Effects of Fibrates in Kidney Disease

A Systematic Review and Meta-Analysis

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Objectives The purpose of this systematic review and meta-analysis was to determine the efficacy and safety of fibrate therapy in the chronic kidney disease (CKD) population.

Background Fibrate therapy produces modest cardiovascular benefits in people at elevated cardiovascular risk. There is limited evidence about the clinical benefits and safety of fibrate therapy in the CKD population.

Methods MEDLINE, EMBASE, and the Cochrane Library were systematically searched (1950 to January 2012) for prospective randomized controlled trials assessing the effects of fibrate therapy compared with placebo in people with CKD or on kidney-related outcomes were included.

Results Ten studies including 16,869 participants were identified. In patients with mild-to-moderate CKD (estimated glomerular filtration rate [eGFR] ≤60 ml/min/1.73 m^2), fibrates improved lipid profiles (lowered total cholesterol [−0.32 mmol/l, p = 0.05] and triglyceride levels [−0.56 mmol/l, p = 0.03] but not low-density lipoprotein cholesterol [−0.01 mmol/l, p = 0.83]; increased high-density lipoprotein cholesterol [0.06 mmol/l, p = 0.001]). In people with diabetes, fibrates reduced the risk of albuminuria progression (relative risk [RR]: 0.86; 95% confidence interval [CI]: 0.76 to 0.98; p = 0.02). Serum creatinine was elevated by fibrate therapy (33 μmol/l, p < 0.001), calculated GFR was reduced (−2.67 ml/min/1.73 m^2, p = 0.01) but there was no detectable effect on the risk of end-stage kidney disease (RR: 0.85; 95% CI: 0.49 to 1.49; p = 0.575). In patients with eGFR of 30 to 59.9 ml/min/1.73 m^2, fibrates reduced the risk of major cardiovascular events (RR: 0.70; 95% CI: 0.54 to 0.89; p = 0.004) and cardiovascular death (RR: 0.60; 95% CI: 0.38 to 0.96; p = 0.03) but not all-cause mortality. There were no clear safety concerns specific to people with CKD but available data were limited.

Conclusions Fibrates improve lipid profiles and prevent cardiovascular events in people with CKD. They reduce albuminuria and reversibly increase serum creatinine but the effects on major kidney outcomes remain unknown. These results suggest that fibrates have a place in reducing cardiovascular risk in people with mild-to-moderate CKD. (J Am Coll Cardiol 2012;60:2061–71) © 2012 by the American College of Cardiology Foundation

The burden of chronic kidney disease (CKD) is large and growing, affecting 10% to 15% of the adult population (1–3). Defined as a glomerular filtration rate (GFR) below 60 ml/min/1.73 m^2 or the presence of other markers of

kidney deterioration including albuminuria or proteinuria (4) CKD is associated with increased risk of kidney failure and cardiovascular events (5–11). While preventing progressive kidney dysfunction is a core aspect of managing these individuals, the risk of cardiovascular disease is greatly elevated in people with CKD and is the leading cause of death in this population (12,13). Treatments that can prevent 1 or both of these adverse outcomes are therefore key to improving the long-term outcomes for this high-risk group.

Accumulating data suggest that a range of interventions that are effective at preventing cardiovascular disease in the general population are likely to be similarly efficacious in people with CKD. Recent evidence suggests that lipid lowering (14), antiplatelet agents (15), and blood pressure lowering (16,17) prevent cardiovascular events in CKD, and the latter may also prevent progression of renal disease (18).

A meta-analysis of studies assessing the effects of fibrates on cardiovascular events in the broader population has reported overall benefit, with consistent evidence of greater effects for subgroups with elevated triglyceride and/or decreased HDL levels (19). However, no adequately powered outcome study of fibrate therapy has been reported to date specifically in the CKD population.

While dyslipidemia is a risk factor for progressive kidney disease (8,10,20,21) the acute elevation of creatinine caused by fibrates (22) has resulted in concerns about the safety of this therapy in the CKD population (23) and there have been conflicting reports regarding the impact of fibrate therapy on kidney function (24,25).

In this systematic review, we sought to synthesize the available clinical trial evidence to better define any benefits of fibrate therapy on kidney-related outcomes and on cardiovascular events in people with CKD, as well as any adverse effects.

Methods

Data sources and searches. We performed a systematic review of the literature according to the PRISMA statement for the conduct of meta-analyses of intervention studies. Relevant studies were identified by searching the following data sources: MEDLINE via Ovid (from 1950 to January 2012), EMBASE (from 1966 to January 2012), and the Cochrane Library database (Cochrane Central Register of Controlled Trials; no date restriction), using relevant text words and medical subject headings that included all spell-

ings of *fibrate, clofibrate, clofibric acid, bezafibrate, gemfibrozil, fenofibrate, procetofen, renal insufficiency, kidney failure, chronic kidney disease, albuminuria, serum creatinine, mortality, cardiovascular disease, myocardial infarction, revascularization,* and *stroke.* The search was limited to randomized controlled trials but without language restriction. Reference lists from identified trials and review articles were manually scanned to identify any other relevant studies. The U.S. government's Clinical Trials database was also searched for randomized trials that were registered as completed but not yet published.

Study selection. The literature search, data extraction, and quality assessment were conducted independently by 2 authors (M.J. and B.Z.) using a standardized approach. All completed randomized controlled trials assessing the effects of a fibrate compared to placebo that reported 1 or more of the primary or secondary outcomes were eligible for inclusion.

