [95% CI, 0.78-0.85]). The stratification by sex did not change the direction or significance of the risk reduction (for women, RR, 0.81 [95% CI, 0.74-0.89] vs RR, 0.82 [95% CI, 0.78-0.85] for men) (Figure 2). The funnel plot for this estimate was asymmetric, suggesting publication bias. Statins were better than placebo in reducing all-cause mortality (RR, 0.81 [95% CI, 0.75-0.88]) (Figure 3). However, the statin benefit in women did not reach statistical significance (RR, 0.92 [95% CI, 0.76, 1.13]) while in men it did (RR, 0.79 [95% CI, 0.72-0.87]).

The interaction between sex and treatment arm was not significant for all-cause mortality ($P = .78$). For the prevention of coronary mortality, statins were better than placebo (RR, 0.73 [95% CI, 0.66-0.80]). Stratification by sex did not change the statin effects (eFigure 1). For the prevention of any MI, statins were better than placebo (RR, 0.73 [95% CI, 0.65-0.81]) (eFigure 2). The same effects were observed for women and men. In the prevention of cardiac interventions, statins were more effective than placebo (RR, 0.76 [95% CI, 0.71-0.82]). Stratification by sex showed a more pronounced statin effect in women than men (RR, 0.69 [95% CI, 0.56-0.85] vs RR, 0.77 [95% CI, 0.71-0.84]), but the absolute risk reduction was similar in both sexes (3% vs 4%) (eFigure 3, Table 3).

Statins were effective preventing recurrence of any stroke com-

Table 1. Summary of Methodologies of Included Trials, Part 1

Trial	Intervention; Cholesterol Level for Inclusion, mg/dL	Baseline LDL, mg/dL	Sample Size, No./Age, Mean, y	Qualifying Event	Women in the Sample, %	Randomization/Blinding
ASCOT-LLA,[24-27] 2003	Atorvastatin, 10 mg/d; TC=<251	131	10 305/63	>3 Cardiovascular risk factors	18.8	Factorial design, 2×2, performed under protocol PROBE by an independent randomization center/yes
LIPID,[28-36] 1998	Pravastatin, 40 mg/d; TC=155-171	W, 158 M, 148.5	9014/62 (median age)	Prior MI or unstable angina in the previous 3-36 mo	17	Stratified by qualifying event, then blocked to keep a ratio of 2:1, acute MI to unstable angina/yes
PROSPER,[48,49] 2002	Pravastatin, 40 mg/d; TC=115-350	W, 154.9 M, 138.5	5804/75 for M, 75.6 for W	Preexisting coronary, cerebral, or peripheral vascular disease	51.7	Simple randomization/yes
4S,[28,39-47] 1994	Simvastatin, 20 mg/d but doubled if LDL not on goal; TC=212-309	W, 189 M, 188	4444/58.2 for M, 60.5 for W	Angina or MI in the prior 3 or 6 mo, respectively	18.5	Sequential allocation stratified per center and then per qualifying event/yes
CARE,[50] 1998	Pravastatin, 40 mg/d; TC=<240, LDL=115-174	W, 140 M, 139	4159/59	Acute MI 3-30 mo prior to randomization	14	Stratified randomization by the center/yes
PLAC-I,[51] 1995	Pravastatin, 40 mg/d; LDL=130-190	164	408/57	Recent MI, coronary stenosis >50% or balloon angioplasty (a third of the sample had interventions)	22.5	The type of randomization not clear, although groups appeared balanced in baseline characteristics/yes
SPARCL,[7-12] 2006	Atorvastatin, 80 mg/d; LDL=100-190	W, 134 M, 132	4731/62 for M, 63.9 for W	TIA or stroke in the prior 6 mo excluding those with history of coronary events	40.4	Simple randomization/yes
MIRACL,[13-19] 2002	Atorvastatin, 80 mg/d; TC<270	124	3086/65	Chest pain plus evidence of MI	34.8	Simple randomization/yes
FLORIDA,[23] 2002	Fluvastatin, 40 mg twice a day; TC<251	134	540/60.5	Acute MI	17	Randomized, but type not disclosed/yes
Fluvastatin on CE,[52] 1999	Fluvastatin, 40 mg/d but doubled if LDL not on goal at week 6; LDL>160	196	365/60	Symptomatic CAD manifested with exercise test or angiographically proven MI	38.4	Randomized, but type not disclosed/yes
CCAIT,[37,38] 1995	Lovastatin, 20 mg/d but increased up to 80 mg/d if LDL not on goal during first 16 weeks; TC=220-230	W, 182 M, 177	331/52.2 for M, 57.6 for W	Symptomatic coronary disease with marker of coronary stenosis on angiography	18.7	Stratified randomization per sex/yes

Abbreviations: CAD, coronary artery disease; LDL, low-density lipoprotein cholesterol; M, men; MI, myocardial infarction; NR, not reported; PROBE, Prospective Randomized Open Blinded End-point; TC, total cholesterol; TIA, transient ischemic attack; W, women.

