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Meta-Analysis of Statin Effects in Women Versus Men

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Objectives The aim of this study was to evaluate the effect of statins in decreasing cardiovascular events in women and men.

Background Published data reviews have suggested that statins might not be as effective in women as in men in decreasing cardiovascular events.

Methods Published data searches and contacts with investigators identified 18 randomized clinical trials of statins with sex-specific outcomes (N = 141,235, 40,275 women, 21,468 cardiovascular events). Odds ratios (ORs) and 95% confidence intervals (CIs) for cardiovascular events were calculated for women and men separately with random effects meta-analyses.

Results The cardiovascular event rate was lower among those randomized to statin intervention than in those randomized to control (low-dose statin in 4 studies, placebo in 11 studies, usual care in 3 studies) and similar in women and men (OR: 0.81, 95% CI: 0.75 to 0.89; $p < 0.0001$, and OR: 0.77, 95% CI: 0.71 to 0.83, $p < 0.0001$, respectively). The benefit of statins was statistically significant in both sexes, regardless of the type of control, baseline risk, or type of endpoint and in both primary and secondary prevention. All-cause mortality was also lower with statin therapy both in women and men without significant interaction by sex (p for interaction = 0.4457).

Conclusions Statin therapy is associated with significant decreases in cardiovascular events and in all-cause mortality in women and men. Statin therapy should be used in appropriate patients without regard to sex. (J Am Coll Cardiol 2012;59:572–82) © 2012 by the American College of Cardiology Foundation

Randomized controlled clinical trials and meta-analyses have shown a benefit of statins in decreasing morbid and mortal cardiovascular events in apparently healthy individuals and in those with clinically evident cardiovascular disease (CVD) (1–6). However, there is insufficient information on the benefits of statins in women especially in primary prevention (7–9). Reviews and meta-analyses have shown improved outcomes with statins in both women and men without significant interaction by sex (10–11). However, they did not show statistically significant effects in women. This could be related to under-representation of women in trials and underscores the need to explore sex-related differences that would provide a basis for clinical strategies to improve outcomes for women (12–15).

The purpose of this report is to present a meta-analysis of sex-specific outcomes in controlled randomized clinical trials of statin therapy.

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Methods

Study selection. The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (16). With Medline, the Cochrane Library, the Central Register of Controlled Trials, Web of Science, and ClinicalTrials.gov, we performed a systematic published data search of randomized clinical trials of statin therapy where sex-specific data were presented through June 30, 2010. Trials were eligible for inclusion in the meta-analysis if they were controlled, randomized, and investigator- and patient-blind and if they presented data by sex. We sought to obtain missing mortality data by contacting the investigators of all studies where sex-specific all-cause mortality data were not published. Studies with fewer than 100 patients or fewer than 5 deaths/randomized group were excluded. With the search strategy described in Online Table 1, we identified 2,332 potentially appropriate titles for possible inclusion in the

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analysis (Fig. 1, Table 1). Each of these titles was evaluated by 2 investigators (W.J.K., J.B.K.) for possible inclusion in the study. Eighteen trials fulfilled all criteria for inclusion in the meta-analysis. The studies were evaluated with regard to the similarity of baseline characteristics, having defined eligibility criteria, blinding, use of placebo or other control, intention-to-treat analysis, information on adherence, and the percentage lost to follow-up (Online Table 2) (17).

Data extraction and quality assessment. The 18 studies that fulfilled the inclusion criteria were categorized as primary prevention (5) (Online References e22–e24,e26,e31,e33,e34) or secondary prevention, (6) (Online References e21,e25,e27–e30,e32,e35,e36) as designed by the investigators. All studies except 1 were funded by the pharmaceutical industry (Online Reference e30). In the majority of the studies, an independent data center was responsible for the data and analysis. The approximate relative potency of the statin used (1 for lovastatin and pravastatin, 2 for simvastatin, 4 for atorvastatin, and 8 for rosuvastatin) and the relative dose used (calculated as the product of the dose and the relative potency) were tabulated. A measure of the use of active therapy in the intervention and control groups (active medication difference [AMD]) was defined as the percentage of patients who actually received active therapy among those randomized to receive it, minus the percentage of those who actually took active therapy among those who were randomized to control. The number of randomized patients, the number of primary endpoints, and the number of deaths in the intervention and control groups were recorded. The difference in the decrease of serum low-density lipoprotein cholesterol (LDL-c) concentration between the intervention and control groups was tabulated for each study. There were no assumptions or modifications made concerning the data included in the analyses. Sex-specific data on the number of randomized patients, the number of primary endpoints, and the number of deaths in the intervention and control groups were recorded.

Abbreviations and Acronyms

CHD = coronary heart disease

CI = confidence interval

CVD = cardiovascular disease

LDL-c = low-density lipoprotein cholesterol

OR = odds ratio

Data synthesis and analysis. Pre-defined outcomes were all-cause mortality and the primary endpoint as defined by the investigators of each study. The rates of occurrence of the primary endpoint and all-cause mortality (where available) in the intervention and control groups were calculated for each study as a whole as well as by sex. Statistical analyses were performed with JMP (version 7.0, SAS Institute, Cary, North Carolina), Comprehensive Meta-Analysis (version 2.2, Biostat, Englewood, New Jersey), and R software (R Project for Statistical Computing). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each endpoint. Weighted pooled treatment

