What primary care clinicians should know about fenofibrate for people with diabetes

Alicia J Jenkins, Andrzej S Januszewski, Emma S Scott, Anthony C Keech

It has been proven that improving modifiable vascular risk factors of diabetes has a positive effect on clinical outcomes. Statins are commonly prescribed for people with type 1 and type 2 diabetes, and their use achieves similar LDL-cholesterol lowering and cardiovascular benefit as people without diabetes. The oral drug fenofibrate is less commonly used than statins, yet has been shown to have major protective effects for people with type 2 diabetes, in particular for microvascular complications. In this article, the authors briefly review fenofibrate, its mechanisms of action, proven clinical benefits in type 2 diabetes and practical aspects of its prescription.

Fenofibrate
Pharmacokinetics
Fenofibrate, a peroxisome proliferator-activated receptor alpha (PPAR-alpha) agonist, is a once-daily oral medication, which predominantly lowers TG and small dense LDL-C and increases HDL-C and apolipoprotein A1 levels, thus reversing a common (adverse) lipid profile in people with type 2 diabetes. The active form of fenofibrate is fenofibric acid, with activation occurring at the gut wall and by circulating esterases. Fenofibric acid’s half-life is approximately 20 hours and it is excreted predominantly renally, with approximately 25% being excreted in faeces (Monthly Index of Medical Specialties [MIMS], 2015; Davis et al, 2011). Due to its predominant renal excretion, fenofibrate dosage is recommended to be reduced with significant renal impairment and is contraindicated if the estimated glomerular filtration rate (eGFR) is less than 10 mL/min/1.73 m².
Handbook, 2015; MIMS, 2015 [Table 1]). There is no consistency in the prescribing practices of fenofibrate globally. Fenofibrate dosage reduction is recommended in Australia, the United Kingdom and the USA if eGFR is <60 mL/min/1.73 m² and in Canada once eGFR <100 mL/min/1.73 m² (Ting et al, 2012).

Mechanisms of action

In addition to direct benefits via improved lipid profiles, there are multiple mechanisms by which fenofibrate may act, and we and others have recently reviewed this area (Ansquer et al, 2009; Chen et al, 2013; Noonan et al, 2013). Activation of the nuclear PPAR-alpha receptor – which is widely expressed, especially in retinal, renal, vascular and neural tissue – by fenofibrate activates or represses over 100 mammalian genes, influencing processes such as lipid, lipoprotein and prostaglandin metabolism, angiogenesis (including via inhibition of anti-vascular endothelial growth factor [VEGF]-related pathways in the eye), apoptosis, inflammation (via NF-κB inhibition) and many intracellular signalling pathways (Chen et al, 2011; Chen et al, 2013; Noonan et al, 2013).

Clinical benefits of fenofibrate in type 2 diabetes

Lipid profile benefit

Fenofibrate lowers fasting TG levels by 20–50% and increases HDL-C levels by 10–20%, though by smaller amounts in people with diabetes, and may lower LDL-C by about 5–20% (Keech et al, 2005). Uncommonly, in the setting of severe hypertriglyceridaemia, LDL-C levels can rise rather than fall, due to fenofibrate promoting VLDL catabolism to LDL, with large drops in TG levels and (unmeasured) VLDL levels. Even without significant LDL-C lowering, fenofibrate redistributes LDL subclasses; lowering levels of small dense (lipid poor) LDL and increasing more buoyant larger (cholesterol rich) LDL particles. There is mixed evidence, reviewed in Tziomalos and Athyros (2006), as to whether fenofibrate lowers levels of proatherogenic/prothrombotic lipoprotein(a).

Severe hypertriglyceridaemia (fasting TG >10mmol/L) can cause acute pancreatitis (O’Callaghan et al, 2014), and fenofibrate (unless contraindicated) should be first-line therapy for the prevention and treatment of this condition.

