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

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P ANCREATITIS HAS A CLINICAL spectrum ranging from a mild, self-limiting episode to a severe or fatal event. Case reports and pharmacoepidemiologic studies have claimed that statins may cause pancreatitis,[1-4] although few of these studies comprehensively considered confounding factors. Very few large randomized trials of statin therapy have published data on incident pancreatitis. Recently reported data from the Study of Heart and Renal Protection (SHARP), a trial comparing combination therapy of simva-

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statin and ezetimibe with placebo on cardiovascular events in patients with chronic kidney disease, demonstrated a reduction in pancreatitis cases in patients receiving simvastatin and ezetimibe, suggesting a possible protective association.[5] In addition, statins reduce bile

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 Unpublished data were obtained from investigators (22 trials).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 I^2 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; $P=.03$; $I^2=0\%$]). 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; $P=.21$; $I^2=0\%$]). Combined results for all 21 statin trials provided RR 0.79 (95% CI, 0.65-0.95; $P=.01$; $I^2=0\%$). 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; $P=.053$; $I^2=0\%$]).

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.

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cholesterol content,[6] 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.[7] This has led to major guidelines for lipid-modifying therapies, including advice to commence triglyceride-lowering therapy, usually fibrates, in persons with moderate and severe hypertriglyceridemia (above 400 to 500 mg/dL [to convert to mmol/L, multiply by 0.0113]).[8,9] However, high-quality evidence for this approach is lacking, and only observational data exist.[10,11] Indeed, there is concern that fibrates might increase the risk of pancreatitis in individuals with triglyceride levels lower than those mentioned in guidelines.[12] Fibrates increase the cholesterol concentration in bile and may increase the risk of gallstones.[13,14] 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.[15] 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[5,16-36] (TABLE 1) and 7 fibrate trials[12,37-43] (TABLE 2) were included in the analyses. Because unpublished data were made available for both the Helsinki Heart Study[40] and its smaller ancillary study[44] conducted in similar groups of participants randomized to the same therapies over the same follow-up times, these results were combined as a single overall study.

Data Sources

Published data for incident pancreatitis were available from 2 statin trials[5,22,36] and 4 fibrate trials.[12,37-39,41] Unpublished data were collected from 19 statin trials[16-21,23-35] and 3 fibrate trials.[40,42,43] 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 lev-

Figure 1. Literature Search
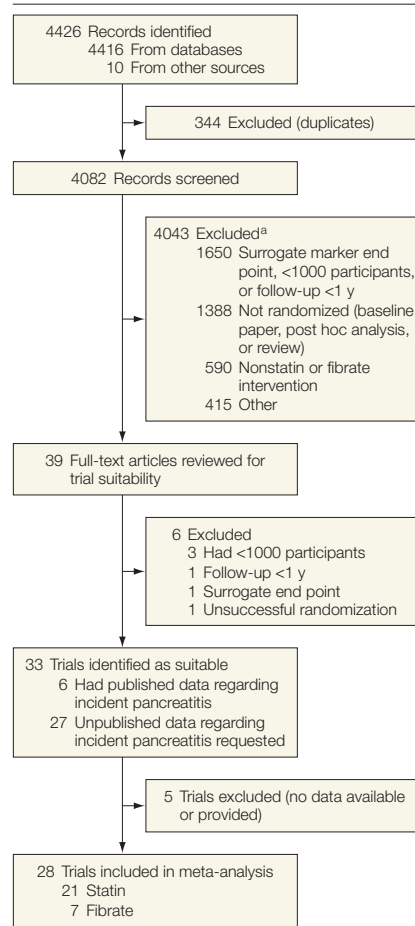
els at 1 year. A PRISMA checklist was provided to the journal at the time of manuscript submission.[45]

