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Lipid Modifying Therapies and the Risk of Pancreatitis: a Meta-Analysis

Short title: statins, fibrates and pancreatitis

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ABSTRACT

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

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

Data Sources: We identified relevant trials in literature searches of MEDLINE, EMBASE and Web of Science (1 January 1994 for statin trials, 1 January 1972 for fibrate trials through 9 June 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 Unpublished data were obtained from investigators (22 trials).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 and fibrate therapy, respectively. Studies with more than 1000 participants followed for over 1 year were included.

Data Extraction: Trial-specific data described numbers of participants developing pancreatitis and change in triglycerides at 1 year. We calculated trial-specific risk ratios (RR) and combined these 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 (standard deviation) follow-up of 4.1 (1.5) years, 309 developed pancreatitis (134 assigned statin, 175 assigned control), RR 0.77 (95% confidence intervals [CI], 0.62-0.97; p=0.027; I^2=0%). In 5 dose-comparison statin trials with 39,614 participants conducted over 4.8 (1.7) years, 156 developed pancreatitis (70 assigned intensive-dose statin, 86 assigned moderate-dose),

RR 0.82 (95% CI, 0.59-1.12; p=0.21; I^2=0%). Combined results for all 21 statin trials provided RR 0.79 (95% CI, 0.65-0.95; p=0.011; I^2=0%). In seven fibrate trials with 40,162 participants conducted over 5.3 (0.5) years, 144 developed pancreatitis (84 assigned fibrate therapy, 60 assigned placebo), RR 1.39 (95% CI 1.00-1.95; p=0.053; I^2=0%).

Conclusion: In a pooled analysis of randomized trial data, use of statin therapy was associated with a lower risk of pancreatitis.

INTRODUCTION

Pancreatitis is a condition with a clinical spectrum ranging from a mild, self-limiting episode to a severe or fatal event. Numerous case-reports and pharmaco-epidemiological studies have stated that statins may be associated with an increased incidence of pancreatitis(1-4) though few 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 simvastatin and ezetimibe with placebo on cardiovascular events in patients with chronic kidney disease, demonstrated a reduction in pancreatitis cases in those on simvastatin and ezetimibe suggesting a possible protective effect (5). In addition, statins reduce bile cholesterol content (6) which may theoretically reduce the risk of developing gallstones, a risk factor for pancreatitis.

Hypertriglyceridemia is the third most common cause of pancreatitis (7). Guidelines for lipid modifying therapies include advice to initiate triglyceride-lowering therapy, usually fibrates, in those with moderate and severe hypertriglyceridemia (above 400 to 500mg/dL) (8;9). However, high quality evidence for this approach is lacking and only observational data exist (10;11). In addition, some evidence suggests that fibrates may be associated with an increased risk of pancreatitis among patients with lower triglyceride levels than the threshold triglyceride level identified in published guidelines (12). Fibrates increase bile cholesterol concentration and may increase the risk of gallstones (13;14). However, few large randomized placebo-controlled trials of fibrate therapy have published data on pancreatitis.

Associations of statin and fibrate medications with pancreatitis are therefore uncertain. We examined the associations between statin and fibrate therapy, respectively, and the incidence of pancreatitis by conducting a collaborative meta-analysis of published and unpublished data from 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 vs. moderate-dose trials) and fibrate therapy, respectively, on cardiovascular events. Inclusion criteria were trials with 1000 or more participants exposed to randomized therapy with a minimum mean follow-up of one year as in previous large statin meta-analyses (15). This was based on the rationale that the large trials contained the vast majority of patient-years of follow-up and would be most likely to employ systematic collection of clinical endpoints and serious adverse events. We excluded trials conducted in patients with previous organ transplant or on hemodialysis, and trials comparing combination therapy to placebo. We searched MEDLINE, EMBASE and Web of Science databases with 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 also searched for additional studies. The Food and Drug Administration Agency website was also searched for trial reports containing relevant data. Abstracts, manuscripts and reports were reviewed independently by 2 readers (D.P. and P.W.) in an unblinded fashion. A third reviewer (N.S.) settled discrepancies. In the small number of trials where published data regarding incident pancreatitis and change in triglyceride levels were available, these data were tabulated. In the majority of trials where 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 seven fibrate trials (**Table 2**) (12;37-43) were included in the analyses. As 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 in one 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 arms in the trials and risk of pancreatitis, we collected data on average change in triglycerides at one year. A PRISMA checklist was provided to the journal at the time of manuscript submission (45).

