Lipid-Modifying Therapies and Risk of Pancreatitis
A Meta-analysis

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Context  Statin therapy has been associated with pancreatitis in observational studies. Although lipid guidelines recommend fibrate therapy to reduce pancreatitis risk in persons with hypertriglyceridemia, fibrates may lead to the development of gallstones, a risk factor for pancreatitis.

Objective  To investigate associations between statin or fibrate therapy and incident pancreatitis in large randomized trials.

Data Sources  Relevant trials were identified in literature searches of MEDLINE, EMBASE, and Web of Science (January 1, 1994, for statin trials and January 1, 1972, for fibrate trials, through June 9, 2012). Published pancreatitis data were tabulated where available (6 trials). Unpublished data were obtained from investigators (22 trials).

Study Selection  We included randomized controlled cardiovascular end-point trials investigating effects of statin therapy or fibrate therapy. Studies with more than 1000 participants followed up for more than 1 year were included.

Data Extraction  Trial-specific data described numbers of participants developing pancreatitis and change in triglyceride levels at 1 year. Trial-specific risk ratios (RRs) were calculated and combined using random-effects model meta-analysis. Between-study heterogeneity was assessed using the I² statistic.

Results  In 16 placebo- and standard care–controlled statin trials with 113,800 participants conducted over a weighted mean follow-up of 4.1 (SD, 1.5) years, 309 participants developed pancreatitis (134 assigned to statin, 175 assigned to control) (RR, 0.77 [95% CI, 0.62-0.97; P = .03; I² = 0%]). In 5 dose-comparison statin trials with 39,614 participants conducted over 4.8 (SD, 1.7) years, 156 participants developed pancreatitis (70 assigned to intensive dose, 86 assigned to moderate dose) (RR, 0.82 [95% CI, 0.59-1.12; P = .21; I² = 0%]). Combined results for all 21 statin trials provided RR 0.79 (95% CI, 0.65-0.95; P = .01; I² = 0%). In 7 fibrate trials with 40,162 participants conducted over 5.3 (SD, 0.5) years, 144 participants developed pancreatitis (84 assigned to fibrate therapy, 60 assigned to placebo) (RR, 1.39 [95% CI, 1.00-1.95; P = .053; I² = 0%]).

Conclusion  In a pooled analysis of randomized trial data, use of statin therapy was associated with a lower risk of pancreatitis in patients with normal or mildly elevated triglyceride levels.

JAMA. 2012;308(8):804-811  www.jama.com

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cholesterol content, which may theoretically reduce the risk of developing gallstones, a risk factor for pancreatitis. Hypertriglyceridemia has been reported to be the third most common cause of pancreatitis. This has led to major guidelines for lipid-modifying therapies, including advice to commence triglyceride-lowering therapy, usually statins, in persons with moderate and severe hypertriglyceridemia (above 400 to 500 mg/dL [to convert to mmol/L, multiply by 0.0113]). However, high-quality evidence for this approach is lacking, and only observational data exist. Indeed, there is concern that statins might increase the risk of pancreatitis in individuals with triglyceride levels lower than those mentioned in guidelines. Fibrates increase the cholesterol concentration in bile and may increase the risk of gallstones. However, few large randomized placebo-controlled trials of fibrate therapy have published data on pancreatitis. Consequently, the associations between both types of lipid-modifying therapy and the risk of pancreatitis are uncertain. We therefore examined the associations between use of a statin or a fibrate and the incidence of pancreatitis by conducting collaborative meta-analyses of published and unpublished data from the relevant large randomized clinical trials.