SI Conversions: To convert all cholesterol values to millimoles per liter, multiply by 0.0259.

pared with placebo (RR, 0.84 [95% CI, 0.76-0.93]). Stratification by sex showed the same statin effect for men (RR, 0.81 [95% CI, 0.72-0.92]), while for women the risk reduction did not reach statistical significance (RR, 0.92 [95% CI, 0.76-1.10]). The interaction between sex and treatment arm was not significant (*P* = .99). Fixed and random models did not differ in any of the tested outcomes and RR by sex except for all-cause mortality in men (fixed effect RR, 0.79 [95% CI, 0.72-0.87] vs random effect RR, 0.83 [95% CI, 0.65-1.05]. This disparity is likely explained by the increased weight attributed to SPARCL[7-12] under the random model. SPARCL is the only trial that had an RR point estimate above 1 for men in statin therapy compared with placebo.

Of the 11 trials included in our analyses, only 3 studies were rated good quality, based on the balanced group characteristics at baseline. The largest studies were of fair quality (LIPID,[28-36] CARE,[50] 4S,[28,39-47] SPARCL,[7-12] and PROSPER[48,49]), and in the remaining trials, the needed information to compare groups was not clearly disclosed.

LIPID PROFILE CHANGE

The pooling of mean differences in lipid profiles revealed very similar changes in lipid profiles for both sexes, which might argue against a differential response in the lipid-lowering effects of statins for both sexes (**Table 4**).

ADVERSE EVENTS

LIPID[33] and SPARCL[7] investigators reported no differences in adverse events by sex. In the CARE trial,[50] women receiving pravastatin were found to have an increased incidence of breast cancer compared with women taking placebo, and PROSPER[48,49] reported increased incidence of new cancer in the pravastatin group compared with the placebo group, but no sex-based rates were reported. The increased can-

Table 2. Summary of Methodologies of Included Trials, Part 2

Trial	Unbalanced Baseline Characteristics/Quality	Patients With Incomplete Data or Censored	Compliance	Concomitant Open-Label Drugs in Women	Follow-up
ASCOT-LLA,[24-27] 2003	No/good	1.1% in active group; 1.2% in placebo group	NR	Yes, equal proportions among groups	3.7 y
LIPID,[28-36] 1998	Yes, women were older, had higher prevalence of angina, HTN, obesity, DM, and higher levels of HDL and LDL/fair	1% of sample included in analysis but not randomized, other losses to follow-up unclear	81% in active group, 76% in placebo group at end of follow-up	Yes, women had lower proportion of aspirin use but higher proportion of CCA, nitrates, diuretics, and ACEi in both placebo and active groups	6.1 y
PROSPER,[48,49] 2002	Yes (unbalanced), women had higher TC, LDL, triglycerides, HTN, and age; less DM and history of vascular disease/fair	25.1% in active group, 25.2% in control group	94% overall, but 10% in active group and 5% in placebo group started open-label statin treatment	Yes, balanced among groups, but types of medications not disclosed	3.2 y
4S,[28,39-47] 1994	Yes (unbalanced), women older, less history of MI or revascularizations, fewer smokers, higher HDL and HTN/fair	No incomplete data reported	86% in placebo group, 90% in simvastatin group	Yes, women with higher nitrates and CCA use	5.4 y
CARE,[50] 1998	Yes, women were older, had higher prevalence of HTN, smoking, and DM, higher TC and HDL than men/fair	Data for MI classification complete for all patients, other outcomes unclear	94% in active group, 86% in placebo group; 8% active and 2% placebo took open-label statins	Yes, women took less aspirin and β-blockers with more CCA and diuretics	5.0 y
PLAC-I,[51] 1995	Not apparent for most covariates but not clearly described/unknown	22% with no follow-up angiography	65.4% Overall	Yes, imbalance seen in the total numbers, but no statistical test performed to evaluate significance	2.3 y
SPARCL,[7-12] 2006	Yes, women were older, had higher TC, LDL, HDL, systolic blood pressure, less prevalent HTN and smoking/fair	3.9% in the active arm, 5% in placebo arm	Not reported, but 25% in placebo arm and 11.4% in active arm took open-label atorvastatin, a net difference of 78% in statins used among groups	Yes, but balanced among groups	4.9 y
MIRACL,[13-19] 2002	No/good	0.5% in active group, 0.2% in placebo group	86% in active group, 88% in placebo group	Yes, but balanced among groups	16 wk
FLORIDA,[23] 2002	No/good	Unclear	87.6%, including temporary and permanent discontinuation	Yes, but balanced among groups	1 y
Fluvastatin on CE,[52] 1999	None apparent, but no statistical testing performed to evaluate significance/unknown	24% of patients lost to follow-up	Not disclosed, but lack of it given as a major reason for 24% loss to follow-up	Yes, but no statistical testing performed to evaluate significance	1 y
CCAIT,[37,38] 1995	Women were more likely to be older, with more prevalent HTN, DM, and angina and less frequent MI; lovastatin-treated women were the oldest of all groups/fair	Unable to determine completion of data to evaluate clinical events rate	>90% in both groups	Yes, no statistical difference reported, but unclear if test was performed for these comparisons	2 y

Abbreviations: ACEi, angiotensin converting enzyme inhibitors; CCA, calcium channel antagonist; DM, diabetes mellitus; HDL, high-density lipoprotein cholesterol; HTN, hypertension; LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; NR, not reported; TC, total cholesterol.

cer risk in the treatment arm has been explained as a result of chance and has not been reproduced in a statin meta-analysis performed by the PROSPER investigators.[49] The 4S,[41,42] ASCOT-LLA,[27] MIRACL,[13] and Fluvastatin on Cardiac Events[52] trials did not find significant differences in adverse effects associated with statins, but no sex-based analysis was reported. PLAC-I[51] reported increased frequency of transaminase elevation in the pravastatin group, but none of the patients discontinued taking the study medication. No sex-based rates were provided. CCAIT[37] and FLORIDA[23] trials did not report adverse events among treated groups.

