

# Effect of Fibrates on Lipid Profiles and Cardiovascular Outcomes: A Systematic Review

Samuel Abourbih,<sup>a,b</sup> Kristian B. Filion, MSc,<sup>a,c,d</sup> Lawrence Joseph, PhD,<sup>c,d</sup> Ernesto L. Schiffrin, MD, PhD,<sup>e</sup> Stephane Rinfret, MD, MSc,<sup>f</sup> Paul Poirier, MD, PhD,<sup>g</sup> Louise Pilote, MD, MPH, PhD,<sup>d,h</sup> Jacques Genest, MD,<sup>i</sup> Mark J. Eisenberg, MD, MPH<sup>a,b,c</sup>

<sup>a</sup>Divisions of Cardiology and Clinical Epidemiology, Jewish General Hospital, Montreal, Quebec; <sup>b</sup>Faculty of Medicine, McGill University, Montreal, Quebec; <sup>c</sup>Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec; <sup>d</sup>Division of Clinical Epidemiology, McGill University Health Center, Montreal, Quebec; <sup>e</sup>Division of Internal Medicine, Jewish General Hospital, Montreal, Quebec; <sup>f</sup>Centre de Recherche de l'Hopital Laval, Quebec, Quebec; <sup>g</sup>Institut de Cardiologie et de Pneumologie, Hôpital Laval, Sainte-Foy, Quebec; <sup>h</sup>Division of Internal Medicine, McGill University Health Center, Montreal, Quebec; <sup>i</sup>Division of Cardiology, Royal Victoria Hospital, Montreal, Quebec.

## ABSTRACT

**OBJECTIVE:** Fibrates might represent a viable treatment option for patients who do not meet their target low-density lipoprotein levels on statins or who are resistant or intolerant to statins. New data from fibrate trials can be synthesized with the existing literature to better estimate their effects.

**METHODS:** We systematically searched the literature to identify randomized, double-blind, placebo-controlled trials examining the effect of fibrates on lipid profiles or cardiovascular outcomes. We estimated the effect of fibrates on the incidence of nonfatal myocardial infarction and all-cause mortality using random effects models.

**RESULTS:** Compared with placebo, fibrates were associated with greater reductions in total cholesterol (range: -101.3 mg/dL to -5.0 mg/dL) and triglycerides (range: -321.3 mg/dL to -20.8 mg/dL), and a greater increase in high-density lipoprotein (range: +1.1 mg/dL to +17.9 mg/dL) in all trials. Fibrates tended to be associated with a greater reduction in low-density lipoprotein (range: -76.3 mg/dL to +38.7 mg/dL) than placebo, although these results were not consistent across all trials. Fibrates were more efficacious than placebo at preventing nonfatal myocardial infarction (odds ratio = 0.78; 95% confidence interval, 0.69-0.89), but not all-cause mortality (odds ratio = 1.05; 95% confidence interval, 0.95-1.15).

**CONCLUSION:** In addition to improving lipid profiles, fibrates are associated with an important decrease in nonfatal myocardial infarction, but do not substantially affect all-cause mortality. Potential applications include treatment for patients with statin resistance or isolated hypertriglyceridemia, or as an adjunct to other lipid-lowering therapies.

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**Conflict of Interest:** Jacques Genest has been on an advisory board for Sanofi-Aventis for the past 3 years and has received honoraria from Sanofi-Aventis. He does not own stock in the company. No other authors have declared any conflicts of interest.

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Requests for reprints should be addressed to Mark J. Eisenberg, MD, MPH, Professor of Medicine, Divisions of Cardiology and Clinical Epidemiology, Jewish General Hospital/McGill University, 3755 Côte Ste-Catherine Road, Suite A-118, Montreal, Quebec, Canada H3T 1E2.

E-mail address: [mark.eisenberg@mcgill.ca](mailto:mark.eisenberg@mcgill.ca)

Statins are currently the drug of choice for achieving target cholesterol goals. However, there are certain patient populations who require cholesterol modification and are refractory or intolerant to statins. In addition, other patients may be receiving the maximal allowable statin dose but are unable to attain their cholesterol goals. Fibrates might represent a viable treatment strategy for these patients; thus, the use of fibrates recently has been examined in 4 large randomized controlled trials. To better understand the effect of fibrates on lipid profiles and cardiovascular outcomes, data from these recent trials need to be evaluated in the context of the existing fibrate literature. Consequently, the objective of this study was to systematically review the medical literature examining the effect of fibrates on lipid profiles and cardiovascular outcomes, including nonfatal myocardial infarction and all-cause mortality.

