Chapter 3. Systematic Review of Lipid Lowering Treatment to Reduce Risk of Coronary Heart Disease in Women

Introduction

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, 2] Among white women, the cumulative risk of developing CHD between 50 and 94 years of age is 46 percent and the cumulative risk of dying from CHD is 31 percent.[3]

Elevated total cholesterol, low density lipoprotein-C (LDL-C) and triglycerides, and low high density lipoprotein-C (HDL-C) 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 interventions on clinical outcomes. Several randomized clinical trials have evaluated the effect of lipid lowering with drugs on risk of CHD events, both in persons with known cardiovascular disease and in those without CHD.[7-11] 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. Finally, some of the trials that did include women reported aggregate events (e.g. 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A previous systematic review of lipid lowering therapy in women included only studies published before 1995 and is now outdated.[12] A more recent systematic review that included only trials of statin drugs found that both women and men treated with statins had a 30 percent reduction in risk of major CHD events.[13] However, this review did not address outcomes other than major CHD events in women, did not stratify by primary or secondary prevention and did not include data from recent large trials.

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. We will assess the effects of lipid lowering on total mortality, CHD mortality, nonfatal myocardial infarction (MI), CHD events and revascularization procedures in women with and without prior CHD.

Methodology

Data sources

We searched PubMed®, the Cochrane Database, and DARE for articles published in English and other languages from 1966 through January 2002. We also reviewed bibliographies and asked peer reviewers (Appendix A) to identify additional articles.

Search Terms

Search terms were developed in collaboration with a medical librarian and included the following:

Limits	publication dates 1966 to January 2002, human *Not:* practice guideline, letter, editorial, review, meta-analysis, infant, newborn, preschool child, child
Predictor	hyperlipidemia and anticholesteremic agents, antilipemic agents, simvastatin, lovastatin, pravastatin, atorvastatin, fluvastatin, gemfibrozil, cholestyramine, cholestpol, niacin
Outcomes	cardiovascular diseases, heart diseases, myocardial ischemia, coronary disease

Inclusion Criteria

To be included, articles were required to fit the following criteria:

1) Randomized clinical trials of outpatients with or without known CHD.
2) Treatment duration of at least one year.
3) Study population classified as either primary (participants without prior CHD) or secondary prevention (participants with prior CHD).
4) Data on women provided.
5) Impact of lipid lowering with drug treatment assessed for at least one of the following clinical outcomes: total mortality, CHD mortality, nonfatal MI, CHD events or revascularization procedures. Coronary events included ischemic coronary syndromes and nonfatal myocardial infarction. CHD procedures included coronary bypass graft surgery and percutaneous coronary angioplasty or stenting.
6) Published between January 1, 1966 and January 30, 2002. Articles published outside this date range recommended by peer reviewers were included.

We excluded studies that only provided evidence on the effect of treatment on changes in lipids, angiographic findings or other intermediate outcomes. For studies with multiple publications, only data from the most comprehensive or most recent publication were used.

Article Identification

An initial search using the terms listed above identified articles that potentially provided evidence. Two University of California, San Francisco (UCSF)-Stanford Evidence-based Practice Center (EPC) physician investigators reviewed the titles and excluded those that clearly did not provide data on humans or clearly did not address the question.

The abstracts of the remaining articles were reviewed independently by two UCSF-Stanford EPC physician investigators and coded using the categories listed below. Disagreements were discussed and the following consensus codes were entered into a database (Access, Microsoft Corporation):

RQ	Research question - the article clearly does not address the research question.
R	Review – the study is a review that does not contain primary data.
NSD	Not appropriate study design - The article is not a randomized clinical trial.
NH	No humans - the study clearly does not include data on humans.
E_1	Eligible – the study may contain primary evidence regarding the research question in women and will be reviewed in full-text.

Articles coded E_1 were retrieved and the full text was reviewed independently by two UCSF-Stanford EPC investigators. Names of authors and titles of journals were obscured before articles were reviewed.

Obtaining Unpublished Results

Some eligible studies included women in the study population, but did not report findings separately by gender. In these instances we attempted to contact authors to obtain these data. If we did not receive a response after the first contact, a second attempt was made. We contacted 13 authors[11, 14-27] and received data from two.[16, 25, 26]

Quality Assessment

The full text of each eligible study was reviewed independently by two UCSF-Stanford physician investigators, who completed a quality evaluation form (Appendix B). All of the studies included in this systematic review are randomized clinical trials. To be categorized as *good quality*, articles were required to meet the following additional parameters:

- Inclusion/exclusion criteria clear and appropriate.
- Randomization allocation concealed.
- Control group received placebo.
- Participants and research staff blinded to intervention.
- More than 75 percent complete followup.

