

Use of Fibrates and Cancer Risk: A Systematic Review and Meta-Analysis of 17 Long-Term Randomized Placebo-Controlled Trials

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Abstract

Background: Fibrates comprise a class of well-established antilipidemic agents that significantly reduce cardiovascular events. Given the concerns of cancer with fibrate therapy, we undertook a systematic review and meta-analysis to investigate the effects of fibrates on cancer outcomes.

Methods: We systematically searched Medline, Scopus, SCI Expanded, and the Cochrane Library for studies published up to 2012. We included randomized controlled trials (RCTs) that evaluated a fibrate therapy compared with placebo, had a minimum duration of two years, and reported data on the incidence of and/or deaths from cancer during the trial. Reviews of each study were performed and the relative data were abstracted. Pooled relative risk estimates (RR) and 95% confidence intervals (CIs) were calculated using the inverse variance weighted approach. Subgroup, sensitivity and meta-regression analyses were also conducted.

Results: Seventeen RCTs, involving 44,929 participants with an average follow-up of 5.2 years, contributed to the analysis. The degree of variability between trials was consistent with what would be expected to occur by chance alone. The quantitative synthesis of data retrieved from the RCTs was not indicative of a fibrate effect on cancer incidence (780 [fibrate] vs 814 [control]; RR = 1.02, 95% CI 0.92–1.12) or cancer death (385 [fibrate] vs 377 [control]; RR = 1.06, 95% CI: 0.92–1.22). When the analysis was restricted to major RCTs, the results did not substantially change. Similarly, we found no evidence of differential effects by length of follow-up or type of fibrate. Insignificant results were also obtained for the role of fibrates in cancers of the respiratory tract, breast, colon, gastrointestinal tract, prostate, genitourinary tract, or in melanoma.

Conclusion: Our findings demonstrate that fibrates have a neutral effect on cancer outcomes. However, it is important to continue monitoring their long-term safety profiles.

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Introduction

Fibrates comprise an important class of therapeutic agents for the management of dyslipidemia. They are agonists of the peroxisome proliferator-activated receptors alpha (PPAR- α), which are mainly expressed in liver, heart and skeletal muscle [1]. Fibrates have been shown to stimulate the expression of genes involved in fatty acid and lipoprotein metabolism, resulting in a shift from hepatic fat synthesis to fat oxidation [2]. This leads to a substantial reduction in serum triglycerides and an increase in high-density lipoprotein cholesterol levels. Though cardiovascular protection using antilipidemic agents has largely been dominated by the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) since the 1990s, fibrates have been particularly useful in patients with primary hypertriglyceridemia, mixed hyperlipidemia, and in patients with type 2 diabetes and dyslipidemia characterized by high triglyceride and low high-density lipoprotein cholesterol concentrations.

However, in the current era of intensive lipid-lowering therapies to reduce the risk of cardiovascular disease, there is still debate regarding the potential relationship between fibrates use and cancer. Concerns about a possible increase in cancer-related deaths arose initially due to fibrates' contribution to the total mortality observed during the "in-trial" period of the World Health Organization (WHO) cooperative study [3], although subsequent extended follow-up showed a smaller difference in incidence of and death rates from cancer between treatment and control arms [4,5]. On the other hand, a review of rodent carcinogenicity tests reported that lipid-lowering drugs, including fibrates, initiate or promote cancer in rats and mice [6]. However, in most of the reviewed studies the doses used were substantially higher than the recommended doses for humans and the employed bioassays were criticised for being inadequate to predict carcinogenicity in humans [7].

Given that the use of fibrates has steadily increased during the past decade [8], more knowledge is needed on the relationship between these medications and cancer. To address this issue, we conducted a systematic review and meta-analysis of randomized placebo-controlled trials published in the peer-reviewed literature.

Materials and Methods

Search Strategy

To identify the studies of interest, we systematically searched the following databases: (i) Medline, (ii) Scopus, and (iii) Science Citation Index Expanded, from the date of inception of each database to January 2012. Search terms included: “fibrate” or “fibric acid” or “fenofibrate” or “bezafibrate” or “ciprofibrate” or “clofibrate” or “gemfibrozil”. The search was limited to randomized controlled trials (RCTs), human subjects. The Cochrane Central Register of Controlled Trials was also reviewed. The title and abstract of studies identified in the computerized search were scanned to exclude any that were clearly irrelevant. The full text of the remaining articles was read to determine whether it contained information on the topic of interest. The reference lists of the articles were reviewed to identify citations to other studies of the same topic. No language restrictions were imposed.

Inclusion and Exclusion Criteria

The studies considered in this meta-analysis were RCTs that evaluated exposure to fibrates and cancer risk. They were considered eligible if they had evaluated a fibrate therapy compared with placebo, they had a minimum duration of two years, and reported data on the incidence of and/or deaths from cancer during the trial. We excluded trials that evaluated multi-interventional therapies where the effect of the fibrate could not be separated out.

We did not assess the methodological quality of the primary studies as quality assessment in meta-analysis is controversial and results can be highly misleading [9,10]. Instead, we performed subgroup and sensitivity analyses according to study characteristics.