## MATERIALS AND METHODS

We systematically searched the English literature to identify randomized, double-blind, placebo-controlled trials examining the effects of fibrates on lipid profiles and cardiovascular outcomes. We restricted our search to the 3 fibrates (bezafibrate, fenofibrate, and gemfibrozil) currently available. This systematic review is presented according to the guidelines set forth by the Quality of Reporting of Meta-analyses group.<sup>1</sup>

We conducted our search using the MEDLINE and EMBASE databases and the Cochrane Controlled Trials Register. Our search was limited to randomized controlled trials published in English before June 2007. Our keyword search included the following terms: *Antara*, *bezafibrate*, *Bezalip*, *fenofibrate*, *fibric acid*, *gemfibrozil*, *Lipofen*, *Lopid*, *procetofen*, *Tricor*, and *Triglide*.

We restricted our review to double-blind, placebo-controlled trials randomizing  $\geq 100$  patients and to those with  $\geq 8$  weeks of follow-up. These restrictions were used to ensure that only the highest quality trials were included. For each included trial, we extracted information using a standardized data abstraction form. Abstraction was performed in duplicate, and disagreements were resolved by consensus or a third reviewer. We recorded data regarding study characteristics, patient characteristics, lipid profiles, cardiovascular outcomes, and safety. When studies presented data for multiple follow-up visits, we used the longest follow-up period. Lipid data were recorded in conventional units (milligrams/deciliter).

## Statistical Analysis

We used random effects meta-analysis models to estimate the effect of fibrates on nonfatal myocardial infarction and all-cause mortality. These analyses were carried out using Review Manager software, version 4.2 (<http://www.cc-ims.net/RevMan>).

Estimates are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Because of the continuous nature of the lipid profile data and the varying follow-up times of identified trials, we were unable to statistically pool data describing the effect of fibrates on lipid profiles.

## RESULTS

Our literature search identified 1376 potentially relevant studies (Figure 1). We eliminated 1280 of these studies on the basis of their abstracts. We retrieved the full text for the remaining 96 studies, 76 of which were subsequently

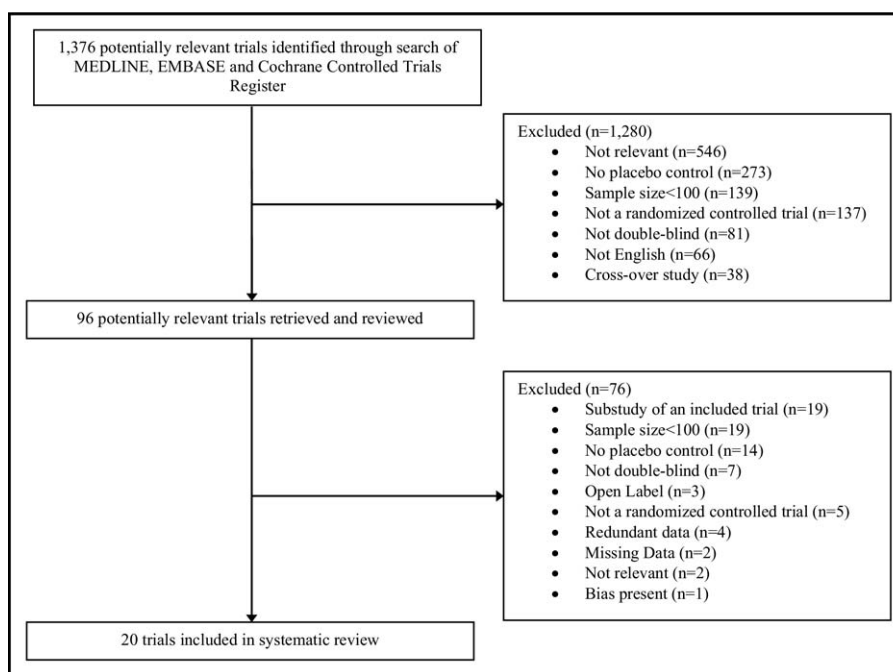
excluded. Thus, our systematic review included 20 randomized controlled trials, including 4 of bezafibrate, 9 of fenofibrate, and 7 of gemfibrozil. These trials randomized a total of 25,655 patients (bezafibrate = 4984 patients, fenofibrate = 12,398 patients, gemfibrozil = 8273 patients). The trial and patient characteristics are described in Table 1.

### Bezafibrate

We identified 4 trials of bezafibrate that met our inclusion criteria, 3 of which examined its effect on lipid profiles. The largest of these trials was the Bezafibrate Infarction Prevention trial (n = 3090), a secondary prevention trial in patients with coronary heart disease.<sup>2</sup> In this study, patients with moderately elevated total cholesterol (180-250 mg/dL) and low high-density lipoprotein (HDL) ( $\leq 45$  mg/dL) were randomized to receive 400 mg of bezafibrate daily or placebo. The primary end point was a composite of fatal myocardial infarction, nonfatal myocardial infarction, or sudden death. After a mean treatment duration of 6.2 years, patients randomized to bezafibrate experienced a substantial decrease in triglycerides ( $-20.8$  mg/dL) and increased HDL ( $+17.9$  mg/dL). These patients also had small improvements in low-density lipoprotein (LDL) and total cholesterol ( $-6.5$  mg/dL and  $-4.5$  mg/dL, respectively). In the placebo group, triglycerides changed by  $+4.6$  mg/dL, HDL changed by  $+3.5$  mg/dL, total cholesterol changed by  $-0.2$  mg/dL, and LDL changed by  $-1.3$  mg/dL over this same period. At the study close, the authors found no difference in the incidence of the primary end point between treatment groups. However, in a post hoc analysis, the authors found that bezafibrate therapy led to a greater reduction in the