All other trials were considered *fair quality*. Disagreements between reviewers regarding quality parameters were decided by discussion and consensus.

Data Abstraction

Two UCSF-Stanford EPC physician investigators independently reviewed the full text of each eligible study and completed a data abstraction form (Appendix C). We abstracted information on the study population (primary prevention trials were defined as those that included individuals without known CHD; secondary prevention trials included individuals with known CHD), inclusion criteria, length of followup, numbers of men and women, participant characteristics such as age, other cardiovascular risk factors and cardiac medication use, baseline and followup lipoprotein values and all clinical outcomes that were measured. When possible, data were abstracted for men and women separately. Disagreements were discussed and decided by consensus.

Data Management and Archive

We entered all identified titles and abstracts in an EndNote® file (Niles Software, Inc.) that includes searchable key words as codes for eligibility. Information on all articles that were reviewed in full text was transferred from EndNote® to a relational database (Access, Microsoft® Corporation) that allows us to categorize each article by reason for exclusion. Quality assessment data for each eligible study were also entered in the Access database, allowing us to categorize eligible articles by quality. Selected data were transferred to a flatfile database (EXCEL, Microsoft® Corporation) for preparation of evidence tables and calculation of summary estimates, confidence intervals and tests of heterogeneity.

The full-text articles that were retrieved, and the abstraction forms for each article are filed by topic and question in Dr. Grady's offices at the UCSF Mt. Zion Women's Health Clinical Research Center.

Data Analyses

The primary outcome of each clinical trial was expressed as the relative risk (RR) among treated compared to untreated study participants. Summary estimates of RR and 95 percent confidence intervals (CI) were calculated using the Mantel-Haenszel method and both fixed and random effects models. Results of the fixed and random effects models were similar, and we report only the findings of the random effects model. To avoid calculation problems associated with zero cells, 0.5 was added to all cells to calculate variances and standard deviations.[28] The significance level for all tests of outcome was set at 0.05. All findings were assessed for heterogeneity using a standard Chi-square test and Q statistic with critical value set at 0.10. All analyses were performed separately for the findings of primary and secondary prevention studies. Subgroup analyses were performed by type of drug treatment (statins vs. others), and by good vs. fair quality.

Publication bias usually occurs if small studies with unremarkable findings (relative risks about 1.0) are not published while small studies with markedly positive findings (in this case, low relative risks) are published. We calculated the correlation between individual study weight (1/variance) and relative risk using a nonparametric correlation coefficient (Kendall's Tau) with critical value set at 0.10 to assess potential publication bias. Statistically significant correlation of study weight and relative risk suggests publication bias.

Results

Results of Study Identification

Our searches identified 1,335 titles. After eliminating ineligible studies by review of titles and abstracts, we reviewed the full text of 120 articles. We identified 20 studies that fit all inclusion criteria, but only 9 provided outcomes stratified by sex.[7-9, 11, 27, 29-39] We contacted the principal investigators of the studies that did not provide data for women to request this information.[11, 14-27] We received data on women from two investigators.[16, 25, 26] Thus, 11 studies (represented by 19 articles) were found to be both eligible and to contain data stratified by sex for inclusion in the systematic review.[7-9, 11, 16, 25-27, 29-39] One additional study did not meet inclusion criteria because it did not provide data on any of the clinical outcomes of interest and the study population was equally divided between persons with prior CHD and those without prior CHD and separate estimates for the effects of lipid lowering in primary and secondary prevention were not published.[40]

Description of Eligible Studies

Characteristics of the 11 eligible trials are described in Evidence Table 6. The numbers of participants in each trial ranged from 151 to 20,536 and 15 to 50 percent of participants were women. The total number of women included in the trials was 15,917, but almost two thirds were from two studies.[11, 39] 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 4.7 years. Seven of the trials were classified as secondary prevention and four were classified as primary prevention (Evidence Table 6). Eligibility criteria for 5 trials required at least mild hyperlipidemia,[7, 16, 25, 26, 31, 39] four required a range of cholesterol levels that would include some participants in the normal range[9, 11, 27, 34] and 2 included participants regardless of cholesterol levels.[29, 30] Three trials assessed the effects of clofibrate[29, 30] or colestipol[31] and eight assessed the efficacy of treatment with statins (lovastatin,[9, 25, 26] simvastatin,[7, 11, 39] pravastatin[16, 27, 34]).