METHODS

We gathered data from large randomized end-point trials primarily designed to assess the effects of statin therapy (including both placebo- and standard care–controlled trials plus intensive-dose/moderate-dose trials) or fibrate therapy on cardiovascular events. Inclusion criteria were trials with 1000 or more participants exposed to randomized therapy with a minimum mean follow-up of 1 year, as in previous large meta-analyses of statin trials. We excluded trials conducted in patients with previous organ transplantation or those receiving hemodialysis as well as trials comparing combination therapy with placebo. We searched MEDLINE, EMBASE, and Web of Science databases using the terms statin, HMG CoA reductase inhibitor, and fibrate and also names of individual statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin) and fibrates (bezafibrate, ciprofibrate, clofibrate, fenofibrate, gemfibrozil) as title words and keywords, limited to studies defined as randomized controlled trials, to identify relevant studies performed in adult patients (initial search on October 28, 2011; search updated June 9, 2012) and published from January 1, 1972 (fibrate trials), or January 1, 1994 (statin trials), until June 9, 2012 (FIGURE 1), without language restrictions. Reference lists for the studies identified in the literature search were searched for additional studies. The US Food and Drug Administration website was also searched for trial reports containing relevant data. Abstracts, manuscripts, and reports were reviewed independently by 2 readers (D.P., P.W.) in an unblinded fashion. A third reviewer (N.S.) settled discrepancies. In the small number of trials in which published data regarding incident pancreatitis and change in triglyceride levels were available, these data were tabulated. In the majority of trials in which no relevant data were available, trial investigators were contacted with a request to provide the required information.

After the full articles were reviewed and data were received from collaborators, 21 statin trials and 7 fibrate trials (TABLE 1) and 344 excluded (duplicates) 4082 records screened 4426 records identified 4416 from databases 805 39 full-text articles reviewed for 4092 records screened 39 full-text articles reviewed for unpublished data 5 trials excluded (no data available or provided) 28 trials included in meta-analysis 7 fibrate 21 statin 6 had published data regarding 5 trials included as suitable 27 unpublished data regarding incident pancreatitis 6 had published data regarding incident pancreatitis 3 had <1000 participants 1 follow-up <1 y 1 surrogates end point 1 unsuccessful randomization 1388 not randomized (baseline paper, post hoc analysis, or review) 590 nonstatin or fibrate intervention 415 other a most records excluded for more than 1 reason, with only the strongest reason recorded.

Quality Assessment

Two authors (D.P., P.W.) used an established tool, the Jadad score, to independently evaluate the quality of each trial. The Jadad score is designed to assess trials with regard to method of randomization, whether the trial is double-blinded, and whether withdrawals/dropouts are described, resulting in a score of up to 5 points. A third reviewer (N.S.) was available to resolve any disagreement by consensus and discussion.

End Points

A patient was considered to have developed pancreatitis during the trial if this event was recorded as diagnosis or provided). The PRISMA checklist was provided to the journal at the time of manuscript submission.

Data Sources

Published data for incident pancreatitis were available from 2 statin trials and 4 fibrate trials. Unpublished data were collected from 19 statin trials and 3 fibrate trials. To examine whether there was a relationship between the extent of triglyceride lowering between active and control therapy groups in the trials and risk of pancreatitis, we collected data on average change in triglyceride levels at 1 year. A PRISMA checklist was provided to the journal at the time of manuscript submission.

Quality Assessment

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End Points

A patient was considered to have developed pancreatitis during the trial if this event was recorded as diagnosis or provided). The PRISMA checklist was provided to the journal at the time of manuscript submission.
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was recorded as an adverse event or serious adverse event. This information was identified using different approaches across the trials, namely text word searches of adverse event reports, including self-reported hospitalization data, for pancreatitis; Medical Dictionary for Regulatory Activities event classification; and International Classification of