Data Extraction

Two reviewers (SB, GN) abstracted the data independently. The following information was collected from each study: (i) publication data: first author's last name, year of publication and geographical location of the study; (ii) study design; (iii) number of participants; (iv) population characteristics; and (v) interventions' parameters including type of drug, dose and duration. Study-level risk ratios and their 95% confidence intervals (CIs) were estimated by reconstructing contingency tables based on the number of patients randomly assigned and the number of patients who had experienced cancer events (intention-to-treat analysis). When no cancer events occurred in either or both arms, a continuity correction of 0.5 was added to each cell of the respective contingency table. Non-melanoma skin cancers were not included in the analysis because they were neither recorded nor routinely reported in the primary studies. Differences in data extraction were resolved by consensus, referring back to the original article.

Quantitative Data Synthesis

We used the inverse variance weighted approach to calculate summary effect-estimates. Outcome reporting bias was evaluated using the Begg-Mazumdar adjusted rank correlation test [11] and the Egger regression asymmetry test [12]. To evaluate whether the results of the studies were homogeneous, we used the Cochran's Q test [13]. We also calculated the quantity I^2 [14,15] that describes

the percentage variation across studies that is due to heterogeneity rather than chance. We regarded an I^2 value less than 40% as indicative of “not important heterogeneity” and a value higher than 75% as indicative of “considerable heterogeneity” [16].

Subgroup analyses by fibrate type were also performed to investigate potentially different effects on risk. We, then, conducted a sensitivity analysis by restricting the meta-analysis: (i) to trials with a minimum duration of 5 years, (ii) to trials that enrolled at least 1,000 subjects, and (iii) to major trials that fulfilled both previous criteria. Last, we performed site-specific analyses to evaluate the association between fibrate use and type of cancer diagnosis (cancer subtypes: respiratory, breast, genitourinary, prostate, gastrointestinal, colorectal and melanoma). In those analyses, only RCTs reporting at least one site-specific new cancer diagnosis were included.

We also conducted a meta-regression analysis [17] to investigate the impact of certain study characteristics on the study estimates of relative risk. We first converted all risk ratios by logarithmic transformation to achieve more symmetrical distributions. The natural logarithm of the risk ratio was the dependent variable, and (i) the mean age of participants at enrollment, and (ii) the mean duration of follow-up, were entered as covariates. This analysis was an indirect way to deal with aspects such as the possibility of effect modification by age, and to examine for increasing or decreasing risks with increasing duration of drug use, a feature often associated with causal relationships. We applied a weighted regression model, so that the more precise studies have more influence in the analysis. The weight for each trial was equal to the inverse of the sum of the within-trial variance and the residual between-trial variance, which corresponds to a random effects meta-regression analysis [18]. Estimation of the residual between-trial variance was based on a restricted maximum likelihood method [19].

This work was performed in accordance with the PRISMA statement for the conduct of meta-analyses of intervention studies [20]. For all tests, a probability level lower than 0.05 was considered statistically significant. All statistical tests were two-sided. Stata 9 software was used for the statistical analyses (Stata Corp., College Station, Texas, USA).

Results

Search Results

Our initial search yielded 3,586 literature citations (Figure 1). However, most abstracts were duplicates or did not specifically address the topic of our analysis and were excluded from full-text review. We retrieved 127 potentially relevant manuscripts. The full text was read and the reference lists were checked. We identified 20 studies of fibrates [3,21–39], which conformed to our inclusion criteria. Seventeen of these [3,21–36] evaluated adverse effects and reported data on the incidence of and/or deaths from cancer during the trial, and we were able to conduct post-hoc analyses to calculate risk ratios. For several studies, additional usable data were extracted from other publications [40–44]. All 17 studies were randomized placebo-controlled trials, and all but one [23] were double-blind.

A total of 44,929 individuals participated in these trials; 21,627 in treatment groups and 23,302 in placebo groups. The participants had a mean age of 55 years at enrollment, and the average follow-up was 5.2 years. A total of 232,000 person-years were reached. Sixteen RCTs reported data on cancer deaths during the trial [3,21–23,25–36]. The overall cancer mortality was 1.82% (762 cancer deaths during the follow-up) corresponding to a rate of 0.36% per year. On the other hand, 10

