Fibrate therapy for dyslipidaemia and prevention of cardiovascular disease

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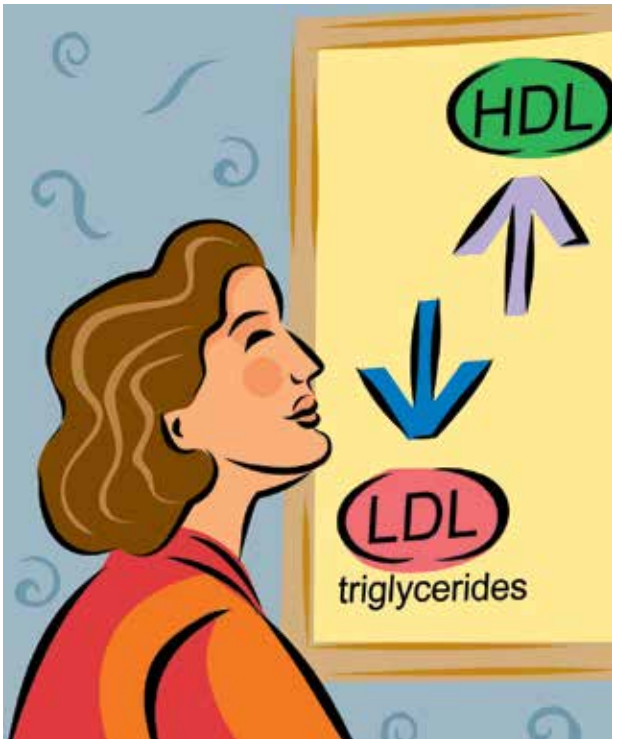
The main use of fibrates is for the treatment of dyslipidaemia to lower plasma triglyceride levels and to raise HDL-cholesterol (HDL-C) levels. The effects of fibrates on LDL-cholesterol levels vary. Fibrates may be used either as monotherapy or in combination with statins. When combined with statins, fenofibrate is the preferred fibrate as it has a low risk of myopathy. The benefits of fibrate therapy in preventing ischaemic cardiovascular disease events appear to be confined to patients with baseline dyslipidaemia (raised triglyceride levels and/or low HDL-C levels).

What are fibrates?

Fibrates are peroxisome proliferator-activated receptor-alpha agonists, which activate several genes involved in lipid metabolism. This results in reduced synthesis and increased catabolism of triglyceride-rich lipoproteins, including very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL) and chylomicrons.[1-3] Levels of small dense LDL particles also reduce with fibrate therapy, with potentially beneficial changes in the size distribution of LDL particles, despite occasional minimal changes in plasma levels of LDL-cholesterol (LDL-C).[1-3] Plasma HDL-cholesterol (HDL-C) levels may increase by 5 to 25% with fibrate therapy.[4]

What are the indications for fibrate therapy?

Fibrates are mainly used to lower triglyceride levels and prevent the major complications of hypertriglyceridaemia. These complications include ischaemic cardiovascular disease (CVD) from excess levels of triglyceride-rich lipoproteins (VLDL and IDL),[5-10] and acute pancreatitis from excess levels of plasma chylomicrons.[1]



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Key points

- **Fibrates are first-line drugs for the treatment of patients with high triglyceride levels and have variable effects on reducing LDL-cholesterol levels, for which statins are first-line therapy.**
- **Fibrate therapy reduces concentrations of atherogenic small dense LDL-cholesterol, while raising HDL-cholesterol and lowering triglyceride levels. These changes are likely to be protective against ischaemic cardiovascular disease.**
- **Several randomised controlled trials have consistently shown reduction of ischaemic heart disease events with fibrate therapy. This is confined to patients with dyslipidaemia (low HDL-cholesterol and/or high triglyceride levels).**
- **Fenofibrate is preferred to gemfibrozil when combined with a statin because of a lower risk of muscle side effects.**

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What are the nonlipid effects of fibrate therapy?

Fibrate therapy decreases plasma uric acid levels and has anti-inflammatory properties by decreasing levels of interleukin-6, fibrinogen, cell-adhesion molecules and C-reactive protein.[1,2] These properties are consistent with antiatherogenic effects on lipid metabolism.