Vascular complications

The FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) and ACCORD (Action to Control Cardiovascular Risk in Diabetes) Lipid studies are two large trials that aimed to examine the effects of long-term fibrate therapy on coronary heart disease event rates in people with diabetes. Whilst the primary end-points of the FIELD (n=9795; Keech et al, 2005) and ACCORD Lipid (n=5518; ACCORD Study Group, 2010a) studies of fenofibrate were not positive overall, in both studies these same end-points were positive among individuals with typical diabetic dyslipidaemia. Both trials also showed similar lipid benefits: TC, LDL-C and TG reduction of 11%, 12% and 29% respectively and HDL-C increase of 5%, in fenofibrate-allocated group, relative to placebo in FIELD (Keech et al, 2005) and 4.1%, 1.3% and 21.9% reduction and 4.6% increase respectively in ACCORD Lipid (ACCORD Study Group, 2010a). This pattern is identical to three earlier fibrate studies (Manninen et al, 1992; Robins et al, 2001; Tenenbaum et al, 2005), where cardiovascular benefits are largely limited to those with HDL-C and TG abnormalities, though the reasons for this remains poorly understood. Furthermore, fenofibrate had many statistically and clinically significant benefits on pre-stated cardiovascular and microvascular end-points in both trials, summarised in Table 2.

<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73 m²)</th>
<th>Dose</th>
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<tbody>
<tr>
<td>&gt;60</td>
<td>145 mg once daily</td>
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<tr>
<td>20–60</td>
<td>96 mg once daily</td>
</tr>
<tr>
<td>10–20</td>
<td>48 mg once daily</td>
</tr>
<tr>
<td>&lt;10</td>
<td>Contraindicated</td>
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</table>

eGFR=estimated glomerular filtration rate.

| “There is no consistency in the prescribing practices of fenofibrate globally.” |
In FIELD, fenofibrate reduced silent myocardial infarction by 16%, acute coronary syndromes by 18%, hospitalisations for revascularisations by 21%, and lowered CVD events in high TG/low HDL-C individuals with type 2 diabetes by 11% (Keech et al, 2005; Burgess et al, 2007). Also in the FIELD Study, fenofibrate significantly reduced the need for any ocular laser treatment by 37%, including 36% for maculopathy and 38% for proliferative DR (Keech et al, 2007; Noonan et al, 2013). Fenofibrate was also renoprotective for both eGFR and albuminuria (Davis et al, 2011). Amputations (of any vascular type) were also reduced by 37% in the FIELD study, being driven by a 47% reduction in first minor amputation without large-vessel disease and 19% (non-significant) reduction of first major or minor amputation in patients with large-vessel disease (Rajamani et al, 2009). Peripheral neuropathy, as assessed by light touch sensation using a 10 g monofilament, was also significantly reduced and even reversed by fenofibrate (Noonan et al, 2013; Rajamani et al, 2015).

The ACCORD Lipid Study, in which all patients were on background statin therapy (simvastatin 20–40 mg), also demonstrated similar benefits for CVD in people with dyslipidaemia and type 2 diabetes (Riddle, 2010), and more generally for retinopathy (ACCORD Study Group, 2010b) and nephropathy (Papademetriou et al, 2015). The ACCORD Study group have not reported amputation data. Clinical benefits are summarised in Table 2. Importantly, all the reported microvascular benefits of fenofibrate were shown to occur independently of traditional lipid levels. This is in contrast to the CVD event reductions and, of note, CVD events were significantly reduced in people with type 2 diabetes with marked dyslipidaemia (27% relative risk reduction; 95% confidence interval [CI], 9–42; \( P=0.005 \) [Scott et al, 2009]).

Based on the FIELD and ACCORD Lipid retinopathy outcomes, the Therapeutic Goods Administration (TGA) approved oral fenofibrate for use in Australia for the secondary prevention of DR in type 2 diabetes. As yet there are no published trials of fenofibrate use in type 1 diabetes or type 2 diabetes alongside laser, intra-ocular VEGF injections and corticosteroid injections, but such trials are in progress.