## CLINICAL SIGNIFICANCE

- In addition to improving lipid profiles, fibrates are associated with an important decrease in nonfatal myocardial infarction when compared with placebo.
- Fibrates do not seem to substantially affect all-cause mortality rates.
- Physicians should consider their use as monotherapy in patients who are intolerant or resistant to statins, in patients who have hypertriglyceridemia, or as an adjunct to statin therapy.



**Figure 1** Flow diagram of randomized controlled trials included in systematic review.

cumulative probability of primary end points in patients with high baseline triglycerides ( $\geq 200$  mg/dL).

Studies conducted by Pauciullo et al<sup>3</sup> and Elkeles et al<sup>4</sup> also found improvements in lipid profiles among patients treated with bezafibrate compared with placebo. Both studies found more pronounced differences for triglycerides and HDL than for LDL, which is consistent with the results of the Bezafibrate Infarction Prevention trial.

### Fenofibrate

We identified 9 fenofibrate trials that met our inclusion criteria, including the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial conducted by Keech et al.<sup>5</sup> In this 5-year study, the largest fibrate trial reported to date, approximately 10,000 diabetic patients were randomized to 200 mg of micronized fenofibrate daily or placebo, and the primary end point was a composite of coronary heart disease death or nonfatal myocardial infarction. Fenofibrate decreased total cholesterol by 31.1 mg/dL, LDL by 24.7 mg/dL, and triglycerides by 23.5 mg/dL. HDL was increased by 1.1 mg/dL. In the placebo group, the lipid changes were as follows: total cholesterol  $-18.3$  mg/dL, LDL  $-18.1$  mg/dL, triglycerides  $+11.9$  mg/dL, and HDL  $+0.7$  mg/dL. All lipid parameters were significantly different between fenofibrate and placebo groups at the end of follow-up. The number of patients who experienced the primary composite outcome was similar in treatment and placebo groups (256 and 288, respectively). However, patients randomized to fenofibrate had significantly fewer nonfatal myocardial infarctions than those randomized to placebo (158 vs 207).

Other smaller trials, including the Diabetes Atherosclerosis Intervention Study, also found that fenofibrate has substantial effects on triglycerides and modest effects on LDL and total cholesterol.<sup>6-12</sup> In addition, these smaller trials reported more impressive changes in HDL than reported in the FIELD trial. Because these studies were of shorter duration, it is possible that the beneficial effect of fenofibrate on HDL attenuates over time. This hypothesis is supported by evidence from the FIELD trial, where investigators noted a maximal difference in HDL levels between treatment and placebo groups after 4 months of treatment, followed by a convergence over time.<sup>5</sup> It also is possible that these differences can be explained by publication bias.

### Gemfibrozil

The use of gemfibrozil has been investigated in 2 large randomized controlled trials, the Helsinki Heart Study and the Veterans Affairs HDL Intervention Trial, as well as 5 smaller trials.<sup>13-19</sup> In the Helsinki Heart Study, men with high baseline LDL were randomized to 1200 mg gemfibrozil daily or placebo. The primary end points of this trial were fatal and nonfatal myocardial infarction and cardiac death. Investigators found that, in the gemfibrozil-treated group, total cholesterol was decreased by 22.9 mg/dL, LDL was decreased by 15.2 mg/dL, and triglycerides were decreased by 61.2 mg/dL. HDL increased by 3.9 mg/dL in these patients. In the placebo group, total cholesterol increased by 2.8 mg/dL, LDL increased by 2.7 mg/dL, and triglycerides increased by 1.7 mg/dL. HDL decreased by 0.3 mg/dL in the placebo group. Compared with placebo, gemfibrozil reduced the incidence of the composite end point by 34.0% (95% CI, 8.2-52.6).