Quality Assessment

Two authors (D.P., P.W.) used an established tool, the Jadad score, to independently evaluate the quality of each trial.[46] 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

was recorded as an adverse event or serious adverse event. This information was identified using different approaches across the trials,[1] namely text word searches of adverse event reports, including self-reported hospitalization data, for *pancreatitis*[2]; Medical Dictionary for Regulatory Activities event classification[3]; and *International Classification of*

Table 1. Baseline Data From 21 Large Statin Trials

Source	No. Statin	No. Control	Treatment, Active/Control	Follow-up, y	Trial Population (Triglyceride Inclusion Criteria)	Age, y	Triglycerides Baseline, Mean (SD), mg/dL	Triglycerides Difference at 1 y, %
Placebo- and Standard Care–Controlled Trials								
4S,[16] 1994	2223	2221	Simvastatin (10-40 mg)/placebo	5.4[a]	Angina or previous MI (triglycerides ≤222 mg/dL)		134 (45)	18
WOSCOPS,[17] 1995	3302	3293	Pravastatin (40 mg)/placebo	4.9	Male, hypercholesterolemia, no history of MI (NR)	55	164 (69)	15
CARE,[18] 1996	2081	2078	Pravastatin (40 mg)/placebo	5.0[a]	MI in previous 3-20 mo (triglycerides <350 mg/dL)	59	156 (61)	14[b]
AFCAPS/TexCAPS,[19] 1998	3304	3301	Lovastatin (20-40 mg)/placebo	5.2	Average cholesterol levels, no CVD (triglycerides ≤400 mg/dL)	58	181 (75)	14
LIPID,[20] 1998	4512	4502	Pravastatin (40 mg)/placebo	6.1	Hospitalization for unstable angina or previous MI (triglycerides <445 mg/dL)	62[a]	140[a]	11[b]
GISSI Prevenzione,[21] 2000	2138	2133	Pravastatin (20 mg)/standard care	2.0[a]	Recent MI (NR)		166 (89)	−4
HPS,[5,22] 2002	10 269	10 267	Simvastatin (40 mg)/placebo	5.4	CVD or diabetes (NR)	65	187 (125)	19
PROSPER,[23] 2002	2891	2913	Pravastatin (40 mg)/placebo	3.3	Age 70-82 y with CVD or risk factors (triglycerides <534 mg/dL)	75	138 (62)	17
GREACE,[24] 2002	800	800	Atorvastatin (to achieve LDL-C <100 mg/dL)/standard care	3.0	CHD (triglycerides <400 mg/dL)	59	181	28
ASCOT-LLA,[25] 2003	5168	5137	Atorvastatin (10 mg)/placebo	3.3[a]	Hypertension, no CHD (triglycerides ≤400 mg/dL)	63	147 (80)	23
CARDS,[26] 2004	1428	1410	Atorvastatin (10 mg)/placebo	3.9[a]	Type 2 diabetes mellitus, no CVD (triglycerides ≤603 mg/dL)	62	173 (97)	21
ASPEN,[27] 2006	1211	1199	Atorvastatin (10 mg)/placebo	4.0	Diabetes mellitus (triglycerides ≤600 mg/dL)	61	146[a]	14[c]
MEGA,[28] 2006	3866	3966	Pravastatin (10-20 mg)/no treatment	5.3	Hypercholesterolemia, no previous CHD or stroke (NR)	58	148 (83)	6
CORONA,[29] 2007	2514	2497	Rosuvastatin (10 mg)/placebo	2.7[a]	Systolic heart failure (NR)	73	178 (114)	24[d]
JUPITER,[30] 2008	8901	8901	Rosuvastatin (20 mg)/placebo	1.9[a]	No CVD, no diabetes, hsCRP ≥2.0 mg/L (triglycerides <500 mg/dL)	66[a]	118 (86-169)[a]	17
GISSI-HF,[31] 2008	2285	2289	Rosuvastatin (10 mg)/placebo	3.9[a]	Chronic heart failure (NR)	68	NA	NA
Intensive- vs Moderate-Dose Trials								
PROVE-IT TIMI 22,[32] 2004	2099	2063	Pravastatin (40 mg)/atorvastatin (80 mg)	2.0	Recent hospitalization for ACS (NR)	58	156[a]	21[a]
A to Z,[33] 2004	2265	2234	Placebo + simvastatin (20 mg)/simvastatin (40-80 mg)	2.0[a]	Recent hospitalization for ACS (NR)	61[a]	149 (116-199)[a]	6
TNT,[34] 2005	4995	5006	Atorvastatin (80 mg)/atorvastatin (10 mg)	4.9[a]	Stable CHD (triglycerides ≤600 mg/dL)	61	151 (71)	NA
IDEAL,[35] 2005	4439	4449	Atorvastatin (80 mg)/simvastatin (20-40 mg)	4.8[a]	Previous MI (triglycerides ≤600 mg/dL)	62	149	23
SEARCH,[5,36] 2010	6031	6033	Simvastatin (80 mg)/simvastatin (20 mg)	6.7	Previous MI (NR)	64	169 (107)	9
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.
[a] Median or median (interquartile range).
[b] Average difference over 5 years.
[c] Difference at end of trial.
[d] Difference at 3 months.