Data extraction and quality assessment. Published reports were obtained for each trial and standard information was extracted into a spreadsheet. The data sought included baseline patient characteristics (age, sex, history of diabetes, creatinine, renal function, lipid levels, and body mass index), fibrate used, dose of drug, follow-up duration, change in lipid levels, outcome events, and adverse events. Study quality was judged by the proper conduct of randomization, concealment of treatment allocation, similarity of treatment groups at baseline, the provision of a description of the eligibility criteria, completeness of follow-up, and use of intention-to-treat analysis, and was quantified using the Jadad score (26). Any disagreement in abstracted data was adjudicated by a third reviewer (V.P.). Attempts were made to contact individual authors of included studies to seek additional data wherever possible. A total of 6 authors were contacted, and additional data were received from 1 author.

To investigate the effects of fibrates on major clinical outcomes, additional unpublished summary level data on a subgroup (n = 399) of the VA-HIT (Veterans Affairs High-Density Lipoprotein Intervention Trial) was sought and obtained.

Outcomes. We collected data on lipid profiles (total cholesterol, triglyceride, low-density lipoprotein [LDL], and high-density lipoprotein [HDL]), albuminuria, serum creatinine and renal function changes, end-stage kidney disease (ESKD), major clinical outcomes (cardiovascular events, cardiovascular death, stroke, all-cause mortality), and adverse events.

Data synthesis and analysis. Individual study relative risks (RRs) and 95% confidence intervals (CIs) were calculated from event numbers extracted from each trial before data pooling. In calculating risk ratios, the total number of patients randomized in each group was used as the denominator. For continuous parameters, weighted mean differences were calculated using end-of-trial mean values, their corresponding standard deviations and treatment arm size. Summary estimates of relative risk ratios were obtained using a random effects model. The percentage of variability

across studies attributable to heterogeneity beyond chance was estimated using the I^2 statistic (27). Potential publication bias was assessed using the Egger test and represented graphically using Begg funnel plots of the natural log of the RR versus its standard error (28).

A 2-sided p value <0.05 was considered statistically significant. Statistical analyses were performed with Stata, version 9.2 (StataCorp, College Station, Texas) and RevMan, version 5.1 (Cochrane IMS, Copenhagen, Denmark).

Results

Search results and characteristics of included studies. The literature search yielded 2,142 articles, of which 26 were reviewed in full text (Fig. 1). Of these, 8 randomized controlled trials published in 10 articles met the inclusion criteria, including a total of 16,869 patients (24,25,29–36). Of the identified articles, 3 were post-hoc analyses (25,33,36) and 2 were subsequent pre-specified analyses (24,34) of randomized controlled trials in people with a previous history of coronary heart disease or type 2 diabetes. Three studies reported the effect of fibrate therapy on lipid profiles in patients with mild to moderate kidney disease

defined as estimated glomerular filtration rate (eGFR) ≤60 ml/min/1.73 m² (31,32,36). Three studies reported the effect of fibrate therapy on serum creatinine levels (29,30,32). Three studies reported sufficient data on renal function changes by treatment allocation for pooling to be possible (25,31,32). Two studies reported major cardiovascular events and all-cause mortality according to baseline eGFR (34,36). The majority of other studies identified by our search did not examine fibrate therapy, examined fibrates in combination with other drug classes, compared fibrates to other drug classes, were not original investigations, or were duplicates of reports already identified.

Table 1 summarizes the characteristics of the included studies. The trials had a sample size that ranged from 24 to 9,795 participants with follow-up periods that ranged from 3 months to 5.1 years. Of the 8 trials identified, 2 were single-center studies, 5 were multicenter studies, and 1 was unspecified. Studies were conducted in some or all of the United States, Canada, Europe, and Oceania. Two trials assessed the effects of gemfibrozil (25,31), 2 assessed bezafibrate (29,30), and 4 assessed fenofibrate (24,32,33,35). The trial results were published between 1992 and 2011.
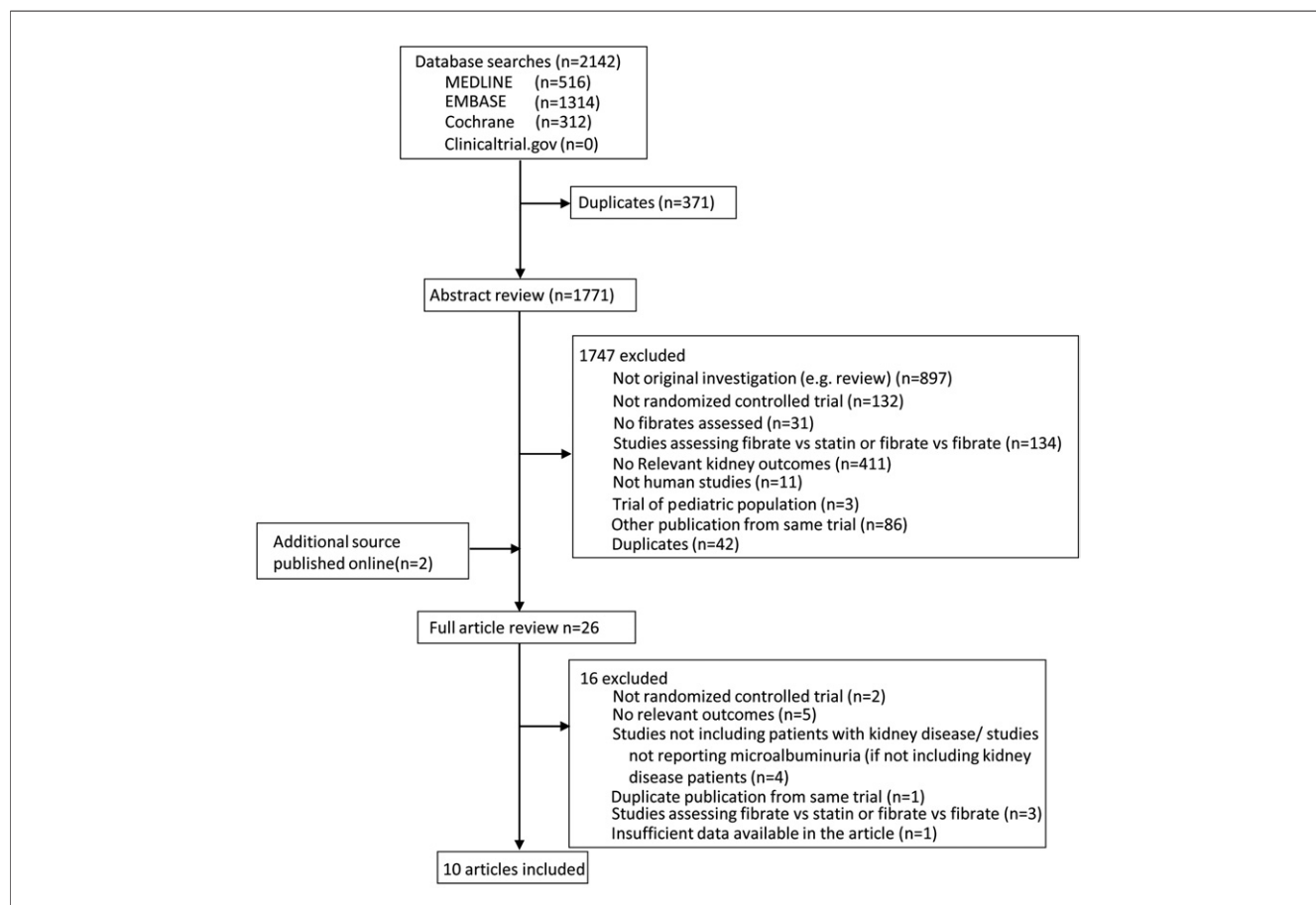