SENSITIVITY ANALYSIS

The RR estimates were not changed by removing the trials with the shortest follow-up (MIRACL[13-19]); less similar qualifying events (ASCOT-LLA[24-27] [mostly excluding clinical events] and SPARCL[7-12] [excluding previous cardiac events]); greater confidence intervals (CCAIT,[37,38] FLORIDA,[23] and Fluvastatin on Cardiac Events[52]); lowest LDL levels at baseline (ASCOT-LLA,[24-27] MIRACL,[13-19] and SPARCL[7-12]); or highest LDL levels at baseline (4S[28,39-47] and Fluvastatin on Cardiac Events[52]). Removing the trial with the oldest population (PROSPER[48,49]) in the comparison of any stroke changed the RR by 10% (from 0.92 to 0.83). Whether this is secondary to the older population of PROSPER[48,49] or the use of a hydrophilic statin is unknown. The removal of the other 3 trials using hydrophilic statins (LIPID,[28-36] CARE,[50] and PLAC-I[51]) plus PROSPER[48,49] brought down the stroke recur-
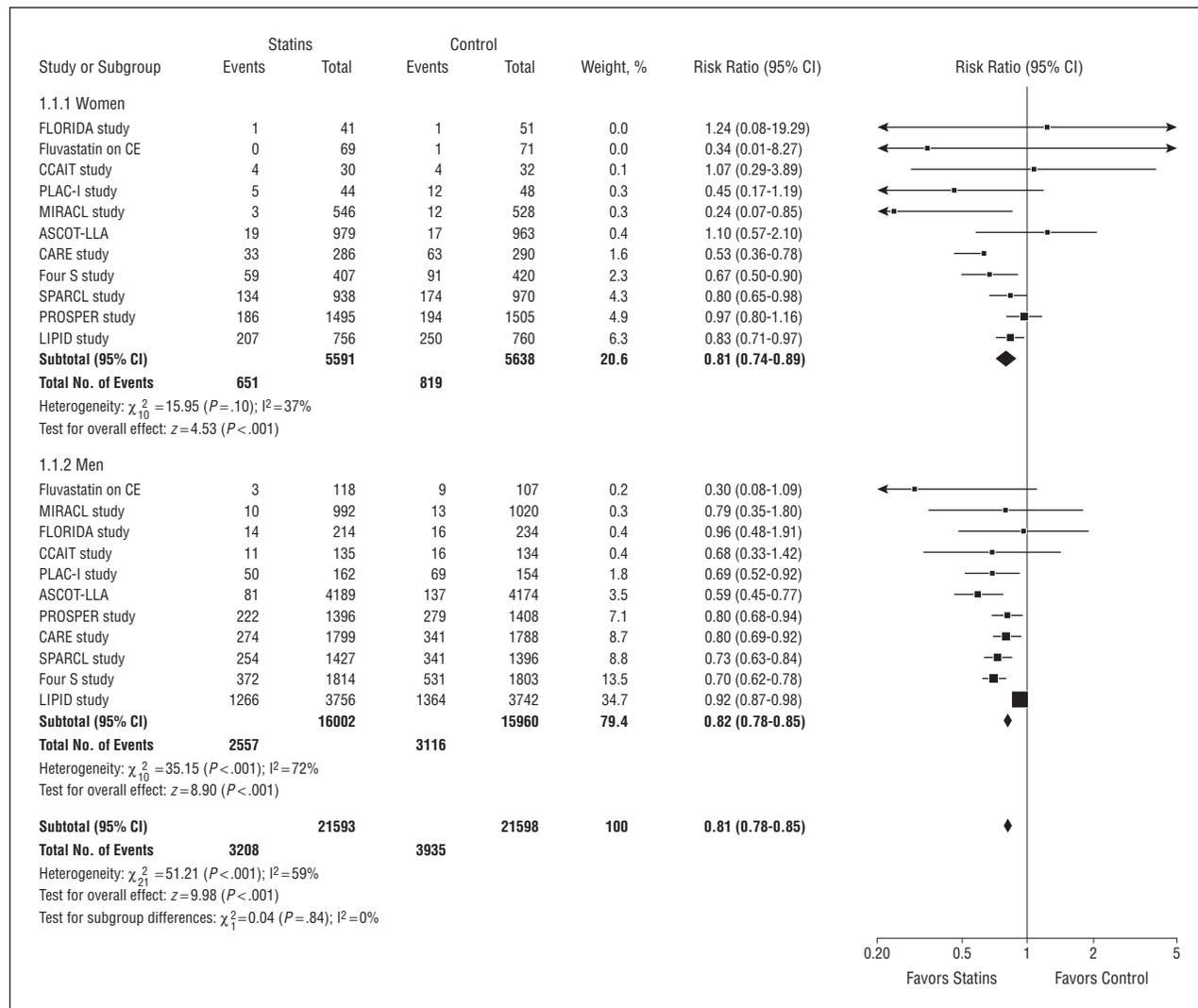
Figure 2. Any cardiovascular event (cardiac and/or cerebrovascular). Risk ratios are based on the fixed Mantel-Haentzl test analysis. ASCOT-LLA indicates Anglo-Scandinavian Cardiac Outcomes Trial–lipid-lowering arm[24-27]; CARE, Cholesterol and Recurrent Events trial[50]; CCAIT, Canadian Coronary Atherosclerosis Intervention Trial[37,38]; FLORIDA, Fluvastatin on Risk Diminishment After Acute Myocardial Infarction trial[23]; Fluvastatin on CE, Fluvastatin on Cardiac Events[52]; LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease[28-36]; M-H, Mantel-Haentzl test; MIRACL, Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering study[13-19]; PLAC-I, Pravastatin Limitation of Atherosclerosis in the Coronary Arteries trial[51]; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk[48,49]; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study[7-12]; 4S, Scandinavian Simvastatin Survival Study.[28,39-47]