Quality Assessment

Two authors (D.P. and 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, thereby allowing 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 a serious adverse event or adverse event. This information was identified using different approaches across the trials, namely (1) text word searches of adverse event reports, including self-reported data of hospitalization, for *pancreatitis*; (2) Medical Dictionary for Regulatory Activities (MedRa) event classification; (3) International Classification of Diseases (ICD) classifications ICD-10 (K85, K86.0, K86.1) or ICD-9 (577.0 and 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 (RR) as the ratio of cumulative

incidence and 95% CIs from the available data for all trial participants at baseline and 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. Statistical heterogeneity across studies was quantified using both the χ^2 (or Cochran Q statistic) and I^2statistics, with p>0.10 considered statistically non-significant. The I^2 statistic is derived from the Q statistic ([$Q-df/Q$]X100) 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 vs. moderate-dose statin trials, were analysed 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; and 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 one year on statins and fibrates respectively, random-effects meta-regression analyses were performed. All p values were 2-sided and p<0.05 was considered statistically significant for the meta-analyses and meta-regression analyses. Analyses were conducted using Stata version 10.1 (StataCorp, College Station, Texas).

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RESULTS

Statin therapy and pancreatitis

Twenty-one randomized clinical trials of statin therapy, two with published data regarding incident pancreatitis and 19 with unpublished data, provided data on 153,414 participants over a weighted mean (standard deviation [SD]) follow-up period of 4.3 (1.6) years. Baseline average triglyceride levels in the trials varied from 118 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 (0.27%) developed pancreatitis (134 assigned statin, 175 assigned control), RR 0.77 (95% CI, 0.62-0.97; p=0.027) (**Table 1**, **Figure 2**). This represents a number needed to treat (NNT) of 1175 (95% CI 693-9195) over 5 years. There was limited heterogeneity between statin trials for incident pancreatitis (χ^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 (0.39%) developed pancreatitis (70 assigned intensive-dose statin, 86 assigned moderate-dose), RR 0.82 (95% CI, 0.59-1.12; p=0.21) (**Table 1**, **Figure 2**). There was again limited heterogeneity between these trials for incident pancreatitis (χ^2=1.29; I^2=0%).

There was no evidence of statistical heterogeneity between the analyses of placebo-controlled trials and intensive vs. moderate- statin dose trials (p=0.79 for interaction).

In the combined dataset of 21 statin trials, 465 (0.30%) developed pancreatitis (204 of whom were assigned to statin therapy or intensive-dose statin therapy, 261 assigned to placebo, standard care or moderate-dose statin therapy respectively), RR 0.79 (95% CI, 0.65-0.95; p=0.011; χ^2=10.48; I^2=0%) (**Table 1**, **Figure 2**). This represents a NNT of 1187 (95% CI 731-4768) over 5 years. There was no evidence of publication bias (p=0.83; **eFigure 1A**). Meta-regression analysis found no relationship across the trials between risk of pancreatitis and reduction in triglyceride levels at one year though this analysis was of limited value given the limited statistical heterogeneity between trial-specific RRs (p=0.23; **eFigure 2A**).

Using a fixed-effects model approach produced identical results (RR 0.79, 95% CI 0.65-0.95; p=0.011) to the random-effects model. In a sensitivity analysis of only the two trials with published data (22;36), 122 (0.37%) developed pancreatitis (52 of 16,300 assigned to statin therapy or intensive-dose therapy, 70 of 16,300 assigned to placebo or moderate-dose statin therapy), RR 0.74 (95% CI 0.52-1.07; p=0.11; χ^2=0.30; I^2=0%).

Fibrate therapy and pancreatitis

Seven randomized clinical trials of fibrate therapy, four with published data and three with unpublished data regarding incident pancreatitis, provided data on 40,162 participants over a weighted mean (SD) follow-up period of 5.3 (0.5) years. Baseline average triglyceride levels in the trials varied from 145 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 (0.36%) developed pancreatitis (84 assigned fibrate therapy, 60 assigned placebo), RR 1.39 (95% CI 1.00-1.95; p=0.053) (**Table 2**, **Figure 3**). This represents a number needed to harm of 935 (95% CI 388- greater than 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=0.59; **eFigure 1B**). Meta-regression analysis found no relationship across the trials between risk of pancreatitis and reduction in triglyceride levels at one year across the trials (p=0.81; **eFigure 2B**) though this analysis was of limited value given the limited statistical heterogeneity between trial-specific RRs, and similar relative reductions in triglyceride levels achieved across the trials.