Figure 1   **Identification of Eligible Studies**

The flowchart depicts the process in which the eligible studies to be included in the systematic review and meta-analysis were identified.

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| Table 1 | Characteristics of Studies Reporting the Effects of Fibrates on Kidney-Related Outcomes |

First Author (Ref. #)	Inclusion Criteria	Treatment Group	Placebo	Design (Country of Origin)	Duration of Follow-Up (Mean)	n	Mean Age (yrs)	Male (%)	Diabetes (%)	Baseline Cholesterol (mmol/l)	Mean Baseline SCr (μmol/l)	Mean Baseline eGFR (ml/min/1.73 m^2)
Barbir et al. (29)	Chol >6.5 mmol/l, TG >2.8 mmol/l	Bezafibrate	Fish oil	Randomized single center (United Kingdom)	3 months	87	53	90	0	7.3	140 ± 4	NR
Bruce et al. (30)	Diabetic nephropathy, mild renal impairment, dyslipidemia (chol >6.2 mmol/l, TG >2.3 mmol/l, HDL <0.9 mmol/l)	Bezafibrate (400 mg daily)	Placebo	Randomized unspecified number of centers (New Zealand)	6 months	24	58	NR	100	7.2	108 ± 27 in bezafibrate 102 ± 17 in placebo	91
Samuelsson et al. (31)	Non-nephrotic, nondiabetic, "moderately advanced CRI"	Gemfibrozil (300–900 mg daily)	Dietary counseling	Randomized single center (Sweden)	1 yr	57	51	75	0	6.30	187	CrCl 35.5
Levin et al. (32)	CrCl 20–74 ml/min1.73 m^2, TG ≥2.23 mmol/l or LDL/HDL chol ratio ≥5; age 20–70 yrs	Fenofibrate (67–201 mg daily)	Dietary counseling	Randomized multicenter (Canada)	6 months	28	57	82	54	6.36	186 ± 72 in fenofibrate 190 ± 96 in placebo	CrCl 46.5
Tonelli et al. VA-HIT post-hoc subgroup (36)	Original trial: age <74 yrs, history of CHD, absence of serious coexisting conditions, HDL ≤1.0 mmol/l, LDL ≤3.6 mmol/l, and TG 3.4 mmol/l. In this publication, mild CRI defined as CrCl 60–75 ml/min and moderate CRI as 30–59.9 ml/min	Gemfibrozil (1,200 mg daily)	Placebo	Randomized multicenter (United States)	5.1 yrs (median)	1,046*	67	100	28	4.5	NR	MDRD 62.1; CrCl 61.5
Tonelli et al. VA-HIT post-hoc subgroup analysis (25)	Original trial: Age <74 yrs, history of CHD, absence of serious coexisting conditions, HDL ≤1.0 mmol/l, LDL ≤3.6 mmol/l, and triglyceride 3.4 mmol/l. In this publication, moderate CRI defined as MDRD GFR 30–59.9 ml/min/1/73 m^2	Gemfibrozil (1,200 mg daily)	Placebo	Randomized multicenter (United States)	5.1 yrs (median)	399†	67	100	30	4.35	NR	MDRD 52.2; CrCl 59.7
Ansquer et al. DAIS post-hoc subgroup analysis (33)	Original trial: Age 40–65 yrs, type 2 DM, lipid profile total cholesterol-to-HDL ratio of 4 plus either LDL 3.5–4.5 mmol/l, trig ≤5.2 mmol/l, or TG 1.7–5.2 mmol/l and LDL ≤4.5 mmol/l	Fenofibrate (200 mg daily)	Placebo	Randomized multicenter (Canada, Finland, France, and Sweden)	3.3 yrs	314‡	57	76	100	5.54	88 ± 18 (fenofibrate arm); 80 ± 9 (placebo arm)	NR