rence RR in women by 13%. The point estimate for men did not change significantly.

Removing the trials with the lowest proportion of women changed the results significantly, particularly LIPID[28-36] and CARE.[50] Removing LIPID[28-36] increased the risk reduction for men by 0.08 (10%) because men in LIPID[28-36] had a higher rate of events than men in the other trials. For coronary mortality outcome, the suppression of CARE[50] made the statin effect in women similar to placebo. The suppression of LIPID[28-36] from the MI outcome increased the risk reduction in women by 38% but reduced it for men by 10%. The suppression of

CARE[50] reduced the benefit in statins therapy in women by 14% making it similar to placebo for the prevention of MI in women. For the prevention of cardiac interventions, removing CARE[50] reduced the stains benefit in women by 15%; this effect was not seen in men.

COMMENT

In our results, statin therapy reduced the recurrence rate of any type of cardiovascular event, all-cause mortality, coronary death, any MI, cardiac intervention, and any stroke type. The stratification by sex showed no statistically significant risk reduc-

tion for women taking statins compared with women taking placebo for the reduction of all-cause mortality and any type of stroke. There was no statistical interaction in these 2 outcomes. In all-cause mortality and stroke, even though the point estimate for women was closer to the null value, the CI still overlapped that of the men. The benefit of statins remained significant for all outcomes in men. Heterogeneity was greater for men than for women in all outcomes except MI, mainly because some trials showed greater reduction in RR for men taking statins than others. However, overall, all the point estimates were below 0, showing consistent directions of the effect. The
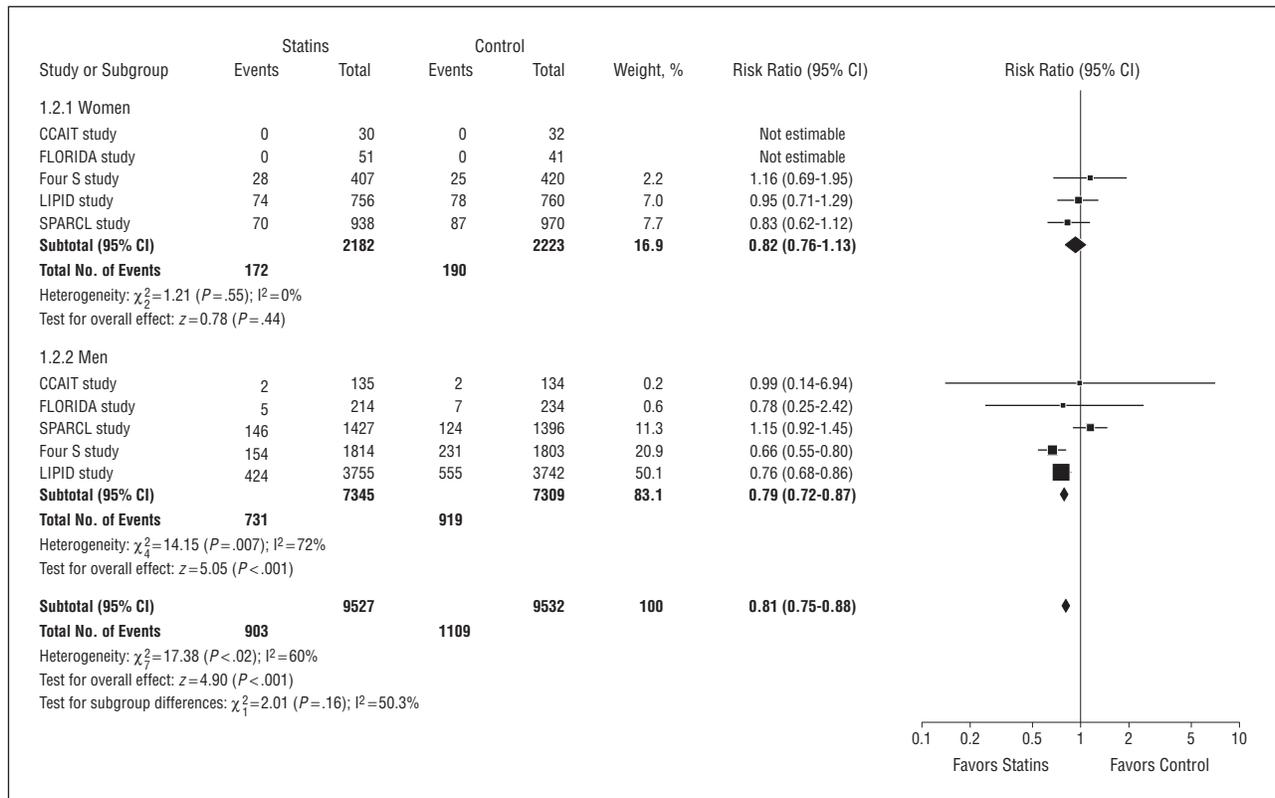
Figure 3

