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# Efficacy and Safety of High-Density Lipoprotein Cholesterol-Increasing Compounds

## A Meta-Analysis of Randomized Controlled Trials

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<b>OBJECTIVES</b>	The aim of this research was to estimate the efficacy and safety of current high-density lipoprotein cholesterol (HDL-C)-increasing drugs.
<b>BACKGROUND</b>	Epidemiologic evidence has shown that HDL-C is inversely related to coronary heart disease (CHD) risk. However, the evidence for reducing CHD risk by raising HDL-C is thin, predominantly due to the paucity of effective and safe HDL-increasing drugs.
<b>METHODS</b>	Randomized controlled trials with fibrates and niacin, published between 1966 through February 2004 (MEDLINE), were retrieved. Information on treatment, baseline characteristics, serum lipids, end points, and side-effects were independently abstracted by two authors using a standardized protocol.
<b>RESULTS</b>	Data from 53 trials (16,802 subjects) using fibrates and 30 trials (4,749 subjects) using niacin were included. Random-effects model showed 11% versus 10% reduction in total cholesterol, 36% versus 20% reduction in triglycerides, 8% versus 14% reduction in low-density lipoprotein cholesterol, and 10% versus 16% increase in HDL-C for fibrates and niacin, respectively. Apart from flushes in the niacin group, both fibrates and niacin were shown to be well-tolerated and safe. Fibrates reduced the risk for major coronary events by 25% (95% confidence interval 10% to 38%), whereas current available data for niacin indicate a 27% reduction.
<b>CONCLUSIONS</b>	Fibrates reduce major coronary events and increase HDL-C levels without significant toxicity. Niacin has a more potent effect on HDL-C levels, whereas data on cardiovascular event rate reduction are limited. Future studies need to evaluate whether additional HDL increase by fibrates or particularly newer niacin formulations on top of statin therapy translates into further event reduction in high-risk subjects, without significant toxicity. (J Am Coll Cardiol 2005;45:185-97) © 2005 by the American College of Cardiology Foundation

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The benefit of statins on cardiovascular (CV) end point reduction in both primary and secondary settings has proven to be a consistent finding throughout a large number of randomized controlled trials. Recently, more intensive low-density lipoprotein (LDL)-lowering was shown to be associated with a further reduction of CV events compared with conventional lipid-lowering (1). However, it should be noted that approximately 70% of CV events have not been prevented in statin trials (2). This staggering number has intensified the search for novel therapeutic targets. The choice of a new target has, to some extent, been directed by the worldwide epidemic of obesity, metabolic syndrome, and type II diabetes mellitus (3), all characterized by a non-LDL-cholesterol (C) dyslipidemia consisting of low high-density lipoprotein cholesterol (HDL-C) and increased triglycerides (TG).

Large-scale population studies have demonstrated that HDL-C is a strong and independent inverse predictor of coronary heart disease (CHD), even in subjects with normal LDL-C levels (4). Accordingly, up to 40% of patients with premature CHD are characterized by low levels of HDL-C.

Using these data, it has been calculated that coronary risk increases by 1% to 3% for every 1% reduction in HDL-C level. As a consequence, increasing HDL-C has emerged as an attractive tool for CV prevention. In support, several classes of drugs with HDL-increasing effects have been associated with reductions in CV event rates. Thus, fibrates, which mediate their HDL increase predominantly by peroxisome proliferator agonist receptor- $\alpha$  activation, have been shown to be associated with an absolute reduction in primary end points of 1.4% and 4.4% in primary (5) and secondary (6) prevention, respectively. In line, nicotinic acid derivatives, mediating HDL increase through a variety of mechanisms (7,8), have been associated with a reduction of CV events in one large monotherapy trial and two small combination secondary prevention trials (9,10). Unfortunately, trials evaluating combination therapy of statins with fibrates or niacin have been hampered because of safety concern.

As HDL-increasing interventions are expected to constitute an important therapeutic option for CV prevention in the next decade, we performed a meta-analysis of all randomized controlled trials using monotherapy of two currently available classes of HDL-increasing compounds (fibrates and nicotinic acid derivatives) in order to provide an accurate and precise estimate of their efficacy as well as their safety.

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**Abbreviations and Acronyms**

CHD	= coronary heart disease
CV	= cardiovascular
ER	= extended-release
HDL-C	= high-density lipoprotein cholesterol
HHS	= Helsinki Heart study
IR	= immediate-release
LDL-C	= low-density lipoprotein cholesterol
SD	= standard deviation
SR	= wax-matrix sustained-release
TC	= total cholesterol
TG	= triglycerides
VA-HIT	= Veterans Affairs High-density lipoprotein Intervention Trial

**METHODS**

**Data sources and study selection.** A literature search of the MEDLINE database (1966 to February 2004) using the medical subject headings fibric acid, fibrates, bezafibrate, ciprofibrate, clofibrate, etofibrate, fenofibrate, gemfibrozil, nicotinic acid, niacin, acipimox, controlled-release, extended-release, immediate-release, sustained-release, lipids, lipoproteins, and CHD was performed. The search was restricted to studies published in English-language journals, conducted in humans, and classified as randomized controlled trials. A manual search was also performed using the authors reference lists from randomized controlled trials and reviews. For inclusion, studies had to meet the following criteria: 1) random allocation of study participants to fibrates or niacin versus a control group or trials with a crossover design; 2) changes in lipids; and 3) intervention duration of  $\geq 3$  weeks. The most common reason for exclusion of trials was missing values (mean or standard deviation [SD]) for serum lipids.

**Data abstraction.** All data were abstracted independently by two authors (R.B. and B.H.) in duplicate using a standardized protocol and reporting form. Disagreements were resolved by consensus. Authors were contacted for additional and missing information. When information of multiple doses and different treatment periods was available, we selected the highest dose and the longest treatment period for the calculations. Study characteristics recorded were as follows: 1) first author's name, year of publication, and journal; 2) number of participants (n); 3) mean age, gender, body mass index; 4) type and dosage of study drug; 5) mean total cholesterol (TC), LDL-C, HDL-C, and TG levels at baseline and follow-up; 6) adverse events; 7) coronary end points; 8) treatment duration; and 9) dyslipidemia. Major coronary events recorded during long-term treatment ( $\geq 2$  years of active treatment) included coronary death (definite), nonfatal myocardial infarction, silent myocardial infarction, coronary revascularization, unstable angina, and sudden cardiac death. In addition, data were abstracted on fatal CHD deaths, stroke, revascularization, non-CV deaths, cancer, and all-cause mortality during

treatment. Adverse events were divided in clinical adverse events and laboratory adverse events. Clinical adverse events were: serious adverse events, gastrointestinal symptoms (defined as abdominal pain, diarrhea, dyspepsia, nausea, and vomiting), skin reactions (defined as pruritus and/or rash), flushes, and gout. Laboratory adverse events were hepatotoxicity (defined as  $>3$  times the upper limit of normal serum glutamic oxalocetic transaminase/serum glutamic pyruvic transaminase value), musculoskeletal symptoms (defined as  $>10$  times the upper limit of normal creatine phosphokinase value and/or myalgia), hyperglycemia (defined as fasting glucose of  $>6.1$  mmol/l or HbA1c  $>7\%$ ).