Table 1. Baseline Data From 21 Large Statin Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>No.</th>
<th>Statin</th>
<th>Treatment, Active/Control</th>
<th>Follow-up, y</th>
<th>Trial Population (Triglyceride Inclusion Criteria)</th>
<th>Age, y</th>
<th>Triglycerides</th>
</tr>
</thead>
</table>
| Placebo- and Standard Care-Controlled Trials
| 4S,16 1994              | 2223| 2221 Simvastatin (10-40 mg)/placebo | 5.4a         | Angina or previous MI (triglycerides ≤222 mg/dL) | 63 (45) | 18           |
| WOSCOPS,17 1995         | 3302| 3293 Pravastatin (40 mg)/placebo    | 4.9          | Male, hypercholesterolemia, no history of MI (NR) | 55 (66) | 15           |
| CARE,18 1996            | 2081| 2078 Pravastatin (40 mg)/placebo    | 5.0a         | MI in previous 3-20 mo (triglycerides <350 mg/dL) | 59 (61) | 14b          |
| AFCAPS/TexCAPS,19 1998  | 3304| 3301 Lovastatin (20-40 mg)/placebo | 5.2          | Average cholesterol levels, no CVD (triglycerides ≤400 mg/dL) | 58 (75) | 14           |
| GISSI-HF,20 2008        |     |                 |                           |              | Hospitalization for unstable angina or previous MI (triglycerides <445 mg/dL) | 62a    | 14b          |
| PROVE-IT TIMI 22,21 2004| 800 | 800 Atorvastatin (to achieve LDL-C <100 mg/dL)/standard care | 3.0          | CHD (triglycerides <400 mg/dL) | 59 (181) | 28           |
| CARDS,22 2004           | 1428| 1410 Atorvastatin (10 mg)/placebo   | 3.9a         | Type 2 diabetes mellitus, no CVD (triglycerides ≤503 mg/dL) | 62 (97) | 21           |
| LIPID,23 1998           | 4512| 4502 Pravastatin (40 mg)/placebo    | 6.1          | Hypertension, no CHD (triglycerides ≤400 mg/dL) | 63 (80) | 23           |
| GISSI Prevenzione,24 2000| 2138| 2133 Pravastatin (20 mg)/standard care | 2.0a         | Recent MI (NR) | 166 (89) | –4           |
| HPS,25,26 2002          | 10269| 10267 Simvastatin (40 mg)/placebo | 5.4          | CVD or diabetes (NR) | 65 (125) | 19           |
| PROSPER,27 2002         | 2891| 2913 Pravastatin (40 mg)/placebo    | 3.3          | Age 70-82 y with CVD or risk factors (triglycerides <534 mg/dL) | 75 (62) | 17           |
| GREACE,28 2002          | 800 | 800 Atorvastatin (10 mg)/placebo    | 3.0          | CHD (triglycerides <400 mg/dL) | 59 (181) | 28           |
| ASCOT-LLA,29 2003       | 5168| 5137 Atorvastatin (10 mg)/placebo   | 3.3a         | Hypertension, no CHD (triglycerides ≤400 mg/dL) | 63 (80) | 23           |
| CARE,30 1996            | 1211| 1199 Atorvastatin (10 mg)/placebo   | 4.0          | Diabetes mellitus (triglycerides ≤600 mg/dL) | 61 (97) | 21           |
| ASPEN,31 2006           | 3866| 3966 Pravastatin (10-20 mg)/no treatment | 5.3          | Hypercholesterolemia, no previous CHD or stroke (NR) | 58 (83) | 6            |
| MEGA,32 2006            | 2514| 2497 Rosuvastatin (10 mg)/placebo   | 2.7a         | Systolic heart failure (NR) | 73 (114) | 24           |
| CORONA,33 2007          | 8901| 8901 Rosuvastatin (20 mg)/placebo   | 1.9a         | No CVD, no diabetes, hsCRP ≤2.0 mg/L (triglycerides <500 mg/dL) | 66a (86-165)a | 17           |
| JUPITER,34 2008         | 2285| 2289 Rosuvastatin (10 mg)/placebo   | 3.9a         | Chronic heart failure (NR) | 68 | NA | NA |
| PROVE-IT TIMI 22,35 2004| 2099| 2063 Pravastatin (40 mg)/atorvastatin (80 mg) | 2.0          | Recent hospitalization for ACS (NR) | 58 (156) | 21           |
| A to Z,36 2004          | 2265| 2234 Placebo + simvastatin (20 mg)/simvastatin (40-80 mg) | 2.0a         | Recent hospitalization for ACS (NR) | 61a (116-199) | 6 |
| TNT,37,38 2005          | 4965| 5006 Pravastatin (80 mg)/atorvastatin (10 mg) | 4.9a         | Stable CHD (triglycerides ≤600 mg/dL) | 61 (71) | NA |
| IDEAL,39 2006           | 4439| 4449 Atorvastatin (80 mg)/simvastatin (20-40 mg) | 4.8a         | Previous MI (triglycerides ≤600 mg/dL) | 62 (149) | 23 |
| SEARCH,40 2010          | 6001| 6033 Simvastatin (80 mg)/simvastatin (20 mg) | 8.7          | Previous MI (NR) | 64 (169) | 10    |