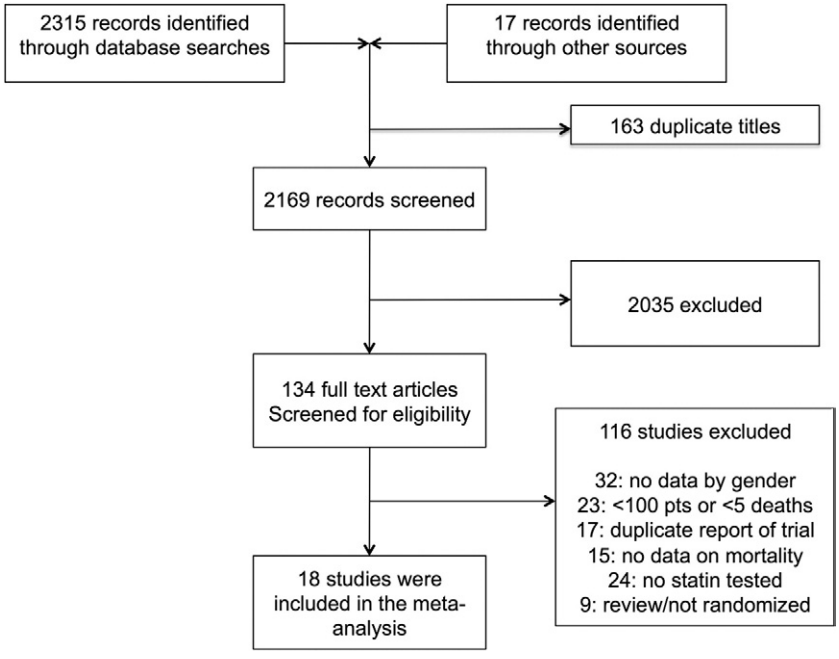

Figure 1 Published Data Search and Selection of Studies Included in the Meta-Analysis

Flow diagram of identification of published records retrieved from published data searches and from other sources (i.e., reading of reviews and prior meta-analyses). Reasons for exclusion of potentially eligible studies are listed.

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Table 1 Descriptors

Study	Primary Versus Secondary	Drug	Dose	Statin Dose	Relative Potency	Relative Dose	Control	Relative Dose Control	Relative Dose Difference (Act-Cntrl)	Follow-Up (Months)
4S	Secondary	Simvastatin	27.0	27.0	2	54.0	Placebo	0	54.0	67.0
AF-TEXCAPS	Primary	Lovastatin	30.0	30.0	1	30.0	Placebo	0	30.0	62.0
ALLHAT-LLT	Primary	Pravastatin	40.0	40.0	1	40.0	Usual Care	0	40.0	58.0
ASCOT-LLA	Primary	Atorvastatin	10.0	10.0	4	40.0	Placebo	0	40.0	40.0
AURORA	Primary	Rosuvastatin	10.0	10.0	8	80.0	Placebo	0	80.0	38.0
CARE	Secondary	Pravastatin	40.0	40.0	1	40.0	Placebo	0	40.0	60.0
CORONA	Secondary	Rosuvastatin	10.0	10.0	8	80.0	Placebo	0	80.0	32.8
GISSI-P	Secondary	Pravastatin	20.0	20.0	1	20.0	Usual Care	0	20.0	23.0
GREACE	Secondary	Atorvastatin	24.0	24.0	4	96.0	Usual Care	0	96.0	36.0
HPS	Primary	Simvastatin	40.0	40.0	2	80.0	Placebo	0	80.0	60.0
JUPITER	Primary	Rosuvastatin	20.0	20.0	8	160.0	Placebo	0	160.0	22.8
LIPID	Secondary	Pravastatin	40.0	40.0	1	40.0	Placebo	0	40.0	73.2
MEGA	Primary	Pravastatin	8.3	8.3	1	8.3	Placebo	0	8.3	63.6
A to Z	Secondary	Simvastatin	80.0	80.0	2	160.0	20 Simvastatin	40	120.0	24.0
PROSPER	Primary	Pravastatin	40.0	40.0	1	40.0	Placebo	0	40.0	38.4
PROVE-IT	Secondary	Atorvastatin	80.0	80.0	4	320.0	40 Pravastatin	40	280.0	24.0
TNT	Secondary	Atorvastatin	80.0	80.0	4	320.0	10 Atorvastatin	40	280.0	58.8
SEARCH	Secondary	Simvastatin	80.0	80.0	2	160.0	20 Simvastatin	40	120.0	80.4

	Active Adherence	Control Adherence	Active in Control	AMD	AMR	% Men	Average Age	% DM	% HTN	% Annual Risk in Control
4S	90.0%	87.0	13.0	77.0	6.92	81	58	4.5	26.0	1.5
AF-TEXCAPS	71.0	63.0	37.0	34.0	1.92	85	58	12.2	22.0	0.5
ALLHAT-LLT	80.0	83.0	17.0	63.0	4.71	49	66	35.2	100.0	2.7
ASCOT-LLA	87.0	91.0	9.0	78.0	9.67	81	63	24.6	100.0	1.1
AURORA	91.7	89.5	10.5	81.2	8.73	62	64	26.0	39.6	14.5
CARE	96.0	92.0	8.0	88.0	12.00	86	59	15.5	42.5	1.7
CORONA	97.3	95.2	4.8	92.5	20.27	86	73	29.5	63.0	10.6
GISSI-P	86.2	81.2	18.8	67.4	4.59	86	60	13.7	36.5	1.8
GREACE	98.8	74.0	26.0	72.8	3.80	79	58	19.5	43.0	1.0
HPS	85.0	83.0	17.0	68.0	5.00	75	64	19.0	41.0	2.6
JUPITER	75.0	75.0	25.0	50.0	3.00	62	66	0.0	56.7	1.2
LIPID	89.0	91.0	9.0	80.0	9.89	83	62	9.0	41.5	1.8
MEGA	90.0	75.0	25.0	65.0	3.60	31	58	21.0	42.0	0.3
A to Z	66.0	68.0	32.0	34.0	2.06	76	61	23.5	50.0	2.3
PROSPER	86.0	86.0	14.0	72.0	6.14	48	75	11.8	61.9	3.2
PROVE-IT	67.0	69.6	30.4	36.6	2.20	79	58	17.6	50.0	1.1
TNT	92.8	94.7	5.3	87.5	17.51	81	61	15.0	54.3	1.2
SEARCH	90.0	93.0	7.0	83.0	12.86	83	64	11.0	42.0	2.4

