Drug Treatment of Hyperlipidemia in Women

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Context Several clinical trials have evaluated the effects of lipid-lowering medications on coronary heart disease (CHD). Many of the trials have not included enough women to allow sex-specific analyses or have not reported results in women separately.

Objectives To assess and synthesize the evidence regarding drug treatment of hyperlipidemia for the prevention of CHD events in women and to conduct a meta-analysis of the effect of drug treatment on mortality.

Data Sources We searched MEDLINE, the Cochrane Database, and the Database of Abstracts of Reviews of Effectiveness for articles published from 1966 through December 2003. We reviewed reference lists of articles and consulted content experts.

Study Selection and Data Extraction Studies of outpatients that had a treatment duration of at least 1 year, assessed the impact of lipid lowering on clinical outcomes, and reported results by sex were included. Outcomes evaluated were total mortality, CHD mortality, nonfatal myocardial infarction, revascularization, and total CHD events. Summary estimates of the relative risks (RRs) with therapy were calculated using a random-effects model for patients with and without a previous history of cardiovascular disease.

Data Synthesis Thirteen studies were included. Six trials included a total of 11 435 women without cardiovascular disease and assessed the effects of lipid-lowering medications. Lipid lowering did not reduce total mortality (RR, 0.95; 95% confidence interval [CI], 0.62-1.46), CHD mortality (RR, 1.07; 95% CI, 0.47-2.40), nonfatal myocardial infarction (RR, 0.61; 95% CI, 0.22-1.68), revascularization (RR, 0.87; 95% CI, 0.33-2.31), or CHD events (RR, 0.87; 95% CI, 0.69-1.09). However, some analyses were limited by too few CHD events in the available trials. Eight trials included 8272 women with cardiovascular disease and assessed the effects of lipid-lowering medications. Lipid lowering did not reduce total mortality in women with cardiovascular disease (RR, 1.00; 95% CI, 0.77-1.29). However, lipid lowering reduced CHD mortality (RR, 0.74; 95% CI, 0.55-1.00), nonfatal myocardial infarction (RR, 0.71; 95% CI, 0.58-0.87), revascularization (RR, 0.70; 95% CI, 0.55-0.89), and total CHD events (RR, 0.80; CI, 0.71-0.91).

Conclusions For women without cardiovascular disease, lipid lowering does not affect total or CHD mortality. Lipid lowering may reduce CHD events, but current evidence is insufficient to determine this conclusively. For women with known cardiovascular disease, treatment of hyperlipidemia is effective in reducing CHD events, CHD mortality, nonfatal myocardial infarction, and revascularization, but it does not affect total mortality.

JAMA. 2004;291:2243-2252 www.jama.com

CORONARY HEART DISEASE (CHD) is the leading cause of death in the United States and half of all deaths from CHD occur in women.[1-3] Elevated levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides and low levels of high-density lipoprotein cholesterol are risk factors for CHD in women.[4-6] Lipid lowering may be achieved with either diet or drugs, but few studies have addressed the effects of dietary and lifestyle interventions on clinical outcomes.

Several randomized clinical trials have evaluated the effect of lipid lowering with drugs on risk of CHD events in persons with known cardiovascular disease and in those without cardiovascular disease.[7-29] Unfortunately, many of the clinical trials of lipid-lowering treatments did not include women and others did not include adequate numbers of women to allow sex-specific analyses. Some of the trials that did report results in women reported aggregate events (eg, major coronary events), but did not report specific outcomes such as CHD death or nonfatal myocardial infarction (MI) separately.

A previous systematic review of lipid-lowering therapy in women included only studies published before 1995 and is now outdated.[30] A more recent review identified several studies of lipid-lowering therapy in women, but did not perform a meta-analysis.[31] LaRosa et al[32] performed a systematic review and meta-analysis that included only trials of statin drugs and found that both women and men treated with statins had a 30% reduction in risk of major CHD events. However, this review did

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CME available online at www.jama.com

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Financial Disclosure: Dr Pignone has received research support from Pfizer and Bayer.
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not address outcomes other than major CHD events in women, did not stratify studies by primary or secondary prevention, and did not include data from recent large trials.

Age is the biggest risk factor for CHD. Women's risk for CHD is lower than that of men at any given age. The onset of CHD in women lags about 10 years behind men. By age 75 years, mortality in women more closely approaches that of men.[33] For persons with similar age and risk factor profiles, many more women than men must be treated to prevent 1 CHD event. Hence, the benefits and risks of treatment may differ for men and women.

Assessing the effect of drug treatment for hyperlipidemia and CHD for primary and secondary prevention is important. The balance between the benefits and risks of treatment will differ depending on a woman's risk of CHD. Women who have known cardiovascular disease are at increased risk for future cardiovascular disease events. Because of this increased risk, fewer women must be treated to prevent a CHD event among women with known cardiovascular disease than among women without cardiovascular disease.

Clinical trials of lipid-lowering therapy usually include individuals either with or without CHD and are therefore classified as either primary or secondary prevention trials. Although women without CHD are at lower risk than women with CHD, factors that influence the degree of CHD risk include age and other risk factors. Thus, the dichotomy of primary and secondary prevention may be somewhat artificial. Risk of CHD is best viewed as a spectrum, depending on age and other risk factors.

