Clinical Outcomes in Statin Treatment Trials
A Meta-analysis

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Objective: To determine the risk of cardiovascular events and death in patients receiving statin treatment for cholesterol regulation.

Methods: Systematic review and meta-analysis of all randomized controlled trials that were published as of April 15, 1997. Primary or secondary prevention trials or regression trials were eligible.

Main Outcome Measures: All-cause mortality, fatal myocardial infarction (MI) or stroke, nonfatal MI or stroke, angina, and withdrawal from the studies. Both random- and fixed-effects models were run for the outcomes of interests, and results are expressed as odds ratios (ORs). Sensitivity analyses tested the impact of the study type and duration, statin treatment type, and control arm event rates. Intent-to-treat denominators were used whenever they were available, and the number needed to treat was calculated when appropriate.

Results: Seventeen studies (21,303 patients) were included (2 secondary prevention studies, 5 mixed primary-secondary prevention population studies, and 10 regression trials). Treatment groups included lovastatin (t = 5), pravastatin (t = 10), and simvastatin (t = 3). For all-cause mortality, the OR was 0.76 (95% confidence interval [CI], 0.67-0.86) in favor of receiving statin treatment; for fatal MI, the OR was 0.61 (95% CI, 0.48-0.78); for nonfatal MI, the OR was 0.69 (0.54-0.88); for fatal stroke, the OR was 0.77 (95% CI, 0.57-1.04); for nonfatal stroke, the OR was 0.69 (95% CI, 0.54-0.88); and for angina, the OR was 0.70 (95% CI, 0.65-0.76).

Conclusions: Patients who received statin treatment demonstrated a 20% to 30% reduction in death and major cardiovascular events compared with patients who received placebo. This advantage was generally present across study types and statin treatment types and for patients with less severe dyslipidemias. The benefit in clinical outcomes was noticeable as early as 1 year.

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STATINS ARE a class of agents that lower plasma cholesterol levels by inhibiting hepatic hydroxymethyl glutaryl coenzyme A reductase. The long-term clinical efficacy for the primary and secondary prevention of cardiovascular outcomes has been difficult to establish because of the enormous sample sizes and lengthy durations such trials require. The efficacy of statin treatment in preventing cardiovascular deaths has been documented in a few large multicenter trials (the Cholesterol and Recurrent Events Trial1-3 and the West of Scotland Coronary Prevention Study [WOSCOPS]4-9); however, long-term studies reporting efficacy in the reduction of all-cause mortality and other types of nonfatal cardiovascular events, such as myocardial infarction (MI) and stroke, are either ongoing or lacking.

The primary objective of this project was to determine the risk of cardiovascular events and death in patients receiving hypolipidemic drugs of the statin class compared with patients receiving placebo or no pharmacological treatment for cholesterol regulation. We conducted a systematic review and meta-analysis of all published randomized controlled trials at least 1 year in duration. Studies of primary or secondary prevention of cardiovascular events and those that measured atherosclerotic lesion regression were included if they reported clinical outcomes.

RESULTS

STUDY CHARACTERISTICS

The initial search of MEDLARS and Current Contents yielded 766 citations. The most frequent reasons for study exclusion were that the study duration was less than 1 year, the trial design was nonrandomized or noncontrolled, there were only active drug control...
METHODS

This meta-analysis adhered to previously described standards for performing meta-analyses,10-12 and it was implemented according to a prospectively written protocol.

LITERATURE SEARCH

A MEDLARS literature search was conducted using the terms anticholesterolemic agents, pravastatin, lovastatin, fluvastatin, atorvastatin, cerivastatin, simvastatin, and human trials. Current Contents CD-ROMs (1994-1997; Institute for Scientific Information, Philadelphia, Pa) were also searched. The publication cutoff date was April 15, 1997; the retrieval cutoff date was May 1, 1997. The computer-based search was supplemented by manually searching the bibliographies of retrieved articles. We also attempted to contact several investigators to identify any new trials or the availability of results for ongoing unpublished trials.

STUDY SELECTION

Studies were considered eligible for this meta-analysis if they were randomized controlled trials, had a parallel design, were primary or secondary prevention studies or regression or restenosis trials, and had a duration of at least 1 year. Eligible studies also had to have more than 10 patients with hypercholesterolemia (as defined by the study investigators) per group and 1 group receiving a monotherapy statin agent vs at least 1 concurrent control arm that used placebo or no pharmacological treatment for cholesterol regulation. Additional inclusion criteria included any indication that subjects were being observed for clinical outcomes (studies with no episodes of the outcomes of interest were retained if the above was satisfied) and publication in English, German, French, Spanish, or Italian.