Continued on next page

effects were calculated for each study as a whole and by sex with random effects models. In addition, analyses were done separately for primary and secondary prevention trials, by level of baseline risk and by type of endpoint. Heterogeneity of the effects was evaluated with the Q statistic. Sensitivity analysis was performed by repeating the analysis 18 times, removing 1 study at a time. Also, analyses were performed by classifying the trials into 3 groups: primary prevention (5) (Online References e22,e33), secondary prevention (6) (Online References e21,e25,e27–e30,e32,e35,e36), and "mixed", which included 5 studies where a significant proportion of patients might have had CVD (Online References e23,e24,e26,e31,e34). Publication bias was examined by performing cumulative meta-analysis, by the Duval and Tweedie's Trim and Fill method (18) and the fail-safe N models of Rosenthal (19) and Orwin (20). The types of these analyses were pre-specified. In addition, analyses were performed by classifying the studies according to annual risk for mortality derived by dividing the observed absolute risk by the duration of the study in years. Meta-analysis was performed by analyzing separately and comparing the 9 studies with the higher annual risk with the 9 studies with the lower annual risk as well as by classifying the studies into high annual risk (2 or higher [6] [Online References e23,e25,e26,e28,e31,e34]), medium (above 1 but lower than 2 [5] [Online References e21,e24,e27,e29,e32,e35,e36]), and low risk (up to 1

Table 1 Continued

Study	% Prior CVD	% Current Smokers	% ASA	LDL Drop Difference, mg/dl	% LDL Drop Difference	Inclusion Criteria	Ref. #
4S	100	25.5	37	68	36.2	CHD; angina and/or MI	e21
AF-TEXCAPS	0	13	17	43	28.7	Average TC and LDL below-average HDL	e22
ALLHAT-LLT	14	23	31	23	15.8	Htn; LDL 120–189 mg/dl (100–129 mg/dl for CHD; ~15% CHD)	e23
ASCOT-LLA	19	33	17	43	32.3	Htn; TC <250 mg/dl	e24
AURORA	40	15	42	40	40.2	Hemodialysis	e26
CARE	100	21	83	38	27.3	AMI; TC <240 mg/dl	e27
CORONA	100	9	60	63	46.2	NYC functional class II–IV ischemic systolic HF	e28
GISSI-P	100	14	50	17	11.2	AMI	e29
GREACE	100	5	88	33	20.7	CHD	e30
HPS	87	14	63	39	29.8	CHD or PVD or cerebrovascular disease or DM	e31
JUPITER	0	16	17	54	50.0	LDL <130 mg/dl and age (≥50 yrs for men, ≥60 yrs for women)	5
LIPID	100	63	83	18	9.0	MI or UA	e32
MEGA	0	21	39	21	13.4	TC 220–270 mg/dl	e33
A to Z	100	41	98	15	13.5	ACS; TC ≥250 mg/dl	e25
PROSPER	44	27	36	50	34.0	CVD or (smoker, HTN, or DM) and TC 155–348 mg/dl	e34
PROVE-IT	100	37	100	33	31.1	ACS	e35
TNT	100	13	88	23	26.3	CHD and LDL <130 mg/dl	e36
SEARCH	100	30	90	15	15.2	MI	6

	Primary Endpoint
4S	Death
AF-TEXCAPS	Fatal MI, nonfatal MI, UA, sudden cardiac death
ALLHAT-LLT	Death
ASCOT-LLA	Nonfatal MI, silent MI, fatal CHD
AURORA	CVD death, nonfatal MI, nonfatal stroke
CARE	Major coronary event (CHD death, nonfatal MI, CABG, PTCA)
CORONA	CVD death, nonfatal MI, nonfatal stroke
GISSI-P	Death, nonfatal MI, nonfatal stroke
GREACE	Death, nonfatal MI, UA, PCI/CABG, CHF, stroke
HPS	Death, nonfatal MI, nonfatal stroke, coronary or noncoronary revascularization
JUPITER	MI, stroke, revascularization, hospitalized UA, CVD death
LIPID	CHD death, nonfatal MI
MEGA	First occurrence of CHD
A to Z	CV death, nonfatal MI, readmission for ACS, stroke
PROSPER	CHD death, nonfatal MI, fatal stroke, nonfatal stroke
PROVE-IT	Death, MI, hospitalized UA, revascularization
TNT	CHD death, nonfatal MI, resuscitated cardiac arrest, fatal or nonfatal stroke, HF hospitalization, peripheral arterial disease
SEARCH	CHD death, MI, stroke, revascularization

4S = Scandinavian Simvastatin Survival Study; ACS = acute coronary syndromes; Act = Active; AF-TEXCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; AMD = active medication difference; AMI = acute myocardial infarction; AMR = active medication ratio; ASA = acetylsalicylic acid; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm; A to Z = Aggrastat to Zocor; AURORA = A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; Avg = average; CABG = coronary artery bypass graft surgery; CARE = Cholesterol and Recurrent Events; Cerebrovasc = cerebrovascular; CHD = coronary heart disease; CHF = congestive heart failure; Cntrl = Control; CORONA = Controlled Rosuvastatin Multinational Study in Heart Failure; CV = cardiovascular; CVD = cardiovascular disease; Diff = difference; DM = diabetes mellitus; GISSI-P = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico – Prevenzione; GREACE = Greek Atorvastatin and Coronary Heart Disease Evaluation; HDL = high-density lipoprotein; HF = heart failure; HPS = Heart Protection Study; HTN = hypertension; JUPITER = Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; LDL = low-density lipoprotein; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; MI = myocardial infarction; PCI = percutaneous coronary intervention; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; PROVE-IT = Pravastatin or Atorvastatin Evaluation and Infection Therapy; PTCA = percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease; SEARCH = Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; Smoke = smoker; TC = total cholesterol; TNT = Treating to New Targets; UA = unstable angina.

[Online References e22,e30,e33]) (21). Also, we performed meta-analysis including the 3 studies (5,14) [Online Reference e33) that reported specific outcomes (stroke, coronary heart disease [CHD] event). We examined, in addition to meta-analysis, effect of sex on outcomes with meta-regression. A more detailed description of the methods is included in the online appendix.