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

Source	No. Fibrate	No. Control	Treatment, Active/Control	Follow-up, y	Trial Population (Triglyceride Inclusion Criteria)	Age, y	Triglycerides Baseline, Mean (SD), mg/dL	Triglycerides Difference at 1 y, %
Coronary Drug Project,[37,38] 1975[b]	1103	2789	Clofibrate/placebo	6.2	Male, previous MI (NR)		184	25
WHO-COOP,[39] 1978[b,d]	5331	5296	Clofibrate/placebo	5.3	Male, upper third of cholesterol range (NR)	46	NA	NA
HHS,[40,44] 1987[c]	2362	2347	Gemfibrozil/placebo	5.0	Male, no CHD or possible symptoms of CHD (NR)	47	177 (119)	35
VA-HIT,[41] 1999[b]	1264	1267	Gemfibrozil/placebo	5.1[a]	Male, CHD (triglycerides ≤300 mg/dL)	64	161 (68)	31
BIP,[42] 2000	1548	1542	Bezafibrate/placebo	6.2	Previous MI or stable angina (triglycerides ≤300 mg/dL)	60	145 (51)	21[e]
FIELD,[12] 2005	4895	4900	Fenofibrate/placebo	5.0[a]	Diabetes mellitus, not taking statin (triglycerides 89-445 mg/dL)	62	174 (78)	30
ACCORD Lipid,[43] 2010	2765	2753	Simvastatin + fenofibrate/ simvastatin + placebo	4.7	Diabetes mellitus, CVD or risk factors (triglycerides <750 mg/dL with no lipid-lowering therapy; <400 mg/dL with therapy)	62	162 (113-229)[a]	20
Total	19 268	20 894		5.3 (0.5)				

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; BIP, Bezafibrate Infarction Prevention; CHD, coronary heart disease; CVD, cardiovascular disease; FIELD, Fenofibrate 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.
[a] Median or median (interquartile range).
[b] Only fatal cases of pancreatitis available.
[c] Includes cases from both the HHS and its ancillary study (age, baseline triglyceride levels, and % difference in triglyceride levels are weighted means).
[d] Includes cases during the trial and during first year after the trial.
[e] 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 χ^2 (or Cochran Q statistic) and I^2 statistics, with $P > .10$ considered statistically nonsignificant. The I^2 statistic is derived from the Q statistic ($[Q - df/Q] \times 100$) and provides a measure of the proportion of the overall variation attributable to between-study heterogeneity.[47]

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 ($\chi^2 = 1.29$; $I^2 = 0\%$).

There was no evidence of statistical heterogeneity between the analyses of placebo-controlled trials and intensive-dose/moderate-dose trials ($P = .79$ for interaction).