**Table 1** Study and Patient Characteristics of Randomized Controlled Trials Examining the Effect of Fibrates on Lipid Profiles and Cardiovascular Outcomes

First Author (year)	Study Population	Active n	Control n	Dose (mg)	Duration (wk)	Male (%)	Age (y)	BMI (kg/m <sup>2</sup> )	Total			
									Cholesterol (mg/dL)	Triglycerides (mg/dL)	LDL (mg/dL)	HDL (mg/dL)
<b>Fenofibrate</b>												
Keech (2005) <sup>5</sup>	Type 2 DM	4895	4900	200	260	63	62	29.8 <sup>a</sup>	194.4	153.5	118.5	42.5
Vakkilainen (2003) <sup>6</sup>	Type 2 DM	198	207	200	156	74	57	28.8	215.1	225.6	130.5	39.6
Farnier (2005) <sup>8</sup>	MxHyperlipid	189	64	160	12	57	53	29.4	264.5	276.5 <sup>a</sup>	165.0	42.5
Farnier (2005) <sup>8b</sup>	MxHyperlipid	185	187	160	12	56	54	29.4	260.6	274.3	160.2	42.5
Farnier (2007) <sup>7</sup>	MxHyperlipid	184	60	160	12	51	54	30.0	255.6	231.1 <sup>a</sup>	162.6	45.3
Farnier (2007) <sup>7c</sup>	MxHyperlipid	183	184	160	12	53	55	29.7	253.5	226.4	162.1	44.7
Knopp (1987) <sup>9</sup>	HyperChol	116	111	300	24	67	52	NR	305.6	193.1	NR	47.5
Davidson (2006) <sup>10</sup>	HypTriglyc	96	50	130	8	61	56	31.0	242.3	479.7	119.3	35.7
Krempf (2000) <sup>11</sup>	HyperChol	69	69	200	13	43	54	24.7	308.2	127.9	225.7	56.8
Krempf (2000) <sup>11d</sup>	HyperChol	69	69	267	13	49	54	24.7	307.6	141.2	225.3	54.1
Krempf (2000) <sup>11d</sup>	HyperChol	66	69	340	13	42	55	24.5	309.6	139.7	225.7	56.0
Krempf (2000) <sup>11d</sup>	HyperChol	67	69	400	13	47	55	24.4	308.2	138.0	226.3	54.7
Seidehamel (1989) <sup>12</sup>	Type 4/5	75	72	300	8	84	52	NR	261.5	614.6	109.9	30.8
Nissen (2007) <sup>38</sup>	AthDyslipid	51	51	200	12	69	54	NR	207.0	246.0 <sup>a</sup>	NR	37.4
<b>Bezafibrate</b>												
BIP (2000) <sup>2</sup>	CAD	1548	1542	400	322	91	60	26.7	212.5	145.0	148.5	34.6
Meade (2002) <sup>39e</sup>	LEAD	783	785	400	239	100	68	NR	216.2 <sup>a</sup>	188.5 <sup>a</sup>	130.7 <sup>a</sup>	43.3 <sup>a</sup>
Pauciuolo (2000) <sup>3f</sup>	CAD	82	80	400	24	78	56	26.7	284.5	260.7	190.5	40.8
Elkeles (1998) <sup>4</sup>	Type 2 DM	81	83	400	156	71	51	28.7	219.5 <sup>a</sup>	191.5 <sup>a</sup>	147.6 <sup>a</sup>	37.8 <sup>a</sup>
<b>Gemfibrozil</b>												
Frick (1987) <sup>18</sup>	Dyslipidemia	2051	2030	1200	262	100	47	26.6	269.8	176.0	188.7	47.3
Rubins (1999) <sup>19</sup>	CAD	1264	1267	1200	265	100	64	29.0	175.0	160.5	111.5	32.0
Frick (1993) <sup>13</sup>	Suspected CAD	311	317	1200	260	100	49	NR	270.1	183.2	188.1	46.3
Vinik (1993) <sup>14</sup>	Type 2 DM	295	147	1200	20	51	59	NR	NR	272.3	NR	NR
Schaefer (1996) <sup>15</sup>	HyperChol	111	118	1200	13	72	52	27.6	289.3	177.2	206.5	34.8
Avogaro (1999) <sup>16</sup>	Type 2 DM	110	107	1200	20	57	59	29.1	NR	317.0	NR	NR
Wiklund (1993) <sup>17</sup>	HyperChol	72	73	1200	12	66	54	NR	281.0	159.8	198.8	46.3

BMI = body mass index; LDL = low-density lipoprotein; HDL = high-density lipoprotein; DM = diabetes mellitus; MxHyperlipid = mixed hyperlipidemia; HyperChol = hypercholesterolemia; HypTriglyc = hypertriglyceridemia; Type 4/5 = type 4 and type 5 hyperlipoproteinemia; AthDyslipid = atherogenic dyslipidemia; CAD = coronary artery disease (coronary heart disease); LEAD = lower-extremity arterial disease; NR = not relevant. All continuous variables are means, unless otherwise noted.

<sup>a</sup>Median.

<sup>b</sup>Fenofibrate 160 mg + ezetimibe 10 mg vs ezetimibe 10 mg.

<sup>c</sup>Fenofibrate 160 mg + ezetimibe 10 mg/simvastatin 20 mg vs ezetimibe 10 mg/simvastatin 20 mg.