DATA EXTRACTION

Eligible studies were blinded as to the source of financial support, authors, and treatment group assignments. Data extraction was performed by 2 reviewers (S.D.R. and I.E.A. or J.E.C.) using the data extraction forms that were developed for this project. Completed data extraction forms were cross-checked against one another; differences were resolved by referring to the original papers or to a third reviewer, if necessary.

The key data elements that were sought from each trial were categorized as follows: study characteristics, patient characteristics, treatment characteristics, and clinical outcomes. Study characteristics included study duration and location; year of publication; active treatment; diet required; study type (ie, primary or secondary prevention, regression or restenosis); and trial assumptions regarding sample size estimates, power calculations, and number of estimated events. In addition, studies were scored using an instrument13 that measures internal validity by scoring randomization, blinding, and withdrawals. A randomized study design earned 1 point; if the randomization method was appropriate (eg, computer generation of random numbers), then an extra point was assigned. If participants were blinded to the identity of the study drug, a point was awarded; if it was expressly stated that the control and experimental interventions were indistinguishable, a second point was awarded. Lastly, if all patients who entered the study were accounted for, a point was awarded. The highest possible score was 5 points; articles that received a score of 3 or higher were considered to be of average to high quality.

The patient characteristics extracted included the number of patients who were randomized and evaluated; sex; age; history of diabetes mellitus, smoking, hypertension, MI, stroke, or angina; and cholesterol levels (total levels, components, and ratios) at baseline and end point. The treatment characteristics were study type; baseline and study cholesterol levels; type of statin therapy received; dosage, schedule, and duration of use; type of comparison group (placebo or no treatment); and the use of concomitant medications. The primary clinical outcomes that were sought from each study were all-cause mortality; sudden or nonsudden death; fatal MI or stroke; nonfatal MI or stroke; and angina (with coronary artery bypass graft [CABG] surgery and percutaneous transluminal angioplasty [PTCA]). A secondary outcome of interest was the total number of withdrawals from the studies, since dropouts or patients who were lost to follow-up could also represent the occurrence of unidentified cardiovascular outcomes.

arms in the study, or clinical results were not reported. Seventeen studies (several with multiple publications) satisfied all criteria for eligibility.1-3,9,14-18,28-38 A list of rejected studies is available from the authors upon request. Study characteristics for the 17 included trials are summarized in Table 1.

The trials were conducted in North America (n = 8), Europe (n = 7), and elsewhere (n = 2). Three studies were 1 to 2 years in duration, 5 were 2 to 3 years, 5 were 3 to 4 years, and 4 were in excess of 4 years. There were no trials in which the entire patient populations were characterized as free of cardiovascular disease. One study was composed of patients with no prior MIs, but included patients with known ischemic heart disease as manifested by angina.1-9 There were 2 secondary prevention trials,1-3,14-18 5 trials with mixed populations of patients (secondary and primary prevention),1-3,9,14-18,28-32 and 10 regression trials.33-58 There were no restenosis trials.

The 17 studies contained 18 treatment groups overall: 4 studies of patients who received lovastatin treatment (5 lovastatin treatment groups), 10 studies of patients who received pravastatin treatment, and 3 studies of patients who received simvastatin treatment. In 6 studies, the protocol required the addition of a second drug (usually a resin) to the treatment regimen if the patients who received statin treatment did not meet certain predefined cholesterol targets.1-3,31-37,39-42,57,58 The studies rarely reported the link between the occurrence of the outcomes of interest and whether such patients were receiving monotherapy or combination therapy. The results of these studies were considered separately in subgroup analyses.

Eleven trials received quality scores of 3 or more, indicating average to superior execution and reporting.

PATIENT CHARACTERISTICS

The meta-analysis included 21 303 randomized patients who were distributed between statin treatments (n = 10 754) and placebo controls (n = 10 525). The dif-
STATISTICAL METHODS

The main hypothesis tested was that the risk of major cardiovascular events and/or death in patients with hypercholesterolemia who receive statin treatment is lower than in similar patients who receive no treatment or placebo. Differences in cardiovascular events and/or mortality of approximately 20% to 30% were expected in an overall control-event rate of between 5% and 10% over 5 years.1-9,14-18 It was also anticipated that for every 1% reduction in cholesterol levels, a 1% to 2% reduction in cardiovascular events and mortality would be observed.19,20

First, the risk of major cardiovascular events and mortality for all patients receiving statin treatment vs controls was tabulated. Only 1 event, the highest level of severity, was listed per patient in the following descending order of events: all-cause mortality, sudden and nonsudden death, fatal MI or stroke, nonfatal MI or stroke, and angina (or CABG or PTCA). Additionally, the efficacy in patient subgroups, the impact of prognostic factors (ie, type of study, type of treatment, and patient characteristics), and the relationship between the risk of events and the degree of cholesterol reduction was assessed as data permitted.