Results

Description of studies. Table 1 includes data on the 18 studies included in the meta-analysis. The statin used in the intervention group was atorvastatin in 4 trials (Online References e24,e30,e35,e36), lovastatin in 1 (Online Reference e22), pravastatin in 6 (Online References e23,e27,e29,

e32–e34), rosuvastatin in 3 (5) (Online References e26,e28), and simvastatin in 4 (6) (Online References e21,e25,e31). Eight trials were designed as primary prevention trials (5) (Online References e22–e24,e26,e31,e33,e34), and 10 were designed as secondary prevention trials (6) (Online References e21,e25,e27–e30,e32,e35,e36). Five of the primary prevention studies included a proportion of patients with CVD (Online References e23,e24,e26,e31,e34). These studies were defined as "mixed" in the sensitivity analysis. Data on all-cause mortality were not available for 5 studies (6) (Online References e24–e26,e28). Overall, the meta-analysis included 141,235 patients, 21,468 primary events, and 13,710 deaths (3,898 deaths in studies with sex-specific mortality data). Different studies used study-specific definitions of primary events (Table 1) and had different durations of follow-up (47.9 ± 18.9 months). The mean relative dose in the intervention group was 98.2 ± 93.5 mg. The mean difference in relative statin dose between the intervention and the control groups was 89.4 ± 79.8 mg. Mean follow-up was 48 ± 19 months. On average, 85.5 ± 9.9% of those randomized to active therapy actually received it compared with 17.2 ± 9.9% of those randomized to the control group. On average, 72.9 ± 15.9% of the patients in the clinical trials were men. The mean age was 62.7 ± 5.1 years. Seventeen percent (17.1 ± 8.8%) of the patients had diabetes, 51.3 ± 21.3% had hypertension, 23.3 ± 13.9% were current smokers, 57.6 ± 29.5% were taking aspirin, and 66.9 ± 42.8% had prior CVD (ranging from 0% in 3 trials to 100% in 10 trials). The difference in LDL-c lowering (compared with baseline) between the intervention and control groups was 35.3 ± 16.3 mg/dl. When expressed as a percentage of the LDL-c at baseline, this difference was 26.7 ± 12% (Table 1).

Primary events in women and men. A statistically significant decrease in the primary endpoint was observed in women (OR: 0.81, 95% CI: 0.75 to 0.89, $p < 0.0001$) as well as in men (OR: 0.77, 95% CI: 0.71 to 0.83, $p < 0.0001$), with similar lowering in both sexes (p for interaction = 0.1837) (Table 2, Online Fig. 1). In women, the benefit with respect to the primary event seemed more pronounced in secondary prevention trials than in primary prevention trials (OR: 0.78, 95% CI: 0.70 to 0.88, $p < 0.0001$, and OR: 0.85, 95% CI: 0.75 to 0.98, p = 0.0209, respectively, p for interaction = 0.3397) (Online Fig. 2). Also, the benefit of the statin intervention was similar in studies where placebo/usual care or low-dose statin were used in the control group (OR: 0.81, 95% CI: 0.72 to 0.91, p = 0.0005 for both types of studies, p for interaction = 0.4545) (Online Fig. 3).

Sensitivity analysis of the primary event in women was performed 18 times with the leave-one-out method, resulting in ORs ranging from 0.80 (95% CI: 0.73 to 0.88, $p < 0.0001$) to 0.83 (95% CI: 0.77 to 0.90, $p < 0.0001$). Publication bias was assessed by performing cumulative meta-analysis with trials ordered by increasing weight and by funnel plot analysis. With cumulative meta-analysis, the associated funnel plot, and the Duval and Tweedie's Trim and Fill method, the effects of statins in lowering the primary endpoint remained statistically significant (OR: 0.84, 95% CI: 0.76 to 0.93, p = 0.035), by including 3 imputed trials (18). Rosenthal's fail-safe N indicated that 152 missing negative studies would be needed to bring the p value of the effect to >0.05 (19). Orwin's fail-safe N needed to bring the OR to 0.95 was 50 (20).

The primary endpoint was also lower in men when all studies were examined (OR: 0.77, 95% CI: 0.72 to 0.84, $p < 0.0001$) and when primary prevention trials were analyzed separately from secondary prevention trials (OR: 0.73, 95% CI: 0.63 to 0.84, $p < 0.0001$ for primary prevention, and OR: 0.79, 95% CI: 0.72 to 0.87, $p < 0.0001$ for secondary prevention, p for interaction by type of prevention 0.2122) (Online Fig. 4). Meta-analysis by level of risk indicated a statistically significant benefit of statin therapy at all levels of risk in both women (OR: 0.88, 95% CI: 0.81 to 0.95, p = 0.0014 for high risk, OR: 0.75, 95% CI: 0.64 to 0.89, p = 0.0011 for medium risk, and OR: 0.59, 95% CI: 0.41 to 0.87, p = 0.0066 for low risk) and men (OR: 0.87, 95% CI: 0.77 to 0.98, p = 0.0254 for high risk, OR: 0.73, 95% CI: 0.67 to 0.80, $p < 0.0001$ for medium risk, and OR: 0.61, 95% CI: 0.41 to 0.92, p = 0.0170 for low risk) for the primary event (Figs. 2 and 3). This more-pronounced benefit in groups at low risk was also observed by meta-regression. Thus, meta-regression showed a statistically significant relationship of annual risk of mortality of each trial to the OR for the primary endpoint in both women (slope of log(OR): 0.01819, 95% CI: 0.00017 to 0.03620, p = 0.04783) and men (slope of log(OR): 0.01925, 95% CI: 0.00819 to 0.03032, p = 0.00065), indicating a greater benefit (lower OR) in low-risk groups. A statistically significant benefit with respect to stroke was observed in the meta-analysis of the 3 studies with sex-specific outcomes (OR: 0.74, 95% CI: 0.55 to 0.99, p = 0.0396 for women, and OR: 0.70, 95% CI: 0.57 to 0.84, p = 0.0002 for men). The benefit for CHD was also statistically significant (OR: 0.78, 95% CI: 0.67 to 0.94, p = 0.0090 for women, and OR: 0.73, 95% CI: 0.66 to 0.81, $p < 0.0001$) (Fig. 4). In the 2 studies with sex-specific reports on adverse effects, there was no significant difference between women and men (JUPITER [Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin], TNT [Treating to New Targets]). In the TNT trial women were slightly more likely to report myalgia in both active and control treatment groups, and there was no difference between treatment groups for women and men.