**Statistical analysis.** The data needed for the measurement of the weighted mean difference were: 1) the mean change in serum lipids (TC, TG, LDL-C, and HDL-C) from baseline to follow-up in milligrams per deciliter (mg/dl); 2) the SD of the mean difference; and 3) the number in each comparison group (n) at follow-up (11).

The estimate of the principal effect was defined as the mean difference in mg/dl between the change in lipid concentrations during active treatment (mean at follow-up minus mean at baseline) and the change during the control period (mean at follow-up minus mean at baseline). This difference is referred to as the net mean change. When the  $SD_{difference}$  was not available in the source papers, authors were contacted. In case of no response or nonavailability of the requested information, we estimated the variance with the following formula (11):

$$\text{Standard error (SE)}_{difference} = \sqrt{[SD_{baseline}^2 / n_{baseline} + SD_{follow-up}^2 / n_{follow-up}]}$$

The  $SD_{difference}$  was calculated from the  $SE_{difference}$  with the following formula:

$$SD_{difference} = SE_{difference} \times \sqrt{n}$$

For the computation of pooled effects, each study was assigned a weight consisting of the reciprocal of its variance. Estimates of the average effect of fibrates or niacin on serum lipids and 95% confidence intervals were calculated with models based on both fixed- and random-effects assumptions. Because substantial variability between observations was indicated by preliminary tests for homogeneity, we have presented the results of random-effects models calculated according to the method of DerSimonian and Laird (12).

Relative risk reduction (RRR) and absolute risk reduction (ABR) were used to measure the effect of fibrates on clinical outcomes. The numbers of various outcomes for both the fibrate and control groups were recorded for each study using  $2 \times 2$  tables.

The number of subjects in the treatment group in whom an end point of interest was observed minus the number of subjects in the control group in whom an end point of interest was observed from each trial was summed, and z statistics were used to test whether the total differed from 0. To calculate the pooled absolute risk, each study was weighted by its sample size  $(N_t \times N_c) / (N_t + N_c)$ , (t =

treatment; c = control). The number needed to treat (NNT) was calculated by taking the reciprocal of the ABR.

Subgroup analyses were performed to examine the effect of fibrates and niacin on serum lipids in subjects with different dyslipidemias. First, the effects were compared in subjects with all lipid disorders, including secondary dyslipidemia. Then we analyzed the effects in subjects with hypercholesterolemia, combined hyperlipidemia, hypertriglyceridemia, low HDL-C, and type II diabetes mellitus. We used the ATP-III classification to define lipid disorders. Trials classified as Frederickson's type IIa hyperlipidemia or with mean baseline TC above 240 mg/dl, mean baseline LDL-C above 160 mg/dl, and without elevated TGs above 200 mg/dl were considered hypercholesterolemia. A trial was considered combined hyperlipidemia if it was classified as Frederickson's type IIb hyperlipidemia or with mean baseline TC above 160 mg/dl, mean baseline LDL-C above 160 mg/dl, and TG above 200 mg/dl. Trials classified as Frederickson's type IV hyperlipidemia with normal mean baseline TC and LDL-C, but TG levels above 200 mg/dl, were considered as hypertriglyceridemia. Trials with mean baseline HDL-C levels below 40 mg/dl were considered as low HDL-C.

## RESULTS

**Study design and participants.** The contents of 409 (275 fibrates and 134 niacin) abstracts or full-text manuscripts were reviewed to determine eligibility for inclusion. Because trials with etofibrate were scarce, we excluded the only trial with this drug. A total of 83 trials (53 trials for fibrates and 30 trials for niacin) met our criteria and were included in the meta-analysis (Tables 1 and 2). The distribution of the 53 trials with fibrates is as follows: 17 trials with gemfibrozil (5,6,13–27), 15 trials with fenofibrate (22,28–41), 13 trials with bezafibrate (22,42–53), 9 trials with clofibrate (21,54–61), and 2 trials with ciprofibrate (62,63). For the 30 trials with niacin, the distribution is as follows: 11 trials with immediate-release niacin (IR-niacin) (54,64–73), 10 trials with acipimox (72,74–82), 6 trials with extended-release niacin (ER-niacin) (67,83–87), and 5 trials with wax-matrix sustained-release niacin (SR-niacin) (64,88–91). From the 83 trials, 6 trials (21,22,54,64,67,72) used multiple treatment arms with more than one fibric acid or nicotinic acid derivative, and 15 trials had different study populations (26,28,31,33,38,44,49,51,53,58,62,68,74,75,81). Overall, in these studies 16,802 subjects were treated with fibrates or placebo, and 4,749 subjects were treated with niacin or placebo. The average length of treatment was 12 and 8 months for fibrates and niacin, respectively. The mean age of patients taking fibrates or niacin was 56 and 58 years, with a male-to-female ratio of 16 to 1 and 7 to 1, respectively. The body mass index of patients in trials with fibrates and niacin was 27 and 28 kg/m<sup>2</sup>, respectively. Twelve trials used random assignment with a crossover design (19,21,26,27,38,40,42,45,51,57,58,61). Subjects with the following dyslipidemias and study populations

were enrolled into the 83 trials: 29 trials with hypercholesterolemia (5,22–25,28,33,34,36,43,49,52,53,55–57,59,60,62,64,67,85–90,92); 25 trials with type II diabetes mellitus (15,17,18,20,29,31,32,37–39,41,43,44,46,50,57,65,68,76–79,81–83); 16 trials with combined hyperlipidemia (21,27,28,33,38,44,49,51,58,62,63,69,72,74,75,80); 10 trials with hypertriglyceridemia (26,30,31,38,42,51,58,61,74,75); 9 trials in subjects with coronary artery disease (6,16,47,48,54,55,64,71,73); and 2 trials in subjects with peripheral arterial disease (48,68). Other rare study populations included healthy subjects (45), type 1 diabetics (53), renal failure (35), and cholelithiasis patients (22).

**Effects of fibrate on lipids.** Fibrate treatment induced significant reductions in serum concentrations of TC, TG, and LDL-C, whereas HDL-C levels were increased (Table 3). The net change in TC was a decrease of 25.5 mg/dl (0.66 mmol/l) (95% confidence interval –29.34 to –21.66 mg/dl,  $p < 0.00001$ ) or 11%. Of the 53 trials, 52 trials (98%) reported a net decrease, and 1 trial (17) (2%) reported a net increase in TC. Although the efficacy of fibrates differed, they all significantly ( $p < 0.00001$ ) reduced TC: fenofibrate (13%), ciprofibrate (13%), bezafibrate (10%), gemfibrozil (9%), and clofibrate (7%).

The net change of TG levels was a decrease of 70.5 mg/dl (0.80 mmol/l) (95% confidence interval –79.78 to –61.22 mg/dl,  $p < 0.00001$ ) or 36%. All 53 trials reported significant ( $p < 0.00001$ ) reductions of TG levels with the following distribution: gemfibrozil (48%), ciprofibrate (45%), fenofibrate (40%), bezafibrate (31%), and clofibrate (18%).