Second, the outcome data from multiple studies were then combined for meta-analysis using both a fixed-effects model21 and a random-effects model.22 The random-effects model was used to take into account possible heterogeneity in the distribution of means and variances among studies. The outcomes of interest were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The natural logarithm of these ratios was used to satisfy the assumptions of normality.23 All meta-analysis results reported here are from random-effects models unless otherwise stated. Odds ratios with 95% CIs for clinical outcomes were computed for all studies together, studies of similar design type (ie, regression, secondary prevention, and mixed), and studies examining the use of similar types of statin treatments. For inclusion in the meta-analyses, 0.5 was added to zero cells for calculation.24

The following formula was used to calculate these values:

$$OR = \frac{pt/(1-p_t)}{pc/(1-p_c)}$$

where $pt$ indicates the probability of an event in the treatment group and $pc$, the probability of an event in the control group.

Statistical heterogeneity was examined by calculating the Cochran Q statistic, which is assumed to have a $\chi^2$ distribution. For the meta-analyses of all outcomes of interest, intent-to-treat (ITT) denominators were used whenever available. Analyses were conducted in 2 ways: by including only studies that reported the ITT denominator and by including the ITT studies and those for which only the evaluable patient denominators were reported. The latter calculations are not reported, however, since they did not change any of the results.

Power estimates derived from previously published projected event rates25 suggested that a meta-analysis sample size in the range of 20,000 patients would be required to achieve at least 80% power to detect a significant difference in treatment groups for the primary outcomes of interest in this study.

Relative risks were estimated to determine the percentage of risk reduction associated with statin treatment. These risks were to be calculated for all statin treatments together and for each statin treatment separately, as data permitted. Absolute risk differences were also estimated, as was the number needed to treat (NNT), which is the inverse of the absolute risk difference.26 The NNT can be interpreted as the number of patients who need to be treated to prevent 1 adverse outcome.

Several subgroup analyses were planned in order to assess the impact of statin treatments by age; sex; baseline lipid levels; and the presence of other cardiovascular risk factors, such as hypertension, smoking, and a history of MI, stroke, or diabetes mellitus, if data permitted.

Multivariate regressions were used to incorporate all significant prognostic variables and their treatment interaction terms. Meta-regression analysis of the effect measures vs absolute or percentage cholesterol reduction was planned,27 if data permitted. Also, control group event rates were used as an index of risk on which to regress statin treatment effects.27

All calculations were performed using SAS software, version 6.12 (SAS Institute Inc, Cary, NC).

Table 3 summarizes the treatment characteristics for each group. The baseline total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels appear comparable across treatment groups. When grouped by the type of statin treatment received, mean baseline TC levels ranged from 6.2 to 6.7 mmol/L (239-259 mg/dL), mean LDL levels from 4.1 to 4.8 mmol/L (158-185 mg/dL), and mean HDL levels from 1.0 to 1.6 mmol/L (39-62 mg/dL).

TREATMENT CHARACTERISTICS

Table 2 summarizes the treatment characteristics for each group. The baseline total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels appear comparable across treatment groups. When grouped by the type of statin treatment received, mean baseline TC levels ranged from 6.2 to 6.7 mmol/L (239-259 mg/dL), mean LDL levels from 4.1 to 4.8 mmol/L (158-185 mg/dL), and mean HDL levels from 1.0 to 1.6 mmol/L (39-62 mg/dL).
dL), and mean HDL levels from 1.1 to 1.2 mmol/L (42-46 mg/dL). No other lipids assays, such as apolipoprotein fractions or cholesterol component ratios, were reported with sufficient frequency to be useful in the meta-analysis.

The starting dosage for the lovastatin treatment studies ranged from 20 or 40 mg once daily up to 40 mg twice a day. For the pravastatin treatment studies, the starting dosage was 15, 20, or 40 mg once daily. The starting dosage for the simvastatin treatment studies was 20 mg once daily. All studies specified a diet for all study patients. Ten of the studies allowed or required the use of concomitant medications. The additional drug therapies included β-blockers, diuretics, angiotensin-converting enzyme inhibitors, calcium channel blockers, and antiplatelet agents or anticoagulants. Cholesterol levels and clinical outcomes of interest were not reported by concomitant medications administered; therefore, this information cannot be analyzed for its impact on the outcomes of interest.