Study or Subgroup	Statins Events	Statins Total	Control Events	Control Total	Weight, %	Risk Ratio (95% CI)
1.2.1 Women						
CCAIT study	0	30	0	32		Not estimable
FLORIDA study	0	51	0	41		Not estimable
Four S study	28	407	25	420	2.2	1.16 (0.69-1.95)
LIPID study	74	756	78	760	7.0	0.95 (0.71-1.29)
SPARCL study	70	938	87	970	7.7	0.83 (0.62-1.12)
Subtotal (95% CI)		2182		2223	16.9	0.82 (0.76-1.13)
Total No. of Events	172		190			

Heterogeneity: $\chi^2_2 = 1.21$ ($P = .55$); $I^2 = 0\%$
Test for overall effect: $z = 0.78$ ($P = .44$)

Study or Subgroup	Statins Events	Statins Total	Control Events	Control Total	Weight, %	Risk Ratio (95% CI)
1.2.2 Men						
CCAIT study	2	135	2	134	0.2	0.99 (0.14-6.94)
FLORIDA study	5	214	7	234	0.6	0.78 (0.25-2.42)
SPARCL study	146	1427	124	1396	11.3	1.15 (0.92-1.45)
Four S study	154	1814	231	1803	20.9	0.66 (0.55-0.80)
LIPID study	424	3755	555	3742	50.1	0.76 (0.68-0.86)
Subtotal (95% CI)		7345		7309	83.1	0.79 (0.72-0.87)
Total No. of Events	731		919			

Heterogeneity: $\chi^2_4 = 14.15$ ($P = .007$); $I^2 = 72\%$
Test for overall effect: $z = 5.05$ ($P < .001$)

Subtotal (95% CI)		9527		9532	100	0.81 (0.75-0.88)
Total No. of Events	903		1109			

Heterogeneity: $\chi^2_7 = 17.38$ ($P < .02$); $I^2 = 60\%$
Test for overall effect: $z = 4.90$ ($P < .001$)
Test for subgroup differences: $\chi^2_1 = 2.01$ ($P = .16$); $I^2 = 50.3\%$

Favors Statins — Favors Control (0.1 0.2 0.5 1 2 5 10)

Figure 3. All-cause mortality. For all abbreviations, data explanation, and study references, see legend to Figure 2.

Figure 4

Study or Subgroup	Statins Events	Statins Total	Control Events	Control Total	Weight, %	Risk Ratio (95% CI)
1.6.1 Women						
FLORIDA study	0	51	0	41		Not estimable
PLAC-I study	0	44	1	48	0.2	0.36 (0.02-8.68)
MIRACL study	3	546	12	528	1.6	0.24 (0.07-0.85)
CARE study	7	286	16	290	2.1	0.44 (0.19-1.06)
LIPID study	33	756	27	760	3.6	1.23 (0.75-2.02)
PROSPER study	70	1495	61	1505	8.0	1.16 (0.83-1.62)
SPARCL study	89	938	107	970	13.9	0.86 (0.66-1.12)
Subtotal (95% CI)		4116		4142	29.4	0.92 (0.76-1.10)
Total No. of Events	202		224			

Heterogeneity: $\chi^2_5 = 10.65$ ($P = .06$); $I^2 = 53\%$
Test for overall effect: $z = 0.91$ ($P = .36$)

Study or Subgroup	Statins Events	Statins Total	Control Events	Control Total	Weight, %	Risk Ratio (95% CI)
1.6.2 Men						
PLAC-I study	0	162	1	154	0.2	0.32 (0.01-7.72)
FLORIDA study	0	214	4	234	0.6	0.12 (0.01-2.24)
MIRACL study	10	992	13	1020	1.7	0.79 (0.35-1.80)
CARE study	47	1799	62	1788	8.2	0.75 (0.52-1.09)
PROSPER study	65	1396	70	1408	9.2	0.94 (0.67-1.30)
LIPID study	136	3756	177	3742	23.4	0.77 (0.62-0.95)
SPARCL study	176	1427	204	1396	27.3	0.84 (0.70-1.02)
Subtotal (95% CI)		9746		9742	70.6	0.81 (0.72-0.92)
Total No. of Events	434		531			

Heterogeneity: $\chi^2_6 = 3.29$ ($P = .77$); $I^2 = 0\%$
Test for overall effect: $z = 3.37$ ($P < .001$)