The net change of LDL-C levels consisted of a decrease of 11.7 mg/dl (0.30 mmol/l) (95% confidence interval –17.86 to –5.59 mg/dl,  $p = 0.0002$ ) or 8%. Bezafibrate (13%;  $p = 0.04$ ), fenofibrate (11%;  $p = 0.01$ ), and ciprofibrate (8%;  $p = 0.005$ ) significantly reduced LDL-C levels, whereas clofibrate (3%;  $p = 0.53$ ) and gemfibrozil (1%;  $p = 0.68$ ) had no significant effect on LDL-C. From the 48 trials, 38 trials (79%) showed a net decrease in LDL-C after treatment with fibrates, whereas in 6 (13%) and 4 (8%) trials LDL-C increased and remained unchanged, respectively. All fibrates, with the exception of clofibrate, significantly ( $p < 0.00001$ ) increased HDL-C concentration by 4.1 mg/dl (0.11 mmol/l) (95% confidence interval 3.34 to 4.91 mg/dl) or 10%. Among the different fibrates, bezafibrate (11%), gemfibrozil (11%), fenofibrate (10%), and ciprofibrate (10%) showed substantial increases in HDL-C levels. From the 53 trials, only 47 trials reported HDL-C outcome. A total of 43 from the 47 eligible trials (91%) showed a net increase of HDL-C levels, whereas 3 trials (6%) with clofibrate and 1 trial with bezafibrate (3%) showed a decrease in HDL-C.

**Adverse effects of fibrates.** Overall, 33% of subjects receiving fibrates experienced adverse effects versus 31% of subjects in the control group (relative risk 1.16; 95% confidence interval 1.03 to 1.32,  $p = 0.02$ ). A larger number of subjects experienced gastrointestinal symptoms in the fibrate drug

**Table 1.** General Characteristics of RCT With Fibric Acid Derivatives

Trial	n, Male/Female	Age, yrs	BMI, kg/m <sup>2</sup>	Dose, mg/day	Duration, weeks	Study Population	TC, mg/dl	TG, mg/dl	LDL, mg/dl	HDL, mg/dl
<b>Ciprofibrate</b>										
Illingworth et al. (62)	31, 8/23	NA	NA	50-100	6	HC & FCH	324	131	249	49
Kontopoulos et al. (63)	60, 53/7	52	NA	100	12	FCH	283	284	167	34
Subtotal	91, 61/30	52	NA		18		297	232	195	39
<b>Clofibrate</b>										
CDP (54)	2,248 men	30-64	NA	1,800	312	CAD	250	266	NA	NA
Cohn et al. (55)	40, NA	49	NA	500	52	CAD	255	191	NA	NA
Crouse et al. (56)	18, NA	54	NA	2,000	24	HC	326	129	248	42
Daubresse et al.* (57)	22, NA	55	NA	2,000	8	DM type 2	216	184	NA	NA
Rabkin et al.* (21)	16, 12/4	50	25	2,000	12	FCH	275	305	169	35
Schneider et al.* (58)	67, 34/33	57	NA	1,200	4	HC, FCH, & HTG	241	403	NA	NA
Sepowitz et al. (59)	33, NA	NA	NA	2,000	36	HC	324	110	256	51
Vecchio et al. (60)	160, NA	18-65	NA	2,000	24	HC	313	130	236	50
Zelis et al.* (61)	12, 7/5	45	NA	2,000	4	HTG	270	429	NA	NA
Subtotal	2,616, 2,301/42	53	25		476		259	261	235	48
<b>Fenofibrate</b>										
Brown et al. (28)	227, 153/74	52	NA	300	24	HC & FCH	306	193	217	48
Cavallero et al. (41)	28 men	52	27	200†	16	DM type 2	196	198	123	34
Feher et al. (29)	32, 18/14	62	28	200†	12	DM type 2	290	275	182	46
Genest et al. (30)	20 men	51	28	200†	8	HTG	222	293	131	27
Goldberg et al. (31)	147, 123/24	52	NA	300	8	DM type 2 & HTG	261	614	110	31
Hodgson et al. (32)	36, 27/9	54	NA	200	12	DM type 2	209	217	130	38
Knopp et al. (33)	36, 33/3	53	26	300	24	HC, FCH	293	185	209	49
Krempf et al. (34)	340, 163/177	18-75	25	200-400†	12	HC	306	138	225	54
Levin et al. (35)	28, 23/5	57	30	67-201†	24	RF	246	390	143	37
Mellies et al. (36)	33, 26/7	49	NA	300	24	HC	306	193	225	43
Playford et al. (37)	40, NA	54	31	200†	12	DM type 2	209	208	126	38
Roglans et al.§ (22)	24, NA	61	30	200	8	Cholelith.	241	142	157	63
Sasaki et al.* (38)	50, 31/19	55	NA	300	8	DM2, FCH, & HTG	241	431	119	40
DAIS (39)	405, 298/107	57	29	200†	158	DM type 2	215	226	132	40
Watts et al.* (40)	11 men	46	31	200†	5	MS	227	215	152	36
Subtotal	1,457, 954/439	55	28		355		262	247	170	44
<b>Bezafibrate</b>										
Alberti et al. (43)	37, NA	55	26	600	12	DM type 2	242	176	162	46
Bradford et al. (44)	82 men	52	26	600	12	DM2, HC, & FCH	266	244	173	37
De Man et al.* (42)	18, 16/2	49	28	400	6	HTG	302	904	101	29
Eagles et al.* (45)	16, 8/8	22	23	400	3	Healthy subjects	182	106	108	NA
Elkeles et al. (46)	164, 117/47	51	29	400	156	DM type 2	220	192	148	38
BIP‡ (47)	3,090, 2,824/266	60	27	400	322	CAD	213	145	149	35
LEADER (48)	1,568 men	69	NA	400	156	PAD	218	213	131	46
Mordasini et al. (49)	18, 7/11	57	NA	600	12	HC & FCH	325	180	195	40
Niort et al. (50)	36, 18/18	47	27	400	4	DM type 2	276	266	164	45
Pazzucconi et al.* (51)	12, 8/4	NA	NA	400	8	FCH & HTG	271	368	157	43
Roglans et al.§ (22)	24, NA	61	30	400	8	Cholelith.	253	264	165	63
BECAIT (52)	81, NA	43	26	600	260	CAD	NA	145	179	40
Winnocour et al. (53)	31, 21/10	50	26	400	12	DM type 1 & HC	278	129	205	55
Subtotal	5,177, 4,669/366	62	27		971		211	178	145	39

*Continued on next page*

treatment group (12% vs. 10%) compared with the control group (relative risk 1.37; 95% confidence interval 1.10 to 1.70,  $p = 0.004$ ). Other adverse effects were skin reactions with a prevalence of 30% and 25% in the treatment and control group, respectively (relative risk 1.03; 95% confidence interval 0.80 to 1.33,  $p = 0.81$ ), musculoskeletal symptoms 3% and 5% in the treatment and control groups, respectively (relative risk 1.23; 95% confidence interval 0.65 to 2.32,  $p = 0.52$ ).