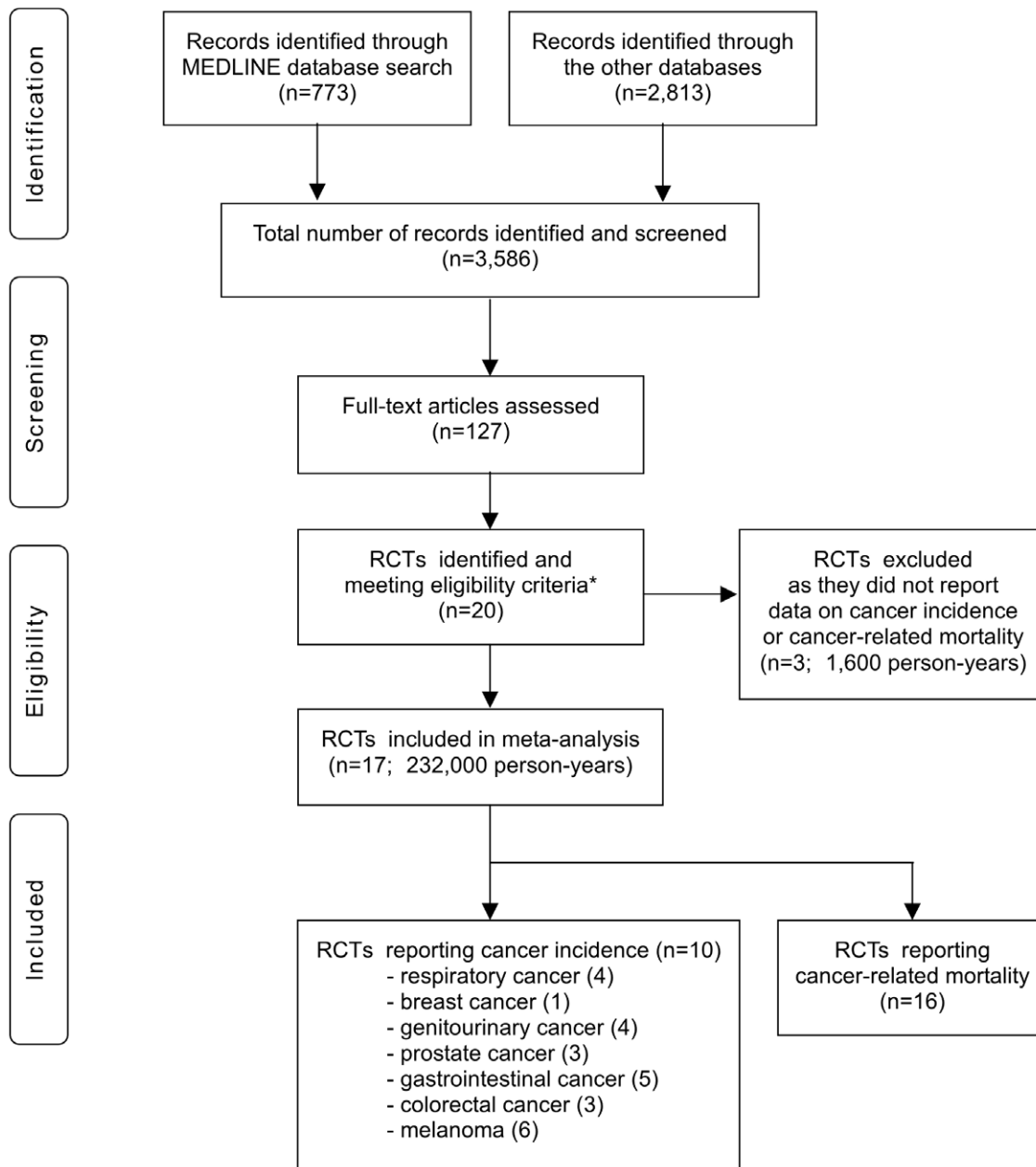


Figure 1. Flow Diagram. Footnote: * To be included in this meta-analysis, studies had to be (i) randomized trials of fibrates, (ii) placebo-controlled, and (iii) have a mean (or median) duration of patient follow-up of at least 2 years.
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RCTs reported data on new cancer diagnoses [3,22,24–26,28–30,32,36]. The overall cancer incidence was 4.48% (1,594 cancer diagnoses) corresponding to a rate of 0.86% per year.

Bezafibrate had been evaluated in four trials [22,24,31,35], clofibrate in six [3,23,25,27,33,34], fenofibrate in three [21,26,28], and gemfibrozil in four trials [29,30,32,36]. Tables 1 & 2 list the RCTs included in the meta-analysis together with the respective trial drug, the number and summary characteristics of patients, the duration of follow-up and the estimated risk ratios and their 95% CIs.

Meta-analysis of Fibrate Use and Cancer Mortality

Sixteen RCTs [3,21–23,25–36] reported data on cancer related-deaths. The meta-analysis of these trials showed no

evidence of an association between fibrate therapy and cancer mortality (RR = 1.06, 95% CI: 0.92–1.22) (Table 3). Figure 2 graphs the risk ratios and the corresponding 95% CIs from the individual studies, and the pooled results. The Cochran's Q test had a p-value of 0.90 and the corresponding I^2 was 0%, which both indicate very small between-studies variability (Table 3). The p-values for the Begg's and the Egger's tests were $p = 0.89$ and $p = 0.18$, respectively, both suggesting that the assumption of no reporting bias is reasonable.

After stratifying the data into subgroups, according to the type of fibrate, we did not find any statistically significant association between bezafibrate, clofibrate, fenofibrate or gemfibrozil use and cancer mortality (Table 3, Figure 3).

Table 1. Characteristics of studies included in the meta-analysis.