All but one of the 11 trials included a placebo control group[39] and all but two were adequately blinded.[31, 39] In all but one of the trials,[31] followup was greater than 75 percent complete. Overall, seven of the trials were rated good quality and four were rated fair (Evidence Table 6).

The clinical outcomes evaluated were total mortality, CHD mortality, nonfatal MI, CHD events and revascularization (Evidence Tables 7 and 8). Most trials were designed to address clinical outcomes, but two were designed to evaluate change in intimal medial thickness of the carotid artery[16, 25, 26] and included clinical events only as secondary outcomes.

For studies with mixed populations (e.g. some participants had CHD and some did not), 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 high risk for CHD outcomes due to presence of CHD risk factors.

Three trials included participants with and without CHD. In the colestipol trial, only 20 percent of participants had CHD and this trial was classified as a primary prevention study.[31] In the Heart Protection Study, 65 percent of participants had known CHD and remaining 35 percent had peripheral vascular disease, cerebrovascular disease or diabetes.[11] Because the majority of participants had CHD and those without CHD were also at very high risk for CHD events, this trial was classified as a secondary prevention study. A recently published trial included older participants with CHD and those at high risk for CHD in approximately equal numbers[40] and did not present results stratified by history of CHD. Because of the equal distribution, we are unable to classify this study as either primary or secondary prevention. In addition, we could not include the results of this trial for any specific coronary disease endpoint because the results for women were only given for the composite outcome of cardiovascular events (CHD mortality, nonfatal MI, fatal stroke and nonfatal stroke).

Findings

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 (Evidence Table 8).

Seven trials assessed the effects of lipid lowering among women with CHD (secondary prevention)[7, 8, 11, 16, 27, 29, 30, 32-37] and included a total of 8,244 women. Two of these trials used clofibrate as the intervention,[29, 30] while five used a statin.[7, 8, 11, 16, 27, 32-37] Both of the trials of clofibrate were rated fair,[29, 30] while all of the statin trials were rated good quality. While seven trials provided data, three were small (22 to 124 women),[16, 29, 30] two were mid-sized (576[8, 34, 35] and 827 women[32, 33]) and only two included more than 1,000 women (1,516[27, 36, 37] and 5,082[11]). Evidence was also limited because several of the trials reported results among women for only one or two of the five outcomes of interest (total mortality, CHD mortality, nonfatal MI, CHD events and revascularization).

Four trials assessed the effects of lipid lowering among women without prior CHD (primary prevention)[9, 25, 26, 31, 38, 39] and included 7,673 women. One of these trials used colestipol as the intervention[31] and the rest used a statin. Two trials[31, 39] were rated fair and the other two good quality.[9, 25, 26, 38] Three of these trials included about 1,000 women or less (441,[25, 26] 997,[9, 38] and 1,184[31]) and one included 5,051.[39] As with the secondary prevention trials, many of these trials reported results among women for only one or two of the five outcomes of interest.

Secondary Prevention

Total mortality. Two trials,[7, 16, 32, 33] both using a statin as the intervention, reported the effect of lipid lowering on mortality among a total of 899 women with CHD (Evidence Table 7). One of these trials[16] enrolled only 22 women, so that essentially all of the data regarding the effects of lipid lowering for secondary prevention of mortality in women comes from one trial that used a statin as the intervention.[7, 32, 33] Neither of the two trials found a reduction in risk of mortality among women (Evidence Table 7), and the summary relative risk was 1.11 (95% CI 0.66-1.87) (Evidence Table 8).

CHD mortality. Five trials reported the effect of lipid lowering on CHD mortality among 1,646 women with CHD (Evidence Table 7). However, three of these trials were small,[16, 29, 30] and two,[7, 8, 32-35] both using a statin as the intervention, provide most of the evidence regarding the effect of lipid lowering on CHD mortality in women with CHD. The findings of these two trials were consistent in showing a reduced risk of CHD death among women treated with lipid lowering compared to controls. The summary relative risk for secondary prevention of CHD mortality was 0.74 (95% CI 0.57-0.96), suggesting a 26 percent reduction in risk of CHD mortality (Evidence Table 8).