Total 76 722 76 692 4.3 (1.6)

Abbreviations: ACS, acute coronary syndromes; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non–Insulin-Dependent Diabetes Mellitus; A to Z, Aggrastat to Zocor; CARDs, Collaborative Atorvastatin Diabetes Study; CHD, coronary heart disease; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; CVD, cardiovascular disease; GISSI-HF, SEARCH Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; GISSI Prevenzione, Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza cardiaca Prevenzione; GREACE, Greek Atorvastatin and Coronary Heart Disease Evaluation; HPS, Heart Protection Study; hsCRP, high-sensitivity C-reactive protein; IDEAL, Incremental Decrease in Events Through Aggressive Lipid Lowering; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C, low-density lipoprotein cholesterol; LIPID, Long-term Intervention With Pravastatin in Ischaemic Disease; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study Group; MI, myocardial infarction; NA, not available; NR, not reported (no triglycerides inclusion or exclusion criteria specified); PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; PROVE-IT TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy; TNT, Treating to New Targets; WOSCOPS, West of Scotland Coronary Prevention Study; 4S, Scandinavian Simvastatin Survival Study.

SI conversion factors: To convert triglyceride values mmol/L, multiply by 0.0113; to convert hsCRP values to nmol/L, multiply by 9.524.

aMedian or median (interquartile range).
bAverage difference over 5 years.
cDifference at end of trial.
dDifference at 3 months.

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Table 2. Baseline Data From Trials Comparing Fibrate Therapy With Placebo

<table>
<thead>
<tr>
<th>Source</th>
<th>No. Treatment, Active/Control</th>
<th>Follow-up, y</th>
<th>Trial Population (Triglyceride Inclusion Criteria)</th>
<th>Age, y</th>
<th>Baseline, Mean (SD), mg/dL</th>
<th>Difference at 1 y, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Drug Project, 1975</td>
<td>1103</td>
<td>Clofibrate/placebo</td>
<td>6.2 Male, previous MI (NR)</td>
<td>46</td>
<td>184</td>
<td>25</td>
</tr>
<tr>
<td>WHO-COOP, 1978</td>
<td>5331</td>
<td>Clofibrate/placebo</td>
<td>5.3 Male, upper third of cholesterol range (NR)</td>
<td>46</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>HHS, 1987</td>
<td>2362</td>
<td>Gemfibrozil/placebo</td>
<td>5.0 Male, no CHD or possible symptoms of CHD (NR)</td>
<td>47</td>
<td>177 (119)</td>
<td>35</td>
</tr>
<tr>
<td>VA-HIT, 1999</td>
<td>1264</td>
<td>Gemfibrozil/placebo</td>
<td>5.1 Male, CHD (triglycerides ≤300 mg/dL)</td>
<td>64</td>
<td>161 (68)</td>
<td>31</td>
</tr>
<tr>
<td>BIP, 2000</td>
<td>1548</td>
<td>Bezafibrate/placebo</td>
<td>6.2 Previous MI or stable angina (triglycerides ≤300 mg/dL)</td>
<td>60</td>
<td>145 (51)</td>
<td>21</td>
</tr>
<tr>
<td>FIELD, 2005</td>
<td>4896</td>
<td>Fenofibrate/placebo</td>
<td>5.0 Diabetes mellitus, not taking statin (triglycerides 89-445 mg/dL)</td>
<td>62</td>
<td>174 (78)</td>
<td>30</td>
</tr>
<tr>
<td>ACCORD Lipid, 2010</td>
<td>2765</td>
<td>Simvastatin + fenofibrate/ simvastatin + placebo</td>
<td>4.7 Diabetes mellitus, CVD or risk factors (triglycerides &lt;750 mg/dL with no lipid-lowering therapy; &lt;400 mg/dL with therapy)</td>
<td>62</td>
<td>162 (113-229)</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>19 268</td>
<td>20 894</td>
<td>5.3 (0.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; BIP, Bezafibrate Infarction Prevention; CHD, coronary heart disease; CVD, cardiovascular disease; FIELD, Fibrate Intervention and Event Lowering in Diabetes; HHS, Helsinki Heart Study; MI, myocardial infarction; NA, not available; NR, not reported (no triglycerides inclusion or exclusion criteria specified); VA-HIT, Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial; WHO-COOP, World Health Organization Co-operative Trial.