The goal of this systematic review is to critically assess the available clinical trial evidence regarding drug treatment of hyperlipidemia for the prevention of CHD events and death in women. The effects of lipid-lowering therapy on total mortality, CHD mortality, nonfatal MI, CHD events, and revascularization procedures in women with and without prior cardiovascular disease will be assessed.

METHODS

MEDLINE, the Cochrane Database, and the Database of Abstracts of Reviews of Effectiveness were searched for articles published in English and other languages from 1966 through January 2002. Search terms were developed in collaboration with a medical librarian and included *hyperlipidemia and anticholesteremic agents*, *antilipemic agents*, *simvastatin*, *lovastatin*, *pravastatin*, *atorvastatin*, *fluvastatin*, *gemfibrozil*, *cholestyramine*, *colestipol*, *niacin and cardiovascular diseases*, *heart diseases*, *myocardial ischemia*, and *coronary disease*. Bibliographies were also reviewed and content experts were asked to identify additional articles. To update the review, an additional search of articles published from January 2002 through December 2003 was conducted.

Studies were included if they (1) were randomized clinical trials of outpatients with or without known cardiovascular disease, (2) had a treatment duration of at least 1 year (assuming that clinical events would be unlikely in a shorter period), (3) classified the study population as either primary (participants without prior cardiovascular disease) or secondary prevention (participants with prior cardiovascular disease), (4) provided data on women and the effect of lipid-lowering drug therapy was assessed for at least 1 clinical outcome (total mortality, CHD mortality, nonfatal MI, CHD events, or revascularization procedures). Coronary events included ischemic coronary syndromes and nonfatal MI. Treatment procedures for CHD included coronary artery bypass graft surgery and percutaneous coronary angioplasty or stenting. Studies were excluded if they provided evidence on the effect of treatment on changes in lipids, angiographic findings, or other intermediate outcomes only. For studies with multiple publications, data from the most comprehensive or most recent publication were used primarily and other articles were used as supplements.

Two physicians reviewed the titles of the initial search and excluded those that did not provide data on humans, did not meet the inclusion criteria, or did not address the question. Eligible articles were reviewed independently by 2 investigators, who were blinded to names of authors and the titles of journals.

Quality was evaluated for each article. To be categorized as *good quality*, articles were required to have clear and appropriate inclusion and exclusion criteria; concealed randomization allocation; a group that served as a "control" and received placebo treatment; participants and research staff blinded to an intervention; and more than 75% complete follow-up. Trials that did not meet these criteria were considered *fair quality*. All disagreements between reviewers regarding quality parameters were also decided by discussion and consensus.

Several studies did not publish results by sex. We contacted the authors of studies that included women in the study population, but did not report results separately by sex to attempt to obtain this information. If we did not receive a response after the first contact, a second attempt was made. If no contact was made after 2 attempts, we did not include the study.

The primary outcome of each clinical trial was expressed as the relative risk (RR) among treated compared with untreated study participants. Summary estimates of RRs and 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel method for fixed effects and the DerSimonian and Laird random-effects model. Results of the fixed- and random-effects models were similar. Findings from the random-effects model are reported herein. To avoid calculation problems associated with zero cells, 0.5 was added to all cells to calculate variances and SDs.[34,35] The significance level for all tests of outcome was set at $P<.05$. All findings were assessed for heterogeneity using a standard χ^2 test and q statistic with a critical value set at 0.10.

Because statins are the mainstay of contemporary care, we planned a subgroup analysis by type of drug (statins vs others). An additional planned subgroup analysis compared good- with

fair-quality studies. A final subgroup analysis was to include the Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) study in both the primary and secondary prevention results to assess its impact. (PROSPER could not be classified as either primary or secondary prevention.)

Publication bias can occur if small studies with unremarkable findings (RRs of about 1.0) are not published while small studies with markedly positive findings (in this case, low RRs) are published. To assess potential publication bias, we calculated the correlation between individual study weight (1 divided by variance) and RR, using a nonparametric correlation coefficient (Kendall τ) with critical value set at 0.10. Statistically significant correlation of study weight and RR is interpreted as evidence of possible publication bias. This work was conducted as part of a larger project, which is described in full in an Agency for Healthcare Research and Quality report.[36]

RESULTS

Characteristics of Included Studies

Our original searches identified 1335 titles and our supplemental search for articles published from January 2002 through December 2003 identified an additional 396 articles. After eliminating ineligible studies by review of titles and abstracts, we reviewed the full text of 121 articles. Twenty-one studies were identified that fit all inclusion criteria, but only 9 (some of which had multiple publications) provided outcomes stratified by sex.[7,8,10,11,14-19,21-23,25,26]

We contacted the principal investigators of the 12 studies to request data on women.[10,12,13,20,24,28,37-46] We received data on women from 4 study investigators.[12,13,20,24,37] Thus, 13 studies (represented by 23 articles) were found to be both eligible and to contain data stratified by sex for inclusion in the systematic review.[7,8,10-27,47,48] In the Heart Protection Study, 65% of participants had known CHD and the remaining 35% had peripheral vascular disease, cerebrovascular disease, or diabetes.[10,29] The CHD outcomes in women with and without CHD have recently been published separately. The Heart Protection Study is included as both a primary and a secondary prevention study.[29] One additional study (PROSPER) did not meet inclusion criteria because the study population was equally divided between persons with or without prior CHD. Separate estimates for the effects of lipid-lowering therapy in primary and secondary prevention in PROSPER were not published or available. In addition, although this study provided information on composite CHD outcomes (CHD events), it did not provide data on any of the individual clinical outcomes of interest in women.[28] Because of the potential importance of this large recent trial, we decided to conduct sensitivity analyses whereby we assessed the impact on outcomes of including it as either a primary or a secondary prevention study.