Subtotal (95% CI)		13862		13884	100	0.84 (0.76-0.93)
Total No. of Events	636		755			

Heterogeneity: $\chi^2_{12} = 15.29$ ($P < .23$); $I^2 = 22\%$
Test for overall effect: $z = 3.31$ ($P < .001$)
Test for subgroup differences: $\chi^2_1 = 1.23$ ($P = .27$); $I^2 = 18.8\%$
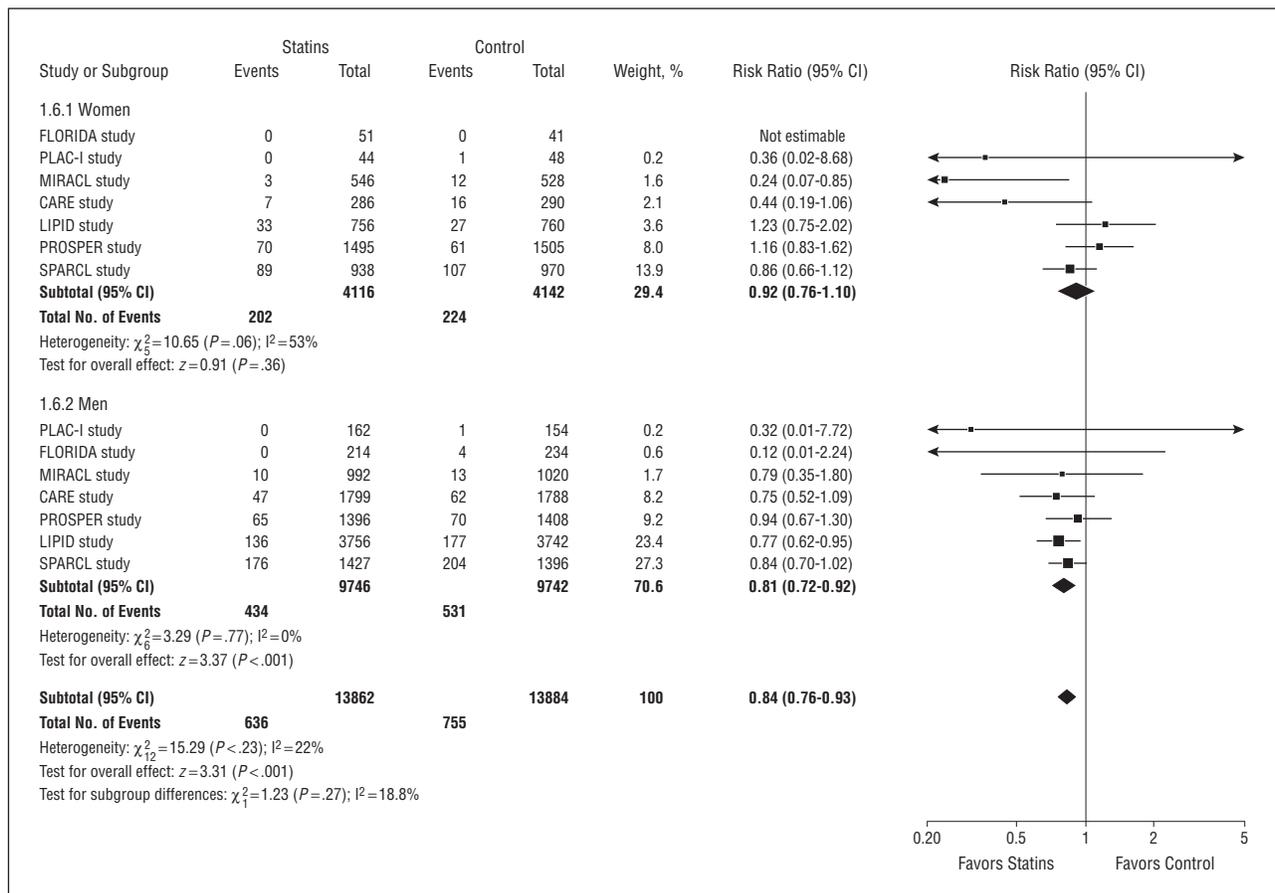
Favors Statins — Favors Control (0.20 0.5 1 2 5)

Figure 4. Any stroke (fatal or nonfatal). For all abbreviations, data explanation, and study references, see legend to Figure 2.

Table 3. Summary of Effect Estimates of Statins vs Placebo, Crude and Stratified by Sex