Table 1   Continued

First Author (Ref. #)	Inclusion Criteria	Treatment Group	Placebo	Design (Country of Origin)	Duration of Follow-Up (Mean)	n	Mean Age (yrs)	Male (%)	Diabetes (%)	Baseline Cholesterol (mmol/l)	Mean Baseline SCr (µmol/l)	Mean Baseline eGFR (ml/min/1.73 m²)
ACCORD (35)	Type 2 DM being treated with simvastatin	Fenofibrate (160 mg daily initially)	Placebo	Randomized multicenter (United States and Canada)	4.7 yrs	5518	62	69	100	4.53	80 ± 18	>50 (97%)
Davis et al. (24) and Ting et al. (34) FIELD pre-specified analyses	Original trial: age 50–75 yrs, type 2 DM according to WHO criteria and not on statin therapy	Fenofibrate (200 mg daily)	Placebo	Randomized multicenter (Australia, New Zealand, and Finland)	5 yrs	9795	62	63	100	5.0	77.7 ± 15.9 (fenofibrate arm); 77.4 ± 15.7 (placebo arm)	NR

*Original trial (VA-HIT [Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial]) included 2,531 participants of whom 1,046 participants had chronic renal insufficiency (CRI) defined by creatinine clearance of ≤75 ml/min. †Original trial (VA-HIT) included 2,531 participants of whom major cardiovascular outcomes for 399 participants were separately sought and obtained from study investigators. ‡Original trial (DAIS [Diabetes Atherosclerosis Intervention Study]) included 418 participants of whom 314 participants had urinary albumin measurements available.

CHD = coronary heart disease; chol = cholesterol; CrCl = creatinine clearance; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MDRD = Modification of Diet in Renal Disease; NR = not reported; RCT = randomized controlled trial; TG = triglyceride; WHO = World Health Organization.

The mean age of the study participants ranged between 51 and 67 years. Males represented the majority of the participants in all but 1 of the studies identified (1 did not report the proportion of sex), ranging from 63% to 100% (29,31–33,35–38). Four studies were undertaken exclusively among patients with diabetes (24,30,33,35). Five studies had specific lipid profile requirements for trial entry (25,29,30,32,33).

In multicenter studies, 2 studies reported the use of a central laboratory for the measurement of albuminuria and/or serum creatinine (32,35), 2 reported the use of 2 core laboratories (33,37), and 1 reported using local laboratories located in the area of the participating sites (38).

The risk of bias was assessed using key indicators of trial quality (Online Table 1). Earlier smaller studies provided few details about the process of randomization, concealment of allocation, and the use of intention-to-treat analysis techniques. Double blinding was reported to have been used in 4 studies (32,35,37,38), with 1 reporting that renal outcomes such as serum creatinine measurements were performed by individuals blinded to study treatment (38). Overall, 4 trials had a Jadad score of 4 (24,25,32,35), 1 scored 3 (33), 2 scored 2 (29,31), and 1 scored 1 (30). In sensitivity analyses that excluded the studies with a Jadad score of ≤3, the overall point estimates for the key outcomes including lipid profiles and serum creatinine were similar to the primary analysis.

Effects of fibrate therapy. LIPID PROFILES. In patients with mild-to-moderate kidney disease, fibrate therapy significantly lowered total cholesterol (−0.32 mmol/l; 95% CI: −0.64 to −0.00 mmol/l; p = 0.05) and triglyceride levels (−0.56 mmol/l; 95% CI: −1.06 to −0.06 mmol/l; p = 0.03), but had no effect on LDL levels (−0.01 mmol/l; 95% CI: −0.11 to 0.09; p = 0.83). There was evidence of moderate (I^2 = 48%, p = 0.15) and significant (I^2 = 72%, p = 0.03) heterogeneity for the outcomes of total cholesterol and triglyceride levels, respectively. Fibrate therapy significantly increased HDL levels (0.06 mmol/l; 95% CI: 0.04 to 0.08 mmol/l; p < 0.001) with no evidence of heterogeneity of effects (I^2 = 0.0%, p = 0.50) (Fig. 2). Gemfibrozil, compared with fenofibrate, tended to be more efficacious in improving triglyceride levels but not total cholesterol, LDL, or HDL levels.

ALBUMINURIA. Three trials, including 14,385 participants and 3,883 events, reported data regarding the progression of albuminuria (24,35). In type 2 diabetes patients, fibrate therapy reduced the risk of albuminuria progression (relative risk [RR]: 0.86; 95% CI: 0.76 to 0.98; p = 0.02), with moderate evidence of heterogeneity (I^2 = 63%, p for heterogeneity = 0.06) (Fig. 3). Two trials, including 2,152 participants and 919 events, reported data regarding the regression of albuminuria (24,33) with fibrate therapy significantly increasing the likelihood of albuminuria regression (RR: 1.19; 95% CI: 1.08 to 1.31; p = 0.0005) (Fig. 3).