Characteristics of the 13 eligible trials are described in TABLE 1. The numbers of participants in each trial ranged from 151 to 20536 and 15% to 50% of participants were women. The total number of women included in the trials was 17891, but almost two thirds were from 2 studies.[10,15] Information on the ethnicity of participants was not provided in most trials. Duration of treatment ranged from 2.8 to 6.1 years and averaged 4.6 years. Six of the trials were classified as primary prevention and 8 were classified as secondary prevention (Outcomes from the Heart Protection Study have been published separately for those with and without CHD and are therefore included for both primary and secondary prevention). Eligibility criteria for 7 trials required at least mild hyperlipidemia,[7,11-13,15,20,27,37] 4 required a range of cholesterol levels that would include some participants in the "normal" range,[8,10,21,24] and 2 included participants regardless of cholesterol levels.[16,17] Two trials assessed the effects of clofibrate,[16,17] one examined colestipol,[11] one used cholestyramine,[37] and 9 assessed the efficacy of treatment with statins (lovastatin,[8,12,13] simvastatin,[7,10,15] pravastatin,[20,21,24] and atorvastatin).[27]

All but 1 of the 13 trials included a placebo-control group,[15] and all but 2 were adequately blinded.[11,15] In all but 1 of the trials,[11] follow-up was more than 75% complete. Overall, 9 of the trials were rated good quality and 4 were rated fair.

The clinical outcomes evaluated were total mortality, CHD mortality, nonfatal MI, CHD events, and revascularization. Most trials were designed to address clinical outcomes, but 3 were designed to evaluate change in intimal medial thickness of the carotid artery or coronary angiographic changes[12,13,20,37] and included clinical events only as secondary outcomes.

For studies with mixed populations (eg, some participants had CHD and some did not) that did not report results separately for primary and secondary prevention, the trial was classified as primary or secondary prevention based on the status of the majority of participants. Participants in most of the trials classified as primary prevention were at increased risk for CHD outcomes due to the presence of CHD risk factors.

Two trials included participants with and without CHD and did not report results separately for primary and secondary prevention. In the Colestipol trial, only 20% of participants had CHD and this trial was classified as a primary prevention study.[11] The recently published PROSPER study included older participants with CHD and those at high risk for CHD in approximately equal numbers,[28] and did not present results stratified by history of CHD. We performed sensitivity analyses including this study as both a primary and a secondary prevention study.

For each outcome, we assessed the effects of lipid lowering separately for primary and secondary prevention studies. We also calculated summary estimates based on the findings of all eligible studies; those that used a statin as the lipid-lowering agent and those that were rated good quality.

Characteristics of Excluded Studies

Eight studies that included women were not included in our meta-analysis be-

cause data for women were not published and not available. Seven of the 8 studies were secondary prevention studies.[39,40,42-46] Of the 3299 participants in these studies, 509 (15.4%) were women. Most had a primary focus on angiographic outcomes, but all reported some clinical outcomes. All 7 of these studies reported a reduction in clinical outcomes among those treated for hyperlipidemia, although not all were statistically significant.

One study, the Pravastatin Multinational Study for Cardiac Risk Patients[38] was defined as a primary prevention study. Eligible participants had at least 2 cardiac risk factors, one of which was a history of MI. Approxi-