Outcome or Subgroup (Studies, No.)	Participants, No.	Absolute Event Rate, %		Risk Ratio[a]	Absolute Risk Reduction[a]	I² Heterogeneity, %
		Statins	Placebo			
Any cardiovascular event (cardiac and/or cerebrovascular) (n=11)	43 191	14.9	18.2	0.81 (0.78 to 0.85)	−0.03 (−0.05 to −0.02)	59
Women	11 229	11.6	14.5	0.81 (0.74 to 0.89)	−0.03 (−0.05 to −0.01)	37
Men	31 962	16.0	19.5	0.82 (0.78 to 0.85)	−0.04 (−0.06 to −0.02)	72
All mortality (n=5)	19 059	9.5	11.6	0.81 (0.75 to 0.88)	−0.02 (−0.03 to −0.01)	60
Women	4405	7.9	8.5	0.92 (0.76 to 1.13)	−0.01 (−0.02 to 0.01)	0
Men	14 654	9.5	11.6	0.79 (0.72 to 0.87)	−0.03 (−0.04 to −0.02)	72
Coronary mortality (n=3)	17 621	6.9	9.5	0.73 (0.66 to 0.80)	−0.03 (−0.03 to −0.02)	28
Women	2919	5.2	7.2	0.73 (0.55 to 0.96)	−0.02 (−0.04 to 0.00)	0
Men	14 702	7.2	10.0	0.73 (0.65 to 0.81)	−0.03 (−0.04 to −0.02)	66
Any myocardial infarction (fatal and nonfatal) (n=4)	13 916	7.2	10.0	0.73 (0.65 to 0.81)	−0.03 (−0.04 to −0.02)	0
Women	2246	6.6	9.6	0.69 (0.52 to 0.91)	−0.03 (−0.05 to −0.01)	33
Men	11 670	7.4	10.0	0.73 (0.65 to 0.83)	−0.03 (−0.04 to −0.02)	0
Cardiac intervention (CABG or PCI) (n=4)	18 316	10.9	14.2	0.76 (0.71 to 0.82)	−0.03 (−0.04 to −0.02)	50
Women	4092	6.8	9.8	0.69 (0.56 to 0.85)	−0.03 (−0.05 to −0.01)	5
Men	14 224	9.4	14.3	0.77 (0.71 to 0.84)	−0.04 (−0.05 to −0.02)	69
Any stroke (fatal and nonfatal) (n=7)	27 746	4.6	5.4	0.84 (0.76 to 0.93)	−0.01 (−0.01 to 0.00)	22
Women	8258	4.9	5.4	0.92 (0.76 to 1.10)	−0.00 (−0.01 to 0.01)	53
Men	19 488	4.5	5.4	0.81 (0.72 to 0.92)	−0.01 (−0.01 to 0.00)	0

Abbreviations: CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention.
[a] Based on the fixed Mantel-Haentzl test analysis, reported as risk ratio (95% CI) or absolute risk reduction (95% CI).

Table 4. Lipid Profile Changes From Baseline in Available Studies

Study	Statin Used	Sex	Active Group Mean Difference From Baseline				Placebo Group Mean Difference From Baseline			
			TC	LDL	HDL	Trg	TC	LDL	HDL	Trg
CARE[50]	Pravastatin, 40 mg/d	M	−19	−28	+5	−14	NA	NA	NA	NA
		F	−20	−28	+4	−13				
CCAIT[37,38]	Lovastatin, 20 mg/d[a]	M	−20	−28	+7.7	−8	−1.2	−1.4	+2.9	+4.4
		F	−24	−32	+5.4	−8.4	−2.4	−2.9	+3.4	+1.5
SPARCL[7-12]	Atorvastatin, 80 mg/d	M	−39	−26.7	+7	−11.2	−4.4	−2.6	+3.2	+5.6
		F	−35.3	−23.2	+4.6	−10.5	−9.1	−5.7	+4.2	+3.2
4S[28,39-47]	Simvastatin, 20 mg/d[a]	M	−25.1	−34	+6.9	−15.8	NA	NA	NA	NA
		F	−26.4	−37.4	+7.2	−15.5				
Average	All	M	−25.8	−29.2	+6.7	−11.9	−2.8	−2	+3.1	+5
		F	−26.4	−30.2	+5.3	−11.9	−5.8	−4.3	+3.8	+2.4

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not available; TC, total cholesterol; Trg, triglycerides.
[a] Dose doubled if LDL levels not at goal.

only exception we found to this was SPARCL,[7-12] in which men had no statistically significant benefit provided by statins in the prevention of all-cause mortality. The funnel plot was asymmetric in the only outcome fit for this test (any cardiovascular event). Whether this asymmetry represents a publication bias is less certain. The inclusion of small trials with somehow more pronounced effect size might be indicative of this type of bias, but the selection of a highly specific population in these small trials, where greater risk modification is expected, could be a valid alternative explanation for the lack of funnel plot symmetry. There is no evidence of significant loss to follow-up that could have biased the reported outcomes: the reported follow-up rate was relatively good in all trials.

The concomitant use of medications in groups is also of concern, especially when unequally distributed among men and women. The administration of antiplatelet agents seemed lower in 2 of the trials that provided a large amount of cases (ie, greater weight in the final risk ratio): LIPID[28-36] and CARE.[50] Women also had overall greater prevalence of hypertension and were older than men in most of the trials (LIPID,[28-36] PROSPER,[48,49] 4S,[28,39-47] CARE,[50] SPARCL[7-12] [greater systolic blood pressure], and CCAIT[37,38]), and these differences somehow conferred a somehow worse cardiovascular profile in studied women than in studied men. Although identifying the reasons for these differences was not the goal of the meta-analysis, these results add to the cumulative evidence that women are undertreated for cardiovascular disease.[53-57] The results of this meta-analysis also underscore the low rate of women being enrolled in cardiovascular prevention clinical trials.