SERUM CREATININE AND RENAL FUNCTION. Serum creatinine was significantly elevated with fibrate therapy (32.6
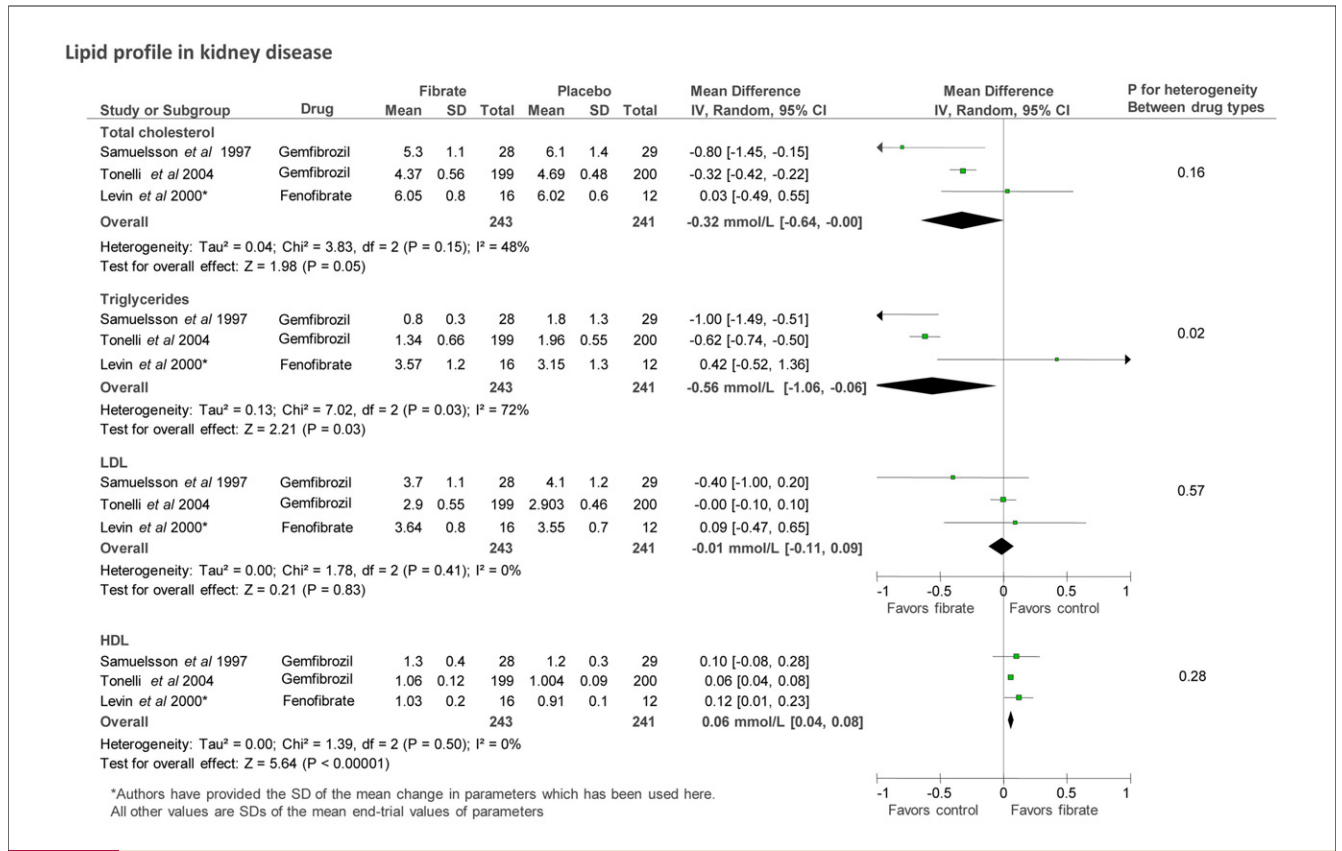
Figure 2   Effect of Fibrates on Lipid Profiles

Effect of fibrates (gemfibrozil and fenofibrate) compared with placebo on total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). CI = confidence interval.

μmol/l; 95% CI: 21.6 to 43.7 μmol/l; p < 0.001), and eGFR was reduced (-2.67 ml/min/1.73 m^2; 95% CI: -4.81 to -0.54 ml/min/1.73 m^2) with no evidence of heterogeneity (I^2 = 0.0%, p > 0.50 for both serum creatinine and eGFR changes) (Fig. 4).

One study measured kidney function in a subset of the total population after study medication had been ceased. A reduction in eGFR was noted during study treatment, but this was reversed off therapy where eGFR levels were higher in the group that had been treated with long-term fenofi-
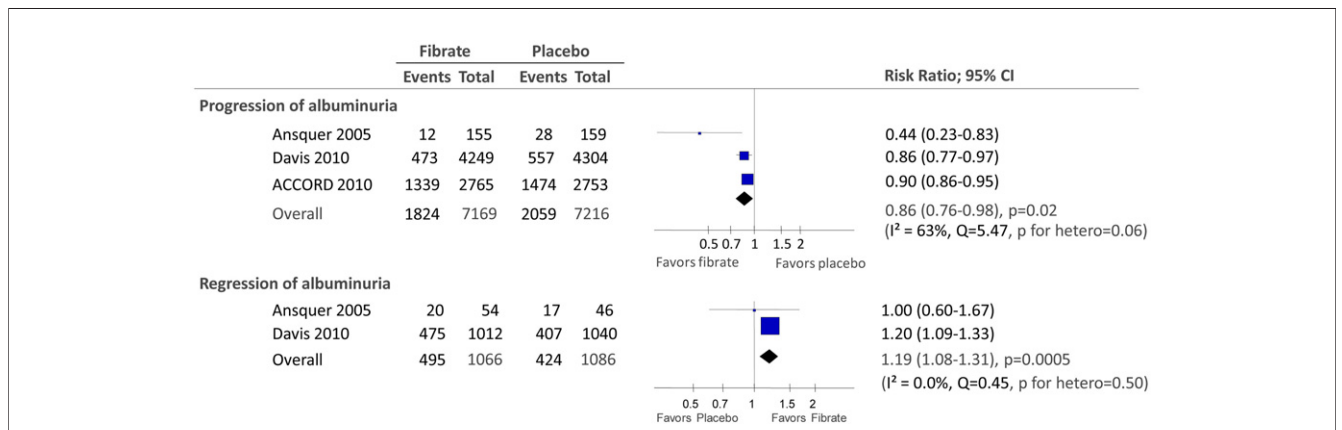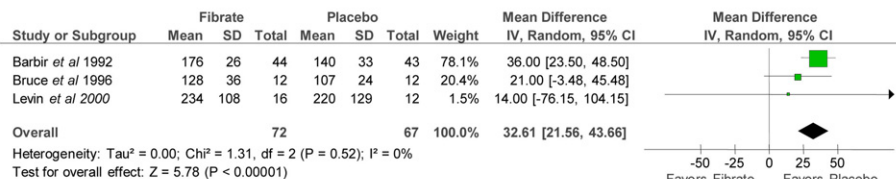