Table 1. Characteristics of Drug Treatment Studies for Hyperlipidemia in Women

Source	No. /Total (%)	Mean Age, y	CHD, %*	Lipid Entry Criterion	Drug Name	Mean Follow-up, y	Outcomes	Quality Rating
Primary Prevention								
Colestipol Study,[11] 1978	1184/2278 (52)	57	20	Total cholesterol >250 mg/dL	Colestipol	3	Total or CHD mortality	Fair
ACAPS,[12,13] 1992-1994	445/919 (48)	61	0	LDL-C, 130-159 mg/dL with other risk factors; LDL-C, 160-189 mg/dL with none or 1 risk factor	Lovastatin	2.8	Total or CHD mortality or nonfatal MI	Good
AFCAPS/TEXCAPS,[8,14] 1998-2001	997/6605 (15)	62	0	Total cholesterol, 180-264 mg/dL; LDL-C, 130-190 mg/dL; and HDL-C, <47 mg/dL	Lovastatin	5.2	Total or CHD mortality or nonfatal MI with revascularization	Good
HPS,†[10,29] 2002-2003	1816/5963 (30)	NA	0	Total cholesterol >135 mg/dL	Simvastatin	5	CHD events	Good
ALLHAT,[15] 2002	5051/10 355 (49)	NA	14	LDL-C, 100-189 mg/dL	Pravastatin	4.8	Total mortality or CHD events‡	Fair
ASCOT-LLA,[27] 2003	1942/10 305 (19)	NA	0	Total cholesterol >252 mg/dL	Atorvastatin	3.3	CHD events§	Good
Secondary Prevention								
Scottish Society of Physicians,[16] 1971	124/717 (17)	54	100	None	Clofibrate	6	CHD mortality or nonfatal MI	Fair
Physicians of the Newcastle upon Tyne Region,[17] 1971	97/497 (20)	54	100	None	Clofibrate	5	CHD mortality or nonfatal MI	Fair
NHLBI Type II,[37] 1984	28/143 (20)	NA	100	LDL-C in upper 10th percentile of general population	Cholestyramine	5	CHD or total mortality or nonfatal MI	Good
4S,[7,18,19] 1994-1997	827/4444 (19)	61	100	Total cholesterol, 213-309 mg/dL	Simvastatin	5.4	Total or CHD mortality, nonfatal MI with revascularization, or CHD events‖	Good
PLAC-II,[20] 1995	22/151 (15)	NA	100	LDL-C in 60th-90th percentile for age and sex	Pravastatin	3	Total or CHD mortality, nonfatal MI	Good
CARE,[21-23] 1996-1999	576/4159 (14)	61	100	Total cholesterol <240 mg/dL and LDL-C, 115-174 mg/dL	Pravastatin	5	Total or CHD mortality, nonfatal MI with revascularization, or CHD events‡	Good
LIPID,[24-26,48] 1998-2003	1516/9014 (17)	62	100	Total cholesterol, 155-271 mg/dL	Pravastatin	6.1	CHD events,‡ total or CHD mortality, or nonfatal MI with revascularization	Good
HPS,†[10,29] 2002-2003	3266/14 573 (22)	NA	100	Total cholesterol >135 mg/dL	Simvastatin	5	CHD events	Good

Abbreviations: ACAPS, Asymptomatic Carotid Artery Progression Study; AFCAPS/TEXCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; CARE, Cholesterol and Recurrent Events trial; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; HPS, Heart Protection Study; LDL-C, low-density lipoprotein cholesterol; LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease; MI, myocardial infarction; NA, not available; NHLBI, National Heart, Lung, and Blood Institute; PLAC-II, Pravastatin, Lipids and Atherosclerosis in the Carotid Arteries; 4S, Scandinavian Simvastatin Survival Study.
SI conversion factor: To convert cholesterol to mmol/L, multiply by 0.0259.
*Defined as history of MI or angina.
†This study included women both with and without CHD. CHD events that occurred during this study were defined as CHD mortality, nonfatal MI, stroke, or revascularization.
‡Defined as CHD mortality or nonfatal MI.
§Defined as CHD mortality, nonfatal MI, unstable angina, or sudden cardiac death.
‖Defined as CHD mortality, nonfatal MI, or resuscitated cardiac arrest.

mately one third of the participants had a history of CHD. Of the 1062 participants, 247 (23%) were women. Overall, a reduction in CHD events was seen among those treated with pravastatin.

Assessments for Heterogeneity and Publication Bias

There was no statistical evidence of heterogeneity in any of the overall summary estimates of the effect of lipid lowering on any outcome. There was no evidence of publication bias in any of the summary estimates.

Primary Prevention

Six trials assessed the effects of lipid lowering among women without prior cardiovascular disease[8,11-15,27] and included 11 435 women. One of these trials used colestipol as the intervention[11] and the rest used a statin. Two trials[11,15] were rated fair and the other 4 were rated as good quality.[8,12-14,29,48] Many of these trials reported results among women for only 1 or 2 of the 5 outcomes of interest. The summary results were similar when restricting the analyses to only studies rated good quality.

Total Mortality. Four trials[8,11-15] reported the effect of lipid lowering on mortality among 7677 women without prior cardiovascular disease (TABLE 2). Two of the trials reported a lower risk of mortality in women treated with lipid-lowering agents compared with controls (Table 2). The summary RR for primary prevention of mortality was 0.95 (95% CI, 0.62-1.46).

CHD Mortality. Three trials[8,11-14] reported the effect of lipid-lowering agents on CHD mortality among 2626 women without prior cardiovascular disease (Table 2). One of these trials[11] used colestipol as the intervention, while the other two used a statin. One of the 3 trials reported a lower risk of CHD mortality in women treated with lipid-lowering agents compared with controls.[12,13] The summary RR for primary prevention of CHD mortality was 1.07 (95% CI, 0.47-2.40).

Nonfatal MI. Two trials[8,12-14] reported the effect of lipid-lowering agents on risk for nonfatal MI in 1442 women without prior cardiovascular disease (Table 2). Both of these trials used a statin drug and both found a reduced risk of nonfatal MI among women treated with lipid-lowering agents. The summary RR for primary prevention of nonfatal MI was 0.61 (95% CI, 0.22-1.68). Although the summary RR suggests a 39% reduction in risk of nonfatal MI among treated women, the 95% CI is wide, reflecting the small number of events across the trials.

Revascularization. Only 1 trial reported the effect of statin therapy for primary prevention of revascularization procedures in women.[8,14] The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS) found an RR of 0.87 (95% CI, 0.33-2.31).