Using a fixed-effects model approach produced identical results to the random-effects model (RR 1.39, 95% CI 1.00-1.95; p=0.053). In a sensitivity analysis of only the four trials with published data (12;37;39;41), 69 (0.26%) developed pancreatitis (44 of 12,593 assigned to fibrate therapy, 25 of 14,252 assigned to placebo), RR 1.75 (95% CI 1.07-2.86; p=0.026; 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 both statin compared with placebo and 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 pharmaco-epidemiological 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 lower risk of pancreatitis overall. Though 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 associations between statin use and both a reduction in bile cholesterol and reduced risk of gallstones on statins suggest the possibility of a protective effect (6;49). Furthermore, studies conducted in animal models suggest the possibility that statin therapy may be associated with benefit for both 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 that fibrate therapy should be prescribed for patients with moderately elevated triglyceride levels and higher (>500mg/dL and >400mg/dL respectively). This is based on the rationale that hypertriglyceridemia is a well-recognized cause for pancreatitis and that lowering triglycerides should therefore be clinically beneficial

(7). However, no convincing trial data exist to support the hypothesis that fibrate therapy is associated with prevention of pancreatitis for patients with hypertriglyceridemia. Participants in the Coronary Drug Project assigned to clofibrate had a 50% higher incidence of cholelithiasis or cholecystitis than those on placebo (13) and gallstones are a well-known 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 are associated with a higher 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 though the total number of cases was small (40;41;43). Our analysis did not demonstrate an association between fibrate therapy and the risk of pancreatitis though we may have lacked statistical power to show an increased risk in patients with slightly elevated triglycerides (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 while the number of cases of pancreatitis was small in this trial population at low risk of pancreatitis, it raises questions regarding the choice of lipid modifying agents in hypertriglyceridemic patients. In those with slightly elevated triglycerides, statin therapy appears better supported by the available data than fibrates for preventing pancreatitis. Lifestyle modifications also remain important to improve lipid profiles in such individuals. In those patients with severe

hypertriglyceridemia, a trial comparing fibrates and statins for preventing pancreatitis would be clinically valuable.

Strengths of this meta-analysis include the following: first, the meta-analysis was conducted using data from randomized trials which avoids most of the potential bias of unmeasured confounders encountered in observational studies. Second we included data from almost all the relevant trials, both published and unpublished, thereby maximizing power and providing the best answer possible with existing data. Limitations include the following: first, pancreatitis was not a pre-specified endpoint 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, respectively, 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 where there were relatively few events which were dominated by two trials (12;43), should be interpreted with caution. Third, as 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 or alcohol. Data on alcohol use was not available. 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 exclusion criteria, 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 of therapy with

the extent of triglyceride lowering. And fifth, as 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

Study concept and design: Preiss, Tikkanen, McMurray

Acquisition of data: Preiss, Tikkanen, Lovato, Elam, LaRosa, DeMicco, Colhoun, Goldenberg, Ford, Pedersen, Keech, McMurray, Ridker, Kjekshus

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CONFLICTS OF INTEREST

The majority of trials in this manuscript were funded partly or wholly by industry and all authors except D.P., P.W., M.J.M., T.M.M. and N.S. were investigators in at least one trial. D.P., P.W., I.F., L.C.L., I.G., M.J.M., T.M.M., J.K., J.J.V.M. report no conflicts of interest. M.J.T. has received honoraria from Pfizer and consultant fees from Amgen Inc. M.B.E. has acted as Consultant and/or Speaker, for Abbott/Solvay, Merck Schering Plough and Pfizer Canada (Category 3). J.C.L. has received consultancy fees from Pfizer, and AstraZeneca and has participated in clinical trials funded by Pfizer. D.A.D. is a full time employee of Pfizer. H.M.C. has received honoraria for advisory board participation and speaker fees from Pfizer. T.R.P. has received speakers honoraria, consulting fees or research grants from Merck, AstraZeneca, AMGEN, Roche and Novartis. A.C.K. has received honoraria, research and/or travel grants from Abbott, Merck Sharpe & Dohme, Bristol-Myers Squibb, Novartis, Eli Lilly, Pfizer, Roche Diagnostics, Solvay and AstraZeneca. P.M.R. has received research grant support from AstraZeneca and Novartis; consultancy fees from Merck, Genzyme, Vascular Biogenics, ISIS, and Boston Diagnostics; and is 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. N.S. has consulted for and received lecture fees from Merck, Pfizer, and AstraZeneca, and has received research grant support from Pfizer.