Figure 3   Effect of Fibrates on Albuminuria

Effect of fibrates on the progression and regression of albuminuria. CI = confidence interval.
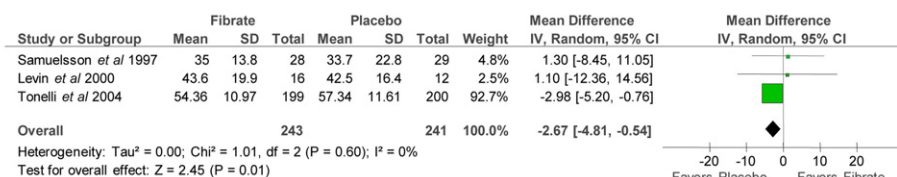
Figure 4   **Effect of Fibrates on Serum Creatinine and Kidney Function**

Effect of fibrates on kidney-related outcomes including serum creatinine and kidney function measured by the glomerular filtration rate. Samuelsson et al. (31) measured glomerular filtration rate (GFR) based on plasma or renal clearance of ^{51}Cr-EDTA; Levin et al. (32) measured creatinine clearance; Tonelli et al. (38) calculated estimated GFR using the MDRD (Modification of Diet in Renal Disease) study equation. CI = confidence interval.

brate (total eGFR loss 5.8 vs. 9.9 ml/min/1.73 m², p < 0.001) (24).

END-STAGE KIDNEY DISEASE. Two studies, with follow-up durations of 1 and 5 years, including 9,852 participants among whom 50 events were observed reporting on the effect of fibrates on ESKD (24,31) and found no clear effect (Fig. 5) (RR: 0.85; 95% CI: 0.49 to 1.49; p = 0.575).

MAJOR CARDIOVASCULAR OUTCOMES. Two studies that included 12,326 participants over a follow-up duration of 5 years reported the effect on major cardiovascular events (n = 1,970), cardiovascular death (n = 377), stroke (n = 467), and all-cause mortality (n = 1,097) according to baseline renal function (25,34). Patients with moderate renal impair-

ment fibrate therapy produced a 30% (p = 0.004) reduction in the risk of major cardiovascular events with no evidence of heterogeneity (I² = 0.0%, p = 0.72) and a 40% (p = 0.032) reduction in the risk of cardiovascular death with no evidence of heterogeneity (I² = 0.0%, p = 0.44) (Fig. 6). Fibrate therapy had no clear effect on cardiovascular death in patients with eGFR ≥60 ml/min/1.73 m² (p for heterogeneity = 0.066). Fibrate therapy had no overall effect on the risk of stroke or all-cause mortality (Fig. 6).

ADVERSE EVENTS. There were several adverse outcomes reported although only by a limited number of trials. One study reported mild gastrointestinal symptoms in the gemfibrozil group (6 of 28) (31) with another reporting epigastric pain in
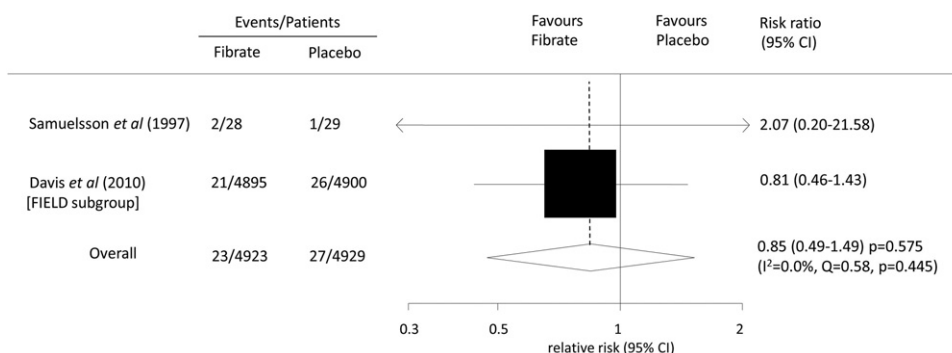