Fenofibrate, unlike gemfibrozil, reversibly increases serum homocysteine, creatinine and cystatin levels. The increase in creatinine levels observed with fenofibrate therapy is reversible on drug withdrawal, and long-term follow up in the Fenofibrate Intervention and Event Lowering in Diabetes study showed some improvement in renal function in patients treated with fenofibrate compared with placebo.[11] In patients with chronic kidney disease, the dose of fenofibrate should be reduced as there is an increase in plasma levels of the drug and consequently an increased risk of side effects at the usual dose (this does not occur with use of gemfibrozil).[1,2]

Fibrates and hypertriglyceridaemia

Patients with elevated triglyceride levels (moderate 4.5 to 11.0 mmol/L and severe more than 11.0 mmol/L) often respond well to fibrate therapy with a reduction in triglyceride levels by more than 50%.[1-3] Hypertriglyceridaemia most commonly occurs in association with uncontrolled diabetes or excessive alcohol consumption, especially binge drinking. Less frequent causes include hypothyroidism, renal disease and excessive consumption of refined carbohydrates or fats (see the box on this page). Drug therapy is often required for patients with these conditions.[1-3] Uncommon genetic causes of hypertriglyceridaemia, such as mutations of the apoA5 or lipoprotein lipase genes,

Common causes of hypertriglyceridaemia

- Diabetes (uncontrolled)
- Alcohol excess
- Exogenous oestrogen (oral contraceptive pill, hormone replacement therapy)
- Endogenous oestrogen (pregnancy)
- Hypothyroidism
- Severe proteinuria (nephrotic syndrome)
- Excessive consumption of refined carbohydrates
- Inadequate fasting before blood sampling (sampling during postprandial lipaemia)
- Drugs: amiodarone, alpha-interferons, beta blockers, bile acid resins, L-asparaginase, protease inhibitors, sirolimus, tamoxifen, thiazides, corticosteroids, tretinoin, atypical antipsychotics
- Familial hypertriglyceridaemia, familial combined hyperlipidaemia, type III hyperlipoproteinaemia