CHD Events. Four trials, all using a statin as the intervention,[8,10,14,15,27,29] reported the effect of lipid lowering on risk for CHD events in 9806 women without prior cardiovascular disease (Table 2). There was a significant reduction in CHD events in the Heart Protection Study (HPS), which included only diabetic women, but not in the other studies. The results of these trials are inconsistent and the summary RR for primary prevention of CHD events was 0.87 (95% CI, 0.69-1.09). Although the summary estimate suggests a reduction in CHD events, the small number of events limits the ability to draw a firm conclusion about the true magnitude of effect.

Statins. Because statins are the most commonly used and recommended treatment of hyperlipidemia, we conducted separate analyses including only those studies that used a statin as the intervention. Evidence on the primary prevention effects of drugs other than statins is limited because only 1

Table 2. Individual and Summary Results of Primary Prevention Studies*

	Placebo, No.		Intervention, No.			
	Events	At Risk	Events	At Risk	RR (95% CI)	*P* Value for Heterogeneity
Total Mortality						
Colestipol	21	583	20	601	0.92 (0.51-1.69)	
ACAPS	5	227	0	218	0.09 (0.01-1.70)	
AFCAPS/TEXCAPS	7	498	11	499	1.53 (0.62-3.81)	
ALLHAT	NR†	2540	NR†	2511	0.98 (0.83-1.17)	
Total and summary	UC	3848	UC	3829	0.95 (0.62-1.46)	.98
CHD Mortality						
Colestipol	9	583	10	601	1.08 (0.44-2.63)	
ACAPS	1	227	0	218	0.35 (0.01-8.47)	
AFCAPS/TEXCAPS	0	498	1	499	2.99 (0.12-73.3)	
Total and summary	10	1308	11	1318	1.07 (0.47-2.40)	.87
Nonfatal MI						
ACAPS	3	227	1	218	0.35 (0.04-3.31)	
AFCAPS/TEXCAPS	6	498	4	499	0.69 (0.21-2.28)	
Total and summary	9	725	5	717	0.61 (0.22-1.68)	.70
Revascularization						
AFCAPS/TEXCAPS	8	498	7	499	0.87 (0.33-2.31)	
CHD Events						
AFCAPS/TEXCAPS	13	498	7	499	0.55 (0.22-1.34)	
ALLHAT	NR†	2540	NR†	2511	1.02 (0.81-1.28)	
ASCOT-LLA	17	963	19	979	1.10 (0.57-2.12)	
HPS	168	902	130	914	0.76 (0.62-0.94)	
Total and summary	UC	4903	UC	4903	0.87 (0.69-1.09)	.17

Abbreviations: CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction; NR, number of events not reported; RR, relative risk; UC, unable to calculate total due to actual numbers of events not reported.
*See footnotes to Table 1 for specific information regarding each study.
†Calculations for the summary RR performed using reported RRs and 95% CIs.

trial addressed the impact of a nonstatin drug.[11] The summary RRs were similar for all outcomes when findings were restricted to those studies using a statin.

PROSPER Study. The PROSPER study could not be classified as a primary or secondary prevention trial (due to 50% of participants in each group).[28] To determine the impact of including the PROSPER study, we performed a sensitivity analysis by adding the results of the cardiovascular disease outcomes from the PROSPER study to the primary prevention results. The summary RR for primary prevention of CHD events including the results of this trial was essentially unchanged (summary RR, 0.90; 95% CI, 0.77-1.05).

Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial. Forty-four percent of the women in the primary prevention studies were enrolled in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The results of this study have been challenged because it was unblinded, 32% of the usual care participants started taking lipid-lowering drugs at some point during the study, and a smaller than expected differential in total cholesterol was found between the treatment and usual care groups (9.6%), which is less than half the average for 8 other long-term statin trials with at least 1000 participants.[15] Hence, we repeated the analyses, excluding ALLHAT to determine the impact on the results. The RR for total mortality is 0.99 (95% CI, 0.52-1.80) when ALLHAT is excluded, which is essentially unchanged from the original primary prevention summary score. However, when excluding ALLHAT, the RR for CHD events is 0.77 (95% CI, 0.64-0.94), suggesting a larger effect and narrower 95% CIs.

Secondary Prevention

Eight trials assessed the effects of lipid-lowering agents among women with cardiovascular disease[7,10,16-26,29,48] and included a total of 8272 women. Two of these trials used clofibrate as the intervention, 1 used cholestyramine, and 5 used a statin. Both of the trials of clofibrate were rated fair,[16,17] while the cholestyramine trial and all of the statin trials were rated as good quality. Several of the trials reported results among women for only 1 or 2 of the 5 outcomes of interest (total mortality, CHD mortality, nonfatal MI, CHD events, and revascularization).

Total Mortality. Four trials,[7,20,37,48] 3 using a statin and 1 using cholestyramine as the intervention drugs, reported the effect of lipid lowering on mortality among a total of 2393 women with cardiovascular disease (TABLE 3). One of these trials[20] enrolled only 22 women and another[37] enrolled only 28 women. All of the data regarding the effects of lipid-lowering agents for secondary prevention of mortality in women comes mainly from 2 trials that used a statin as the intervention drug.[7,24] Only 1 of these trials suggested a reduction in risk of mortality among women and the summary RR was 1.00 (95% CI, 0.77-1.29).