Figure 5   **Effect of Fibrates on End-Stage Kidney Disease**

Effect of fibrates on progression to end-stage kidney disease. CI = confidence interval.
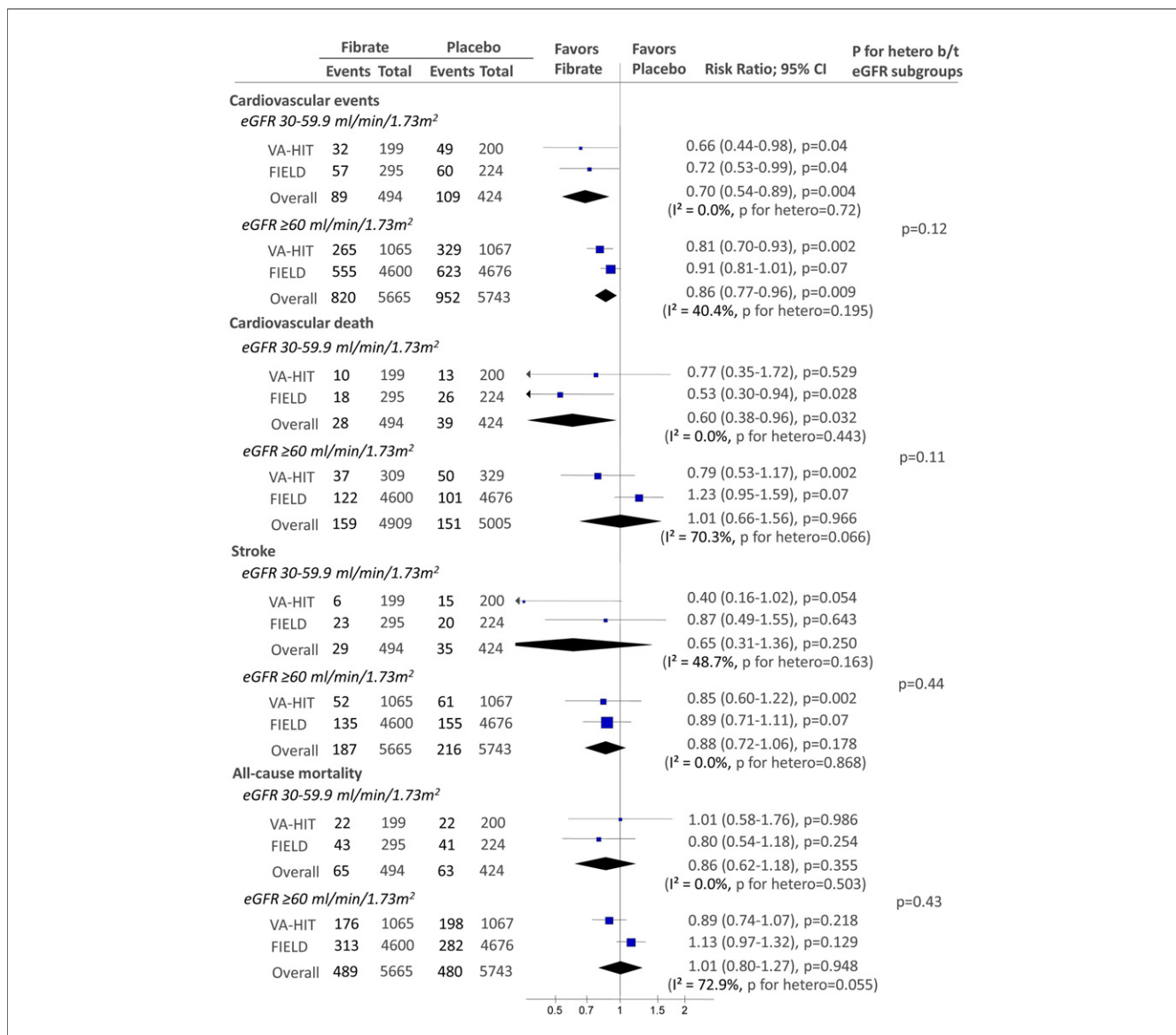
Figure 6   Effect of Fibrates on Major Clinical Outcomes in Patients With CKD

Effect of fibrates on cardiovascular disease and all-cause mortality according to estimated glomerular filtration rate (eGFR) category.
CI = confidence interval; CKD = chronic kidney disease.

1 patient receiving fenofibrate (1 of 12) (31). One study reported no differences in depression, nondermatological malignancy, or skin cancer (25). Nausea, leg cramps, headaches, tonsillitis, and gouty arthritis were also reported (29). One study conducted in people with type 2 diabetes, reported a small increase in the risk of pancreatitis (23 [0.5%] vs. 40 [0.8%]; p = 0.031) and pulmonary embolism (32 [0.7%] vs. 53 [1%]; p = 0.022). However, these results were not specific for the CKD subgroup but were for the entire trial (37).

Due to limited availability of data and differences in reporting methods, it was not possible to quantitatively combine adverse events to produce a summative result.

PUBLICATION BIAS. Formal statistical testing to assess for publication bias was not possible due to the limited avail-

ability of data and different reporting methods employed by the studies. However, examination of funnel plots of outcomes with 3 or more studies did not suggest the presence of publication bias (Online Fig. 1).

Discussion

This quantitative review has 2 major findings. First, the available data suggests that fibrate therapy reduces the risk of cardiovascular events in patients with CKD including protection against cardiovascular death. The effects in people with CKD appeared at least as large as the effects in people with normal kidney function, although formal statistical testing to confirm this was limited by sample size. Second, the available data demonstrates that fibrate therapy

is associated with an acute reduction in eGFR. A recent post hoc analysis of the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study suggested that this is likely to be reversible and that it may mask an underlying benefit for kidney function. Further support for this is provided by the observed reductions in proteinuria with fenofibrate. There were no clear safety concerns specific to the CKD population identified, but available data were limited. While a large outcome trial conducted specifically in this population is required to more clearly define these effects, the available data support the overall safety and potential benefits of this class of agents (39,40).

The graded association between CKD stage and cardiovascular risk highlights the urgent need to identify beneficial therapies for this population (41). Fibric acid derivatives are effective in improving lipid profiles and reducing the risk of cardiovascular events with evidence showing greater efficacy of fibrates in people with baseline hypertriglyceridemia (19,42). The higher levels of triglycerides and the lower HDL levels in the CKD population therefore provide a strong rationale for expecting greater magnitudes of benefit in CKD. Other mechanisms specific to CKD populations could also explain our findings. For example, levels of kidney function and albuminuria have been shown to be strong and independent predictors of cardiovascular risk, and it is possible that the observed beneficial effects on albuminuria (and perhaps the putative benefits for kidney function suggested in the FIELD study) could also lead to long-term cardiovascular benefit. These results suggest net benefit if fibrates are used more widely in people with kidney disease. However, there are currently no data available for individuals with more severe levels of kidney dysfunction (eGFR <30 ml/min/1.73 m^2), and the available data come from subgroup analyses of trials in broader populations. Of note, the recent SHARP (Study of Heart and Renal Protection) trial clearly demonstrated that statin-based LDL lowering prevents cardiovascular events in CKD patients, particularly those with early disease (14). Few of the participants in the trials included in the current review were treated with statins, so that the effects of combined treatment remain uncertain. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial participants all received statins but the effects on cardiovascular outcomes in the CKD population have not been reported. This would be of great interest. Nonetheless, a new trial specifically designed and powered to define the potential protective effects of these agents in people with a range of levels of kidney dysfunction treated with statins would therefore be valuable.