Changes in lipid levels were reported and were usually the mean over the duration of the study. Mean TC levels were reduced by 20.8%, 19.5%, 22.0%, and 0.6% for lovastatin, pravastatin, and simvastatin treatments and placebo, respectively. Mean LDL cholesterol levels were reduced by 28.1%, 28.8%, 34.6%, and 17.2% for lovastatin, pravastatin, and simvastatin treatments and placebo, respectively. Mean HDL cholesterol levels were increased by 5.8%, 5.0%, and 7.3%, for lovastatin, pravastatin, and simvastatin treatments, respectively. Mean HDL cholesterol levels were decreased by 0.2% for patients who received placebo.

**PRIMARY CLINICAL OUTCOMES**

Table 4 summarizes the primary clinical outcomes overall and by the type of statin treatment. In 1 study, zero events were reported in a monitored population. For inclusion in the meta-analyses, all zero cells were treated as 0.5. When data were not reported, the study was dropped from the analysis.

Overall, there were 1132 deaths from all causes (4.8% of patients randomized to statin treatment groups and 6.3% of patients randomized to placebo groups). The absolute difference of 1.5% is a relative decrease of approximately 24% for patients who received statin treatment relative to controls. The NNT is 67, which means that 67 patients need to be treated with statins in order to pre-
vent 1 death. The rate for all-cause mortality was 0.6% for lovastatin, 4.4% for pravastatin, and 7.3% for simvastatin treatments. In this case and in all instances described below, the clinical event rate by the type of statin treatment received was confounded by study type; therefore, comparisons cannot be made. An analysis of mortality rates by sudden vs nonsudden death was not possible because of insufficient reporting of these data.

Fatal MIs occurred in 1.0% of patients who received statin treatment and in 1.6% of patients who received placebo overall. This 0.6% absolute reduction in patients who received statin treatment translates to a relative decrease of 38% and an estimated NNT of 166 patients to prevent 1 fatal MI. The frequency of fatal MIs was 0.2% for lovastatin, 0.9% for pravastatin, and 1.3% for simvastatin treatments.

Fatal strokes were reported in 20 patients who received statin treatment and in 19 patients who received placebo. The distribution by study type was 3 patients in regression studies (statin treatment, n = 0; placebo, n = 3), 26 patients in secondary prevention trials (statin treatment, k = 14; placebo, k = 12), and 10 patients in mixed studies (statin treatment, n = 6; placebo, n = 4). In addition, 1 study combined fatal strokes with nonfatal strokes (statin treatment, n = 54; placebo, k = 78). If all confirmed fatal strokes are combined with the aforementioned 132 unspecified strokes, the total is 171 strokes and the overall frequency is 0.8% for patients who received statin treatment and 1.0% for those who received placebo. The frequencies by type of statin treatment are 0% for lovastatin, 0.9% for pravastatin, and 0.6% for simvastatin.

Nonfatal MIs were reported in 4.7% of patients who received statin treatment and in 7.0% of patients who received placebo. The absolute difference of 2.3% translates to a relative decrease of 33% in nonfatal MIs in patients who received statin treatment. Therefore, the NNT is 43, which implies that 43 patients need to be treated

Table 3. Study and Patient Characteristics by Type of Statin Treatment*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Lovastatin, 20/40 mg</th>
<th>Pravastatin, 15/20/40 mg</th>
<th>Simvastatin, 20 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>1037</td>
<td>7161</td>
<td>2556</td>
<td>10525</td>
</tr>
<tr>
<td>Randomized†</td>
<td>1037</td>
<td>7161</td>
<td>2545</td>
<td>10512</td>
</tr>
<tr>
<td>Type of study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regression</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Secondary</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mixed</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Baseline cholesterol levels, mmol/L (mg/dL)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6.2 (239)</td>
<td>6.4 (247)</td>
<td>6.7 (259)</td>
<td>6.5 (251)</td>
</tr>
<tr>
<td>LDL</td>
<td>4.1 (158)</td>
<td>4.5 (174)</td>
<td>4.8 (185)</td>
<td>4.5 (174)</td>
</tr>
<tr>
<td>HDL</td>
<td>1.2 (46)</td>
<td>1.1 (42)</td>
<td>1.2 (46)</td>
<td>1.1 (42)</td>
</tr>
<tr>
<td>Study cholesterol levels, mmol/L (mg/dL) [% change]‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4.9 (189)[-20.8]</td>
<td>5.2 (201)[-19.5]</td>
<td>5.0 (193)[-22.0]</td>
<td>6.4 (247)[-0.6]</td>
</tr>
<tr>
<td>LDL</td>
<td>3.0 (116)[-28.1]</td>
<td>2.9 (112)[-28.8]</td>
<td>4.7 (181)[-34.6]</td>
<td>3.8 (147)[-17.2]</td>
</tr>
<tr>
<td>HDL</td>
<td>1.2 (46)[-5.8]</td>
<td>1.1 (42)[-5.0]</td>
<td>1.2 (46)[-7.3]</td>
<td>1.1 (42)[-0.2]</td>
</tr>
</tbody>
</table>

* LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.
† Evaluated patient values were substituted for the unreported values found in the Monitored Atherosclerosis Regression Study47-50 and Santinga et al51; this explains the discrepancy in the total number of patients randomized in Tables 2 and 3.
‡ Values are means.