Study	Location	Agent	Design	N	(active/ placebo)	Mean age (yrs)	Follow-up (yrs)	Study population
ACCORD [21], 2010	USA, Canada	Fenofibrate	r, db, pc	5518	(2765/2753)	62.2	5.0	Type 2 DM
BECAIT [22], 1996	Sweden	Bezafibrate	r, db, pc	92	(47/45)	42.0	5.0	CAD
Begg Study [23], 1971	Scotland	Clofibrate	r, pc	155	(76/79)	56.0	3.5	Peripheral arteriopathy
BIP [24], 2000	Israel	Bezafibrate	r, db, pc	3090	(1548/1542)	60.1	6.2	CAD
CDP [25], 1975	USA, Puerto Rico	Clofibrate	r, db, pc	3892	(1103/2789)	52.0	6.2	CAD
DAIS [26], 2001	Canada, Finland, France, Sweden	Fenofibrate	r, db, pc	418	(207/211)	56.8	3.3	Type 2 DM
DIS [27], 1991	Germany	Clofibric acid	r, db, pc	761	(379/382)	46.0	5.0	NIDDM
FIELD [28], 2005	Australia, New Zealand, Finland	Fenofibrate	r, db, pc	9795	(4895/4900)	62.2	5.0	Type 2 DM
HHS [29], 1987	Finland	Gemfibrozil	r, db, pc	4081	(2046/2035)	47.3	5.0	Dyslipidemia
HHS ancillary [30], 1993	Finland	Gemfibrozil	r, db, pc	628	(311/317)	48.6	5.0	Suspected CAD
LEADER [31], 2002	United Kingdom	Bezafibrate	r, db, pc	1568	(783/785)	68.2	4.6	LEAD
LOCAT [32], 1997	Finland	Gemfibrozil	r, db, pc	395	(197/198)	59.2	2.5	CAD
NEWCASTLE [33], 1971	England	Clofibrate	r, db, pc	497	(244/253)	52.5	3.6	CAD
SCOTTISH [34], 1971	Scotland	Clofibrate	r, db, pc	717	(350/367)	52.1	3.4	CAD
SENDCAP [35], 1998	United Kingdom	Bezafibrate	r, db, pc	164	(81/83)	50.9	3.0	Type 2 DM
VA HIT [36], 1999	USA	Gemfibrozil	r, db, pc	2531	(1264/1267)	64.0	5.1	CAD
WHO [3], 1978	Scotland, Hungary, Czech Rep.	Clofibrate	r, db, pc	10627	(5331/5296)	45.9	5.3	High-cholesterol population

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; BECAIT, Bezafibrate Coronary Atherosclerosis Intervention Trial; BIP, Bezafibrate Infarction Prevention; CDP, Coronary Drug Project; DAIS, Diabetes Atherosclerosis Intervention Study; DIS, Diabetes Intervention Study; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; HHS, Helsinki Heart Study; LEADER, Lower Extremity Arterial Disease Event Reduction; LOCAT, Lipid Coronary Angiography Trial; SENDCAP, St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention; VA HIT, Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial; WHO, World Health Organization; r, randomized; db, double-blind; pc, placebo-controlled; DM, Diabetes Mellitus; CAD, Coronary Artery Disease; NIDDM, Non-Insulin-Dependent Diabetes Mellitus; LEAD, Lower Extremity Arterial Disease.

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When the analysis was restricted to studies with a minimum duration of 5 years (9 trials), we also found no evidence of an association (RR = 1.08, 95% CI: 0.93–1.26). Similarly, when only RCTs that enrolled at least 1,000 subjects contributed to the analysis (7 trials), the pooled effect estimate remained insignificant (RR = 1.08, 95% CI: 0.94–1.24) (Table 3, Figure 3). Finally, we performed a meta-analysis of six major trials [3,21,25,28,29,36] that fulfilled both previous criteria. Once again, there was no statistically significant association between fibrate use and cancer mortality (RR = 1.09, 95% CI: 0.94–1.27). In this restricted analysis, there was no evidence of reporting bias (Begg's $p = 0.99$, Egger's $p = 0.89$) or heterogeneity (Cochran's Q test: $p = 0.49$, $I^2 = 0\%$) (Table 3).

Meta-regression analysis, using the mean age of participants and the mean duration of follow-up as covariates, did not reveal any significant association (Table 4).

Meta-analysis of Fibrate Use and Cancer Incidence

Ten RCTs [3,22,24–26,28–30,32,36] reported data on new cancer diagnoses. The quantitative synthesis of these studies provided no evidence of an association between fibrate use and cancer incidence. The calculated effect estimate indicated a neutral effect of fibrates (RR = 1.02, 95% CI: 0.92–1.12) (Table 3). Figure 4 presents a forest plot of the risk ratios and their 95% CIs from the 10 primary studies, and the pooled estimates. Reporting bias (Begg's $p = 0.72$; Egger's $p = 0.28$) or significant heterogeneity

(Cochran's $p = 0.75$; $I^2 = 0\%$) were not detected in this analysis (Table 3).

The subgroup analysis, according to the type of fibrate, did not demonstrate any significant association between bezafibrate, clofibrate, fenofibrate or gemfibrozil use and cancer incidence (Table 3, Figure 5).