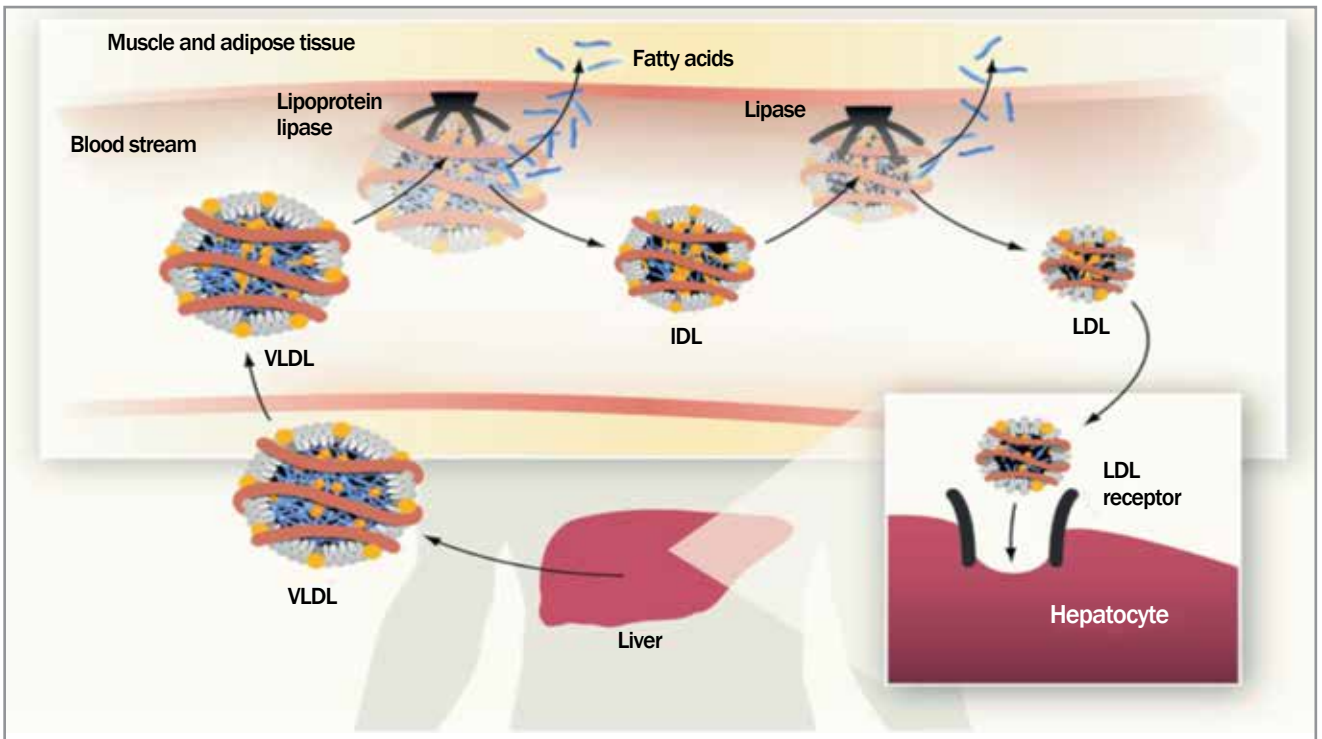

Figure 1. Normal lipoprotein metabolism. The liver secretes very low density lipoproteins (VLDL) into plasma, where they are converted to intermediate lipoproteins (IDL) and then low-density lipoproteins (LDL) by lipoprotein lipase and hepatic lipase. Hepatic uptake of LDL and VLDL remnants occurs via LDL receptors.[12]

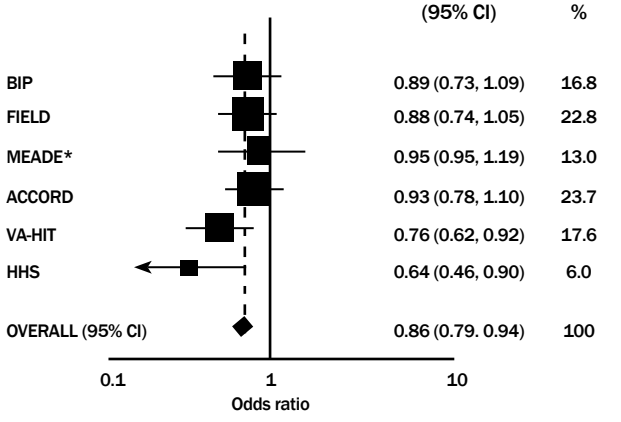

Figure 2. Meta-analysis of reduction of risk of main coronary events in patients of all ages treated with fibrates.[7,13]

Abbreviations: ACCORD = Action to Control Cardiovascular Risk in Diabetes; BIP = Bezafibrate Infarction Prevention; CI = confidence interval; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; HHS = Helsinki Heart Study; VA-HIT = Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial.

* This refers to the Lower Extremity Arterial Disease Event Reduction Trial.

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are resistant to fibrates and other drug therapy. The major complication of severe hypertriglyceridaemia is recurrent acute pancreatitis, and the major complication of moderate hypertriglyceridaemia is CVD.[5-11]

Mild hypertriglyceridaemia refers to triglyceride levels between 2.3 and 4.4 mmol/L. Lifestyle modification often results in significant improvement in triglyceride levels, and drug therapy is usually required in the minority of patients. Either fibrate or statin monotherapy may be effective in controlling mild hypertriglyceridaemia, and may achieve target triglyceride levels of less than 1.5 mmol/L.[1-3] Statins are first-line therapy for mild hypertriglyceridaemia because of their predictable effects on lowering levels of LDL-C; however, moderately high doses of more potent statins may be required for optimal triglyceride control. In general, statins are more effective at lowering LDL-C levels in patients with higher baseline triglyceride levels, in higher doses and with increasing statin potency. Nevertheless, statin therapy alone may not achieve target triglyceride levels and a combination of statin and fenofibrate therapy may be required.[1-3] The addition of omega-3 fatty acids (2 to 4 g/day) may also assist in achieving target triglyceride levels. In patients with severe hypertriglyceridaemia, restriction of dietary refined carbohydrates, fats and alcohol are required.

Fibrates and LDL-C reduction

The effect of fibrates on LDL-C levels depends to a large extent on the baseline lipid profile. Patients with hypercholesterolaemia alone may experience a 10 to 20% reduction in LDL-C levels when treated with fibrate monotherapy. In patients with borderline high and high triglyceride levels who are treated with fibrates, LDL-C levels often do not change, whereas LDL-C levels may increase in patients with very high triglyceride levels.

Fibrates may be effective in patients who cannot tolerate statins and in those whose LDL-C levels remain above target. Fibrates are therefore alternative second-line therapy after ezetimibe for these patients, and nicotinic acid is the alternative second-line add-on therapy to ezetimibe therapy.