Table 4. Primary Clinical Outcomes*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Lovastatin</th>
<th>Pravastatin</th>
<th>Simvastatin</th>
<th>All Statins</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>5 (0.6) [914]</td>
<td>301 (4.4) [6917]</td>
<td>187 (7.3) [2556]</td>
<td>493 (4.8) [10387]</td>
<td>639 (6.3) [10199]</td>
</tr>
<tr>
<td>Sudden death</td>
<td>0 [454]</td>
<td>1 (0.1) [784]</td>
<td>29 (1.2) [2427]</td>
<td>30 (0.8) [3665]</td>
<td>44 (1.3) [3511]</td>
</tr>
<tr>
<td>Nonsudden death</td>
<td>0 [289]</td>
<td>1 (0.1) [784]</td>
<td>. . .</td>
<td>1 (0.1) [1073]</td>
<td>0 [924]</td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>2 (0.2) [914]</td>
<td>65 (0.9) [6992]</td>
<td>32 (1.3) [2556]</td>
<td>99 (1.0) [10462]</td>
<td>168 (1.6) [10287]</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>0 [749]</td>
<td>60 (0.9) [6841]</td>
<td>14 (0.6) [2223]</td>
<td>74 (0.8) [9813]</td>
<td>97 (1.0) [9633]</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>10 (1.6) [625]</td>
<td>297 (4.3) [6992]</td>
<td>174 (6.8) [2556]</td>
<td>481 (4.7) [10173]</td>
<td>710 (7.0) [10136]</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0 [460]</td>
<td>45 (1.0) [4554]</td>
<td>61 (2.7) [2223]</td>
<td>106 (1.5) [7237]</td>
<td>159 (2.2) [7211]</td>
</tr>
<tr>
<td>Angina or CABG or PTCA</td>
<td>8 (4.9) [165]</td>
<td>766 (11.0) [6992]</td>
<td>593 (23.2) [2556]</td>
<td>1367 (14.1) [9713]</td>
<td>1764 (18.2) [9677]</td>
</tr>
<tr>
<td>Total withdrawals</td>
<td>28 (1.7) [165]</td>
<td>1248 (18.6) [6711]</td>
<td>305 (11.9) [2556]</td>
<td>1581 (16.8) [9432]</td>
<td>1849 (19.7) [9396]</td>
</tr>
</tbody>
</table>

* Values are number of patients (percentage) [sample size]. The Cholesterol and Recurrent Events Trial5-3 combined fatal and nonfatal strokes (statin treatment, n = 54; placebo, n = 78). CABG indicates coronary artery bypass graft surgery; PTCA, percutaneous transluminal coronary angioplasty.
to prevent 1 nonfatal MI. The proportions of patients who were randomized and experienced nonfatal MIs were 1.6% for lovastatin, 4.3% for pravastatin, and 6.8% for simvastatin treatments.

There were 106 nonfatal strokes reported in patients who received statin treatment and 159 in patients who received placebo, yielding approximate proportions of 1.5% of patients who received statin treatment and 2.2% of patients who received placebo—a 32% reduction in patients who received statin treatment. In some studies, transient ischemic attacks were not distinguished from confirmed strokes; therefore, totals were used in these computations. With an absolute difference of 0.7%, the NNT is estimated at 143 patients who need to be treated to prevent 1 nonfatal stroke. The frequencies are 0% for lovastatin, 1.0% for pravastatin, and 2.7% for simvastatin treatments.

Episodes of angina or nonelective CABG or PTCA procedures were often reported together; therefore, totals were also used in these computations. The total number of events was 1367 in the statin treatment groups and 1764 in the placebo groups. Therefore, the approximate proportions of patients who experienced angina or nonelective CABG or PTCA were 14.1% of patients who received statin treatment and 18.2% of patients who received placebo. The absolute difference of 4.1% translates to a 23% reduction in episodes of angina or nonelective CABG or PTCA in patients who received statin treatment. The corresponding NNT is 24, implying that approximately 24 patients need to be treated to prevent 1 such event. The proportions of patients with angina or nonelective CABG or PTCA were 4.9% for lovastatin, 11.0% for pravastatin, and 23.2% for simvastatin treatments. As noted above, for all of the event frequencies by the type of statin treatment received, there is confounding by study type that prevents comparisons among types of statin treatment. For these angina events, the frequency by study type was 353 patients in regression studies (statin treatment, n = 148; placebo, n = 205), 2622 in secondary prevention trials (statin treatment, n = 1158; placebo, n = 1464), and 156 in mixed studies (statin treatment, n = 61; placebo, n = 95).