Through the sensitivity analysis, we found that lipophilic statins might be better for women than hydrophilic statins, particularly for stroke prevention. This hypothesis needs to be tested in proper trials powered for sex differences among treatment groups. The PROSPER trial[48,49] suggests that statins might not work as well for old women as for old men. Therefore, age might be an important confounder in the evaluation of statin efficacy. As is already well known, women reach rates of cardiovascular disease similar to men but at an older age than men, almost a decade older. The number needed to treat was the inverse of the absolute risk reduction, and as is summarized in Table 3, the combined absolute risk reduction in women was constantly lower than that in men. In this context, the number needed to treat with statins in women is expectedly higher compared with that of men in the same age group.

Other possible explanations for the differential effects of stains in women include the biological profile particular to women and different interactions between sexual hormones, statins, and endothelial function.[58-62] Although the lipid profile change noted in 4 of the trials analyzed did not show any difference in the lipid profile, particularly LDL level reduction between sexes, others have reported that women less often had LDL goals achieved while treated with statins.[63] An ideal trial to test the hypothesis that statins have a differential effect in women and men should be powered for sex subgroup analysis; it should aim high at equalizing cardiovascular risk factors and medical therapy variables at baseline and follow-up; and it should collect variables that can help understand the presumed difference in statin therapy response by sex such as hormonal levels, inflammatory markers, and markers of atherosclerosis such as coronary calcium level, carotid intima media thickness, and others.

LIMITATIONS

Our study is the result of a systematic review in only 1 database, which introduces bias. It is possible that many other trials were not reported in PubMed or in the journals indexed in this electronic database. Limiting the electronic search to manuscripts published in English introduced language bias. Only 1 person screened the trials and extracted the information, increasing the chances of missed trials and/or misclassification. Owing to the small number of trials included in this meta-analysis, formal testing of publication bias could be performed, and the funnel plot was useful for only 1 outcome. The heterogeneity of reports, the inclusion of at least 5 relatively small studies, and the lack of response of at least 9 qualifying trials make the results of this meta-analysis less conclusive, and the lack of statistical significance in some outcomes might be secondary to these problems.

A major limitation of the conclusion is that women represented only 20% of the population studied. It is likely that the pooled sample was underpowered for women. Since the direction of the statin therapy effects was toward the reduction of event rates in both sexes, the lack of significance could have been related to the small sample size of the comparisons. Overall, the population studied was obtained from hospital-based samples or clinics with no random sampling performed, which raises concerns when applying these results to other populations or groups not included in the trials. Most of the trials were sponsored by the pharmaceutical manufacturers that produced the tested drugs at the time of the trials. The conflict of interest for reporting positive results is latent, although independent statistical analysis, restriction to the cumulative data set, and the expected ethical behavior of researchers offers some reassurance against the reporting bias.

CONCLUSIONS

Statins are effective for the prevention of cardiovascular events for both men and women. Women represented only a fifth of the studied sample, limiting the strength of our conclusions. In our results, the benefit associated with statin administration in women did not reach statistical significance compared with placebo in at least 2 outcomes, all-causes mortality and any stroke type. The reason for this difference is uncertain. One possibility is that the small sample size of women limits the power of the study. In addition, it is possible that the worse cardiovascular profile of women enrolled in studies as well as the lower proportion of antiplatelet agent use could account for some of these differences. Although biological differences need to be further elucidated and are likely to exist, sex-specific disparities in health care and in biomedical research, particularly in cardiovascular health, need to be addressed from a public health perspective by promoting equal access to health care that includes timely screening, diagnoses, and treatment of cardiovascular risk factors and disease.

This meta-analysis supports the use of statins in women for the secondary prevention of cardiovascular events. It also underscores differences in the benefit obtained from statins in women compared with men. These differences are likely secondary to the small proportion of women included in the trials and a worse cardiovascular health status in these same women. Increased awareness of this disparity is needed, and public policies addressing sex-specific differences in cardiovascular health are encouraged.

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INVITED COMMENTARY

Statins Work Just as Well in Women as in Men

Evidence to support the use of statins for preventing recurrent cardiovascular disease (CVD) is strong, derived from individual patient data meta-analysis[1] and from systematic reviews of randomized trials.[2] This evidence underpins the use of statins in clinical guidelines internationally as an uncontroversial treatment for secondary prevention that is both cost-effective and safe.[3-5]

In this issue of The *Archives*, Gutierrez and colleagues[6] present a meta-analysis of statin trials to determine whether the effects are different in men and women. Their literature search was confined to keyword terms in PubMed and English language, and data were extracted by a single investigator—all potential sources of bias. Indeed the basic search for the terms *statins/cholesterol-lowering medications* and *CVD* yields only 5000 articles, of which 878 survive the additional limits imposed. So is it possible that Gutierrez and colleagues have missed some relevant studies?

There have been several recent systematic reviews of statin trials to compare with the analysis by Gutierrez et al,[6] whose limited search and restrictive inclusion criteria resulted in most of the relevant data being lost. Of the 21 trials included in the recent Cholesterol Treatment Trialists (CTT) publication,[7] only 5 were included by Gutierrez and colleagues. Several of the omitted trials would have been eligible for inclusion if the authors had accepted usual-care comparison groups, used in some of the larger randomized controlled trials, and participants without prior cardiovascular disease.

But is it really likely that there are sex differences in treatment effects?