SI conversion factor: To convert triglyceride values to mmol/L, multiply by 0.0113.

aMedian or median (interquartile range).

bOnly fatal cases of pancreatitis available.

Includes cases from both the HHS and its ancillary study (age, baseline triglyceride levels, and % difference in triglyceride levels are weighted means).

Includes cases across the trial and during first year after the trial.

¢Average difference during trial.

Diseases classifications (10th revision: K85, K86.0, K86.1; ninth revision: 577.0, 577.1), according to the preference of each trial’s investigators. All reports of pancreatitis were included, regardless of suggested etiology (information regarding alcohol intake was not available) or whether the condition was described as acute, chronic, or neither, based on the rationale that such additional data may have been largely absent or variably reported across trials.

Statistical Analysis

To identify potential associations of lipid-modifying therapies with the risk of developing pancreatitis, we calculated risk ratios (RRs) as the ratio of cumulative incidence and 95% CIs from the available data for all trial participants at baseline and for those who developed pancreatitis during trial follow-up. Study-specific RRs were pooled using a random-effects model meta-analysis as the preferable approach to manage potential between-study heterogeneity that may have been introduced by the differing methods for identifying participants with incident pancreatitis available in the trials and different trial populations. For trials with no events with randomized or control therapy, a nominal amount (0.5 cases) was added to the results for both trial groups.

Statistical heterogeneity across studies was quantified using both the χ² (or Cochran Q statistic) and I² statistics, with P > .10 considered statistically nonsignificant. The I² statistic is derived from the Q statistic [(Q − df/Q) × 100] and provides a measure of the proportion of the overall variation attributable to between-study heterogeneity.17

Placebo- and standard care–controlled statin trials plus intensive-dose/moderate-dose statin trials were analyzed both separately (with comparison of analyses by fixed-effect inverse-variance method) and in a combined analysis. In sensitivity analyses, only trials with previously published pancreatitis data were examined; fixed-effects model meta-analyses were also performed. We assessed the potential for publication bias through formal statistical testing, namely, funnel plots and Egger tests. To evaluate the potential relationship between the associations of lipid-modifying agents with incident pancreatitis and relative reductions in triglyceride levels achieved at 1 year using statins and fibrates, respectively, random-effects meta-regression analyses were performed.

All P values were 2-sided, and P < .05 was considered statistically significant for the meta-analyses and meta-regression analyses. Analyses were conducted using Stata version 10.1 (StataCorp).

RESULTS

Statin Therapy and Pancreatitis

Twenty-one randomized clinical trials of statin therapy, 2 with published data regarding incident pancreatitis and 19 with unpublished data, provided data on 153 414 participants over a weighted mean follow-up period of 4.3 (SD, 1.6) years. Baseline average triglyceride levels in the trials varied from 118 mg/dL to 187 mg/dL. Trials were of high quality, with a median Jadad score of 5 (range, 3–5) and 100% agreement between reviewers.