<sup>d</sup>Four treatment arms with varying treatment dosages compared using same placebo arm.

<sup>e</sup>Patients with creatinine >135 mg/dL took 400 mg bezafibrate on alternate days.

<sup>f</sup>Bezafibrate 400 mg + fluvastatin 40 mg vs fluvastatin 40 mg.

In the Veterans Affairs HDL Intervention Trial, a secondary prevention trial in men with low HDL (<40 mg/dL), patients were randomized to 1200 mg gemfibrozil daily or placebo.<sup>19</sup> The primary study outcome was nonfatal myocardial infarction or cardiac death. The investigators found that after 1 year of gemfibrozil treatment, triglycerides showed the greatest improvement (−45.5 mg/dL), with more modest improvements in total cholesterol (−5.0 mg/dL) and HDL (+2.0 mg/dL). LDL increased by +1.5 mg/dL in this group. In the placebo group, total cholesterol changed by +2.0 mg/dL, LDL changed by +1.5 mg/dL, triglycerides changed by +5.5 mg/dL, and HDL was unchanged. With the exception of LDL, all lipid values showed greater improvement after gemfibrozil treatment compared with placebo, and the difference persisted throughout the 5-year follow-up. Compared with placebo, gemfibrozil was associated with a relative risk reduction of 22% in the primary composite end point (95% CI, 7-35). Nonfatal myocardial infarction was decreased by 23% (95%

CI, 4-38), but there was no significant difference in cardiac death. The remaining gemfibrozil studies showed similar effects, with triglycerides improving the most after fibrate treatment, and relatively smaller improvements in HDL, LDL, and total cholesterol.

### Effect of Fibrates on Lipid Profiles

All 3 fibrates improve total cholesterol. Gemfibrozil decreased total cholesterol by a range of −41.6 to −5.0 mg/dL, bezafibrate by a range of −56.4 to −5.0 mg/dL, and fenofibrate by a range of −101.3 to −7.8 mg/dL (Table 2). Two fenofibrate trials involved patients with extremely elevated baseline triglycerides.<sup>10,12</sup> If these studies are included, fenofibrate decreased triglycerides by as much as −321.3 mg/dL. When these 2 trials are excluded, all 3 fibrates appear to have similar effects on triglycerides (gemfibrozil −103.0 to −45.5 mg/dL, bezafibrate −99.5 to −20.8 mg/dL, and fenofibrate −120.7 to −23.5 mg/dL)

**Table 2** Baseline and Follow-up Lipid Data of all Studies That Met Inclusion Criteria

First Author (year)	Study Size (n) <sup>a</sup>	Follow-up (wk)	Total Cholesterol (mg/dL)			Triglycerides (mg/dL)			LDL (mg/dL)			HDL (mg/dL)		
			Baseline <sup>b</sup>	Follow-up		Baseline <sup>b</sup>	Follow-up		Baseline <sup>b</sup>	Follow-up		Baseline <sup>b</sup>	Follow-up	
				Tx.	Placebo		Tx.	Placebo		Tx.	Placebo		Tx.	Placebo
<b>Fenofibrate</b>														
Keech (2005) <sup>5</sup>	9795	260	194.4	163.3	176.1	153.5	130.1	165.5	118.5	93.8	100.4	42.5	43.6	43.2
Vakkilainen (2003) <sup>6</sup>	405	172	215.1	193.8	214.7	225.6	151.3	206.2	130.5	122.0	133.2	39.6	41.7	40.5
Farnier (2005) <sup>8</sup>	253	12	264.5	237.6	259.2	276.5	160.9	233.0	165.0	156.9	162.5	42.5	50.5	43.9
Farnier (2005) <sup>8</sup>	372	12	260.6	203.7	228.2	274.3	153.6	243.9	160.2	129.1	137.1	42.5	50.6	44.2
Farnier (2007) <sup>7</sup>	244	12	255.6	218.1	252.6	231.1	135.6	224.1	162.6	137.7	154.8	45.3	53.8	45.3
Farnier (2007) <sup>7</sup>	367	12	253.5	152.2	167.1	226.4	114.8	159.4	162.1	85.8	87.7	44.7	51.0	50.6
Knopp (1987) <sup>9</sup>	227	24	305.6	250.0	311.4	193.1	116.0	200.4	NR	174.0	221.9	47.5	56.7	46.7
Davidson (2006) <sup>10</sup>	146	8	242.3	234.5	235.1	479.7	304.3	482.4	119.3	139.2	119.7	35.7	41.0	35.3
Krempf (2000) <sup>11</sup>	138	13	308.2	228.6	313.5	127.9	85.8	137.2	225.7	152.1	227.4	56.8	59.8	57.5
Seidehamel (1989) <sup>12</sup>	147	8	261.5	226.2	268.4	614.6	293.3	637.1	109.9	148.6	110.9	30.8	38.3	31.5
Nissen (2007) <sup>38</sup>	102	12	207.0	192.9	204.7	246.0	159.0	248.8	NR	114.6	114.1	37.4	42.9	37.2
<b>Bezafibrate</b>														
BIP (2000) <sup>2</sup>	3090	322	212.5	207.5	213.2	145.0	124.2	149.6	148.5	141.5	147.7	34.6	52.5	38.1
Meade (2002) <sup>39</sup>	1568	239	216.2	NR	NR	188.5	NR	NR	130.7	NR	NR	43.3	NR	NR
Paucullo (2000) <sup>3</sup>	162	24	284.5	228.1	233.5	260.7	161.2	247.0	190.5	146.8	146.4	40.8	51.3	39.6
Elkales (1998) <sup>4</sup>	164	156	219.5	204.2	223.9	191.5	127.4	177.0	147.6	127.8	152.1	37.8	40.2	35.5
<b>Gemfibrozil</b>														
Frick (1987) <sup>18</sup>	4081	262	269.8	246.9	272.6	176.0	114.8	177.7	188.7	173.5	191.4	47.3	51.2	47.0
Rubins (1999) <sup>19</sup>	2531	52	175.0	170.0	177.0	160.5	115.0	166.0	111.5	113.0	113.0	32.0	34.0	32.0
Frick (1993) <sup>13</sup>	628	260	270.1	249.2	281.3	183.2	125.7	201.3	188.1	180.3	201.7	46.3	50.4	45.7
Vinik (1993) <sup>14</sup>	442	20	NR	NR	NR	272.3	189.0	275.0	NR	NR	NR	NR	NR	NR
Schaeffer (1996) <sup>15</sup>	305	13	289.3	251.0	287.8	177.2	110.8	185.8	206.5	187.3	208.5	34.8	38.4	35.0
Avogaro (1999) <sup>16</sup>	217	20	NR	NR	NR	317.0	214.0	380.0	NR	NR	NR	NR	NR	NR
Wiklund (1993) <sup>17</sup>	137	12	281.0	239.4	275.3	159.8	91.2	161.9	198.8	165.6	193.8	46.3	53.7	44.8