Fibrate therapy also reduces plasma levels of IDL (see Figure 1).[12] This accounts for the efficacy of fibrates in patients who are homozygous for apoE2 (type III hyperlipidaemia).[1-3]

Fibrate and statin combination therapy

Fibrate monotherapy is not frequently associated with myalgia, although the incidence may be increased with concomitant statin therapy. This especially applies to gemfibrozil, which may result in considerably raised levels of plasma statins when they are used concurrently. Fenofibrate does not result in significant elevation in plasma levels of statins nor does it have any significant effect on the incidence of muscular side effects.[1,3]

Fibrates and CVD prevention

High triglyceride levels, presence of small dense LDL particles, and low HDL-C levels commonly occur together as the 'atherogenic triad', particularly in states of insulin resistance such as obesity, the metabolic syndrome and diabetes. Fibrates are particularly effective in treating the atherogenic triad, and several large trials investigating fibrates have shown a reduction in coronary artery disease events, which is mainly confined to patients with the atherogenic triad in those with and without diabetes (Figure 2).[7,13]

Results of a meta-analysis of reduction of risk of major coronary events in patients of all ages treated with fibrates showed a reduction in these events that was significant in two studies using gemfibrozil (Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial and Helsinki Heart Study), and only trended toward significant in the other fibrate trials (Figure 2).[7,13] It was concluded that fibrates might have a benefit in selected patients in whom statins are not an option and when HDL or triglyceride modification is indicated.[7] Meta-analyses of all fibrate trials have shown a consistent benefit in reducing CVD events in patients with baseline dyslipidaemia (triglyceride levels of 2.3 mmol/L or more and/or low HDL-C levels of less than 1.0 mmol/L in men and less than 1.2 mmol/L in women).[5-11]

Conclusion

Fibrates have proven to be useful drugs for lipid control, especially in patients with combined hyperlipidaemia who have underlying insulin resistance (obesity, metabolic syndrome and type 2 diabetes; see the box on page 15). Combination therapy with statins is often required for optimal lipid control in these patients, and fibrates may also be combined with other lipid-modifying agents.

Summary: recommendations for clinical use of fibrates

The following recommendations apply to the use of fibrates in clinical practice for the management of dyslipidaemia and prevention of cardiovascular disease. These recommendations are made in the context of LDL-cholesterol (LDL-C) control as first priority in lipid management, usually with statin therapy, and after exclusion of secondary causes of dyslipidaemia, especially poor glycaemic control and hypothyroidism.

- Fibrates are first-line therapy for improving triglyceride levels in patients with fasting triglyceride levels of 4.5 mmol/L or more. Statins and/or fish oils used as second-line therapy may further improve triglyceride control.
- Statins are first-line therapy for improving the lipid profile in patients with fasting triglyceride levels of less than 4.5 mmol/L.
- In patients with normal triglyceride levels (less than 2.3 mmol/L) who are intolerant to statins, either fibrates or ezetimibe can be considered as first-line therapy for LDL-C control, although fibrates are preferred for patients with low HDL-cholesterol (HDL-C) levels.
- In patients with triglyceride levels of 2.3 to 4.5 mmol/L who are intolerant to statins, fibrates are first-line therapy for improving the overall lipid profile, including levels of triglycerides, LDL-C and HDL-C . Many of these patients have the metabolic syndrome and low HDL-C levels.
- In patients with normal or near-normal triglyceride levels, fibrate monotherapy may be effective for LDL-C control; however, in those with hypertriglyceridaemia, LDL-C levels increase with fibrate therapy. This is associated with a potentially beneficial shift in LDL particle size from small dense to larger, less dense and less atherogenic particles.
- In patients who are intolerant to statins, fibrates can be used in combination with ezetimibe to improve LDL-C control.
- When used with statin therapy, fenofibrate is preferred to gemfibrozil because fenofibrate is less likely to cause adverse effects on skeletal muscle.
- Fibrates (either alone or as fenofibrate in combination with statins) can be considered for the prevention of ischaemic cardiovascular disease in patients with dyslipidaemia (fasting triglyceride levels of 2.3 mmol/L or more and/or low HDL-C levels of less than 1.0 mmol/L in men and less than 1.2 mmol/L in women). Meta-analyses of fibrate trials have shown no consistent cardiovascular disease benefit in patients who have normal triglyceride levels and/or HDL-C levels.
- The dose of fenofibrate needs to be reduced in patients with impaired renal function; maximum daily doses of 96 mg and 48 mg are used for those with creatinine clearance of 21 to 60 mL/min and 10 to 20 mL/min, respectively.

Several studies investigating fibrates, either as monotherapy or in combination with statins, have shown benefit in the prevention of ischaemic CVD, particularly in patients with baseline dyslipidaemia (elevated triglyceride levels and/or low HDL-C levels). We recommend adding fenofibrate to statin therapy in patients with residual dyslipidaemia (triglyceride level of 2.3 mmol/L or more and/or low HDL-C levels of less than 1.0 mmol/L in men and less than 1.2 mmol/L in women). **CT**

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