Lastly, we recorded the total number of reported patient withdrawals for any reason. One thousand five hundred eighty-one patients (16.8%) withdrew in the statin treatment groups and 1849 (19.7%) in the placebo groups. The withdrawal rate was 17.0% for lovastatin, 18.6% for pravastatin, and 11.9% for simvastatin treatments. Five studies did not report total withdrawals.

**META-ANALYSES**

The ORs and 95% CIs for all clinical outcomes are shown by the type of study in Table 5 and by the type of statin treatment in Table 6. For all studies combined, patients who received statin treatment had a statistically significant advantage for all-cause mortality and all other outcomes assessed except fatal stroke and withdrawals, for which there was a nonsignificant trend in favor of statin treatment. In the mixed population studies, the advantage

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**Table 5. Odds Ratios (ORs) for Clinical Outcomes of Statin Treatment vs Placebo by Type of Study**

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>All Studies</th>
<th>Mixed Prevention Studies</th>
<th>Secondary Prevention Studies</th>
<th>Regression Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. OR (95% CI) NNT</td>
<td>No. OR (95% CI)</td>
<td>No. OR (95% CI)</td>
<td>No. OR (95% CI)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>14 0.76 (0.67-0.86) 67</td>
<td>4 0.77 (0.59-0.99)</td>
<td>2 0.79 (0.60-1.04)</td>
<td>8 0.52 (0.32-0.85)</td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>14 0.61 (0.49-0.78)</td>
<td>4 0.71 (0.47-1.07)</td>
<td>2 0.53 (0.38-0.74)</td>
<td>8 0.72 (0.31-1.66)</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>10 0.77 (0.57-1.04)</td>
<td>4 1.26 (0.44-3.66)</td>
<td>2 0.80 (0.50-1.27)</td>
<td>4 0.43 (0.08-2.39)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>13 0.66 (0.57-0.77)</td>
<td>3 0.58 (0.30-1.14)</td>
<td>2 0.66 (0.50-0.87)</td>
<td>8 0.69 (0.44-1.09)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>7 0.69 (0.54-0.88)</td>
<td>4 0.82 (0.54-1.24)</td>
<td>1 0.63 (0.46-0.88)</td>
<td>3 0.52 (0.20-1.38)</td>
</tr>
<tr>
<td>Angina</td>
<td>12 0.70 (0.65-0.76)</td>
<td>4 0.45 (0.13-1.50)</td>
<td>2 0.71 (0.65-0.78)</td>
<td>7 0.66 (0.53-0.83)</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>11 0.80 (0.61-1.04)</td>
<td>3 0.95 (0.85-1.05)</td>
<td>2 0.56 (0.28-1.08)</td>
<td>6 0.90 (0.62-1.31)</td>
</tr>
</tbody>
</table>

*Includes studies with intent-to-treat denominators. ORs are derived from random-effects model meta-analysis. CI indicates confidence interval; NNT, number needed to treat; and NA, not applicable.

†Heterogeneity test result was significant.

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**Table 6. Odds Ratios (ORs) for Clinical Outcomes of Statin Treatment vs Placebo by Type of Statin Administered**

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Lovastatin Treatment Studies</th>
<th>Pravastatin Treatment Studies</th>
<th>Simvastatin Treatment Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. OR (95% CI)</td>
<td>No. OR (95% CI)</td>
<td>No. OR (95% CI)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>3 0.42 (0.19-1.37)</td>
<td>8 0.84 (0.71-0.98)</td>
<td>3 0.67 (0.55-0.81)</td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>3 0.61 (0.11-3.31)</td>
<td>8 0.69 (0.51-0.94)</td>
<td>3 0.48 (0.32-0.73)</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>2 0.70 (0.04-11.24)</td>
<td>7 0.71 (0.51-0.99)</td>
<td>1 1.16 (0.54-2.48)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>2 0.92 (0.40-2.10)</td>
<td>8 0.70 (0.60-0.81)</td>
<td>3 0.78 (0.54-2.4)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>1 0.09 (0.01-1.63)</td>
<td>5 0.80 (0.54-1.17)</td>
<td>1 0.63 (0.46-0.88)</td>
</tr>
<tr>
<td>Angina</td>
<td>1 0.61 (0.25-1.49)</td>
<td>8 0.71 (0.64-0.80)</td>
<td>3 0.69 (0.61-0.79)</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>1 1.60 (0.73-3.47)</td>
<td>7 0.72 (0.46-1.40)</td>
<td>3 0.80 (0.68-0.95)</td>
</tr>
</tbody>
</table>

*Includes studies with intent-to-treat denominators. ORs are derived from random-effects model meta-analysis. CI indicates confidence interval.