Hepatotoxicity occurred in 6.4% of subjects receiving fibrates versus 6.1% in the control group (relative risk 1.23;

95% confidence interval 0.98 to 1.53,  $p = 0.07$ ). Serious adverse effects occurred in 12% versus 13% of patients, respectively (relative risk 1.02; 95% confidence interval 0.88 to 1.17,  $p = 0.83$ ), whereas cancer prevalence was 4.1% versus 3.7% of subjects (relative risk 0.93; 95% confidence interval 0.80 to 1.08,  $p = 0.35$ ). Subject withdrawal was similar (15%) between the treatment and the control group. There was no significant difference in adverse effects between the different fibrates.

**Effects of fibrates on coronary end points.** Eight long-term clinical end point intervention trials using fibrates were

**Table 1 Continued**

Trial	n, Male/Female	Age, yrs	BMI, kg/m <sup>2</sup>	Dose, mg/day	Duration, weeks	Study Population	TC, mg/dl	TG, mg/dl	LDL, mg/dl	HDL, mg/dl
Gemfibrozil										
Dumont et al. (13)	64 men	46	31	1,200	24	Obesity	218	230	145	33
HHS (5)	4,081 men	47	27	1,200	260	HC	289	176	162	47
LOCAT (14)	595 men	59	27	1,200	128	Post-CABG	200	140	145	32
Kahri et al. (15)	20, 18/2	56	27	1,200	12	DM type 2	NA	NA	NA	43
Knipscheer et al. (16)	33 men	49	NA	1,200	12	CAD	270	322	187	31
Lahdenpera et al. (17)	16, 14/2	55	27	1,200	12	DM type 2	226	275	130	43
Leaf et al.* (18)	13, 7/6	49	NA	1,200	8	DM type 2	472	2,502	NA	23
Miller et al.* (19)	14 men	35	NA	1,200	12	Low HDL-C	147	101	93	34
O'Neal et al. (20)	26, 17/9	58	32	1,200	24	DM type 2	240	350	141	33
Rabkin et al.* (21)	16, 12/4	50	25	1,200	12	FCH	275	305	169	35
VA-HIT (4)	2,531 men	64	29	1,200	265	CAD	175	161	112	32
Roglans et al.§ (22)	24, NA	61	30	900	8	Cholelith.	251	149	163	60
Vanhanen et al. (23)	19, 10/9	56	28	1,200	12	HC	292	174	181	48
Wiklund et al. (24)	137, 91/46	54	26	1,200	12	HC	282	156	195	48
Yoshida et al. (25)	19, 10/9	55	25	900	8	HC	256	218	179	43
Yuan et al.* (26)	18, 16/2	48	29	1,200	6	HTG & HC	247	269	170	40
Zambon et al.* (27)	35, 26/9	53	28	1,200	8	FCH	292	290	200	37
Subtotal	7,461, 7,339/98	54	28		823		242	174	144	41
Pooled	16,802, 15,330/982	56	27		2,643		237	194	148	41

\*Crossover design; †micronized fenofibrate; ‡baseline SD was used as an estimate of the SD of the follow-up; §trial had different treatment arms with more than one fibric acid derivatives. To convert values for cholesterol to mmol/l, multiply by 0.02586; to convert values for triglycerides to mmol/l, multiply by 0.01129.

BECAIT = Bezafibrate Coronary Atherosclerosis Intervention trial; BIP = Bezafibrate Infarction Prevention trial; BMI = body mass index; CAD = coronary artery disease; CABG = coronary artery bypass grafting; CDP = Coronary Drug Project; cholelith. = cholelithiasis; DAIS = Diabetes Atherosclerosis Intervention study; DM = diabetes mellitus; (F) CH = (familial) combined hyperlipidemia; HC = hypercholesterolemia; HDL = high-density lipoprotein cholesterol; HHS = Helsinki Heart Study; HTG = hypertriglyceridemia; LDL = low density lipoprotein cholesterol; LEADER = Lower Extremity Arterial Disease Event Reduction; LOCAT = Lipid Coronary Angiography trial; NA = not available; PAD = peripheral arterial disease; RCT = randomized controlled trial; RF = renal failure; TC = total cholesterol; TG = triglycerides; VA-HIT = Veterans Affairs High-Density Lipoprotein Intervention trial; Y&O = young and old subjects.

included (5,6,14,39,47,48,52,54). Overall, 1,609 major coronary events and 675 coronary deaths occurred in subjects in the control group, whereas 892 events and 398 deaths occurred in those allocated to active treatment (Table 4). Pooled results indicated significant reductions in the risk for major coronary events ( $p < 0.001$ ), but not for coronary deaths. Treatment with fibrates reduced risk of major coronary events by 25% (95% confidence interval 11% to 37%,  $p < 0.001$ ). Only the Veterans Affairs High-Density Lipoprotein Intervention trial (VA-HIT) and the Helsinki Heart Study (HHS) showed statistically significant reductions in major coronary events ( $p < 0.001$ ). Other long-term trials (i.e., Bezafibrate Coronary Atherosclerosis Intervention trial, Bezafibrate Infarction Prevention study, and Bezafibrate treatment in the Lower Extremity Arterial Disease Event Reduction trial) exhibited tendencies toward a statistically significant ( $p = 0.07$ ) reduction in major coronary events. No statistically significant reductions were found in mortality due to coronary cause or all-cause (Table 4). The NNT for all fibrates to prevent one major coronary event was 33 for four years. Noncardiovascular mortality was similar in active treatment and control groups (relative risk 1.10; 95% confidence interval 0.96 to 1.26,  $p = 0.18$ ). The total number of enrolled women was 373 compared with 13,945 men.

**Effects of niacin on lipids.** Niacin treatment was associated with significant reductions in serum concentrations of TC, TG, LDL-C, and HDL-C (Table 5). The net change of TC levels was a decrease of 25.5 mg/dl (0.66 mmol/l)

(95% confidence interval  $-31.80$  to  $-19.13$  mg/dl,  $p < 0.00001$ ), corresponding with 10%. Of the 27 trials with TC outcome, 22 trials (81%) reported a net decrease, and 5 trials (19%) reported a net increase of TC. The SR-niacin and IR-niacin formulations were most effective with a 15% and 13% decrease in TC, respectively.

The net change of TG levels consisted of a decrease of 47.0 mg/dl (0.53 mmol/l) (95% confidence interval  $-60.72$  to  $-34.67$  mg/dl,  $p < 0.00001$ ), corresponding with 20%. A total of 25 trials (86%) reported a net decrease, and 4 trials (14%) reported an increase of TG levels from a total of 29 trials. Among all the niacin formulations, IR-niacin and ER-niacin showed the most substantial reductions of TG levels of 26% and 20%, respectively.

The net change of LDL-C levels was a decrease of 20.6 mg/dl (0.53 mmol/l) (95% confidence interval  $-28.24$  to  $-13.02$  mg/dl,  $p < 0.00001$ ), corresponding with 12%. The SR-niacin, IR-niacin, and ER-niacin showed significant reductions of LDL-C concentration of 19%, 15%, and 10%, respectively. Acipimox was the only drug associated with a mean increase of LDL-C of approximately 3% ( $p = 0.60$ ).