When we restricted the analysis to studies with a minimum duration of 5 years (8 trials), we also found no evidence of association (RR = 1.02, 95% CI: 0.93–1.13). Similarly, when only RCTs with a minimum duration of 5 years and more than 1,000 participants (6 trials) [3,24,25,28,29,36] contributed to the analysis, the summary effect estimate suggested a neutral effect of fibrates on cancer incidence (RR = 1.02, 95% CI: 0.93–1.13; Begg's $p = 0.99$; Egger's $p = 0.60$; Cochran's $p = 0.57$; $I^2 = 0\%$) (Table 3, Figure 5).

No statistically significant differences were observed between patients receiving fibrate vs placebo for any of the prespecified cancer subtypes (Table 3, Figure 5). Heterogeneity or reporting bias were not observed in any of these site-specific analyses ($p > 0.14$ for all) with the exception of gastrointestinal cancer (Egger's $p = 0.033$; Table 3).

Last, in the meta-regression analysis, the results did not show any impact of either the mean age of participants or the duration of follow-up on the study estimates of relative risk (Table 4).

In a re-analysis, excluding all trials reporting zero cancer events in either or both arms, no statistically or clinically meaningful

Table 2. Incidence of and/or deaths from cancer in the randomized placebo-controlled trials of fibrates.

Study	Incident cancer, n (%*)				Cancer deaths, n (%*)			
	Fibrate	Placebo	RR	95% CI	Fibrate	Placebo	RR	95% CI
ACCORD [21], 2010	–	–	–	–	57 (2.06)	58 (2.11)	0.98	(0.68–1.40)
BECAIT [22], 1996	1 (2.13)	1 (2.22)	0.96	(0.06–14.85)	0 (0.00)	0 (0.00)	0.96	(0.02–47.30)
Begg Study [23], 1971	–	–	–	–	0 (0.00)	0 (0.00)	1.04	(0.02–51.71)
BIP [24], 2000	85 (5.49)	91 (5.90)	0.93	(0.70–1.24)	–	–	–	–
CDP [25], 1975	32 (2.90)	79 (2.83)	1.02	(0.68–1.54)	10 (0.91)	24 (0.86)	1.05	(0.51–2.20)
DAIS [26], 2001	5 (2.42)	7 (3.32)	0.73	(0.23–2.26)	0 (0.00)	3 (1.42)	0.15	(0.01–2.80)**
DIS [27], 1991	–	–	–	–	2 (0.53)	3 (0.79)	0.67	(0.11–4.00)
FIELD [28], 2005	393 (8.03)	373 (7.61)	1.05	(0.92–1.21)	168 (3.43)	148 (3.02)	1.14	(0.91–1.41)
HHS [29], 1987	25 (1.22)	29 (1.43)	0.86	(0.50–1.46)	10 (0.49)	11 (0.54)	0.90	(0.38–2.12)
HHS ancillary [30], 1993	5 (1.61)	4 (1.26)	1.27	(0.35–4.70)	0 (0.00)	2 (0.63)	0.20	(0.01–4.23)
LEADER [31], 2002	–	–	–	–	47 (6.00)	47 (5.99)	1.00	(0.68–1.48)
LOCAT [32], 1997	3 (1.52)	7 (3.54)	0.43	(0.11–1.64)	0 (0.00)	0 (0.00)	1.01	(0.02–50.41)
NEWCASTLE [33], 1971	–	–	–	–	3 (1.23)	1 (0.40)	3.11	(0.33–29.70)
SCOTTISH [34], 1971	–	–	–	–	3 (0.86)	5 (1.36)	0.63	(0.15–2.61)
SENDCAP [35], 1998	–	–	–	–	0 (0.00)	0 (0.00)	1.02	(0.02–51.02)
VA HIT [36], 1999	125 (9.89)	138 (10.89)	0.91	(0.72–1.14)	45 (3.56)	51 (4.03)	0.88	(0.60–1.31)
WHO [3], 1978	106 (1.99)	85 (1.60)	1.24	(0.93–1.64)	40 (0.75)	24 (0.45)	1.66	(1.00–2.74)

*Crude rates;

**Reported in Saha et al. [43].

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; BECAIT, Bezafibrate Coronary Atherosclerosis Intervention Trial; BIP, Bezafibrate Infarction Prevention; CDP, Coronary Drug Project; DAIS, Diabetes Atherosclerosis Intervention Study; DIS, Diabetes Intervention Study; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; HHS, Helsinki Heart Study; LEADER, Lower Extremity Arterial Disease Event Reduction; LOCAT, Lipid Coronary Angiography Trial; SENDCAP, St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention; VA HIT, Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial; WHO, World Health Organization; RR, relative risk (risk ratio); CI, confidence interval.

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differences occurred vs the initial analyses (both for cancer mortality and cancer incidence).