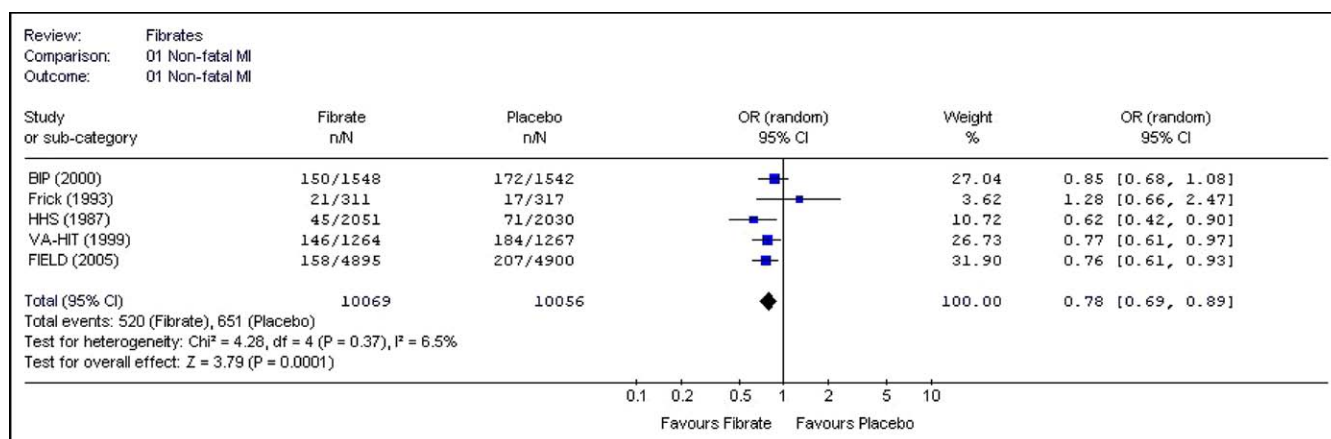
BIP = Bezafibrate Infarction Prevention; NR = not relevant.  
<sup>a</sup>Study size is the total number of patients at randomization.  
<sup>b</sup>Baseline refers to the average of the treatment and placebo groups at baseline.

(Table 2). Fibrates had more modest effects on LDL and HDL (Table 2).