In the combined data set of 21 trials, 465 participants (0.30%) developed pancreatitis (of whom 204 were assigned to statin therapy or intensive-dose statin therapy and 261 were assigned to placebo, standard care, or moderate-dose statin therapy, respectively) (RR, 0.79 [95% CI, 0.65-0.95; $P = .01$; $\chi^2 = 10.48$; $I^2 = 0\%$]) (Table 1, Figure 2). This represents a number needed to treat of 1187 (95% CI, 731-4768) over 5 years. There was no evidence of publication bias ($P = .83$) (eFigure 1A, available at http://jama.com). Meta-regression analysis found no relationship across the trials between risk of pancreatitis and reduction in triglyceride levels at 1 year, although this analysis was of limited value given the limited statistical heterogeneity between trial-specific RRs ($P = .23$) (eFigure 2A).
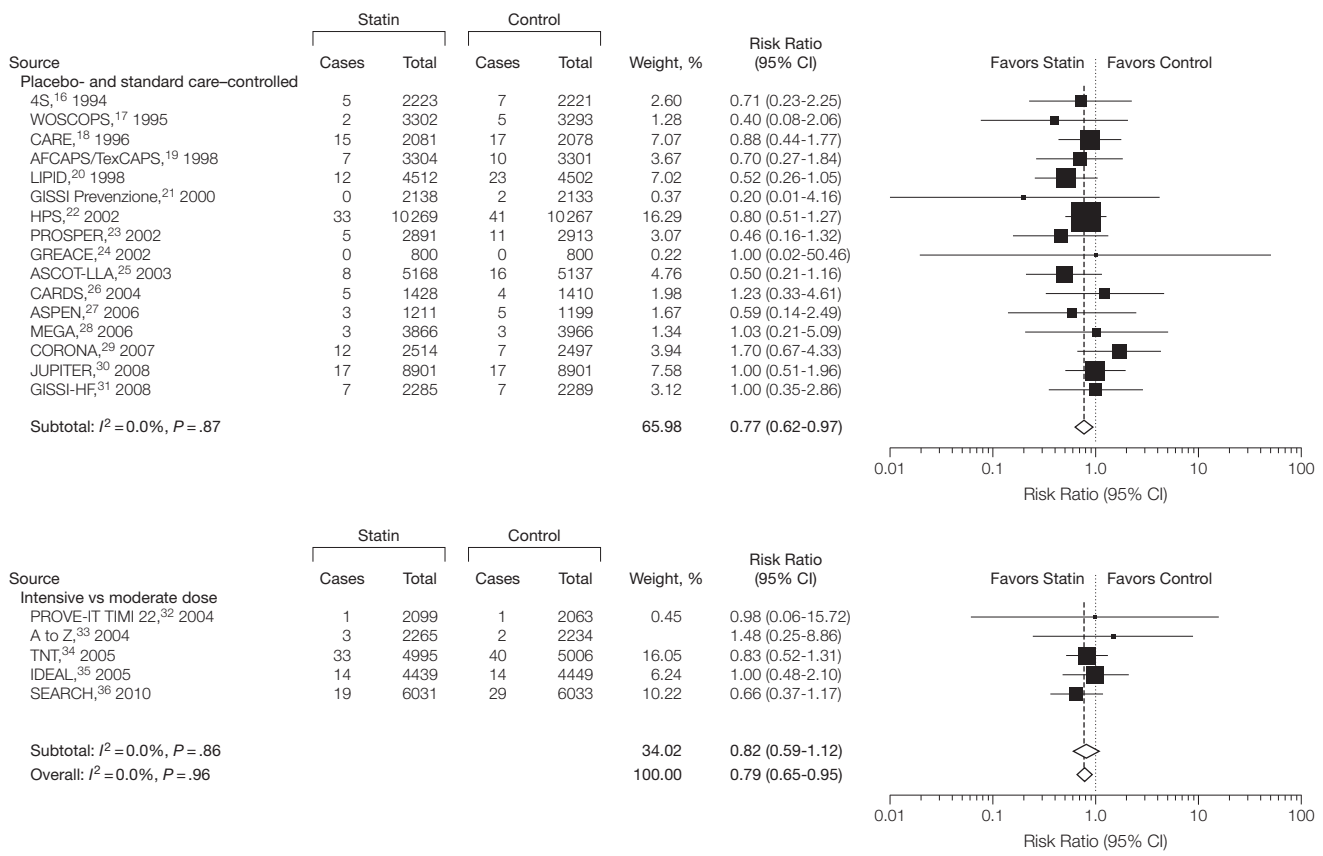
Using a fixed-effects model approach produced results (RR, 0.79 [95% CI 0.65-0.95; $P = .01$]) identical to those of the random-effects model. In a sensitivity analysis of only the 2 trials with published data,[22,36] 122 participants (0.37%) developed pancreatitis (52/