Discussion

Fibrates comprise a class of lipid-lowering agents that significantly reduce cardiovascular events through a substantial reduction in serum levels of triglycerides and modest effects on levels

of low-density and high-density lipoprotein cholesterol [45,46]. The concerns that lipid-lowering drugs (including fibrates) might increase the risk of cancer have been present for three decades [6,47–51]. However, while for the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) several meta-analyses of existing data have convincingly demonstrated that they do not cause any substantial change in overall [52,53] or site-specific

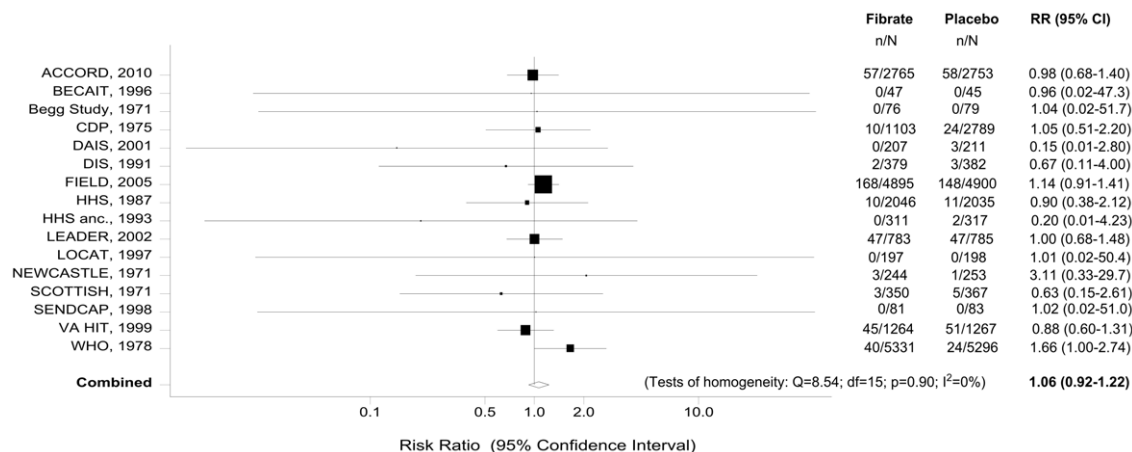


Figure 2. Forest plot of the meta-analysis of fibrate use and cancer deaths. Footnote: The risk ratios and their 95% confidence intervals are displayed on a logarithmic scale. The size of the data markers represents the relative weight of the trial according to size and occurrence of the outcome being measured.

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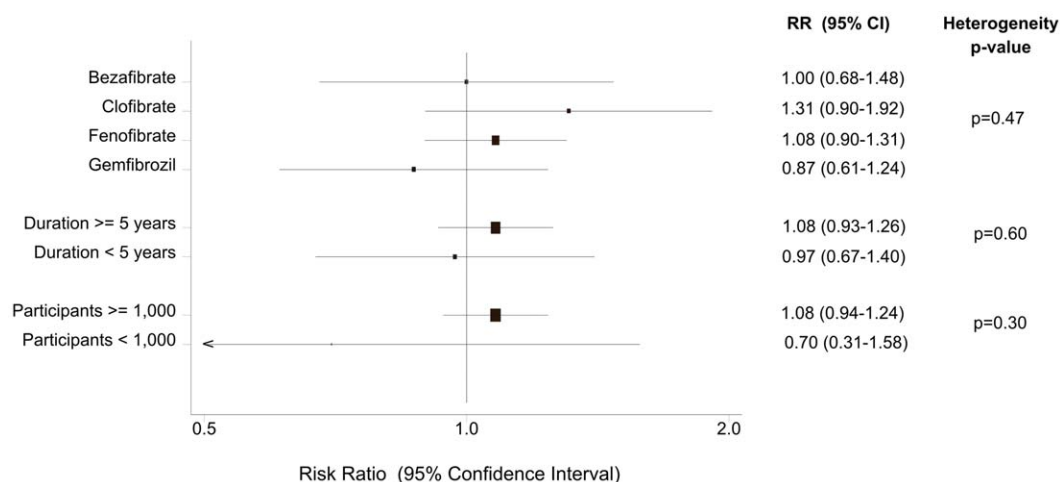
Table 3. Fibrate use and cancer risk: Meta-analysis and subgroup analysis.