### Meta-analysis of Cardiovascular Outcomes

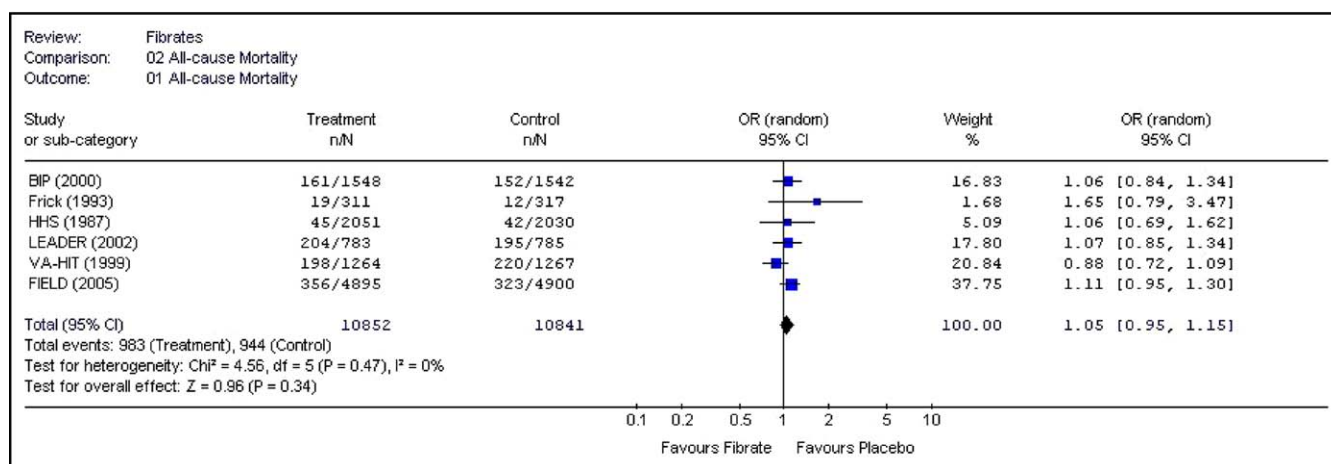
The only 2 cardiovascular outcomes that were consistently reported across most studies were nonfatal myocardial in-

faction and all-cause mortality. Consequently, these were the only 2 outcomes that we were able to include in our meta-analysis. We found that fibrate therapy was associated with a clinically important decrease in nonfatal myocardial infarction compared with placebo use (OR = 0.78; 95% CI, 0.69-0.89) (Figure 2). Our analysis also suggests that fibrate



**Figure 2** Forest plot of the effect of fibrate treatment on nonfatal myocardial infarction. BIP (2000) was a bezafibrate trial. Frick (1993), HHS (1987), and VA-HIT (1999) were gemfibrozil trials. FIELD (2005) was a fenofibrate trial. MI = myocardial infarction; OR = odds ratio; CI = confidence interval; BIP = Bezafibrate Infarction Prevention; HHS = Helsinki Heart Study; VA-HIT = Veterans Affairs HDL Intervention Trial.





**Figure 3** Forest plot of the effect of fibrate treatment on all-cause mortality. BIP (2000) and LEADER (2002) were bezafibrate trials. Frick (1993), HHS (1987), and VA-HIT (1999) were gemfibrozil trials. FIELD (2005) was a fenofibrate trial. OR = odds ratio; CI = confidence interval; BIP = Bezafibrate Infarction Prevention; HHS = Helsinki Heart Study; VA-HIT = Veterans Affairs HDL Intervention Trial.

therapy has little effect, if any, on all-cause mortality (OR = 1.05; 95% CI, 0.95-1.15) (Figure 3). There were insufficient data to examine the effect of individual fibrates on these outcomes.

### Adverse Events Analysis

Overall, 6.3% of patients randomized to fibrate therapy withdrew because of adverse events, compared with 4.6% of those randomized to placebo. The proportion of patients who experienced side effects was similar between groups (64% and 65%, respectively), with the most common being gastrointestinal symptoms. Myalgia was rare and of similar incidence between groups (2.3% and 2.2%, respectively). Rhabdomyolysis occurred in 3 patients taking fenofibrate and 1 patient taking placebo in the FIELD study. There were no other reported cases of rhabdomyolysis. There was no increase in the rate of cholelithiasis in patients treated with fibrates. The number of cancer diagnoses also was similar among those randomized to fibrate or placebo (241 and 255, respectively).

### DISCUSSION

Our study was designed to examine the effect of fibrates on lipid profiles and cardiovascular outcomes. We found that fibrates as a class substantially decrease triglycerides and have more modest effects on LDL, HDL, and total cholesterol compared with placebo. Individual fibrates appeared to have similar effects on lipid profiles with some minor differences. Bezafibrate may have a slightly greater beneficial effect on HDL than the other fibrates, and fenofibrate may improve total cholesterol more than bezafibrate and gemfibrozil. As a class, fibrates also considerably reduce the number of nonfatal myocardial infarctions, but do not seem to greatly affect all-cause mortality. Statins as a class have similar effects on nonfatal myocardial infarction (relative

risk = 0.74; 99% CI, 0.70-0.79).<sup>20</sup> Statins also lower all-cause mortality, with relative risks between 0.78 and 0.89, depending on the statin.<sup>21</sup> This important effect on all-cause mortality is not shared with the fibrates.

