

Chapter 5: Triglyceride-lowering treatment in adults

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5.1: In adults with CKD (including those treated with chronic dialysis or kidney transplantation) and hypertriglyceridemia, we suggest that therapeutic lifestyle changes be advised. (2D)

RATIONALE

Non-pharmacological treatment of high triglycerides

TLC includes dietary modification, weight reduction, increased physical activity, reducing alcohol intake, and treatment of hyperglycemia (if present). Evidence that TLC will reduce serum TGs in patients with CKD is weak. However, the elements of TLC are unlikely to lead to harm and may improve general health. In the opinion of the Work Group, it is reasonable to advise patients with high fasting levels of serum TGs (> 5.65 mmol/l [> 500 mg/dl]) to adopt TLC. Dietary changes that may reduce serum TGs include a low-fat diet ($< 15\%$ total calories), reduction of monosaccharide and disaccharide intake, reducing the total amount of dietary carbohydrates, and use of fish oils to replace some long-chain TGs. Dietary modification should be used judiciously, if at all, in individuals who are malnourished. This is a weak recommendation that is based on very low quality evidence.

Pharmacological treatment of high triglycerides: effects on risk of pancreatitis

Although previous guidelines have suggested the use of fibric acid derivatives for preventing pancreatitis from severe hypertriglyceridemia,¹ the evidence supporting the safety and efficacy of this approach is extremely weak, especially in patients with CKD. Therefore, the Work Group no longer recommends this approach, especially since statins appear to prevent pancreatitis in people with normal or mildly elevated TGs.⁸⁸

Fibric acid derivatives could be considered for the rare patients with CKD and markedly elevated fasting levels of serum TG (> 11.3 mmol/l [> 1000 mg/dl]). If such therapy is prescribed, fibric acid derivatives must be dose-adjusted for kidney function. There is limited evidence to recommend one fibric acid derivative over another in the setting of CKD and therefore any of the alternatives may be used. As mentioned in Chapter 2, concomitant therapy with both a fibric acid derivative and a statin is not recommended in patients with CKD due to the potential for toxicity.

Nicotinic acid has not been well studied in advanced CKD and therefore is not recommended for treatment of severe hypertriglyceridemia, given the risk of toxicity (especially flushing and hyperglycemia).

The Work Group considered a weak recommendation against the use of fibric acid derivatives in people with CKD. However, in the judgment of the Work Group, there is insufficient evidence to recommend for or against the use of fibric acid derivatives in this population. Treatment with fibric acid derivatives might be warranted in patients who place a relatively high value on preventing pancreatitis, and a relatively low value on the risks of polypharmacy and drug toxicity.

Pharmacological treatment of high triglycerides: effects on cardiovascular risk

A meta-analysis of data from 18 randomized trials involving 45,058 participants drawn from the general population (i.e., not specific to CKD) demonstrated a modest 10% RR reduction (95% CI 0–18; $p = 0.048$) in major cardiovascular events and a 13% RR reduction in coronary events (95% CI 7–19; $p < 0.0001$) for fibrate therapy. But such benefits are smaller than the 20% reduction in vascular events and 10% reduction in mortality demonstrated by statins per mmol/l reduction in LDL-C.^{14,89,90}

As mentioned in Chapter 1, the dyslipidemia associated with CKD appear particularly suited to therapy with fibric acid derivatives, which alter triglyceride-rich lipoproteins more than LDL-C, the main target of statins. This observation has raised the hypothesis that fibrates might be especially effective for preventing vascular events in CKD populations.

Randomized treatment trials that examined the effect of fibrates relative to placebo in patients with diabetes and CKD are summarized below. The Veterans' Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) found evidence that gemfibrozil reduces risk of major cardiovascular events (i.e., fatal CHD, nonfatal MI, and stroke) by 42% compared with placebo (RR 0.58; 95% CI 0.38–0.89) in a *post hoc* analysis of 297 individuals with low eGFR (GFR < 75 ml/min/1.73 m²) and diabetes.⁹¹

The Diabetes Atherosclerosis Intervention Study (DAIS)⁹² and the FIELD study⁹³ reported that fenofibrate treatment significantly lowered the risk of developing new-onset microalbuminuria compared with placebo (RR 0.87 in patients with type 2 diabetes; 95% CI 0.77–0.97). In a pooled analysis of these two trials, fenofibrate also promoted regression from microalbuminuria to normoalbuminuria (RR1.15; 95% CI 1.04–1.28; $n = 2260$). None of the other trials of fibrate therapy in diabetes reported CVD or kidney disease outcomes for the subgroup of patients with CKD.