	N	Pooled effect estimate		Tests of homogeneity			Tests for reporting bias	
		RR	(95% CI)	Q (d.f.)	p-value	I ²	Begg's p	Egger's p
Cancer Deaths:								
All RCTs	16	1.06	(0.92–1.22)	8.54 (15)	0.90	0%	0.89	0.18
Bezafibrate	3	1.00	(0.68–1.48)	0.00 (2)	0.99	0%	0.99	0.79
Clofibrate	6	1.31	(0.90–1.92)	2.88 (5)	0.72	0%	0.99	0.32
Fenofibrate	3	1.08	(0.90–1.31)	2.26 (2)	0.32	12%	0.30	0.077
Gemfibrozil	4	0.87	(0.61–1.24)	0.90 (3)	0.83	0%	0.31	0.43
Duration ≥5 years	9	1.08	(0.93–1.26)	5.85 (8)	0.66	0%	0.75	0.34
Participants ≥1,000	7	1.08	(0.94–1.24)	4.55 (6)	0.60	0%	0.99	0.84
Both previous criteria	6	1.09	(0.94–1.27)	4.40 (5)	0.49	0%	0.99	0.89
Cancer Incidence:								
All RCTs	10	1.02	(0.92–1.12)	5.89 (9)	0.75	0%	0.72	0.28
Bezafibrate	2	0.93	(0.70–1.24)	0.00 (1)	0.98	0%	0.99	–
Clofibrate	2	1.16	(0.92–1.47)	0.57 (1)	0.45	0%	0.99	–
Fenofibrate	2	1.05	(0.92–1.20)	0.41 (1)	0.52	0%	0.99	–
Gemfibrozil	4	0.89	(0.73–1.10)	1.47 (3)	0.69	0%	0.73	0.64
Duration ≥5 years	8	1.02	(0.93–1.13)	3.95 (7)	0.79	0%	0.99	0.81
Participants ≥1,000	6	1.02	(0.93–1.13)	3.84 (5)	0.57	0%	0.99	0.60
Both previous criteria	6	1.02	(0.93–1.13)	3.84 (5)	0.57	0%	0.99	0.60
Respiratory Cancer	4	0.99	(0.71–1.37)	1.36 (3)	0.72	0%	0.99	0.92
Breast Cancer	1	0.98	(0.63–1.53)	–	–	–	–	–
Genitourinary Cancer	4	1.11	(0.89–1.38)	2.05 (3)	0.56	0%	0.73	0.89
Prostate Cancer	3	1.25	(0.96–1.63)	1.24 (2)	0.54	0%	0.99	0.99
Gastrointestinal Cancer	5	0.91	(0.73–1.14)	5.29 (4)	0.26	24%	0.46	0.033
Colorectal Cancer	3	0.98	(0.71–1.34)	3.96 (2)	0.14	49%	0.99	0.43
Melanoma	6	0.54	(0.22–1.31)	5.50 (5)	0.36	9%	0.99	0.66

RR, risk ratio; CI, confidence interval; d.f., degrees of freedom.
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cancer risk [54–59], this is the first meta-analysis that focuses specifically on the relationship between fibrates and cancer.

Our study encompassed 17 randomized placebo-controlled trials involving 45,000 individuals with a broad range of baseline characteristics, and accrued a total experience of 232,000 person-

**Figure 3. Fibrate use and cancer deaths: Subgroup analyses.**

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Table 4. Meta-regression's results.

	Univariable analysis		
	Ratio of RR	(95% CI)	p-value
Cancer Deaths:			
- Mean age of participants (per 10-year increase)	0.89	(0.71–1.12)	0.33
- Mean duration of follow-up (per 1-year increase)	1.19	(0.81–1.74)	0.37
Cancer Incidence:			
- Mean age of participants (per 10-year increase)	0.92	(0.79–1.08)	0.33
- Mean duration of follow-up (per 1-year increase)	1.03	(0.85–1.25)	0.73

RR, risk ratio; CI, confidence interval.

Results are exponentiated regression coefficients and their 95% CIs, which show the proportional change in risk ratio for every one scale increase.

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years. The analysis did not provide any evidence that the use of fibrates significantly affects the incidence of cancer or cancer-related death. When the analysis was restricted to major RCTs, the results remained practically unchanged. Similarly, when bezafibrate, clofibrate, fenofibrate and gemfibrozil were evaluated alone, we found no impact on cancer outcomes. No significant results were also noted for cancers of the respiratory tract, breast, colon, gastrointestinal tract, prostate, genitourinary tract, or skin (melanoma) when fibrates were used.

The neutral results of the present study are in line with several well-designed observational studies that have analysed overall cancer [60,61] and site-specific cancers [62–64] in fibrate users, and exclude the strong protective effect of fibrates found in the PRIME study [65]. This large observational cohort, suggesting that cancer mortality was significantly lower in fibrate users as compared with untreated dyslipidemic subjects (hazard ratio: 0.52, 95% CI: 0.28–0.97), may have been affected by uncontrolled (unmeasured) or residual confounding or other biases, problems known to plague even well-designed observational studies because they lack the experimental random allocation of the intervention necessary to test exposure-outcome hypotheses [66].

Our study has several merits. We have conducted an extensive literature search to retrieve all relevant eligible trials. Moreover,

the absence of significant between-study heterogeneity, the small likelihood of important reporting bias, as well as the stability of results in subgroup and sensitivity analyses, reinforce our confidence in the validity of the conclusion that fibrate use has a neutral effect on cancer outcomes. The strengths of this quantitative synthesis should be, however, weighed against some limitations. First, the trials included in this meta-analysis were not designed to specifically analyze the relationship between fibrates and cancer risk. They have assessed cancer outcomes as secondary (safety) endpoints. Thus, problems in cancer detection and reporting may exist. However, the definition used and the surveillance intensity were consistent within each study for the fibrate and placebo groups, so the relative impact should still be accurate. Second, our search was restricted to published studies and we did not seek for unpublished/original data. However, we did not impose any exclusion criteria with regard to language, place of publication or study quality. Last, a main issue remaining beyond our control is cancer latency. As the exposure and follow-up times only lasted for nearly five years, estimates of cancer risk resulting from longer exposure to fibrates are not possible. Thus, our results should be interpreted with caution.