Niacin treatment significantly increased HDL-C with 6.7 mg/dl (0.17 mmol/l) (95% confidence interval 5.10 to 8.44 mg/dl,  $p < 0.00001$ ), or 16%. Among the different niacin formulations, IR-niacin (23%), ER-niacin (22%), and SR-niacin (13%) had the strongest HDL-increasing capacity ( $p < 0.00001$ ), whereas acipimox only induced a 7% increase ( $p = 0.10$ ). From the 25 trials, 21 trials (84%)

**Table 2.** General Characteristics of RCT With Nicotinic Acid Derivatives

Trial	n, Male/Female	Age, yrs	BMI, kg/m <sup>2</sup>	Dose, mg/day	Duration, weeks	Study Population	TC, mg/dl	TG, mg/dl	LDL, mg/dl	HDL, mg/dl
<b>IR-niacin</b>										
Brown et al.‡ (64)	29 men	49	27	2,000	112	CAD	299	191	215	46
CDP (54)	2,248 men	30-64	NA	1,800	312	CAD	250	266	NA	NA
Garg et al.* (65)	13 men	59	30	4,500	8	DM type 2	259	450	131	29
King et al.*† (66)	28 men	60	NA	1,500	12	Healthy	192	197	123	32
Knopp et al.‡ (67)	109, 111/36	55	28	1,500-3,000	16	HC	276	158	200	45
ADMIT study (68)	468, 432/36	66	28	3,000	60	DM2 & PAD	213	176	137	41
Mostaza et al.* (69)	13, NA	38-69	24-36	1,500-3,000	8	CH	264	322	163	33
Vega et al.* (70)	61 men	59	28	4,500	8	Low HDL-C	194	147	122	32
Wink et al. (71)	38, 23/15	63	NA	100	12	CAD	193	182	111	47
O'Kane et al.‡ (72)	16, NA	52	26	3,000	12	FCH	338	270	232	52
O'Keefe et al.† (73)	39, NA	NA	NA	3,000	18	CAD	228	287	134	36
Subtotal	3,062, 2,945/87	62	28		578		244	243	147	41
<b>SR-niacin</b>										
Aronov et al.* (88)	89, 71/18	50	27	1,500-2,000	16	HC	278	171	198	46
Keenan et al. (89)	201, NA	50	27	1,000-2,000	8	HC	264	144	184	50
Vacek et al. (90)	25, 17/8	59	NA	1,200	12	HC	277	173	209	45
Keenan et al. (92)	158, 106/61	20-70	NA	1,000-2,000	8	HC (Y&O)	261	149	182	49
Lavie et al.† (91)	34 men	NA	NA	3,000	12	Low HDL & CAD	196	205	142	26
Brown et al.‡ (64)	29 men	49	27	2,000	64	CAD	299	191	215	46
Subtotal	536, 257/87	46	27		120		264	158	186	47
<b>ER-niacin</b>										
Davignon et al. (85)	79, 55/24	50	NA	1,000-2,000	8	HC	314	176	233	45
Knopp et al.‡ (67)	149, 113/36	54	28	1,500	16	HC	276	158	200	45
Morgan et al. (86)	122, 78/44	52	28	1,000-2,000	16	HC	274	147	201	43
Goldberg et al. (87)	131, 77/54	54	28	1,000-3,000	26	HC	300	191	216	45
Grundy et al. (83)	146, 86/60	60	33	1,000-1,500	16	DM type 2	NA	268	103	41
Kuvin et al. (84)	21, 17/4	63	NA	1,500	12	Low LDL & CAD	143	192	72	36
Subtotal	648, 426/222	55	29		94		282	191	170	43
<b>Acipimox</b>										
Ball et al. (74)	52, 44/10	36-63	NA	750	12	FCH & HTG	302	412	NA	45
Crepaldi et al. (75)	130, 85/45	48	26	750-1,200	8	HC, FCH & HTG	284	322	185	39
Davoren et al. (76)	60, 43/17	60	28	500	12	DM type 2	216	190	NA	43
Dean et al. (77)	48, 32/16	56	NA	750	12	DM type 2	253	261	160	44
Fulcher et al.*† (78)	30, 25/5	59	26	750	12	DM type 2	242	258	155	39
Koev et al. (79)	121, 60/61	56	27	750	12	DM type 2	268	264	NA	44
O'Kane et al.‡ (72)	21, NA	52	26	750	12	FCH	338	270	232	52
Otto et al. (80)	18, 11/7	49	27	500-750	24	CH	350	292	238	43
Taskinen et al.* (81)	11 men	41	NA	750-1,200	8	DM2 & HTG	247	593	107	NA
Vaag et al. (82)	12, 10/2	58	30	750	12	DM type 2	230	222	154	38
Subtotal	503, 321/163	48	27		124		271	292	180	43
Pooled	4,749, 3,949/559	58	28		916		262	239	167	43

\*Crossover design; †control group was dietary; ‡trial had different treatment arms with more than one nicotinic acid derivatives. To convert values for cholesterol to mm/l multiply by 0.02586; to convert values for triglycerides to mm/l, multiply by 0.01129.

ER-niacin = extended-release niacin; IR-niacin = immediate-release niacin; SR-niacin = wax-matrix sustained-release niacin; Y-O = young and old subjects; other abbreviations as in Table 1.

showed a net increase of HDL-C levels, whereas 4 trials (16%) (3 with acipimox and 1 with SR-niacin) reported a slight decrease in HDL-C concentration.

**Adverse effects of niacin therapy.** Because the high drop-out rate (75%) of the largest IR-niacin trial would dominate the outcome of the safety analysis (54) compared with newer niacin formulations, we did not pool safety data of this trial with other niacin formulations. The most common adverse effect in subjects who received niacin was skin flushing. Overall, 70% of subjects receiving niacin experienced flushes, in contrast with 4% of subjects who received placebo (relative risk 7; 95% confidence interval 3.98 to 12.26,  $p <$

0.00001). The distribution of flushes in the various niacin formulations showed that subjects with IR-niacin had the highest prevalence of flushing up to 85% (relative risk 14; 95% CI 4.94 to 38.90). Other formulations with a high rate of flushes included ER-niacin 66% (relative risk 5; 95% confidence interval 3.36 to 7.51), whereas flushes seemed to occur less in SR-niacin (26%) and acipimox (22%). Flushing was the main reason for subject withdrawal.