Meta-regression showed a statistically significant relationship between the benefit of statin therapy and the difference in LDL-c lowering between intervention and control groups (slope log(OR) vs. LDL: −0.00416, 95% CI: −0.00642 to −0.00910, p = 0.0003) (Online Fig. 5).

Pairwise comparisons of the primary event for women versus men did not show a significant difference between

Table 2 Primary Events by Sex

Study	Men Primary Events Active	Men Active (n)	Men Primary Events Control	Men Control (n)	Men Primary Event Active AR	Men Primary Event Control AR	Men Primary Event RR
4S	155	1,814	231	1,803	8.5	12.8	66.7
AF-TEXCAPS	109	2,805	170	2,803	3.9	6.1	64.1
ALLHAT-LLT	406	2,659	398	2,645	15.3	15.0	101.5
ASCOT-LLA	81	4,189	137	4,174	1.9	3.3	58.9
AURORA	247	851	267	872	29.0	30.6	94.8
CARE	384	1,795	469	1,788	21.4	26.2	81.6
CORONA	554	1,921	577	1,910	28.8	30.2	95.5
GISSI-P	97	1,854	113	1,830	5.2	6.2	84.7
GREACE	50	624	101	632	8.0	16.0	50.1
HPS	1,666	7,727	2135	7,727	21.6	27.6	78.0
JUPITER	103	5,475	181	5,526	1.9	3.3	57.4
LIPID	622	3,756	777	3,742	16.6	20.8	79.8
MEGA	40	1,228	65	1,248	3.2	5.3	62.5
A to Z	239	1,716	272	1,680	13.9	16.2	86.0
PROSPER	222	1,396	279	1,408	15.9	19.8	80.3
PROVE-IT	376	1,634	424	1,617	23.0	26.2	87.8
TNT	1,113	4,054	1330	4,045	27.5	32.9	83.5
SEARCH	1,277	5,005	1325	5,007	25.5	26.5	96.4

	Women Primary Events Active	Women Active (n)	Women Primary Events Control	Women Control (n)	Women Primary Event Active AR	Women Primary Event Control AR	Women Primary Event RR
4S	27	407	25	420	6.6	6.0	111.4
AF-TEXCAPS	7	499	13	498	1.4	2.6	53.7
ALLHAT-LLT	260	2,511	277	2,540	10.4	10.9	94.4
ASCOT-LLA	19	979	17	963	1.9	1.8	109.9
AURORA	149	538	141	512	27.7	27.5	100.6
CARE	46	286	80	290	16.1	27.6	58.3
CORONA	138	593	155	587	23.3	26.4	88.1
GISSI-P	23	284	23	303	8.1	7.6	106.7
GREACE	13	176	27	168	7.4	16.1	46.0
HPS	367	2,542	450	2,540	14.4	17.7	81.5
JUPITER	39	3,426	70	3,375	1.1	2.1	54.9
LIPID	112	756	134	760	14.8	17.6	84.0
MEGA	26	2,638	36	2,718	1.0	1.3	74.4
A to Z	91	549	99	552	16.6	17.9	92.4
PROSPER	186	1,495	194	1,505	12.4	12.9	96.5
PROVE-IT	94	465	120	446	20.2	26.9	75.1
TNT	292	941	347	961	31.0	36.1	85.9
SEARCH	200	1,026	228	1,026	19.5	22.2	87.7

AR = absolute risk; RR = relative risk; other abbreviations as in Table 1.

men and women ($\log(OR)_{men} - \log(OR)_{women}$) = −0.026, SD = 0.062, p = 0.68) in multivariate meta-regression. This corresponds to an OR ratio (ORmen/ORwomen) of 0.77 ± 0.54, a nonsignificant trend for men to benefit more from statins. Also, a significant difference in all-cause mortality was not observed (log(OR): difference = −0.002, SD = 0.215, p = 0.993, indicating a nearly identical effect of statins in women and men, OR: 0.998).

To examine whether differences in primary events in women versus men were influenced by trial characteristics, we performed multivariate meta-regression analyses. They showed a trend implying that men might be more likely to benefit from active therapy than women (Online Appendix).

All-cause mortality in men and women. All-cause mortality was lower in women when all studies were examined (OR: 0.90, 95% CI: 0.82 to 0.99, p = 0.0344) (Table 3, Online Fig. 6) as well as when primary prevention trials were analyzed separately (OR: 0.87, 95% CI: 0.78 to 0.97, p = 0.0142, p for interaction = 0.5122). The effect on all-cause mortality in women was not statistically significant for secondary prevention trials (OR: 1.03, 95% CI: 0.84 to 1.25, p = 0.7926). All-cause mortality was also lower in men when all studies were examined (OR: 0.84, 95% CI: 0.77 to 0.92, p = 0.0003) (Online Fig. 6) as well as when the secondary prevention trials were analyzed (OR: 0.76, 95% CI: 0.66 to 0.87, p = 0.0001). In men, all-cause mortality was not significantly lower in the intervention group for primary prevention trials (OR: 0.92 95% CI: 0.84 to 1.01, p = 0.0664). However, there was no statistically significant interaction between the decrease