In 16 placebo- and standard care–controlled statin trials with 113 800 participants conducted over 4.1 (SD, 1.5) years, 309 participants (0.27%) developed pancreatitis (134 assigned to statin, 175 assigned to control) (RR, 0.77 [95% CI, 0.62-0.97; P = .03]) (Table 1, FIGURE 2). This represents a number needed to treat...
of 1175 (95% CI, 693-9195) over 5 years. There was limited heterogeneity between trials for incident pancreatitis ($\chi^2=9.11; I^2=0\%$).

In 5 dose-comparison statin trials with 39 614 participants conducted over 4.8 (SD, 1.7) years, 156 participants (0.39%) developed pancreatitis (70 assigned to intensive dose, 86 assigned to moderate dose) (RR, 0.82 [95% CI, 0.59-1.12; $P=.21$]) (Table 1, Figure 2). There was again limited heterogeneity between these trials for incident pancreatitis ($\chi^2=1.70; I^2=0\%$).

There was no evidence of statistical heterogeneity between the analyses of placebo-controlled trials and intensive-dose/moderate-dose trials ($P=.86$; RR, 0.82 [95% CI, 0.59-1.12]). There was no evidence of publication bias ($P=.83$) (eFigure 2A).

Using a fixed-effects model approach produced results (RR, 0.79 [95% CI 0.65-0.95; $P=0.01$]) identical to those of the random-effects model. In a sensitivity analysis of only the 2 trials with unpublished data,22,36 122 participants (37% of those assigned to fibrate therapy) developed pancreatitis (52/16 300 assigned to statin therapy or intensive-dose therapy, 70/16 300 assigned to placebo or moderate-dose statin therapy) (RR, 0.74 [95% CI, 0.52-1.07; $P=.11$; $\chi^2=0.30; I^2=0\%$]).

**Fibrate Therapy and Pancreatitis**

Seven randomized clinical trials of fibrate therapy (4 with published data and 3 with unpublished data regarding incident pancreatitis) provided data on 40 162 participants over a weighted mean follow-up period of 5.3 (SD, 0.5) years. Baseline average triglyceride levels in the trials varied from 145 mg/dL to 184 mg/dL. Trials were of high quality, with a median Jadad score of 5 (range, 5-5) and 100% agreement between reviewers. During this time, 144 participants (36%) developed pancreatitis (84 assigned to fibrate therapy, 60 assigned to placebo) (RR, 1.39 [95% CI, 1.00-1.95; $P=.053$]) (Table 2, Figure 3). This represents a number needed to harm...
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Figure 3. Meta-analysis of Incident Pancreatitis in 7 Large Fibrate Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>Fibrates Cases</th>
<th>Control Cases</th>
<th>Weight, %</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Drug Project, 1975</td>
<td>0</td>
<td>1103</td>
<td>1.11</td>
<td>1.00 (0.05-20.71)</td>
</tr>
<tr>
<td>WHO-COPP, 1978</td>
<td>3</td>
<td>5331</td>
<td>1.29</td>
<td>6.95 (0.36-134.66)</td>
</tr>
<tr>
<td>HHS, 1987</td>
<td>3</td>
<td>2362</td>
<td>5.89</td>
<td>0.50 (0.12-1.95)</td>
</tr>
<tr>
<td>VA-HIT, 1989</td>
<td>1</td>
<td>1264</td>
<td>1.47</td>
<td>1.00 (0.06-16.04)</td>
</tr>
<tr>
<td>BIP, 2000</td>
<td>6</td>
<td>1548</td>
<td>8.62</td>
<td>1.00 (0.32-3.10)</td>
</tr>
<tr>
<td>Field, 2005</td>
<td>40</td>
<td>4895</td>
<td>142.83</td>
<td>1.74 (1.04-2.91)</td>
</tr>
<tr>
<td>ACCORD Lipid, 2010</td>
<td>31</td>
<td>2765</td>
<td>38.59</td>
<td>1.34 (0.78-2.31)</td>
</tr>
<tr>
<td>Overall: F = 0.0%, P = .61</td>
<td></td>
<td>100.00</td>
<td>1.39</td>
<td>1.00-1.95</td>
</tr>
</tbody>
</table>

For abbreviations, see Table 2. Size of data markers indicates relative weight of the study (from random-effects analysis).