Approximately 13% of the subjects in the niacin group withdrew from the study, compared with 6% in the placebo group (relative risk 1.87; 95% confidence interval 1.19 to 2.93,  $p = 0.006$ ). The subject withdrawal rate was distrib-

**Table 3.** Net Change in Serum Lipids Concentration in Subjects Treated With Fibric Acid Derivatives as Compared With the Control Group

Index	No. of Trials	No. of Subjects	Net Change (mg/dl)	95% CI (Random)	Percent Change
Total cholesterol					
Bezafibrate	13*	5,177	-21.4	-27.59 to -15.11	-10.1
Ciprofibrate	2	91	-36.9	-52.59 to -21.21	-12.6
Clofibrate	8	2,616	-16.8	-19.87 to -13.68	-6.5
Fenofibrate	15*	1,457	-34.9	-46.50 to -23.35	-13.3
Gemfibrozil	16*	7,441	-21.3	-28.78 to -13.90	-8.8
Pooled	54	16,782	-25.5	-29.34 to -21.66	-10.8
Triglycerides					
Bezafibrate	13*	5,177	-54.7	-69.54 to -39.83	-30.7
Ciprofibrate	2	91	-104.3	-171.06 to 37.56	-45.0
Clofibrate	7	2,582	-46.6	-63.94 to -29.31	-17.9
Fenofibrate	15*	1,457	-99.0	-130.04 to -67.97	-40.1
Gemfibrozil	16*	7,441	-83.3	-99.92 to -66.58	-47.9
Pooled	53	16,748	-70.5	-79.78 to -61.22	-36.3
LDL cholesterol					
Bezafibrate	13*	5,177	-18.1	-35.22 to -0.93	-12.5
Ciprofibrate	2	91	-15.9	-27.00 to -4.83	-8.4
Clofibrate	4	278	-7.3	-30.01 to 15.46	-3.1
Fenofibrate	15*	1,457	-17.8	-32.06 to -3.48	-10.5
Gemfibrozil	15*	7,428	-1.7	-9.74 to 6.35	-1.2
Pooled	49	14,431	-11.7	-17.86 to -5.59	-7.8
HDL cholesterol					
Bezafibrate	12*	5,161	+4.3	3.35 to 5.15	+11.0
Ciprofibrate	2	91	+3.9	2.27 to 5.52	+10.0
Clofibrate	4	278	-0.1	-3.11 to 2.99	-0.2
Fenofibrate	15*	1,457	+4.5	3.24 to 5.74	+10.2
Gemfibrozil	17*	7,461	+4.4	2.98 to 5.86	+10.7
Pooled	50	14,448	+4.1	3.34 to 4.91	+10.0

\*No. of trials includes trials with more than one fibrin acid treatment arm. To convert values for cholesterol to mm/l, multiply by 0.02586; to convert values for triglycerides to mm/l, multiply by 0.01129; net change is expressed as the change during active treatment minus the change during control.

CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

uted as follows: IR-niacin (20.2% in the niacin group vs. 8.6% in the control group), ER-niacin (19.7% vs. 10.2%), acipimox (4.3% vs. 4.6%), and SR-niacin (2.9% vs. 0%), respectively; IR-niacin had the highest prevalence for subject withdrawal (relative risk 4.06; 95% confidence interval 1.44 to 11.44,  $p = 0.008$ ). The relative risk for subject withdrawal during ER-niacin was lower than during IR-niacin (relative risk 1.51; 95% confidence interval 0.63 to 3.61,  $p = 0.35$ ).

Gastrointestinal symptoms had a prevalence of 23% and 15% in the treatment and control group, respectively (relative risk 1.57; 95% confidence interval 1.05 to 2.34,  $p = 0.03$ ); ER-niacin 35% vs. 24% (relative risk 1.95; 95% confidence interval 0.91 to 4.14,  $p = 0.08$ ); IR-niacin 20% vs. 20% (relative risk 1.24; 95% confidence interval 0.47 to 3.29,  $p = 0.66$ ); SR-niacin 15% vs. 5% (relative risk 5.21; 95% confidence interval 0.36 to 75.18,  $p = 0.23$ ); and acipimox 11% vs. 8% (relative risk 1.48; 95% confidence interval 0.79 to 2.78,  $p = 0.22$ ). Other adverse effects were skin reactions, 11% and 5% (relative risk 2.71; 95% confidence interval 1.48 to 4.97,  $p = 0.001$ ), and musculoskeletal symptoms, 1% and 0.1% (relative risk 2.87; 95% confidence

interval 0.49 to 16.91,  $p = 0.24$ ), respectively. Hepatotoxicity occurred in 2.1% of subjects receiving niacin versus 0.3% in the control group (relative risk 3.15; 95% confidence interval 1.85 to 7.85,  $p = 0.01$ ).

Hyperglycemia had an occurrence rate of 2.3% versus 0.4% in the niacin and the control group, respectively (relative risk 3.04; 95% confidence interval 1.28 to 7.21,  $p = 0.01$ ). From all the niacin derivatives, ER-niacin and IR-niacin had the highest prevalence of, respectively, 4% (relative risk 5.67; 95% confidence interval 1.06 to 30.30,  $p = 0.04$ ) and 2.3% (relative risk 2.79; 95% confidence interval 0.89 to 8.73,  $p = 0.08$ ).

**Sensitivity and subgroup analysis.** Comparison of the fixed-effects with the random-effects model resulted in comparable changes for lipid efficacy. For fibrates, the numbers were -15 versus -25 mg/dl for TC, -51 versus -70 mg/dl for TG, -13 versus -12 mg/dl for LDL-C, and +4 versus +4 mg/dl for HDL-C, respectively. The numbers for niacin were -24 versus -25 mg/dl for TC, -36 versus -47 mg/dl for TG, -20 versus -21 mg/dl for LDL-C, +7 versus +7 mg/dl for HDL-C, respectively. Subgroup analyses for serum lipids by fibrates and niacin in