In conclusion, the synthesis of existing data from randomized placebo-controlled trials supports a neutral effect of fibrates on

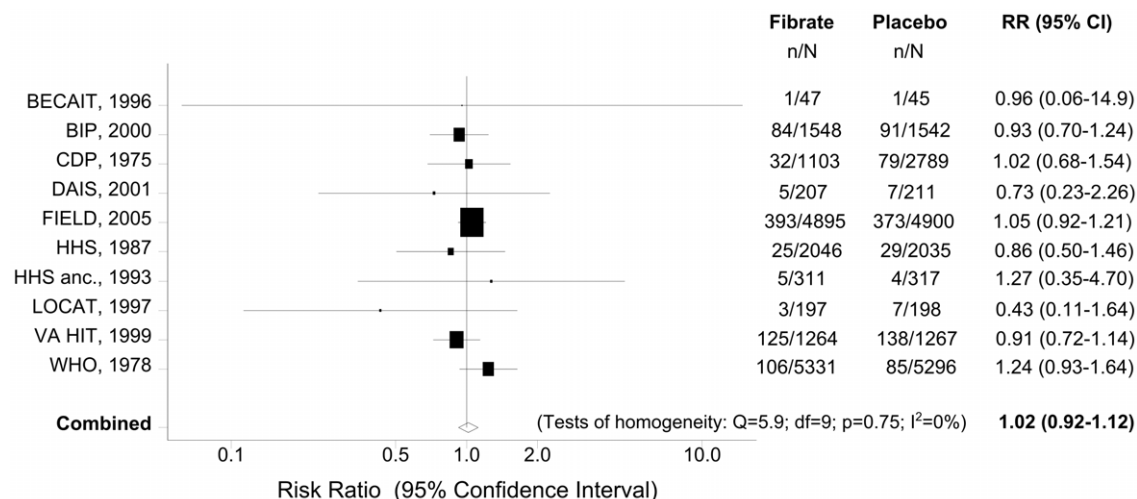


Figure 4. Forest plot of the meta-analysis of fibrate use and cancer incidence. Footnote: The risk ratios and their 95% confidence intervals are displayed on a logarithmic scale. The size of the data markers represents the relative weight of the trial according to size and occurrence of the outcome being measured.

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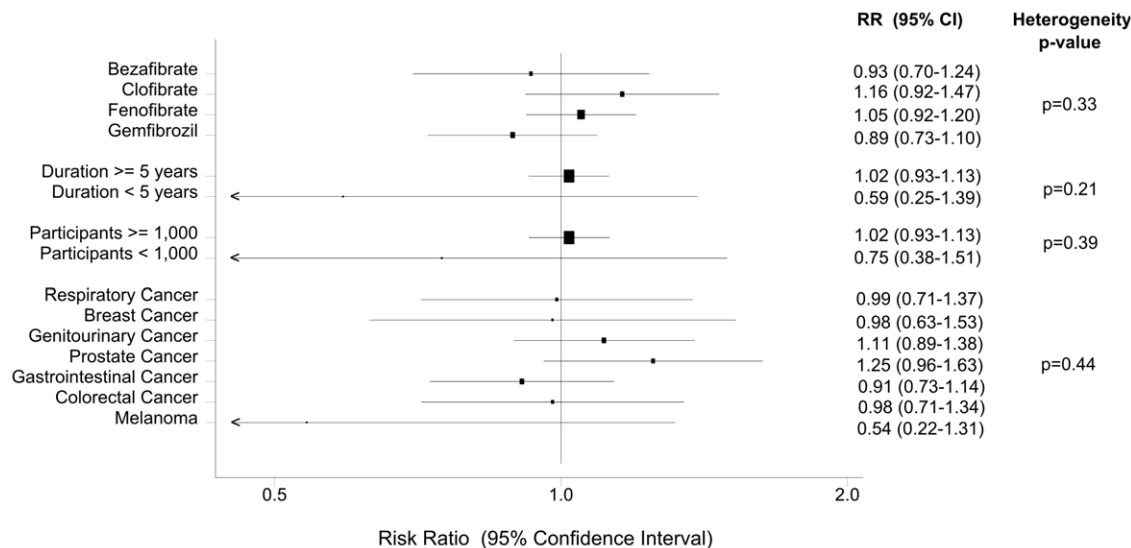


Figure 5. Fibrate use and cancer incidence: Subgroup analyses.
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cancer risk in the short term. We found no site-specific type of cancer whose risk was affected by fibrates, or subtype of fibrates that influenced the risk of cancer. However, given the steadily increasing use of fibrates during the past decade [8], and the indications for long-term and perhaps lifelong use, it is important to continue monitoring their long-term safety profiles.

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Data Access and Responsibility

Stefanos Bonovas had full access to all the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis and acts as guarantor of the paper.

Author Contributions

Study idea: SB. Study design: SB PB. Literature search: SB GN. Data collection: SB GN. Statistical analysis: SB. Data interpretation: SB GN PB. First version of the manuscript: SB. Critical revision for important intellectual content: SB GN PB. Final approval of the version to be published: SB, GN, PB.

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