As well as uncertainty about efficacy, the use of fibrates in patients with kidney disease has been limited due to safety concerns related to the documented increases in serum creatinine (43,44), associations with increased hospitalization and nephrologist consultations (45), and with uncertainty about the implications for longer-term renal outcomes. The National Kidney Foundation and the National Lipid Association have both made recommendations for the cautious use of fibrates in patients with CKD based on this perceived risk (40). Drug-induced elevations in serum creatinine have been reported in those with mild to moderate renal failure (46) and renal transplant recipients (47,48), however, the mechanism behind this elevation is unclear. A potential mechanism explaining the change in serum creatinine with fibrate therapy is interference in the generation of vasodilatory prostaglandins by fibrates due to the activation of peroxisome proliferator–activated receptors (49) causing a change in renal blood flow and consequently increasing serum creatinine and reducing GFR. Hottelart and colleagues reported that serum creatinine was elevated with fenofibrate but without evidence of a reduction in GFR as assessed by inulin clearances (46). The authors proposed that creatinine production may be increased with fibrate therapy but that GFR remains unchanged. These potential explanations have supported the view that the drug-induced elevations in serum creatinine does not reflect a true deterioration of renal function and many studies reporting this rise as a transient phenomenon have further strengthened this view (44,50). Indeed, the reduction in eGFR may not be paralleled by a reduction in directly measured GFR using inulin (24,37). Post-trial studies of the FIELD and ACCORD trials have explored the drug-induced serum creatinine elevation and have improved our knowledge regarding the safety of fibrate therapy. A post-hoc analysis from the FIELD study reported that plasma creatinine levels in a cohort of 661 "substudy washout participants" 8 weeks after withdrawal from study treatment were significantly lower in participants who had received fenofibrate compared to placebo (p < 0.001) suggesting longer-term renoprotective effects despite the initially elevated serum creatinine (24). Similarly, reversibility in acute increases in creatinine has been described amongst participants in the ACCORD study (50). Taken together, these results suggest that the acute changes in creatinine with fibrate therapy do not translate into adverse effects on major clinical renal outcomes, and indeed suggest the possibility of long-term renal benefit. This provides another strong rationale for an outcome trial specifically conducted in people with CKD. Adverse events reporting was inconsistent, limiting the conclusions that can be drawn, however, no specific adverse outcomes were noted to be specifically elevated in CKD.

This systematic review has comprehensively searched the literature for available evidence regarding the effects of fibrate therapy in patients with CKD. It highlights the relative paucity of data in the field, particularly in patients with advanced kidney disease (eGFR <30 ml/min/1.73 m^2). In addition, the risk of bias assessments of the individual trials have shown that some of the studies were of suboptimal quality in terms of providing adequate descriptions of allocation concealment and lacking the use of double-blinding. Adequate reporting of quality indicators is a validated measure of the quality of trial conduct, strongly related to the internal validity of randomized controlled trials (51). Therefore,

selection bias may be a possibility in some of these trials. The lack of double-blinding may leave open the possibility of information and ascertainment bias, which may particularly be an issue when assessing subjective outcomes such as renal outcomes (52). These biases could lead to overestimation of benefit or underestimation of harm.

Study limitations. This review has limitations primarily resulting from the scarcity of current trial evidence. Although we were able to obtain new unpublished data to assess the effects of fibrate therapy on major clinical outcomes, only 2 trials (both of which were conducted in people with type 2 diabetes) reported outcomes by baseline level of kidney function. Insufficient data were available to allow separate analysis of effects in people with and without diabetes. The majority of the studies identified were small and lacked power to detect clinically important effects of fibrates, particularly on advanced renal outcomes such as ESKD. None of the studies we identified included people with advanced CKD (eGFR <30 ml/min/1.73 m^2) and therefore our results cannot be extrapolated to these individuals. One study reported the use of fish oil as the placebo, which may be a potential confounder as fish oil is known to modify lipid profiles, however, the inclusion of this study does not substantially impact on the overall outcome of this review as the study did not contribute to the results on lipid profile or cardiovascular outcomes. In addition, differences in reporting methods restricted the pooling of data. Performing analyses based on published summary level data limited the capacity to fully explore the effects of fibrate therapy in CKD patients and there remains significant potential for an overview based on individual patient data to provide more insight into the effects of fibrates based on CKD stage.

Conclusions

Fibrate therapy improves lipid profiles and prevents cardiovascular events in people with kidney disease. Albuminuria is also improved in patients with type 2 diabetes mellitus and while serum creatinine is increased there is no evidence that this translates into long-term adverse effects on kidney function in any population studied. Patients with advanced CKD represent a high-risk population and our findings suggest that assessing the benefits of fibrates in people with advanced CKD should be a high priority. In the meantime, these results suggest that fibrates could be used more broadly in patients with mild to moderate CKD to prevent cardiovascular disease.

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Key Words: chronic kidney disease ■ fibrate ■ meta-analysis ■ systematic review ■ triglyceride cholesterol.

▶ **APPENDIX**

For a supplementary table and figure, please see the online version of this article.