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

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Article points

1. Major clinical trials have demonstrated protective effects of oral fenofibrate against diabetic retinopathy (DR), nephropathy and some cardiovascular events in people with type 2 diabetes.
2. There are multiple mechanisms by which fenofibrate may protect against the vascular and neurologic complications of diabetes, including molecular and cell-signalling effects, modulation of lipids, effects on growth factors and anti-inflammatory and anti-oxidant properties.
3. Fenofibrate has been approved by the Therapeutic Goods Administration for the secondary prevention of DR in type 2 diabetes, but does not have a specific PBS-listing for this indication. However, most people with type 2 diabetes qualify under current lipid/cardiovascular disease risk criteria, exactly the same as they qualify for statins.

Key words

- Cardiovascular disease
- Fenofibrate
- Risk factors

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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.

Diabetes mellitus affects approximately 8% of Australians and is associated with high rates of vascular complications, including diabetic retinopathy (DR), nephropathy, neuropathy and cardiovascular disease (CVD), which are associated with high personal burden and healthcare costs. Major risk factors for diabetic complications include long diabetes duration, poor glycaemic control, hypertension, smoking, renal dysfunction, dyslipidaemia and adiposity (Pedersen and Gaede, 2003; Jenkins et al, 2004). There are proven therapies relating to modifiable risk factors that improve diabetes outcomes, though unfortunately many individuals do not meet all recommended treatment targets. Lipid drugs, in particular "statins", are commonly prescribed for people with type 1 and type 2 diabetes, and they gain similar LDL-cholesterol (LDL-C) lowering and CVD benefit as people without diabetes (Cholesterol Treatment Trialists' [CTT] Collaborators, 2008). The triglyceride (TG)-lowering/HDL-C-elevating 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, we 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 Specialities [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 m^2 (Australian Medicines

Table 1. Recommended fenofibrate dose in Australia accordingly to eGFR (creatinine clearance; MIMS, 2015).

eGFR (mL/min/1.73 m²)	Dose
>60	145 mg once daily
20–60	96 mg once daily
10–20	48 mg once daily
<10	Contraindicated

eGFR=estimated glomerular filtration rate.

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*.

"There is no consistency in the prescribing practices of fenofibrate globally."

Table 2. Percentage reduction of vascular complications with fenofibrate relative to placebo in the FIELD and ACCORD Lipid studies.

Outcomes	FIELD	ACCORD Lipid
Primary outcomes*	-11 (Keech et al, 2005)	-8 (ACCORD Study Group, 2010a)
Secondary outcomes		
Silent myocardial infarction	-16 (Burgess et al, 2010)	Not available
Death from cardiovascular cause†	-4 (Burgess et al, 2010)	-14 (ACCORD Study Group, 2010a)
Coronary revascularisation‡	-21¶ (Keech et al, 2005)	-6 (ACCORD Study Group, 2010a)
Stroke (fatal or non-fatal)	-10¶ (Keech et al, 2005)	+5 (ACCORD Study Group, 2010a)
Any amputation due to diabetes	-36¶ (Rajamani et al, 2009)	Not available
Microvascular outcomes		
Retinopathy§	-37¶ (Keech et al, 2007)	-40¶ (ACCORD Study Group, 2010b)
Albuminuria‖	-14 (Keech et al, 2005; Davis et al, 2011)	-8¶ (ACCORD Study Group, 2010a)
First minor (only) amputation	-46¶ (Rajamani et al, 2009)	Not available

*FIELD: First myocardial infarction or coronary heart disease death; ACCORD Lipid: First non-fatal myocardial infraction or stroke or death from cardiovascular causes.

†FIELD: Fatal myocardial infarction; ACCORD Lipid: Death from cardiovascular cause.

‡FIELD: Coronary revascularisation; ACCORD Lipid: Revascularisation or hospitalisation for congestive heart failure (together with primary outcome).

§FIELD: All events, laser treatment; ACCORD Lipid: Laser treatment and/or vitrectomy and/or 3-step Early Treatment Diabetic Retinopathy (ETDR) scale progression.

‖FIELD: Progression (normo- to microalbuminuria or from micro- to macroalbuminuria) separately, FIELD study also reported a significant 18% increase in albuminuria regression (from macro- to microalbuminuria or from micro- to normoalbuminuria) in response to fenofibrate therapy versus placebo (Keech et al, 2005; Davis et al, 2011); ACCORD Lipid: microalbuminuria incidence (post-randomisation).

¶$P<0.05$ (unadjusted for multiple comparisons).

FIELD=Fenofibrate Intervention and Event Lowering in Diabetes; ACCORD=Action to Control Cardiovascular Risk in Diabetes.

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 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 m^2), 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.