**Table 4.** Risk Reduction for Major Coronary Events and Deaths From Coronary Disease, Cardiovascular Disease

	No. of Events		Relative Risk Reduction, % (95% CI)	Absolute Risk Reduction per 1,000 (95% CI)	No. Needed to Treat (95% CI)	p Value
	Control	Fibrate				
Major coronary events	1,609	892	25 (10 to 38)	30 (10 to 50)	33 (20-100)	<0.001
CDP, 1975 (54)	839	309	9 (-3 to 20)	20 (10 to 50)		0.13
HHS, 1987 (5)	84	56	30 (5 to 48)	10 (0 to 30)		<0.001
BECAIT, 1997 (52)	11	3	25 (16 to 92)	210 (50 to 370)		0.07
LOCAT, 1997, (14)	7	7	-1 (-181 to 64)	0 (-40 to 40)		<0.001
BIP, 2000 (47)	232	211	9 (-8 to 24)	10 (-10 to 40)		0.07
VA-HIT, 2001 (4)	275	219	20 (6 to 32)	40 (10 to 70)		<0.001
LEADER, 2002 (48)	111	49	56 (39 to 68)	80 (50 to 110)		0.07
DAIS, 2003 (39)	50	38	21 (-16 to 45)	50 (-30 to 130)		0.23
Coronary deaths	675	398	10 (-2 to 20)	10 (0 to 10)		100 (0-100)
CDP	392	135	13 (-5 to 27)	20 (10 to 40)	0.14	
HHS	12	11	9 (-105 to 60)	0 (-10 to 10)	0.08	
BIP	88	95	-8 (-42 to 19)	0 (-20 to 10)	0.73	
VA-HIT	118	93	21 (-2 to 39)	20 (0 to 40)	0.08	
LEADER	65	64	1 (-37 to 29)	0 (-30 to 30)	0.73	
Cardiovascular deaths	840	480	8 (-3 to 18)	0 (-10 to 10)	—	0.39
CDP	528	191	9 (-6 to 21)	20 (-10 to 40)		0.24
HHS	23	21	-98 (-556 to 40)	0 (-10 to 0)		0.68
BIP	88	95	-8 (-42 to 19)	0 (-20 to 10)		0.58
VA-HIT	127	96	67 (-23 to 81)	0 (0 to 10)		0.68
LEADER	74	77	-4 (-41 to 23)	0 (-30 to 30)	0.58	
Noncardiovascular deaths	348	344	-7 (-24 to 7)	0 (-10 to 0)	—	0.33
CDP	42	23	-38 (-129 to 16)	10 (-20 to 0)		0.21
HHS	19	23	-20 (-119 to 35)	0 (-10 to 0)		0.64
BIP	64	66	-3 (-44 to 27)	0 (-20 to 10)		0.66
VA-HIT	93	102	-10 (-44 to 16)	0 (-20 to 20)		0.64
LEADER	121	127	-5 (-32 to 16)	-10 (-40 to 30)	0.66	
All-cause deaths	1,201	835	2 (-7 to 10)	0 (-10 to 10)	—	0.66
CDP	583	221	4 (-10 to 17)	10 (-20 to 40)		0.55
HHS	42	45	-6 (-61 to 30)	0 (-10 to 10)		0.36
BIP	152	161	-5 (-24 to 11)	-10 (-30 to 20)		0.46
VA-HIT	220	198	10 (-8 to 24)	20 (-10 to 50)		0.36
LEADER	195	204	-5 (-20 to 8)	-10 (60 to -30)		0.46
DAIS	9	6	30 (-92 to 75)	10 (-20 to 50)		0.49

Major coronary events included coronary death, definite nonfatal myocardial infarction, and silent myocardial infarction.  
 CI = confidence interval; other abbreviations as in Table 1.

subjects with all lipid disorders, hypercholesterolemia, combined hyperlipidemia, type II diabetes mellitus, and low HDL-C showed moderate differences (Table 6).

**DISCUSSION**

Statin therapy has been accepted as standard therapy to lower CV risk. However, because the majority of CV events cannot be prevented with statins (2), despite their extensive LDL-lowering and weak HDL-increasing (5%) properties, this has prompted us to focus the present analysis on efficacy and safety of HDL-increasing compounds offering the potential for future combination therapy. The choice for HDL-increasing strategies as second target after LDL-lowering reflects both solid epidemiologic data as well as the advent of numerous options for selective HDL-increase within the next few years. To date, two compounds, currently available for clinical use, fit this profile: fibric acid and nicotinic acid derivatives.

**Lipid profile changes.** A consistent HDL-increasing effect of approximately 10% was found for fibrates. This effect was

more pronounced in patients with combined hyperlipidemia and/or hypercholesterolemia ranging from 11% up to 16%. The HDL increase by niacin exceeded that of fibrate therapy approximately 1.6-fold, ranging from 7% up to 23%. The effects of IR-niacin (23%) and ER-niacin (22%) were more pronounced than those observed during SR-niacin (13%) or acipimox (7%) therapy. Of note, the consistency of this observation seriously questions the use of the latter compounds as a means of achieving HDL increases.

With regard to TG, significant reductions were achieved by all fibrates, ranging from 18% up to 48%. This effect of fibrates was consistent throughout the different forms of dyslipidemia included in the present analysis. The efficacy of niacin or its derivatives toward TG lowering was less pronounced when compared with fibrate therapy, ranging from 17% to 26%. The reductions in TC and LDL-C during fibrate therapy ranged between 7% and 13% and 8% and 13%, respectively. Niacin and its derivatives were shown to be slightly more effective in reducing LDL-C levels than fibrates.

**Table 5.** Net Change in Serum Lipids Concentration in Subjects Treated With Nicotinic Acid Derivatives as Compared With the Control Group

Index	No. of Trials	No. of Subjects	Net Change (mg/dl)	95% CI (Random)	Percent Change
<b>Total cholesterol</b>					
Acipimox	10*	503	-9.4	-21.97 to 3.11	-3.5
ER-niacin	5*	502	-20.8	-33.92 to -7.61	-7.4
IR-niacin	11*	3,062	-30.7	-41.26 to -20.05	-12.6
SR-niacin	6*	536	-38.6	-49.02 to -28.18	-14.6
Pooled	32	4,603	-25.5	-31.80 to -19.13	-9.7
<b>Triglycerides</b>					
Acipimox	10*	503	-66.4	-109.83 to -22.96	-22.7
ER-niacin	6*	648	-37.2	-53.65 to -20.72	-19.5
IR-niacin	11*	3,062	-64.0	-77.92 to -50.16	-26.4
SR-niacin	6*	536	-27.1	-32.27 to -21.95	-17.2
Pooled	33*	4,749	-46.9	-60.72 to -34.67	-20.0
<b>LDL cholesterol</b>					
Acipimox	7*	270	+5.1	-14.08 to 24.21	+2.8
ER-niacin	6*	648	-16.2	-25.06 to -7.40	-9.5
IR-niacin	10*	814	-22.7	-34.75 to -10.64	-15.4
SR-niacin	6*	536	-37.5	-46.63 to -28.40	-19.1
Pooled	29	2,268	-20.63	-28.24 to -13.02	-12.4
<b>HDL cholesterol</b>					
Acipimox	9*	492	+3.0	-0.58 to 6.57	+7.0
ER-niacin	6*	648	+9.2	6.96 to 11.42	+21.9
IR-niacin	10*	814	+9.2	8.56 to 9.91	+22.5
SR-niacin	6*	536	+6.0	5.15 to 6.74	+12.7
Pooled	29	2,490	+6.7	5.10 to 8.44	+15.7

\*No. of trials includes trials with more than one fibric acid treatment arm. To convert values for cholesterol to mm/l, multiply by 0.02586; to convert values for triglycerides to mm/l, multiply by 0.01129; net change is expressed as the change during active treatment minus the change during control. To convert values for cholesterol to mm/l, multiply by 0.02586; to convert values for triglycerides to mm/l, multiply by 0.01129.

CI = confidence interval; other abbreviations as in Tables 1 and 2.

**Safety.** The incidence of adverse effects in subjects receiving fibrates was increased compared with placebo (relative risk 1.16,  $p = 0.02$ ). The most common side effects during fibrate therapy were skin reactions (30%) and gastrointestinal symptoms (12%). Other adverse events like hepatotoxicity (6%) and musculoskeletal symptoms (3%) occurred much less frequently. The withdrawal rate from the trials was 15% in both the fibrate and the placebo group. Previous reports have addressed concerns with regard to using fibrates in view of a potential increase in the risk of death from noncoronary causes and/or the induction of cancer (93). In the present meta-analysis, we could not find any increase in noncoronary mortality and/or the prevalence of cancer. Notably, in view of the predefined inclusion criteria for studies with regard to available lipid profile data and treatment arms with the combination of both drugs, we

were unable to include the data from the World Health Organization cooperative trial on primary prevention of CHD by clofibrate. Because adverse effects on overall mortality in previous analyses were largely explained by the results of the latter study, it is in line with expectations that we did not find a negative effect. In view of the large number of subjects included in the present meta-analysis, it appears safe to conclude that fibrate therapy is well-tolerated without conveying additional risks.