Nonfatal MI. Five trials reported the effect of lipid lowering on risk for nonfatal MI in 1,646 women with CHD (Evidence Table 7). Three of these trials were small[16, 29, 30] and two trials, both using a statin as the intervention,[7, 8, 32-35] provide most of the evidence regarding the effect of lipid lowering for secondary prevention of nonfatal MI in women. Both of these two trials showed a reduced risk for nonfatal MI and the summary relative risk was 0.64 (95% CI 0.50-0.82), suggesting a 36 percent reduced risk (Evidence Table 8).

CHD events. Four trials, all using a statin as the intervention, reported the effect of lipid lowering on CHD events in 8,001 women with CHD (Evidence Table 7). These trials consistently found a reduced risk of CHD events among women,[7, 8, 11, 27, 32-37] with a summary relative risk of 0.79 (95% CI 0.72-0.88), suggesting a 21 percent reduced risk of CHD events among women with CHD (Evidence Table 8).

Revascularization. Two trials, both using a statin as the intervention, reported the effect of lipid lowering for secondary prevention of revascularization procedures in 1,403 women with CHD (Evidence Table 7). Both of these trials found a reduction in risk among treated women and the summary relative risk was 0.70 (95% CI 0.42-1.16). Although the summary relative risk suggests a 30 percent reduction in risk of revascularization, this finding was not statistically significant (Evidence Table 8).

Drug class and study quality. Only two studies, including a total of 221 women, addressed the impact of lipid lowering drugs other than statins.[29, 30] Thus, evidence on the effect of non-statin drugs is limited. However, the summary ORs were similar for all outcomes when findings were restricted to those studies using a statin. Both of the studies that used a non-statin drug were rated fair quality,[29, 30] and all five of the trials that used a statin were rated good quality. Thus, the summary ORs are also unchanged when the results are restricted to good quality studies.

Sensitivity analyses. One trial that we included with the secondary prevention studies enrolled a mixed population of persons with and without CHD and reported the effect of statin treatment on risk for CHD events.[11] Because 65 percent of the participants had prior CHD and the rest had vascular disease or diabetes, we included the results of this trial as secondary prevention. We also performed a sensitivity analysis excluding the results of this trial. The summary relative risk for secondary prevention of CHD events excluding the results of this trial was essentially unchanged (summary relative risk 0.74; 95% CI 0.61-0.91). We also performed a sensitivity analysis by adding the results of the cardiovascular disease outcomes from the PROSPER trial to the summary results for secondary prevention of CHD events.[40] The summary relative risk for secondary prevention of CHD events including the results of this trial was essentially unchanged (summary relative risk 0.76; 95% CI 0.72-0.87).

Primary Prevention

Total mortality. Four trials[9, 25, 26, 31, 38, 39] reported the effect of lipid lowering on mortality among 7,673 women without prior CHD (Evidence Table 7). One of these trials[31] used colestipol as the intervention, while the rest used a statin. One of the trials reported a lower risk of mortality in women treated with lipid lowering compared to controls, but the other three did not (Evidence Table 7). The summary relative risk for primary prevention of mortality was 0.95 (95% CI 0.62-1.46) (Evidence Table 8).

CHD mortality. Three trials[9, 25, 26, 31, 38] reported the effect of lipid lowering on CHD mortality among 2,622 women without prior CHD (Evidence Table 7). One of these trials[31] used colestipol as the intervention, while the other two used a statin. One of the three trials reported a lower risk of CHD mortality in women treated with lipid lowering compared to controls,[25, 26] but the others did not. The summary relative risk for primary prevention of CHD mortality was 1.07 (95% CI 0.47-2.40).

Nonfatal MI. Two trials[9, 25, 26, 38] reported the effect of lipid lowering on risk for nonfatal MI in 1,646 women without prior CHD (Evidence Table 7). Both of these trials used a statin as the intervention, and both found a reduced risk of nonfatal MI among women treated with lipid lowering. The summary relative risk for primary prevention of nonfatal MI was 0.61 (95% CI 0.22-1.68). Although the summary relative risk suggests a 39 percent reduction in risk of nonfatal MI among treated women, this finding was not statistically significant.

CHD events. Two trials, both using a statin as the intervention,[9, 38, 39] reported the effect of lipid lowering on risk for CHD events in 6,048 women without prior CHD (Evidence Table 7). The results of these trials are inconsistent, and the summary relative risk for primary prevention of CHD events was 0.87 (95% CI 0.50-1.49).

Revascularization. Only one trial reported the effect of statin therapy for primary prevention of revascularization procedures in women[9, 38] (Evidence Table 7). This trial found a relative risk of 0.87 (95% CI 0.33-2.31).