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FIGURE LEGENDS

Figure 1. Flow Diagram of the Literature Search

Figure 2. Meta-analysis of incident pancreatitis in twenty-one large statin trials

Footnote: for abbreviations see Table 1; data marker size indicates relative weight of the study

Figure 3. Meta-analysis of incident pancreatitis in seven large fibrate trials

Footnote: for abbreviations see Table 2; data marker size indicates relative weight of the study

Table 1. Baseline data from twenty large statin trials

Trial	Year published	N on statin	N on control	Treatment (active / control)	Follow up (years)	Trial population (triglyceride inclusion criteria)	Age (years)	Baseline triglycerides (mg/dL)	% difference in triglycerides between treatment and control arms at 1 year
PLACEBO- AND STANDARD CARE-CONTROLLED TRIALS									
4S (16)	1994	2223	2221	S10-40mg / placebo	5.4*	Angina or previous MI (triglycerides ≤222mg/dL)	-	134 (45)	18
WOSCOPS (17)	1995	3302	3293	P40mg / placebo	4.9	Male, hypercholesterolemia, no history of MI (-)	55	164 (69)	15
CARE (18)	1996	2081	2078	P40mg / placebo	5.0*	MI in previous 3 to 20 months (triglycerides <350mg/dL)	59	156 (61)	14∫
AFCAPS TexCAPS (19)	1998	3304	3301	L20-40mg / placebo	5.2	Average cholesterol levels, no CVD (triglycerides ≤400mg/dL)	58	181 (75)	14
LIPID (20)	1998	4512	4502	P40mg / placebo	6.1	hospitalization for unstable angina or previous MI (triglycerides <445mg/dL)	62*	140*	11∫
GISSI-Prev. (21)	2000	2138	2133	P20mg / standard care	2.0*	Recent MI (-)	-	166 (89)	-4
Heart Protection Study (5;22)	2002	10269	10267	S40mg / placebo	5.4	CVD or diabetes (-)	65	187 (125)	19
PROSPER (23)	2002	2891	2913	P40mg / placebo	3.3	Age 70-82 years with CVD or risk factors (triglycerides <534mg/dL)	75	138 (62)	17
GREACE (24)	2002	800	800	A to achieve LDLc <100mg/dL / standard care	3.0	CHD (triglyceride <400mg/dL)	59	181	28
ASCOT-LLA (25)	2003	5168	5137	A10mg / placebo	3.3*	Hypertension, no CHD (triglyceride ≤400mg/dL)	63	147 (80)	23
CARDS (26)	2004	1428	1410	A10mg / placebo	3.9*	Type 2 diabetes mellitus, no CVD (triglyceride ≤603mg/dL)	62	173 (97)	21
ASPEN (27)	2006	1211	1199	A10mg / placebo	4.0	DM (triglyceride ≤600mg/dL)	61	146*	14‡
MEGA (28)	2006	3866	3966	P10-20mg / no	5.3	Hypercholesterolemia, no	58	148 (83)	6

				treatment		previous CHD or stroke (-)			
CORONA (29)	2007	2514	2497	R10mg / placebo	2.7*	Systolic heart failure (-)	73	178 (114)	24**
JUPITER (30)	2008	8901	8901	R20mg / placebo	1.9*	No CVD, no diabetes, hsCRP ≥2.0mg/L (triglycerides <500mg/dL)	66*	118 (86-169)*	17
GISSI-HF (31)	2008	2285	2289	R10mg / placebo	3.9*	Chronic heart failure (-)	68	-	-
INTENSIVE VS. MODERATE DOSE TRIALS									
PROVE-IT TIMI 22 (32)	2004	2099	2063	P40mg / A80mg	2.0	Recent hospitalization for ACS (-)	58	156*	21*
A to Z (33)	2004	2265	2234	Placebo – S20mg / S40-80mg	2.0*	Recent hospitalization for ACS (-)	61*	149 (116-199)*	6
TNT (34)	2005	4995	5006	A80mg / A10mg	4.9*	Stable CHD (triglyceride ≤600mg/dL)	61	151 (71)	-
IDEAL (35)	2005	4439	4449	A80mg / S20-40mg	4.8*	Previous MI (triglyceride ≤600mg/dL)	62	149	23
SEARCH (5;36)	2010	6031	6033	S80mg / S20mg	6.7	Previous MI (-)	64	169 (107)	9
TOTAL	**-**	**76722**	**76692**		**4.3 (1.6)**	**-**	**-**	**-**	**-**