CHD Mortality. Seven trials reported the effect of lipid-lowering agents on CHD mortality among 3190 women with cardiovascular disease (Table 3). However, 4 of these trials were small.[16,17,20,37] Three[7,18,19,21-24,48] of the 4 used a statin as the intervention and provide most of the evidence regarding the effect of lipid-lowering agents on CHD mortality in women with cardiovascular disease. The findings from these 3 trials were consistent in showing a reduced risk of CHD death among women treated with lipid-lowering medications compared with controls. The summary RR for secondary prevention of CHD mortality was 0.74 (95% CI, 0.55-1.00), suggesting a 26% reduction in risk of CHD mortality (Table 3).

Nonfatal MI. Seven trials reported the effect of lipid-lowering agents on risk for nonfatal MI in 3190 women with cardiovascular disease (Table 3). Four of these trials were small.[16,17,20,37] Three trials[7,18,19,21-24,48] use a statin as the intervention and provide most of the evidence regarding the effect of lipid lowering for secondary prevention of nonfatal MI in women. Six of the trials showed a reduced risk for nonfatal MI (summary RR, 0.71; 95% CI, 0.58-0.87). The summary RR suggests a 29% reduced risk for nonfatal MI.

Revascularization. Three trials, all using a statin as the intervention, reported the effect of lipid lowering for secondary prevention of revascularization procedures in 2919 women with cardiovascular disease (Table 3).[10,21-26] All of these trials found a reduction in risk among treated women and the summary RR was 0.70 (95% CI, 0.55-0.89), suggesting a 30% reduced risk of revascularization among women with cardiovascular disease (Table 3).

Total CHD Events. Several studies reported on total CHD events, which were defined as CHD mortality or nonfatal MI in the Cholesterol and Recurrent Events (CARE) and Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) studies. In the Scandinavian Simvastatin Survival Study (4S), CHD events were defined as CHD mortality, nonfatal MI, or resuscitated cardiac arrest and in the HPS as CHD mortality, nonfatal MI, stroke, or revascularization. CARE, LIPID, 4S, and HPS used a statin as the intervention drug and reported a lipid-lowering effect in 6185 women with cardiovascular disease for total CHD events (Table 3). All found a reduced risk of total CHD events among women,[7,10,18,19,21-26,48] with a summary RR of 0.80 (95% CI, 0.71-0.91), suggesting a 20% reduced risk of total CHD events among women with cardiovascular disease.

Statins. Because statins are the most commonly recommended treatment of hyperlipidemia, we conducted separate analyses including only those studies that used a statin as the intervention. Only 3 studies, including a total of 249 women, addressed the impact of lipid-lowering drugs other than statins.[16,17,37] Thus, evidence on the effect of nonstatin drugs is limited. However, the summary RRs were similar for all outcomes when findings were restricted to those studies using a statin.

Study Quality. Two of the studies that used a nonstatin drug were rated as fair quality[16,17] and one was rated as good quality.[37] All 5 of the trials that used a statin were rated as good quality. The summary RRs are similar when the results are restricted to good-quality studies.

PROSPER Study. The PROSPER study could not be classified as a primary or secondary prevention trial due to 50% of participants being in each group.[28] To determine the impact of adding the PROSPER study, we performed a sensitivity analysis by adding the results of the cardiovascular disease outcomes from the PROSPER study to the secondary prevention results. Including the results of this trial in the summary RR of CHD events resulted in an RR that was essentially unchanged (summary RR, 0.84; 95% CI, 0.74-0.95).

COMMENT

Our systematic review found that pharmacological lipid-lowering therapy, primarily with statin drugs, reduced the risk of CHD events for women with cardiovascular disease. In women without cardiovascular disease, the effect of lipid-lowering therapy was not clear because of the relatively small number of events in the primary prevention trials. For the trials reporting total mortality, lipid lowering did not appear to have a beneficial effect for women with or without previous cardiovascular disease over the 2.8- to 6-year study period in the available trials, although a longer length of follow-up may be necessary to find a reduction in mortality. In addition, the women in these studies were all relatively young, which might also limit the ability to find an effect on total mortality.

Although 21 clinical trials on lipid-lowering therapy included women, only 9 published results by sex. By contacting study investigators, we obtained data on women from 4 additional trials. Thus, we were able to analyze results from 13 trials that included 17 891 women. However, complete data on total mortality, CHD mortality, nonfatal MI, CHD events, and revascularization procedures were not available from each trial, limiting our ability to assess the effect of lipid lowering on some outcomes. Only 4 studies, including a total of 1433 women, addressed the effect of lipid-lowering drugs other than statins. Thus, evidence on the effect of nonstatin drugs is limited. In addition, because results were generally not published for differing drug doses, no information regarding dose is available.