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; $P = .11$; $\chi^2 = 0.30$; $I^2 = 0\%$]).
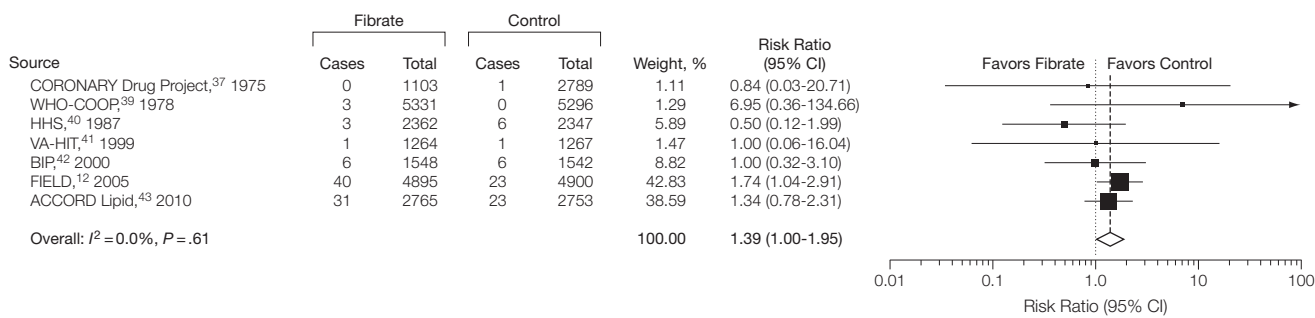
Fibrate Therapy and Pancreatitis

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 (0.36%) 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 2. Meta-analysis of Incident Pancreatitis in 21 Large Statin Trials

Source	Statin Cases	Statin Total	Control Cases	Control Total	Weight, %	Risk Ratio (95% CI)
Placebo- and standard care–controlled						
4S,[16] 1994	5	2223	7	2221	2.60	0.71 (0.23-2.25)
WOSCOPS,[17] 1995	2	3302	5	3293	1.28	0.40 (0.08-2.06)
CARE,[18] 1996	15	2081	17	2078	7.07	0.88 (0.44-1.77)
AFCAPS/TexCAPS,[19] 1998	7	3304	10	3301	3.67	0.70 (0.27-1.84)
LIPID,[20] 1998	12	4512	23	4502	7.02	0.52 (0.26-1.05)
GISSI Prevenzione,[21] 2000	0	2138	2	2133	0.37	0.20 (0.01-4.16)
HPS,[22] 2002	33	10269	41	10267	16.29	0.80 (0.51-1.27)
PROSPER,[23] 2002	5	2891	11	2913	3.07	0.46 (0.16-1.32)
GREACE,[24] 2002	0	800	0	800	0.22	1.00 (0.02-50.46)
ASCOT-LLA,[25] 2003	8	5168	16	5137	4.76	0.50 (0.21-1.16)
CARDS,[26] 2004	5	1428	4	1410	1.98	1.23 (0.33-4.61)
ASPEN,[27] 2006	3	1211	5	1199	1.67	0.59 (0.14-2.49)
MEGA,[28] 2006	3	3866	3	3966	1.34	1.03 (0.21-5.09)
CORONA,[29] 2007	12	2514	7	2497	3.94	1.70 (0.67-4.33)
JUPITER,[30] 2008	17	8901	17	8901	7.58	1.00 (0.51-1.96)
GISSI-HF,[31] 2008	7	2285	7	2289	3.12	1.00 (0.35-2.86)
Subtotal: $I^2 = 0.0\%$, $P = .87$					65.98	0.77 (0.62-0.97)