†Heterogeneity test result was significant.
might be a useful index of cardiac risk, we regressed the ORs for the same outcome. Both ORs were statistically significant in favor of statin treatment. When studies were subgrouped by whether they added a second cholesterol-regulating drug to the statin treatment, there was no difference in the OR for all-cause mortality between the 5 studies that allowed the addition of a second drug (OR, 0.70; 95% CI, 0.41-1.20) and the 9 studies in which no second drugs were added (OR, 0.70; 95% CI, 0.60-0.82). The OR for these latter 9 studies is statistically significant, whereas the OR for the former 5 is not. When studies were subgrouped by quality score, the 6 studies with low scores (≤2) had an OR of 0.47 (95% CI, 0.24-0.93) for all-cause mortality, while those with higher scores (>2) had an OR of 0.77 (95% CI, 0.68-0.87) for the same outcome. Both ORs remain statistically significant in favor of statin treatment.

To test the hypothesis that control arm event rates might be a useful index of cardiac risk, we regressed the treatment effect size (logarithmic OR) on the frequency of all-cause mortality and all MI, fatal and nonfatal, in the control groups. However, neither analysis approached statistical significance (all-cause mortality, P = .70; all MI, P = .17), suggesting that in this set of studies, the hypothesis was rejected. This finding is consistent with the observation that the statin treatment effect size for most measured clinical outcomes is relatively constant across study types, which presumably include patients with different underlying levels of cardiac risk.

Clinical outcomes within the patient subgroups of interest were so infrequently reported, they were unanalyzable. Next, a stepwise multivariate regression analysis was fitted to the data to assess the impact of several factors (sex, age, hypertension, smoking status, diabetes, and baseline cholesterol level) on clinical outcomes. These analyses were not fruitful because of inconsistency in the reporting of patient demographic characteristics across the studies.

To explore concerns that the observed statin treatment effects might be swayed by the largest studies in the set, 2 large studies (WOSCOPS and the Scandinavian Simvastatin Survival Study) were dropped, 1 at a time, from the set of studies to determine what effect this would have on the overall results. In both cases, when the ORs were recalculated for the remainder, the results did not change significantly.

Lastly, studies were grouped and displayed using I-beam figures to show all-cause mortality and MIs. In Figure 1 and Figure 2, ORs are ordered by the duration of the study from shortest to longest. In Figure 3, ORs are grouped by study type. In Figure 4, ORs are ordered by control-event rates from lowest to highest. No trends are apparent.

**COMMENT**

This meta-analysis of the clinical outcomes of statin treatment included all relevant randomized controlled trials with results published as of April 15, 1997, that were at
least 1 year in duration and that reported at least some of the clinical outcomes of interest. Our main hypothesis was confirmed. In general, a 20% to 30% reduction in the risk of death or major cardiovascular events was observed in patients who received statin treatment compared with patients who received placebo. The advantage was generally present across different study types, including regression studies that were not individually designed to capture differences in clinical outcomes as primary end points. The outcomes that reached statistical significance included stroke, angina, and MI. The advantage of statin treatment was seen in studies that were previously thought to be too short to demonstrate clinical outcomes and in studies with patients with less severe dyslipidemias.1-3

While a few previous statin treatment studies have demonstrated significant reductions in cardiovascular events, the proof of benefit for other categories of clinical outcomes has been less persuasive. In particular, statin treatment–associated reductions in all-cause mortality, stroke, and angina had not been demonstrated conclusively at the time we began this review.30 Subsequent to the completion of our review, a similar meta-analysis was published that also found a statin treatment benefit regarding total mortality and stroke.30 Although the latter review contains somewhat different study eligibility criteria (and therefore different studies were analyzed), as well as different categorization by study types and different statistical methods, the main results are similar. Our review has also extended the range of benefit to include angina-related events. Subsequent to this review, the results of the Air Force/Texas Coronary Atherosclerosis Prevention Study,51 which examined the primary prevention of acute coronary events with lovastatin treatment in more than 6000 patients who were evaluated for an average of 5 years, have been published. These results also confirm the findings of our review, including the findings relative to angina and to patients with normal baseline cholesterol levels in primary prevention settings. The interim results of the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study,62 with more than 9000 patients, have also been published recently. These results also appear to confirm the clinical benefits of statin treatment in secondary prevention settings for patients with normal baseline cholesterol levels.