Although women were included in 21 trials, results by sex are not available for 8 of these studies, which could potentially bias the results. Of these 8 studies, 7 were secondary prevention studies and 1 was a primary prevention study. In the secondary prevention stud-

Table 3. Individual and Summary Results of Secondary Prevention Studies*

	Placebo, No.		Intervention, No.		RR (95% CI)	*P* Value for Heterogeneity
	Events	Women	Events	Women		
Total Mortality						
NHLBI Type II	0	13	1	15	2.63 (0.12-59.4)	
4S	25	420	27	407	1.11 (0.66-1.87)	
PLAC-II	0	12	0	10	1.18 (0.03-54.81)	
LIPID	78	760	74	756	0.95 (0.71-1.29)	
Total and summary	103	1205	102	1188	1.00 (0.77-1.29)	.63
CHD Mortality						
Scottish Society of Physicians	6	62	1	62	0.23 (0.04-1.32)	
Physicians from Newcastle upon Tyne Region	6	45	1	52	0.20 (0.04-1.13)	
NHLBI Type II	0	13	1	15	2.63 (0.12-59.4)	
4S	17	420	13	407	0.79 (0.39-1.60)	
PLAC-II	0	12	0	10	1.18 (0.03-54.81)	
CARE	14	290	11	286	0.80 (0.38-1.71)	
LIPID	50	760	39	756	0.79 (0.52-1.18)	
Total and summary	93	1602	66	1588	0.74 (0.55-1.00)	.57
Nonfatal MI						
Scottish Society of Physicians	1	62	3	62	0.75 (0.42-1.33)	
Physicians from Newcastle upon Tyne Region	4	45	2	52	0.43 (0.08-2.25)	
NHLBI Type II	0	13	0	15	0.88 (0.02-41.28)	
4S	83	420	53	407	0.66 (0.48-0.90)	
PLAC-II	0	12	0	10	1.18 (0.48-54.81)	
CARE	28	290	14	286	0.51 (0.27-0.94)	
LIPID	61	760	54	756	0.89 (0.63-1.26)	
Total and summary	177	1602	126	1588	0.73 (0.59-0.90)	.59
Revascularization						
4S	42	420	21	407	0.52 (0.31-0.86)	
CARE	65	290	56	286	0.82 (0.64-1.20)	
LIPID	103	760	77	756	0.66 (0.5-0.87)	
Total and summary	210	1470	154	1449	0.70 (0.55-0.89)	.18
CHD Events						
4S	91	420	60	407	0.68 (0.51-0.91)	
CARE	80	290	46	286	0.60 (0.37-0.97)	
LIPID	104	760	90	756	0.87 (0.67-1.13)	
HPS	282	1638	237	1628	0.85 (0.72-0.99)	
Total and summary	557	3108	433	3077	0.80 (0.71-0.91)	.35

Abbreviations: CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction; RR, relative risk.
*See footnotes in Table 1 for specific information regarding each study.

ies, 509 of the 3299 participants were female. All of these secondary prevention studies showed a reduction in CHD events in treated individuals—results which are consistent with all the included secondary prevention studies. Because the overall study results are so similar among included studies, it is unlikely that even if the results for these 509 women could be included in the meta-analysis that they would significantly affect the available results for the 8272 included women.

One primary prevention study did not report sex-specific results. In this study, one third of the participants had known CHD.[38] As in many of the included primary prevention studies, a small proportion of individuals (23%) were female. A reduction in cardiovascular events with treatment was seen in this study and is consistent with the results of the other primary prevention studies. Inclusion of this study, which showed overall effects in the same direction as most of the included studies, and which included only 247 women, is unlikely to have a significant effect on the overall results for primary prevention.

This analysis is based on the most recent available data. However, an important limitation is that not all trials provided sex-specific outcomes and not all trials provided outcomes for all the individual types of CHD events. Clinicians and policymakers could benefit from combining sex-specific data from all of the completed trials in an individual patient-level meta-analysis, which was performed recently for antiplatelet therapy.[49]

A prior systematic review of the findings of clinical trials regarding the effects of lipid-lowering agents among persons without cardiovascular disease, published before the results of the HPS, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA), and ALLHAT were available,[15,27,29] used inclusion criteria and methods similar to ours, but did not stratify the results by sex.[50] Because 90% of the participants included in that review were men, the results primarily reflect the effects of lipid-lowering agents in men. Among (mostly) men, primary prevention with lipid lowering resulted in about a 30% reduced risk for both CHD events and CHD mortality.[50] Another prior review focused on women, but was also published before the results of the HPS, ASCOT-LLA, and ALLHAT were available.[15,27,29] This review found that lipid-lowering agents reduced CHD events in women with cardiovascular disease, but found no significant effect in women without cardiovascular disease, although the numbers of women in the available primary prevention studies were limited.[31] A recent meta-analysis of the effects of statins on low-density lipoprotein cholesterol, CHD, and stroke found that cholesterol lowering with statin drugs reduced the risk of stroke and CHD,[51] however, women were not analyzed separately.

Because women have a lower risk of cardiovascular disease than men at any given age, the number needed to treat (NNT) to prevent 1 CHD event will differ between women and men. For primary prevention, many more women than men need to be treated to prevent 1 CHD event. In a prior meta-analysis of the primary prevention statin studies, which included more than 90% men, the NNT to prevent 1 CHD event was 77.[50] Our summary estimate of the number of women needed to treat to prevent 1 CHD event (which did not include the ALLHAT study because actual numbers of events in women were not provided) was 140. Thus, almost twice as many women than men must be treated for primary prevention to prevent 1 CHD event.