Although statins represent the gold standard for the treatment of dyslipidemia, there remain several potential clinical applications for fibrate therapy. Fibrates represent an important treatment option for patients who are statin-intolerant or resistant. Furthermore, they may be used, with caution, as an adjunct for patients who are receiving the maximum allowable dose of statins but have not yet achieved recommended lipid levels. The efficacy and safety of combination therapy was examined in an open-label trial conducted by Gavish et al,<sup>22</sup> in which patients were randomized to bezafibrate monotherapy, simvastatin monotherapy, or combination therapy involving both bezafibrate and simvastatin. The authors found that combination therapy reduced triglycerides by 42% and total cholesterol by 23%, and increased HDL by 25%. These improvements seen with combined therapy were all greater than the effects of either monotherapy. These results were confirmed in a double-blind randomized controlled trial conducted by Paucullo and colleagues.<sup>3</sup> Both trials found that combination therapy had a similar safety profile as fibrate monotherapy.<sup>3,22</sup> However, previous studies have documented an increased incidence of myopathy and rhabdomyolysis associated with fibrate use.<sup>23-27</sup> In particular, when gemfibrozil is combined with statins, the risk of rhabdomyolysis increases 10-fold or more.<sup>23</sup> Therefore, caution should be exercised when prescribing fibrates with statins. The ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, to be completed in 2009, is examining the combination of fenofibrate with simvastatin in the treatment of type 2 diabetes<sup>28</sup> and will provide further evidence as to the benefits and safety of combination therapy.

Another potential application of fibrates may be in the treatment of hypertriglyceridemia.<sup>29</sup> Our results have shown that all 3 fibrates substantially decrease triglycerides, making them ideally suited for patients with hypertriglyceridemia. High levels of triglycerides have been associated with denser, more atherogenic LDL-c particles.<sup>30,31</sup> Controlling triglycerides seems to be more important than was previously believed, because triglycerides may be an independent risk factor for cardiovascular disease.<sup>32,33</sup> Moreover, data from the FIELD trial have shown that high baseline triglycerides or low baseline HDL predict greater reductions in the risk of cardiovascular disease with fibrate treatment.<sup>34</sup> This effect was present in all subgroups examined.

### Previous Reviews

Previous systematic reviews and meta-analyses have examined the effect of fibrates on lipid profiles and cardiovascular outcomes.<sup>35-37</sup> Birjmohun et al<sup>35</sup> compared the efficacy of fibrates against niacin in their meta-analysis. They found that fibrates had beneficial effects on patients' lipid profile, decreasing triglycerides by 36%, LDL by 8%, and total cholesterol by 11%, and increasing HDL by 10%. They also found that fibrate use was associated with a decrease in major coronary events but had no effect on coronary deaths. Because their search was restricted to MEDLINE, several studies were not included in their analysis, potentially biasing their results and leading to less accurate estimates of treatment effects.

Studer et al<sup>36</sup> conducted a systematic review of fibrates and other lipid-lowering agents to assess their impacts on mortality. This study included 17 fibrate trials, 9 of which examined clofibrate, which is not routinely prescribed in North America. They found that fibrates did not affect all-cause mortality (OR = 1.00; 95% CI, 0.91-1.11), which is consistent with our results. The review conducted by Studer and colleagues did have several important limitations, including the inclusion of nonplacebo control groups, a lipid analysis that only considered total cholesterol, and a cardiovascular analysis that only considered all-cause mortality. A full 3 years have elapsed since the literature searches of both studies by Birjmohun et al<sup>35</sup> and Studer et al<sup>36</sup> were completed. The FIELD trial, as well as several smaller fibrate trials, have been published since these previous searches.<sup>5</sup>

### STUDY LIMITATIONS

Our systematic review has several potential limitations. First, because of varying lengths of follow-up time, missing measures of dispersion such as standard deviations, and the continuous nature of lipid profiles, there were insufficient data available to estimate the effects of fibrates on lipid parameters in a meta-analysis. We also were unable to examine the effects of individual fibrates on cardiovascular outcomes. Second, there was considerable heterogeneity in study designs, patient populations, and interventions (eg, dosage, choice of fibrate, and duration of follow-up). Al-

though we used a random-effects model to account for this heterogeneity, we did not have a sufficient number of studies to run a meta-regression model. Finally, we restricted our systematic review to trials published in English. Thus, our systematic review may be affected by publication or language bias.

### CONCLUSIONS

Fibrates substantially decrease triglycerides, modestly decrease LDL and total cholesterol, and modestly increase HDL. Fibrates also are associated with an important decrease in nonfatal myocardial infarctions, but do not affect all-cause mortality. Consequently, although statins remain the recommended treatment for dyslipidemia, fibrates also might have a role to play. Physicians should consider their use as monotherapy in patients who are intolerant or resistant to statins, in patients who have hypertriglyceridemia, or as an adjunct to statin therapy.

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