As expected, flushes were the most common adverse effect with niacin. Most studies, however, report a decline in the incidence of flushing during prolonged use. Although the SR-niacin and acipimox formulations had a lower incidence of flushes, the HDL-raising efficacy of these compounds is significantly less than the other compounds. There was also a modest increase in gastrointestinal symp-

**Table 6.** Subgroup Analysis With Net Change in mg/dl of Fibric Acid Derivatives and Nicotinic Acid Derivatives in Different Study Populations

	Fibric Acid Derivatives					Nicotinic Acid Derivatives				
	No. of Trials	TC	TG	LDL	HDL	No. of Trials	TC	TG	LDL	HDL
All trials	53	-26	-71	-12	+4	30	-26	-47	-21	+7
Hypercholesterolemia	19	-33	-64	-20	+4	10	-31	-40	-31	+6
Combined hyperlipidemia	11	-38	-89	-17	+4	5	-17	-54	-3	+4
Diabetes mellitus type 2	9	-24	-114	-7	+4	16	-21	-92	-9	+8
Low HDL-C	21	-20	-102	-4	+4	10	-18	-63	-4	+7

Abbreviations as in Table 1.

toms in the niacin group (23%) when compared with the control group (15%). We found relatively little evidence to support the concerns for hepatotoxicity with SR-niacin, because only two of six trials with SR-niacin reported modest elevations of liver enzymes (90,91). Although niacin treatment has been associated with worsening of insulin sensitivity (assessed using euglycemic, hyperinsulinemic clamp technique), only few subjects experienced this side-effect (2%). More importantly, potential changes in glyce-mic control did not result in a need to change the regimen of diabetic control. These findings are consistent with the Arterial Disease Multiple Intervention Trial (ADMIT) study, in which glyce-mic control was affected only temporarily by IR-niacin therapy in 125 diabetics (68).

**CV outcome.** In contrast with the overwhelming number of patients included in statin studies, the number of studies evaluating the effect of fibrates and/or niacin derivatives on CV outcome is limited. Two crucial studies with fibrates comprise the VA-HIT study and the HHS. In the VA-HIT study, the primary end point (nonfatal myocardial infarction or coronary death) frequency was reduced from 21.7% in the control group to 17.3% in the gemfibrozil group, whereas the HDL increase upon gemfibrozil treatment largely predicted CV benefit in multivariate analysis (94). In the HHS, the primary end point (CHD events) was significantly reduced in the gemfibrozil group (2.7%), compared with the control group (4.1%). Other studies using fibrate therapy have yielded less convincing results (Table 4), most likely related to power and patient selection. It remains to be established whether and to what extent the combination of statins and fibrates confers additive protection against CHD. Currently, two studies addressing this issue are the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.

The previously reported interaction between fibrates, particularly gemfibrozil, and statins asks for some degree of caution while implementing combination therapy with these compounds (95).

The number of studies addressing the effect of mono-therapy with nicotinic acid derivatives on CV event outcomes is limited to one study, the coronary drug project. This study reported a modest 11% reduction of CV mortality and a 27% reduction of major coronary events after a follow-up period as long as 10 years (54). However, the use of immediate-release preparations in that study, characterized by multiple daily dosing and a large number of side-effects, resulted in a dropout rate larger than 70% in addition to not-quantified effects due to noncompliance. In this respect, two recent smaller trials evaluating niacin combined with either a bile acid sequestrant or a statin reported impressive HDL increases ranging from 25% to 41% with an unprecedented reduction of CV event rates ranging from 60% to 72% (9,10). Notably, these impressive reduction rates fit nicely to the estimated reduction rates based on the obtained HDL increase in these studies (i.e.,

1% HDL increase being associated with a 1% to 3% reduction in CV events [94]). These data warrant longer and adequately powered studies to verify these promising observations. In line with these results, the combination of clofibrate and niacin showed impressive reductions of 36% to 60% ( $p < 0.01$ ) in CV mortality, which was directly related to serum TG-lowering in the Stockholm Heart study (96). Unfortunately, in view of the predefined inclusion criteria for studies with regard to the treatment arm, we were unable to include the data from this study.

**Study limitations.** Most studies did not report the  $SD_{difference}$ . This was the most common reason to contact the authors. Because the response rate and data availability was disappointing, we had to calculate the  $SD_{difference}$  with the formula mentioned in the Methods section. This resulted in a slightly overestimated  $SD_{difference}$  which in turn, marginally decreased the weight of the studies. Although this is not the ideal situation, this formula provides a generally accepted method to calculate the  $SD_{difference}$ . Another issue is the weighing of continuous data, which is in favor of small studies with homogeneous populations upon pooling of all studies with different numbers of subjects, dyslipidemias, and agents. In the present analyses, we limited this phenomenon by applying a random-effects model.

It must also be noted that, in almost all fibrate intervention trials, mostly men were included, with a male-to-female ratio of 16:1. Awaiting ongoing combination trials using statins and fibrates, one has to be careful before extrapolating all findings toward female patients.

**Clinical perspectives.** The global epidemic of CHD in combination with the inability of statin monotherapy to prevent more than 25% to 30% of CV events emphasizes the need for combination therapies; HDL increase offers a promising target for future CV prevention trials. First, strong observational studies validate the antiatherogenic potential of HDL-C. Second, the prognostic value of HDL-C on CV outcome remains present, even in patients using statin therapy (97). Third, the currently available intervention studies with niacin support an additive beneficial effect of these compounds on top of statin therapy (9,10), and we believe that fibrates may also add to event reduction in combination with statins. Finally, new HDL-increasing strategies with weekly apoAI-Milano infusions are able to induce a 4.2% reduction in plaque volume in a period of five weeks (98). These findings outperform the reduction in plaque volume established after 18 months of intensive LDL-lowering therapy with 80 mg of atorvastatin in the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study, reaching only 0.9% (99). Because the latter changes might be extrapolated to result in a significant improvement in CV outcome during intensive lipid-lowering therapy, the expectations for potent HDL increase combined with intensive LDL-lowering have been raised significantly. The recent reports on significant HDL increases up to 60% during cholesterol ester transfer protein-inhibition with 120 mg of torcetrapib (100) might

bring us a step closer to executing this combined intervention strategy.

In summary, both fibrates and niacin provide a safe and effective way of increasing HDL-C, the latter being the most potent one. Whereas for both, particularly for fibrates, intervention data have emerged to show beneficial effects on CV outcome; their ability to enhance CV event reduction when added to statin monotherapy has been shown in small trials with niacin and may be shown with larger ongoing trials with fenofibrate.

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**Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: A meta-analysis of randomized controlled trials**  
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