For secondary prevention, in which it seems clear that both men and women benefit from treatment, the NNT is similar for men and women. Based on the results of our meta-analysis, the NNT to prevent 1 CHD event among women is 26. A prior meta-analysis, which included primary and secondary prevention trials and assessed the effect of statins on coronary disease found an overall NNT of 28 to prevent 1 CHD event.[32] Including only the secondary prevention studies included in this meta-analysis, the NNT to prevent 1 CHD event is 21. Although men and women were not analyzed separately for this estimate because 83% of the individuals in the included secondary prevention trials were male, this closely represents the NNT for men.

Our findings suggest that among persons without cardiovascular disease, lipid-lowering agents may not be as effective in women as in men without cardiovascular disease. However, our power to observe a modest reduction in CHD risk was limited because the number of events in the 6 available primary prevention trials was small, yielding imprecise effect estimates. In addition, the average length of the follow-up of the primary prevention trials was only 4 years, and it is possible that a longer duration of treatment may have resulted in a larger reduction in CHD outcomes.

Although we could not categorize the recently published PROSPER trial, which assessed the effect of lipid-lowering agents among 2804 men and 3000 women aged 70 to 82 years randomized to pravastatin or placebo and followed up for a mean of 3.2 years as either primary or secondary prevention, we assessed the impact of including PROSPER in both the primary and secondary prevention estimates.[28] About half of the participants in this trial had cardiovascular disease and the others had cardiovascular risk factors. Results were reported for the effect of lipid-lowering agents on cardiovascular events in women (CHD mortality, nonfatal MI, fatal stroke, and nonfatal stroke). The RR of cardiovascular events among women treated with pravastatin was 0.97 (95% CI, 0.80-1.16). Findings were not altered in sensitivity analyses that included the results of this trial as either primary or secondary prevention of CHD events.

There were no clinically important differences in the summary odds ratios when included studies were restricted to those that used a statin as the intervention or were rated as good quality. This is likely because 9 of the 13 included trials used a statin as the intervention and were rated as good quality.

In summary, lipid-lowering therapy appears to reduce the risk of CHD mortality, nonfatal MI, revascularization, and CHD events 20% to 30% in women with prior cardiovascular disease. Currently available evidence is insufficient to determine if lipid-lowering agents reduce CHD events in women with no previous history of cardiovascular disease. For total CHD events, the summary point estimate for risk reduction with lipid lowering is 0.87 (95% CI, 0.69-1.09), suggesting a modest decrease in risk when all available trial data are considered. In addition, exclusion of the ALLHAT trial, which has methodological limitations (crossover, nonblinding, and smaller achieved cholesterol reduction), strengthened the estimate of the lipid-lowering effect and precision (RR, 0.77; 95% CI, 0.64-0.94).

The risk for total mortality was not lower in women treated with lipid-lowering drugs, regardless of whether they had prior cardiovascular disease or not. In the primary prevention studies, there was no reduction in either CHD or total mortality. This may be because lipid lowering does not affect total mortality in women or because there were few deaths in the small, relatively healthy cohorts of women studied, even after summarizing study findings. In most of the studies, the length of follow-up was only 2.8 to 6 years. It is possible that a reduction in total mortality might have been observed with a longer duration of follow-up. For secondary prevention, CHD mortality is reduced, but total mortality is not. Possible explanations include chance, the limitation that not all studies reported both CHD and total mortality, or not all studies could be included in each summary estimate. Another potential explanation might be an increase in a competing cause of mortality, for example, an increase in hemorrhagic stroke with lipid-lowering therapy. However, information on the causes of non-CHD mortality is not available for all the trials, so this possibility cannot be proven. Publication of cause-specific mortality for many of the larger trials could help to clarify the association between lipid-lowering therapy and total mortality.

When making decisions about initiating lipid-lowering therapy in women, clinicians should consider a woman's overall risk for CHD. A global CHD risk-based approach integrates information about lipid levels along with information about other CHD risk factors, including age, blood pressure, tobacco use, and diabetes to make treatment decisions. Decisions about treatment of hyperlipidemia and other CHD risk factors will thus depend not only on the woman's lipid levels, but also her other risk factors for heart disease and her overall risk of experiencing a CHD event over a defined period (usually 10 years).

Global CHD risk can be estimated by using information from large epidemiological cohorts like the Framingham Heart Study. Risk equations derived from the Framingham Study are accurate in classifying women as being at high (>20%), intermediate (10%-20%), or low (<10%) 10-year risk and have been shown to be relatively accurate when applied to other settings within the United States.[52,53]

Future randomized trials should include women in adequate numbers to assess the effects of lipid-lowering therapy on clinical outcomes. Studies that include women should report the effects of lipid lowering on all clinical outcomes stratified by sex and primary or secondary prevention, and should include women with a range of CHD risk levels, particularly women at intermediate (10%-20%) 10-year CHD risk.

Funding/Support: This work was performed by the University of California San Francisco–Stanford Evidence Based Practice Center under contract 290-97-0013 with the Agency for Healthcare Research and Quality.

Disclaimer: No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or of the US Department of Health and Human Services.

Acknowledgment: We thank Paul Varosy, MD, for assistance with article reviews, Lily Chaput, MD, for assistance with literature searches, and Hai Emily Huang, Gaily Szeto, Evan Sloan, and Amy Truong for their assistance with manuscript preparation.

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