In this analysis, we have assumed that there is a consistent class effect for all statin treatments, while recognizing that this has been previously questioned.63,64 There were no differences in clinical results, although there were some differences in the effects of different statin treatments on cholesterol components. It is likely that any such differences resulted from differences in the number and type of studies in each analyzable subset, and until head-to-head comparisons are done, we cannot draw conclusions about differences. However, the clinical benefits observed with statin treatments do not appear to translate to other lipid-lowering agents; reviews and meta-analyses of these agents failed to demonstrate convincing reductions in adverse clinical outcomes.59,65 This may be caused by nothing more than the fact that, compared with older agents, statin treatments lower total and LDL cholesterol levels and increase HDL cholesterol levels to a greater degree. There may also be other mechanisms of action unique to statin treatment, such as reduction in atherosclerotic plaque vulnerability or alteration of macrophage function.66

Future reviewers of the cholesterol-lowering effects of various treatments should assess drug-specific or class-specific effects. Furthermore, patients should be considered to be on a continuum of vasculopathy; therefore, distinctions may not always be necessary among patients with documented prior MIs vs those with only angina vs those with asymptomatic radiologic lesions vs those without signs or symptoms. The underlying risk of adverse outcomes may certainly differ, but atherosclerotic vasculopathy is multifactorial; we are not convinced that differences in risk are always captured cleanly in studies that purport to assess primary prevention vs secondary prevention vs regression. Therefore, we do not believe that primary and secondary prevention and regression should always be analyzed independently of each other. Also, exclusion of short-term studies from re-
views of clinical outcomes may not be warranted, given the findings of our review, which had a cutoff of studies that were 1 year in duration. The review of Hebert et al included studies of even shorter durations. Lastly, distinctions on the basis of baseline cholesterol levels may also be unnecessary, since studies do not show that the low end of the cholesterol continuum has yet been reached in terms of statin treatment benefits.

Unique to this review is the provision of NNTs for statin treatment effects. Number needed to treat is a concept aimed at making investigational trial results more applicable in the clinic. The NNT assists practitioners in weighing the clinical significance of study results, not just statistical significance. For example, our estimate of an NNT of 45 patients (treated for at least 1 year, the minimum duration of any study in this data set) to prevent 1 nonfatal MI can be placed in useful perspective if one recognizes that adoption of the guidelines of the fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure for the treatment of hypertension would result in an NNT of 41 patients in average patients in a clinical trial setting to facilitate patient-specific decision making. This is 1 possible solution of average patients in a clinical trial setting to facilitate patient-specific decision making. This is 1 possible solution of the problem of translating clinical trial results with cholesterol-lowering interventions to real-life patients. Additional examples of NNTs for common clinical conditions have been published elsewhere along with a nomogram that would allow practitioners to go 1 step further and factor in the patient expected event rate for an individual patient with the NNT derived from a set of average patients in a clinical trial setting to facilitate patient-specific decision making. This is 1 possible solution of translating clinical trial results with cholesterol-lowering interventions to real-life patients.

Lastly, although it is unlikely that this review missed any important data published before the search cutoff date, the statin treatment literature is growing quickly, and frequent updates to this review would be valuable, especially to establish efficacy in subgroups that are still underrepresented in individual trials, such as women and the elderly, for whom questions of efficacy of cholesterol lowering still exist.

CONCLUSIONS

We believe this analysis has conclusively demonstrated a beneficial effect of statin treatments on most cardiovascular outcomes, including angina and nonfatal stroke—a benefit not previously demonstrated. We expect the final results of ongoing or of recently completed statin treatment studies (eg, the Plaque Hypertension Lipid-Lowering Italian Study for pravastatin, the Lipoprotein and Coronary Atherosclerosis Study for fluvastatin, the Oxford Cholesterol Study for simvastatin, and the LIPID study for pravastatin) to confirm and extend the results presented here. We recommend ongoing monitoring of the literature, with periodic updating of this database in order to benchmark the track record of the newer statin treatments against these data and to increase the representation of those patient populations that are still underrepresented in this data set.

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REFERENCES

20. The Prospective Pravastatin Pooling Project Investigators. Design, rationale, and baseline characteristics of the Prospective Pravastatin Pooling (PPP) project: a combined analysis of three large-scale randomized trials: Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), Cholesterol and Recurrent Events (CARE), and West of Scotland Coronary Prevention Study (WOSCOPS). Am J Cardiol. 1995;76:899-905.
26. Holme J. Relationship between total mortality and cholesterol reduction as found in the elderly, for whom questions of efficacy of cholesterol lowering still exist.


32. The Pravastatin Multinational Study Group for Cardiac Risk Patients, Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/L (200 to 300 mg/dL) plus two additional atherosclerotic risk factors. Am J Cardiol. 1993;72:1031-1037.