Data presented as mean or mean (SD) unless otherwise indicated; * median or median (interquartile range); ∫ average difference over5 years; ‡ difference at end of trial; ** difference at 3 months; (-) no triglyceride inclusion or exclusion criteria specified for trial

Abbreviations: Scandinavian Simvastatin Survival Study (4S), West of Scotland Coronary Prevention Study (WOSCOPS), Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS TexCAPS), Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID), Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca (GISSI) Prevenzione (Prev), Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study, Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA), Collaborative Atorvastatin Diabetes Study (CARDS), Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT TIMI 22) study, Aggrastat to Zocor (A to Z) study, Treating to New Targets (TNT) study, Incremental Decrease in Events through Aggressive Lipid Lowering (IDEAL) study, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN), Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study Group (MEGA), Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA), JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), GISSI-Heart Failure, SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine); S (simvastatin); P (pravastatin); L (lovastatin); A (atorvastatin); R (rosuvastatin); MI (myocardial infarction); CVD (cardiovascular disease); CHD (coronary heart disease); ACS (acute coronary syndrome); DM (diabetes mellitus)

Table 2. Baseline data from trials comparing fibrate therapy to placebo

Trial	Year published	N on fibrate	N on control	Treatment (active / control)	Follow up (years)	Trial population (triglyceride inclusion criteria)	Age (years)	Baseline triglycerides (mg/dL)	% difference in triglycerides at 1 year
Coronary Drug Project (37;38)†	1975	1103	2789	Clofibrate / placebo	6.2	Male, previous MI (-)	-	184	25
WHO Co-operative Trial (39)†∫	1978	5331	5296	Clofibrate / placebo	5.3	Male, upper third of cholesterol (-)	46	-	-
Helsinki Heart Study** (40;44)	1987	2362	2347	Gemfibrozil / placebo	5.0	Male, No CHD or possible symptoms of CHD (-)	47	177 (119)	35
VA-HIT† (41)	1999	1264	1267	Gemfibrozil / placebo	5.1*	Male, CHD (triglyceride ≤300mg/dL)	64	161 (68)	31
BIP (42)	2000	1548	1542	Bezafibrate / placebo	6.2	Previous MI or stable angina (triglyceride ≤300mg/dL)	60	145 (51)	21‡
FIELD (12)	2005	4895	4900	Fenofibrate / placebo	5.0*	DM, not on statin (triglyceride 89-445mg/dL)	62	174 (78)	30
ACCORD Lipid (43)	2010	2765	2753	Simvastatin + fenofibrate / simvastatin + placebo	4.7	DM, CVD or risk factors (triglycerides <750mg/dL on no lipid lowering therapy; <400mg/dL on therapy)	62	162 (113-229)*	20
TOTAL	**-**	**19268**	**20894**	**-**	**5.3 (0.5)**	**-**	**-**	**-**	**-**

Data presented as mean or mean (SD) unless otherwise indicated; * median or median (interquartile range); † only fatal cases of pancreatitis available; ** includes cases from both the Helsinki Heart Study and its ancillary study (age, baseline triglycerides and % difference in triglycerides are weighted means); ∫ includes cases during the trial and during 1st year after the trial; ‡ average difference during trial; (-) no triglyceride inclusion or exclusion criteria specified for trial

Abbreviations: VA-HIT (Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial), BIP (Bezafibrate Infarction Prevention), FIELD (Fenofibrate Intervention and Event Lowering in Diabetes), ACCORD (Action to Control Cardiovascular Risk in Diabetes), MI (myocardial infarction), CHD (coronary heart disease), DM (diabetes mellitus), CVD (cardiovascular disease)