Source	Statin Cases	Statin Total	Control Cases	Control Total	Weight, %	Risk Ratio (95% CI)
Intensive vs moderate dose						
PROVE-IT TIMI 22,[32] 2004	1	2099	1	2063	0.45	0.98 (0.06-15.72)
A to Z,[33] 2004	3	2265	2	2234		1.48 (0.25-8.86)
TNT,[34] 2005	33	4995	40	5006	16.05	0.83 (0.52-1.31)
IDEAL,[35] 2005	14	4439	14	4449	6.24	1.00 (0.48-2.10)
SEARCH,[36] 2010	19	6031	29	6033	10.22	0.66 (0.37-1.17)
Subtotal: $I^2 = 0.0\%$, $P = .86$					34.02	0.82 (0.59-1.12)
Overall: $I^2 = 0.0\%$, $P = .96$					100.00	0.79 (0.65-0.95)

For abbreviations, see Table 1. Size of data markers indicates relative weight of the study (from random-effects analysis).

Figure 3. Meta-analysis of Incident Pancreatitis in 7 Large Fibrate Trials

Source	Fibrate		Control		Weight, %	Risk Ratio (95% CI)
	Cases	Total	Cases	Total		
CORONARY Drug Project,[37] 1975	0	1103	1	2789	1.11	0.84 (0.03-20.71)
WHO-COOP,[39] 1978	3	5331	0	5296	1.29	6.95 (0.36-134.66)
HHS,[40] 1987	3	2362	6	2347	5.89	0.50 (0.12-1.99)
VA-HIT,[41] 1999	1	1264	1	1267	1.47	1.00 (0.06-16.04)
BIP,[42] 2000	6	1548	6	1542	8.82	1.00 (0.32-3.10)
FIELD,[12] 2005	40	4895	23	4900	42.83	1.74 (1.04-2.91)
ACCORD Lipid,[43] 2010	31	2765	23	2753	38.59	1.34 (0.78-2.31)
Overall: I^2=0.0%, P=.61					100.00	1.39 (1.00-1.95)

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

of 935 (95% CI, 388 to >50 000) over 5 years. There was limited heterogeneity between trials for incident pancreatitis (χ^2=4.48; I^2=0%). Likewise, there was no evidence of publication bias (P=.59) (eFigure 1B). Meta-regression analysis found no relationship across the trials between risk of pancreatitis and reduction in triglyceride levels at 1 year across the trials (P=.81) (eFigure 2B), although this analysis was of limited value given the limited statistical heterogeneity between trial-specific RRs and the similar relative reductions in triglyceride levels achieved across the trials.

Using a fixed-effects model approach produced results identical to those achieved using the random-effects model (RR, 1.39 [95% CI, 1.00-1.95; P=.053]). In a sensitivity analysis of only the 4 trials with published data,[12,37,39,41] 69 participants (0.26%) developed pancreatitis (44/12 593 assigned to fibrate therapy, 25/14 252 assigned to placebo) (RR, 1.75 [95% CI, 1.07-2.86; P=.03; χ^2=1.19; I^2=0%]).

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)[8] and the National Institute for Health and Clinical Excellence (NICE) Type 2 Diabetes guideline[9] 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 hypertriglyc-

eridemia 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.[40,41,43] 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-

tients 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 prespecified 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,[12,43] 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.[5] 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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