Drug class and study quality. Evidence on the primary prevention effects of drugs other than statins is limited as only one trial addressed the impact of a non-statin drug.[31] The summary ORs were similar for all outcomes when findings were restricted to those studies using a statin or to studies rated good quality.

Sensitivity analyses. We performed a sensitivity analysis by adding the results of the cardiovascular disease outcomes from the PROSPER trial to the summary results for primary prevention of CHD events.[40] The summary relative risk for primary prevention of CHD events including the results of this trial was essentially unchanged (summary relative risk 0.97; 95% CI 0.84-1.12).

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 except for secondary prevention of revascularization (Evidence Table 8). There was no evidence of publication bias in any of the summary estimates.

Conclusions

Although 20 clinical trials of the effects of lipid lowering therapy included women, only nine published results by gender. By contacting study investigators, we were successful in obtaining data on women from two additional trials. Thus, we were able to analyze results from 11 trials that included 15,917 women. However, complete data on the five outcomes of interest were not available from each trial, limiting our ability to assess the effect of lipid lowering on some outcomes. Only three studies, including a total of 1,405 women, addressed the impact of lipid lowering drugs other than statins. Thus, evidence on the effect of non-statin drugs is limited.

In the secondary prevention setting, treatment with lipid lowering therapy reduced risk of CHD mortality, nonfatal MI and CHD events in women. Summary estimates suggest a 26 percent reduction in risk of CHD mortality, a 36 percent reduction in risk of nonfatal MI and a 21 percent reduction in risk of a CHD event. There was no evidence of a reduction in risk of total mortality and insufficient evidence to document a reduction in risk of revascularization procedures. In the primary prevention setting, there was insufficient evidence of reduced risk of any clinical outcome in women. The summary relative risk for nonfatal MI was similar to that for secondary prevention (39 percent reduction vs. 36 percent reduction for secondary prevention), but was not statistically significant.

A prior systematic review of the findings of clinical trials of the effects of lipid lowering among persons without CHD used inclusion criteria and methods very similar to ours, but did not stratify the results by gender.[41] Since 90 percent of the participants included in that review were men, the results primarily reflect the effects of lipid lowering in men. Among (mostly) men, primary prevention with lipid lowering resulted in about a 30 percent reduced risk for both CHD events and CHD mortality[41] Our findings suggest that, among persons without CHD, lipid lowering may not be as effective in women as in men without CHD. However, our power to observe a modest reduction in CHD risk was limited because the findings of only four primary prevention trials were available for inclusion in the meta-analysis.

We were unable to include findings from a recently published clinical trial of the effect of lipid lowering among 2,804 men and 3,000 women aged 70 to 82 years randomized to pravastatin or placebo and followed for a mean of 3.2 years.[40] About half of the participants in this trial had vascular disease and the others had vascular risk factors. Results were reported for the effect of lipid lowering on cardiovascular events in women (CHD mortality, nonfatal MI, fatal stroke and nonfatal stroke); the relative risk among women treated with pravastatin was 0.96 (95% CI 0.79-1.18). We could not include these data because we could not categorize the trial as primary or secondary prevention and results in women were only given for cardiovascular events. Given the timeline for this review, we did not have time to contact the authors to request findings stratified by sex, primary vs. secondary prevention and clinical outcomes. However, in sensitivity analyses that included the results of this trial as either primary or secondary prevention of CHD events did not alter the findings.

There were no clinical differences in the summary odds ratios when studies included were restricted to those that used a statin as the intervention or to good quality studies. This is likely because eight of the 11 included trials used a statin as the intervention, and seven of the 11 trials were rated good quality.

In summary, lipid lowering therapy appears to reduce risk of CHD mortality, nonfatal MI and CHD events 25 to 35 percent in women with prior CHD. There was inadequate evidence to document a reduction in risk of any clinical outcome among women without prior CHD. Data were limited, but the risk for total mortality was not lower in women

treated with lipid lowering, regardless of whether they had prior CHD or not. The lack of reduction in risk for mortality in either primary or secondary prevention settings may be because lipid lowering does not affect total mortality in women or because there were few deaths, even after summarizing study findings.

Future Research

Future randomized trials should include women in adequate numbers to assess the effects of lipid lowering on clinical outcomes. Studies that include women should report the effects of lipid lowering on all clinical outcomes stratified by sex and primary vs. secondary prevention.

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