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

Condition	Criteria
Diabetes + age	≥60 years
Diabetes + ethnicity	Indigenous
Type 2 diabetes comorbidities	Microalbuminuria Symptomatic coronary artery disease Symptomatic cerebrovascular artery disease Symptomatic peripheral vascular disease
Diabetes + lipid profile	Fasting total choloesterol >5.5 mmol/L after ≥6 weeks' diet therapy Fasting triglycerides >8 mmol/L
Family history	Premature coronary artery disease Peripheral vascular disease

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 m^2), 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 (by statins). Uniquely among fibrates, fenofibrate can be safely used with statin therapy. Adults with type 2 diabetes who qualify for PBS-subsidised statin therapy also qualify for PBS-subsidised fenofibrate on the same grounds. ■

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 (2010a) Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* **362**: 1563–74

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

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retinopathy progression in type 2 diabetes. *N Engl J Med* **363**: 233–44

Ansquer JC, Foucher C, Aubonnet P, Le Malicot K (2009) Fibrates and microvascular complications in diabetes–insight from the FIELD study. *Curr Pharm Des* **15**: 537–52

Australian Medicines Handbook (2015) *Australian Medicines Handbook 2015.* AMH Pty Ltd, Adelaide, SA. Available at: http://amhonline.amh.net.au/ (accessed 07.10.16)

Burgess DC et al (2007) Abstract 3693: Effects of fenofibrate on silent myocardial infarction, hospitalization for acute coronary syndromes and amputation in type 2 diabetes: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Circulation* **116**(Suppl 16): II_838

Burgess DC, Hunt D, Li L et al (2010) Incidence and predictors of silent myocardial infarction in type 2 diabetes and the effect of fenofibrate: an analysis from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Eur Heart J* **31**: 92–9

Chen Y et al (2011) Mechanisms for the therapeutic effect of fenofibrate on diabetic retinopathy in type 1 diabetes models. Presented at: *American Diabetes Association 71st Scientific Sessions*. San Diego, Ca, USA, June 24–28

Chen Y, Hu Y, Lin M et al (2013) Therapeutic effects of PPAR-alpha agonists on diabetic retinopathy in type 1 diabetes models. *Diabetes* **62**: 261–72

Cholesterol Treatment Trialists' (CTT) Collaborators (2008) Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* **371**: 117–25

Davis TM, Ting R, Best JD et al (2011) Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. *Diabetologia* **54**: 280–90

Jenkins AJ, Rowley KG, Lyons TJ et al (2004) Lipoproteins and diabetic microvascular complications. *Curr Pharm Des* **10**: 3395–418

Jones PH, Davidson MH (2005) Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am J Cardiol* **95**: 120–2

Keech A, Simes RJ, Barter P et al (2005) Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* **366**: 1849–61

Keech AC, Mitchell P, Summanen PA et al (2007) Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* **370**: 1687–97

Manninen V, Tenkanen L, Koskinen P et al (1992) Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation* **85**: 37–45

Monthly Index of Medical Specialities (2015) *Fenofibrates*. Haymarket Media Group Ltd, London, UK. Available at: http://www.mims.com.au (accessed 07.10.16)

Noonan JE, Jenkins AJ, Ma JX et al (2013) An update on the molecular actions of fenofibrate and its clinical effects on diabetic retinopathy and other microvascular end points in patients with diabetes. *Diabetes* **62**: 3968–75

O'Callaghan CJ, Rong P, Goh MY (2014) National guidelines for the management of absolute cardiovascular disease risk. *Med J Aust* **200**: 454–6

Papademetriou V, Lovato L, Doumas M et al (2015) Chronic kidney disease and intensive glycemic control increase cardiovascular risk in patients with type 2 diabetes. *Kidney Int* **87**: 649–59

Pedersen O, Gaede P (2003) Intensified multifactorial intervention and cardiovascular outcome in type 2 diabetes: the Steno-2 study. *Metabolism* **52**(8 Suppl 1): 19–23

Rajamani K, Colman PG, Li LP et al (2009) Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomised controlled trial. *Lancet* **373**: 1780–8

Rajamani K et al (2015) Abstract 18987: Fenofibrate reduces peripheral neuropathy in type 2 diabetes: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. *Circulation* **122**(Suppl 21): A18987

Riddle MC (2010) Effects of intensive glucose lowering in the management of patients with type 2 diabetes mellitus in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Circulation* **122**: 844–6

Robins SJ, Collins D, Wittes JT et al (2001) Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA* **285**: 1585–91

Scott R, O'Brien R, Fulcher G et al (2009) Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetes Care* **32**: 493–8

Tenenbaum A, Motro M, Fisman EZ et al (2005) Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome. *Arch Intern Med* **165**: 1154–60

Ting RD, Keech AC, Drury PL et al (2012) Benefits and safety of long-term fenofibrate therapy in people with type 2 diabetes and renal impairment: the FIELD Study. *Diabetes Care* **35**: 218–25

Tziomalos K, Athyros VG (2006) Fenofibrate: a novel formulation (Triglide) in the treatment of lipid disorders: a review. *Int J Nanomedicine* **1**: 129–47

Vasudevan AR, Jones PH (2006) Effective use of combination lipid therapy. *Curr Atheroscler Rep* **8**: 76–84

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