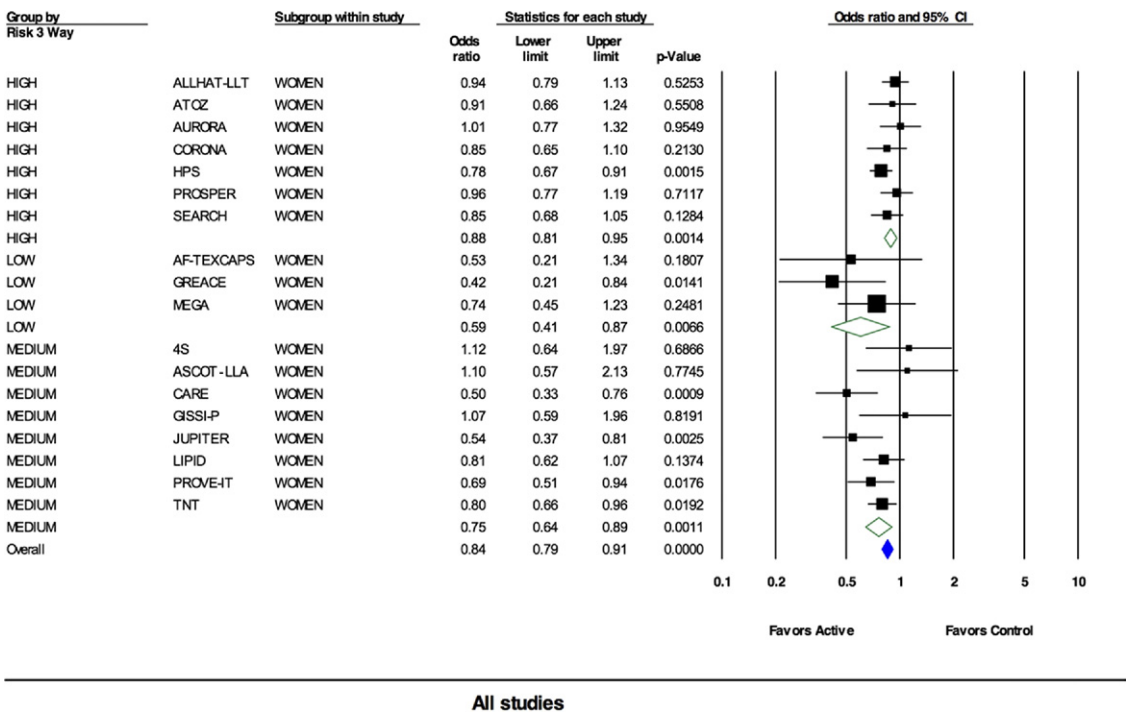

Figure 2 **Forest Plot for the Primary Event by Level of Risk of Participants in Each Study in Women**

Solid squares represent the odds ratios in individual trials and have a size proportional to the inverse of the variance. **Horizontal lines**, **diamonds**, and **squares** denote the 95% confidence intervals (CIs) for individual trials and summary statistics. Pooled estimates were computed from a random effects model. Trial acronyms as in Table 1.

in mortality and type of prevention in men (p for interaction = 0.2122).

Discussion

The findings of this study are consonant with a wealth of information from randomized clinical trials and meta-analyses. The Cholesterol Treatment Trialists' Collaboration individual participant data meta-analyses showed decreases in cardiovascular events and mortality with statin use and that more intensive lowering of LDL-c produced further reductions in cardiovascular events (1,22). Our analysis, indicating a decrease in the primary endpoint and all-cause mortality and a positive association between LDL-c lowering and lower risk, is consistent with the Cholesterol Treatment Trialists' findings. In the present study, the benefit of statins in reducing primary endpoints was observed in women and men and in both primary and secondary prevention without significant difference between the 2 sexes. Lower all-cause mortality was also observed in both women and men. Meta-regression with stepwise variable selection suggested that the benefit was more pronounced in men in studies with higher percentages of smokers or patients with CVD and lower percentage on aspirin. The mortality benefit was statistically significant for primary prevention in women and for secondary prevention in men, although there was no significant interaction by sex in these analyses.

Studies classified as primary prevention frequently include patients with CVD, and the distinction between primary and secondary prevention is ambiguous (21,23). For this reason, we performed analyses by risk level. They indicate a benefit across risk levels in both women and men, and meta-regression shows a relationship between risk and the benefit of statins. The reasons for the more pronounced benefit of statins in studies that enrolled low-risk patients, both by meta-regression and by subsetting, are not known. Also, because the primary endpoint was different across studies, we analyzed the data according to whether the endpoint included or did not include stroke or angina, endpoints more likely to occur in women. The analyses indicated a benefit was shown for studies including either stroke or angina as a component of the combined endpoint. A recent Cochrane report on the use of statins for primary prevention agrees with our finding of reduction of cardiovascular events but does not include sex-specific results (21). The authors stated that caution should be taken in prescribing statins for persons at low cardiovascular risk (below 1% annual all-cause mortality risk). We found a benefit in both women and men in the 3 studies with annual risk 1% or below (Online References e22,e30,e33). However, the costs and