### Clinical aspects
Fenofibrate – which can be prescribed by a GP, specialist doctor, or nurse practitioner with prescribing rights – is usually very well-tolerated.
with low rates (<2%) of side-effects, mainly related to uncommon myalgia (Keech et al., 2005), elevated abnormal liver function tests or photosensitive skin rash (Ansquer et al., 2009). Fenofibrate induces a small increase (averaging about 12%) in serum creatinine levels and a corresponding reduction in calculated (but not real) GFR (Davis et al., 2011; Ting et al., 2012). In the FIELD study, there was a small but statistically significant increase in acute pancreatitis and pulmonary emboli (Keech et al., 2005), not evident in the smaller ACCORD Lipid trial. Hence fenofibrate should be avoided in such patients (except those with severe hypertriglyceridaemia). Fenofibrate, uniquely among fibrates, is metabolised predominantly by pathways distinct from those used for statins clearance. Therefore, as demonstrated by the ACCORD Lipid trial. Hence, among “statin drop-ins” in the FIELD Study, fenofibrate is well-tolerated in combination with statin therapy. Fenofibrate is the only fibrate currently recommended for combination therapy with a statin (Jones and Davidson, 2005; Vasudevan and Jones, 2006), as other fibrates tend to compete with statins for hepatic metabolism pathways.

In conjunction with glucose, blood pressure, weight and LDL-C control and not smoking, fenofibrate should be considered for use in adults with type 2 diabetes and with high TG/low HDL-C for CVD prevention and for those individuals with type 2 diabetes with existent DR, or diabetic macular oedema. As yet, fenofibrate is not indicated in Australia for renoprotection or protection against amputation or diabetic neuropathy. Contraindications to fenofibrate use include severe renal disease (eGFR <10 mL/min/1.73 m²), gallbladder disease, severe liver disease (AST and ALT levels over three times the upper limit of normal range), and previous pancreatitis (unless due to severe hypertriglyceridaemia), pulmonary embolus or fenofibrate hypersensitivity (e.g. photosensitive skin rash; MIMS, 2015). The TGA approved fenofibrate for prevention of established retinopathy progression in December 2013, without a specific Pharmaceutical Benefits Scheme (PBS) listing for this new indication. However, a PBS script for fenofibrate may be given as per the PBS general statement for lipid-lowering drugs, and hence the majority of people with type 2 diabetes are likely to qualify based on high-CVD risk, using the same criteria for PBS-subsidised statin therapy (summarised in Table 3).

Monitoring of fenofibrate should be the same as monitoring of statins (e.g. lipids, renal and liver function and creatine kinase if muscle symptoms arise). If severe renal dysfunction develops (i.e. GFR <60 mL/min/1.73 m²), the fenofibrate dosage should be reduced (Australian Medicines Handbook, 2015).

### Summary

In two major randomised placebo-controlled trials, the FIELD and ACCORD Lipid studies, oral fenofibrate has shown multiple protective effects in adults with type 2 diabetes and to be very well tolerated. In individuals with type 2 diabetes, fenofibrate should be considered in addition to lifestyle changes and blood pressure, glycaemic and LDL-C control. Adults with type 2 diabetes who qualify for PBS-subsidised statin therapy also qualify for PBS-subsidised fenofibrate on the same grounds.

### Table 3. Criteria for Pharmaceutical Benefits Scheme-subsidised statin and/or fibrate therapy.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Diabetes + age</td>
<td>≥60 years</td>
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<tr>
<td>Diabetes + ethnicity</td>
<td>Indigenous</td>
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<tr>
<td>Type 2 diabetes comorbidities</td>
<td>Microalbuminuria, Symptomatic coronary artery disease, Symptomatic cerebrovascular artery disease, Symptomatic peripheral vascular disease</td>
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<tr>
<td>Diabetes + lipid profile</td>
<td>Fasting total cholesterol &gt;5.5 mmol/L after ≥6 weeks’ diet therapy, Fasting triglycerides &gt;8 mmol/L</td>
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<tr>
<td>Family history</td>
<td>Premature coronary artery disease, Peripheral vascular disease</td>
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**Page points**

1. Fenofibrate is the only oral fibrate recommended to be safe to use with a statin due to low risk of rhabdomyolysis.
2. Fenofibrate should be considered in individuals with type 2 diabetes in addition to lifestyle changes and blood pressure, glycaemic and LDL-C control.


ACCORD Study Group (2010b) Effects of medical therapies on


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