COMMENT

This report of pooled randomized trial data demonstrates that use of statin therapy was associated with a reduction in the number of patients developing pancreatitis. Broadly similar results were obtained for statin compared with placebo as well as for intensive-dose statin therapy compared with moderate-dose therapy, in keeping with a dose-dependent association. However, we did not demonstrate an association between use of fibrate therapy and risk of pancreatitis.

Previously published case reports and observational pharmacoepidemiologic studies have demonstrated an association between statin therapy and increased risk of pancreatitis.1-4 However, such analyses are susceptible to bias by unmeasured confounders and to confounding by indication. The present analysis, however, indicates that statin therapy may be associated with a reduced risk of pancreatitis overall. Although we cannot completely exclude the possibility that statin therapy may lead to very occasional idiosyncratic cases of pancreatitis, the randomized trial data appear reassuring. Unlike fibrates, statins are not known to increase the risk of developing gallstones.48 Studies showing both a reduction in bile cholesterol levels and an association with reduced risk of gallstones with statin therapy suggest the possibility of a protective effect.6,49 Furthermore, studies conducted in animal models suggest that statin therapy may be beneficial in both established acute pancreatitis and chronic pancreatitis.50-52

Major guidelines of lipid-modifying therapy such as the National Cholesterol Education Program Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP III) and the National Institute for Health and Clinical Excellence (NICE) Type 2 Diabetes guideline6 suggest the addition of fibrate therapy in patients with moderately elevated triglyceride levels and above (>400 mg/dL and >500 mg/dL, respectively). This is based on the rationale that hypertriglyceridemia is a well-recognized cause of pancreatitis and that lowering of triglyceride levels should be clinically beneficial.7 However, no convincing trial data exist to support use of any agents for prevention of pancreatitis in this clinical situation. Participants in the Coronary Drug Project assigned to clofibrate were at 50% higher risk of developing cholelithiasis or cholecystitis than those receiving placebo,13 and gallstones are a well-recognized cause of pancreatitis. In addition, it has been demonstrated in small clinical studies that both fenofibrate—a fibrate thought less likely to cause gallstones—and bezafibrate increase the cholesterol content of bile, thereby theoretically increasing the risk of developing gallstones.14,53 Following the Coronary Drug Project, other large fibrate trials did not find a significant increase in the incidence of gallbladder disease, although the total number of cases was small.50-52 Our analysis did not demonstrate an association between fibrate therapy and risk of pancreatitis, although the analysis may have lacked statistical power to show an increased risk in patients with slightly elevated triglyceride levels (the range at baseline in the trials we examined was 145-184 mg/dL). It remains possible, however, that fibrates might have a different net effect in patients with higher triglyceride levels.

Although the present results for both statins and fibrates should be considered hypothesis-generating and the number of pancreatitis cases was small in this trial population at low risk of pancreatitis, the analysis raises questions regarding the choice of lipid-modifying agents in pa-
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patients with hypertriglyceridemia. In those with slightly elevated triglyceride levels, statins appear better supported by the available data than fibrates for preventing pancreatitis. Lifestyle modifications also remain important to improve lipid profiles in such individuals. In patients with severe hypertriglyceridemia, a trial comparing fibrates and statins for preventing pancreatitis would be clinically valuable.

Strengths of this meta-analysis are that the analysis was conducted using data from randomized trials, which avoids most of the potential bias of unmeasured confounders encountered in observational studies, and that we were able to include data from almost all of the relevant trials, both published and unpublished, thereby maximizing power and providing the best answer possible with existing data.