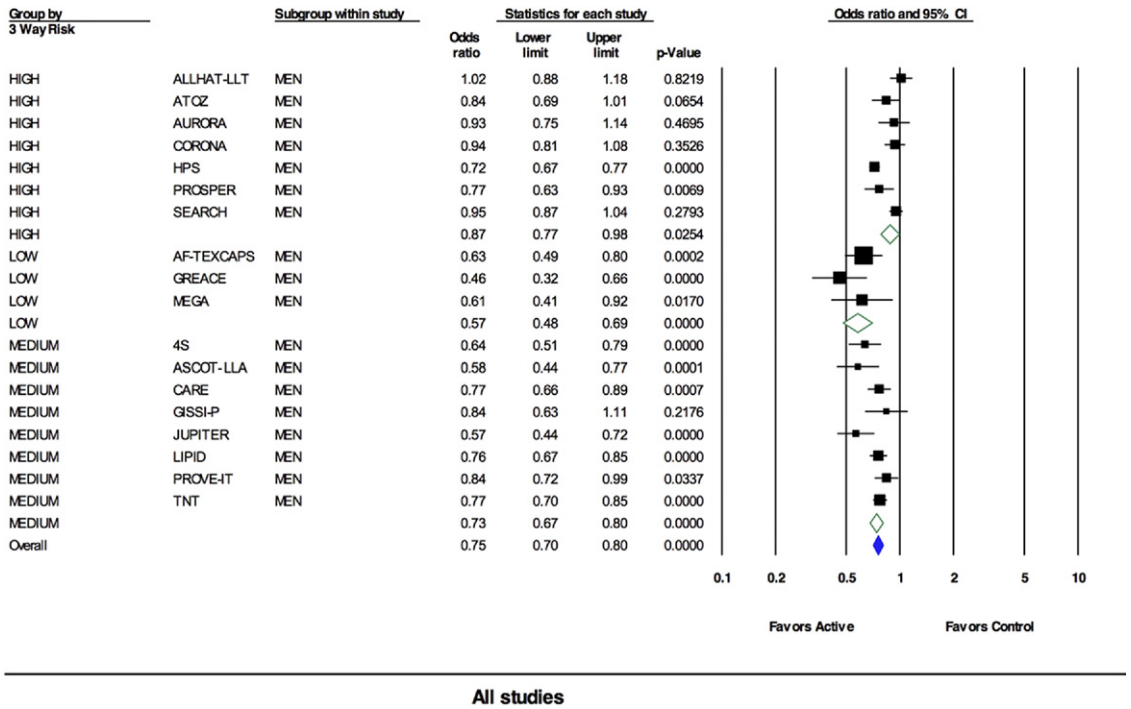

Figure 3 **Forest Plot for the Primary Event by Level of Risk of Participants in Each Study in Men**

Solid squares represent the odds ratios in individual trials and have a size proportional to the inverse of the variance. **Horizontal lines**, **diamonds**, and **squares** denote the 95% confidence intervals (CIs) for individual trials and summary statistics. Pooled estimates were computed from a random effects model. Trial acronyms as in Table 1.

safety of the medications should be considered in addition to the absolute benefit in decreasing events (24). The estimated cost of preventing 1 cardiovascular event with rosuvastatin in the JUPITER trial is $287,000 (21), although with the decrease in the price of generic statins the cost would be lower.

Significant differences between women and men were not observed in the 2 studies reporting sex-specific adverse events, and women are under-represented in clinical trials (5,12,14,25). This underscores the importance of collecting sex-specific data and of increasing the percentage of women in clinical trials.

Although LDL-c is a strong predictor of CHD in both women and men and similar treatment approaches are recommended for both sexes, CHD might have different manifestations in women, and medications might have different effects in women than in men (7–10,12–15). For example, aspirin seems to have differential effects in primary prevention of CVD, with men deriving benefit primarily in reduction of myocardial infarction and women in reduction of ischemic stroke (26). The present study, however, does not indicate any sex differences in the beneficial effects of statins in either primary or secondary prevention.

Previous meta-analyses, most conducted before the publication of the JUPITER trial, have implied that some of the benefits of statins do not pertain to women in primary prevention and that all-cause mortality is not decreased in women (7–10). Rosenberg and Allard (7) have stated that safety meta-analyses do not disaggregate for women and do not consider female vulnerability to statin-induced muscle problems and women-centered concerns such as breast cancer, miscarriage, and birth defects. Wenger et al. (13–15) has emphasized that, as the population ages, the incidence of CVD will increase among women and that the great majority of persons over 80 years are women and are more likely to suffer cardiovascular events. Thus, meta-analyses such as the present study provide important information from a large proportion of the population. Although statin therapy benefits both women and men, lipid-lowering therapy with statin drugs is currently underused. Barham et al. (27), examining a sample of 60 North Carolina primary care practices participating in a randomized practice-based trial, did not find large differences by sex in screening or appropriateness of management. Lifestyle interventions are preferable in primary prevention but they might be difficult to implement and to maintain (28).

Study limitations. Limitations of the study include possible publication bias, although it is unlikely that this has a significant sex-specific effect, because in all trials the hypothesis and the primary endpoints analyzed were not sex-specific. Exclusion of studies without sex-specific data diminishes the number of studies available for the meta-analysis and the power of the analyses. This study indicates that statin therapy is beneficial in both women and men. The trend suggesting higher benefit in men than in women must be interpreted with caution, because