The FIELD study was a large randomized double-blind trial in which 9795 participants aged 50–75 years with type 2

diabetes were allocated to micronized fenofibrate 200 mg daily or matching placebo, and followed for a median of 5 years.⁹³ Patients were eligible if there was no clear indication for, or treatment with, lipid-modifying therapy at study entry, and patients with renal impairment, defined as a plasma creatinine $>130 \mu\text{mol/l}$ ($>1.47 \text{ mg/dl}$), were excluded. There was a significant difference in the proportion of participants with progression of albuminuria, analyzed categorically to/from normo-, micro-, and macro-albuminuria (466 [9.5%] progressing and 462 [9.4%] regressing in the fenofibrate group vs. 539 [11.0%] progressing and 400 [8.2%] regressing in the placebo group; i.e., 2.6% more patients were regressing or not progressing in those allocated fenofibrate than placebo, $p=0.002$). Importantly, only 5% (519 of 9795) of the randomized participants had a baseline eGFR below $60 \text{ ml/min/1.73 m}^2$, so only 117 cardiovascular events occurred in this subgroup. The significant treatment effects presented for those with eGFR below $60 \text{ ml/min/1.73 m}^2$ (for the outcomes of coronary revascularization, cardiovascular mortality, and total cardiovascular events) were based on too few events to be reliable. Hence, there was not good evidence that the treatment effects on vascular outcomes differed between those with and without lower baseline eGFR.

Ting and colleagues also considered whether allocation to fenofibrate affected renal function but were unable to conclusively address this issue due to lack of statistical power.⁹⁴ Another paper, which provides more detailed renal analyses from FIELD, suggested that after excluding the $10\text{--}12 \mu\text{mol/l}$ ($0.11\text{--}0.14 \text{ mg/dl}$) step-rise in creatinine on commencing fenofibrate, allocation to fenofibrate was in fact associated with a slower rate of change in eGFR (-1.19 vs. -2.03 , absolute difference $\sim 1 \text{ ml/min/1.73 m}^2$ per year; $p < 0.001$).⁹⁵ But the inaccuracy of eGFR above $60 \text{ ml/min/1.73 m}^2$ and the use of surrogate outcomes such as rate of change in eGFR and albuminuria remain important caveats. Furthermore, allocation to fenofibrate was also associated with an increased risk of doubling of plasma creatinine (148 [3.0%] vs. 90 [1.8%], $p < 0.001$), which cannot simply be explained by the small step-rise in creatinine.

ACCORD Lipid, the other large randomized trial which investigated the effect of fibrates in type 2 diabetic patients, assessed the addition of fenofibrate 160 mg daily to simvastatin $10\text{--}40 \text{ mg}$ daily (dose modified over time in response to changing guidelines) in 5518 participants.⁹⁶ Again, this study excluded patients with impaired kidney function, creatinine $>133 \mu\text{mol/l}$ ($>1.5 \text{ mg/dl}$), such that only 141 participants had baseline eGFR below $50 \text{ ml/min/1.73 m}^2$. Ultimately too few participants with eGFR $<60 \text{ ml/min/1.73 m}^2$ were included in either FIELD or ACCORD Lipid to provide reliable information on either the safety or efficacy of fenofibrate in this group.

A recent large observational study in patients aged ≥ 66 years demonstrated a clear association between new

prescriptions for fibric acid derivatives and increased SCr levels, as well as a small increase in the risk of hospitalization and nephrologist consultation.⁹⁷ These findings contribute to the uncertainty that fibric acid derivatives would yield net clinical benefit in people with CKD.

For these reasons, use of fibric acid derivatives to reduce cardiovascular risk is not recommended in patients with CKD.

Suggested Audit Criteria

Given the lack of evidence to support this recommendation, no audit criteria are suggested.

KEY POINTS

- TLC should be recommended to adults with CKD and hypertriglyceridemia.
- Fibric acid derivatives are not recommended to prevent pancreatitis or reduce cardiovascular risk in adults with CKD and hypertriglyceridemia.

RESEARCH RECOMMENDATIONS

- There are currently no published randomized trials of fibric acid derivatives in CKD populations and too few participants with CKD were included in previous trials to provide reliable information. Other agents, such as niacin and the cholesteryl ester transfer protein inhibitor anacetrapib are currently being investigated in clinical trials in the general population and deserve investigation in CKD patients.
- CKD registries should report hypertriglyceridemia-induced pancreatitis to identify true incidence.
- Studies should be conducted to confirm that pancreatitis due to TG levels above 11.3 mmol/l (1000 mg/dl) is infrequent in HD patients.

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