This meta-analysis also has several limitations. First, pancreatitis was not a pre-specified end point in the trials, which were primarily designed to assess the effect of lipid-modifying therapy on cardiovascular events. However, limited statistical heterogeneity between trial results for statins and fibrates, plus evidence of a dose-dependent association for statins, provides confidence in the findings. Second, the occurrence of pancreatitis was not recorded in a standardized way, with resultant variation between trials. Therefore, these results, especially for fibrate therapy when there were relatively few events dominated by 2 trials, should be interpreted with caution.

Third, because it was felt unlikely that the cause of pancreatitis would have been consistently recorded in an accurate way across trials, we were unable to examine specific causes such as gallstones. Likewise, we were unable to separate reports of pancreatitis into acute and chronic cases. However, given that the majority of trials used the presence of hepatobiliary disease as an exclusion criterion, it is highly likely that the majority of cases included in this report represent de novo acute pancreatitis. This is supported by evidence from SHARP. Fourth, we did not have access to individual-participant data, which may have reduced our ability to identify any relationship with the extent of triglyceride lowering. Fifth, because the trials tended to exclude participants with marked hypertriglyceridemia, these findings may not necessarily be generalizable to that specific group of patients.

In summary, pooled analyses of randomized trial data suggest that statin therapy is associated with a reduction in the risk of pancreatitis in patients with normal or mildly elevated triglyceride levels.

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Author Contributions: Dr Preiss had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Preiss, Tikkanen, McMurray. Acquisition of data: Preiss, Tikkanen, Ford, Lovato, Elam, LaRosa, Demicco, Colhoun, Goldenberg, Pedersen, Keech, Ridker, Kjekshus, McMurray. Analysis and interpretation of data: Preiss, Tikkanen, Welsh, LaRosa, Demicco, Colhoun, Goldenberg, Murphy, MacDonald, Keech, Ridker, Sattar, McMurray. Drafting of the manuscript: Elam, LaRosa, Sattar, McMurray. Critical revision of the manuscript for important intellectual content: Preiss, Tikkanen, Welsh, Ford, Lovato, Elam, LaRosa, Demicco, Colhoun, Goldenberg, Murphy, MacDonald, Pedersen, Keech, Ridker, Kjekshus, McMurray. Statistical analysis: Preiss. Obtained funding: Pedersen. Administrative, technical, or material support: Welsh, Ford, Demicco, Goldenberg, Keech, Ridker. Study supervision: Ford, LaRosa, Pedersen, Sattar, McMurray.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. The majority of trials discussed in this article were funded partly or wholly by industry, and the following authors have received honoraria from Abbott/Solvay, Merck Schering Plough, and Pfizer: Ford, Pedersen, and McMurray. The remaining authors have no disclosures.

The majority of trials included in this meta-analysis were funded partly or wholly by industry. Dr Ford reports receiving consulting fees from Pfizer and AstraZeneca and participating in clinical trials funded by Pfizer. Dr Colhoun reported receiving honoraria for advisory board participation and speaking fees from Pfizer. Dr DeMicco reported receiving speakers honoraria, consulting fees, or research grants from Merck, AstraZeneca, AMGEN, Roche, and Novartis. Dr Keech reported receiving honoraria and research or travel grants from Abbott, Merck Sharpe & Dohme, Bristol-Myers Squibb, Novartis, Eli Lilly, Pfizer, Roche Diagnostics, Solvay, and AstraZeneca. Dr Ridker reported receiving research grant support from AstraZeneca and Novartis, receiving consulting fees from Merck, Genzyme, Vascular Bio- genics, ISIS, and Boston Diagnostics; and being listed as a co-inventor on patents held by the Brigham and Women’s Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to AstraZeneca and Siemens. Dr Sattar reported consulting for and receiving lecture fees from Merck, Pfizer, and AstraZeneca and receiving research grant support from Pfizer. No other authors reported disclosures.

Funding/Support: This project was not supported by external funding. Dr Welsh is supported by British Heart Foundation fellowship grant FS/10/005/28147. Role of the Sponsor: The British Heart Foundation had no role in the design and conduct of the study, the collection, analysis, and interpretation of data, or the preparation, review, or approval of the manuscript.


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