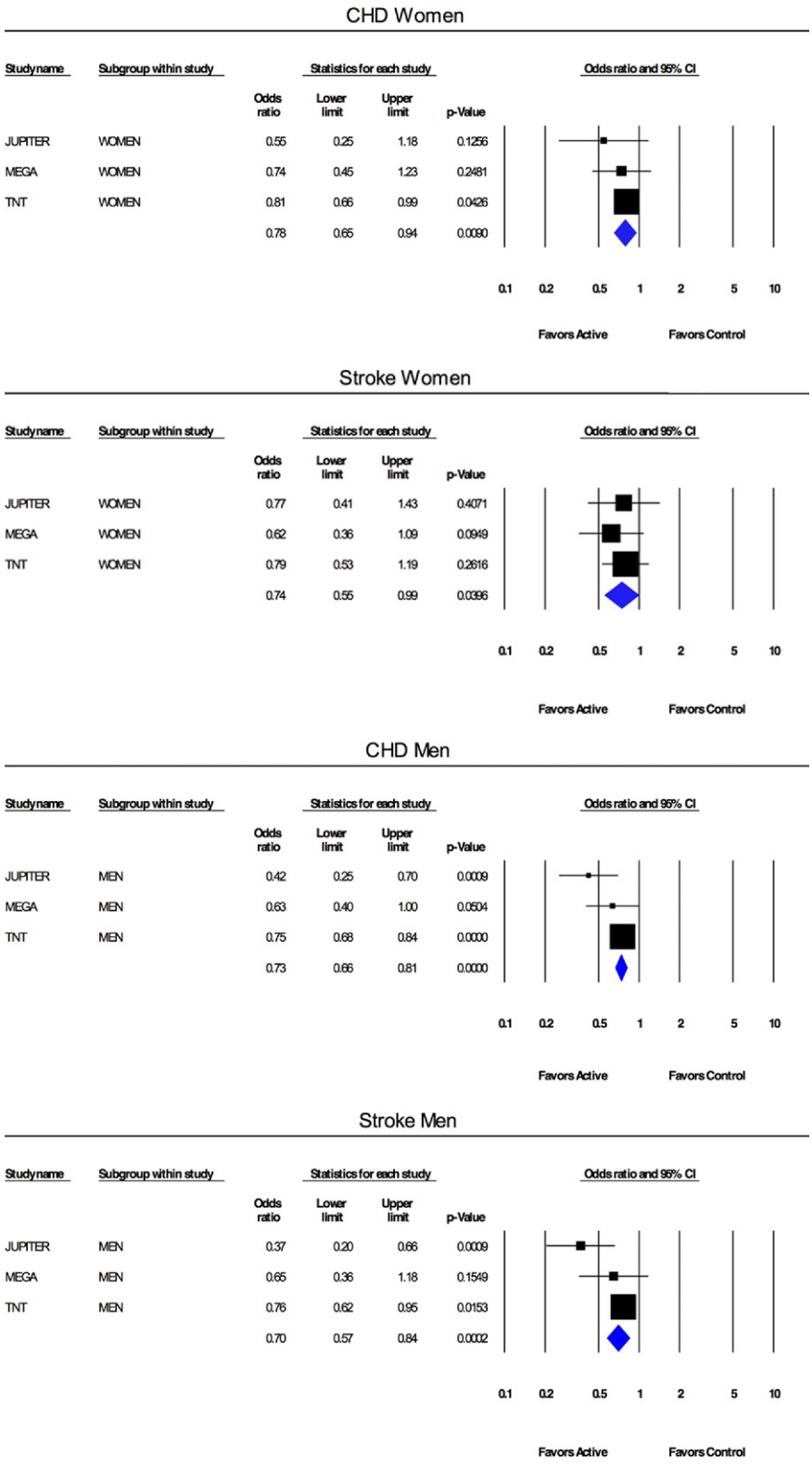

Figure 4 **Forest Plots for CHD Event and for Stroke in Women and Men**

Solid squares represent the odds ratios in individual trials and have a size proportional to the inverse of the variance. **Horizontal lines**, **diamonds**, and **squares** denote the 95% confidence intervals (CIs) for individual trials and summary statistics. Pooled estimates were computed from a random effects models. Trial acronyms as in Table 1.

Table 3 All-Cause Mortality by Sex

Study	Men Deaths Active	Men Active (n)	Men Deaths Control	Men Control (n)	Men Death Active AR	Men Death Control	Men Death RR
4S	155	1,814	231	1,803	8.5	12.8	66.7
AF-TEXCAPS	69	2,805	70	2,803	2.5	2.5	98.5
ALLHAT-LLT	406	2,659	398	2,645	15.3	15.0	101.5
ASCOT-LLA	—	—	—	—	—	—	—
AURORA	—	—	—	—	—	—	—
CARE	159	1,795	173	1,788	8.9	9.7	91.5
CORONA	—	—	—	—	—	—	—
GISSI-P	55	1,854	76	1,830	3.0	4.2	71.4
GREACE	19	624	32	632	3.0	5.1	60.1
HPS	1,102	7,727	1245	7,727	14.3	16.1	88.5
JUPITER	138	5,475	170	5,526	2.5	3.1	81.9
LIPID	424	3,756	555	3,742	11.3	14.8	76.1
MEGA	21	1,228	27	1,248	1.7	2.2	79.0
A to Z	—	—	—	—	—	—	—
PROSPER	178	1,396	171	1,408	12.8	12.1	105.0
PROVE-IT	34	1,634	52	1,617	2.1	3.2	64.7
TNT	226	4,054	237	4,045	5.6	5.9	95.1
SEARCH	—	—	—	—	—	—	—

	Women Deaths Active	Women Active (n)	Women Deaths Control	Women Control (n)	Women Death Active AR	Women Death Control	Women Death RR
4S	27	407	25	420	6.6	6.0	111.4
AF-TEXCAPS	11	499	7	498	2.2	1.4	156.8
ALLHAT-LLT	260	2,511	277	2,540	10.4	10.9	94.9
ASCOT-LLA	—	—	—	—	—	—	—
AURORA	—	—	—	—	—	—	—
CARE	21	286	23	290	7.3	7.9	92.6
CORONA	—	—	—	—	—	—	—
GISSI-P	17	284	12	303	6.0	4.0	151.1
GREACE	4	176	8	168	2.3	4.8	47.7
HPS	226	2,542	262	2,540	8.9	10.3	86.2
JUPITER	60	3,426	77	3,375	1.8	2.3	76.8
LIPID	74	756	78	760	9.8	10.3	95.4
MEGA	22	2,638	39	2,718	0.8	1.4	58.1
A to Z	—	—	—	—	—	—	—
PROSPER	120	1,495	135	1,505	8.0	9.0	89.5
PROVE-IT	12	465	14	446	2.6	3.1	82.2
TNT	58	941	45	961	6.2	4.7	131.6
SEARCH	—	—	—	—	—	—	—

Abbreviations as in Tables 2 and 3.

the power of the study in this respect was low (24%). Analysis of patient-level data that might be available will provide more precise estimates than those presented in this report (1,22). It is possible that such analyses, although showing benefits of statin therapy in women, will reveal a more pronounced benefit in men among certain subsets, because trends in that direction were observed in this study. However, we should not overinterpret the data of the 18 trials that represent, to our knowledge, all available information at the time of this report.

Conclusions

Statins decrease cardiovascular events and all-cause mortality in both women and men. The effect on cardiovascular events is present in both primary and secondary prevention trials. Therefore, statin therapy should be used in appropriate patients without regard to sex. It seems that, with respect to statin therapy, what is good for the gander is good for the goose (29).

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Key Words: cardiovascular disease ■ LDL ■ lipids ■ statins ■ women.

APPENDIX

For supplementary text, tables, figures, and references, please see the online version of this article.