Fibrates in Perspective

Answering an Age-Old Question

Although fibrates have been used to treat dyslipidemia since the 60s, recent studies have shown their effectiveness in the treatment of hypercholesterolemia, low HDL cholesterol, high triglycerides, and overall cardiovascular risk reduction as well.

T.K. Lee, FRCPC, MSc, MB, BSc

The use of HMG-coenzyme A reductase inhibitors (*i.e.*, statins) appears to be well established in dyslipidemic patients for reducing cardiovascular events. The role of the fibric acid derivatives (*i.e.*, fibrates) for this purpose may sometimes be less clear.

Fibrates, beginning with clofibrate in the 60s, were used to treat dyslipidemia before statins were. The fibric acid derivatives currently available for use in Canada are listed in Table 1.

Fibrates are peroxisome proliferator-activated receptors (PPAR-alpha mediators). Their actions are theoretically preferable for reducing cardiovascular risk by elevating high-density lipoprotein cholesterol (HDL-C) levels by 15% to 25%, and reducing triglyceride levels by 35% to 50% (both actions more than with statins). Fibrates also have a modest effect on low-density lipoprotein cholesterol (LDL-C) levels, reducing them by up to 20% (less than with statins). Fibrates, however, modify LDL-C parti-

Hugo's case

Hugo, 65, comes to you for a routine physical examination. On examination he has abdominal obesity with a body mass index of 30 and an average blood pressure of 150/95 mmHg.

His lipid profile shows:

- Total cholesterol: 4.0 mmol/L
- High-density lipoprotein cholesterol (HDL-C): 0.7 mmol/L
- Low-density lipoprotein cholesterol (LDL-C): 2.5 mmol/L
- Triglycerides: 2.3 mmol/L

Management could include:

1. Testing for diabetes because he probably has the metabolic syndrome with insulin resistance.
2. Starting a fibrate to improve his low HDL-C level.
3. Adding a statin if the LDL-C level remains high.
4. All of the above.

What would you do? For a discussion, see page 36.

cles qualitatively from small, dense LDL particles to the larger, and less atherogenic, forms. In addition, they have a variable effect on lipoprotein(a) levels, reduce fibrinogen and plasminogen-activator inhibitor-1 levels, may increase homocysteine levels (fenofibrate, bezafibrate), and reduce uric acid. The clinical significance of these latter effects is uncertain.

When to use a fibrate

The Canadian Working Group on Dyslipidemia recommends the use of fibrates in patients who have not responded adequately to lifestyle modification and diet, and who have high triglyceride levels, normal LDL-C levels, and/or low HDL-C levels. They are also recommended in combination therapy with statins in patients with elevated LDL-C, high triglyceride and low HDL-C levels.[1] It should be noted that the risk of coronary events is high in these patients, where statin therapy alone often does not correct all the lipoprotein abnormalities. Although treatment with fibrates of these residual abnormalities is recommended, evidence for benefit of this second recommendation is presently weak.

About the author ...

Dr. Lee is a clinical professor of medicine at the University of Alberta, and an internist at the Grey Nuns Hospital, Edmonton, Alberta.

Table 1

Fibrates available in Canada

1. Clofibrate (no longer used much)
2. Gemfibrozil (Lopid®; a generic formulation is also available)
3. Fenofibrate (Lipidil®, Lipidil Micro®, Lipidil Supra®)
4. Bezafibrate (Bezalip®)
5. Ciprofibrate (not readily available, special release only)

Fibrates are commonly used in the following situations (Table 2):

Patients with the "metabolic syndrome". (*i.e.*, insulin resistance with impaired glucose tolerance or Type 2 diabetes). These patients characteristically have abdominal obesity, hypertension and dyslipidemia, comprising low HDL-C and elevated triglyceride levels.[2] The combination of an elevated triglyceride level with an increased waist circumference can predict the presence of insulin resistance.[3]

Patients with very high triglyceride levels (typically over 11 mmol/L to 12 mmol/L), at risk of acute pancreatitis, where drug therapy may need to be started concomitantly with other measures. Other examples where patients present with significant hypertriglyceridemia are newly diagnosed diabetics, human immunodeficiency virus-positive patients taking protease inhibitors, and those patients with familial hypertriglyceridemia (a rare condition).

In combination therapy with statins. Fibrates are commonly used in patients with familial combined dyslipidemia who have

Table 2

Situation where fibrates are commonly used

1. Patients with low HDL-C/high triglycerides (the metabolic syndrome, *e.g.*, impaired glucose tolerance or Type 2 diabetes).
2. Patients with very high trigylcerides.
3. In combination therapy, usually with statins.

elevated levels of LDL-C and triglycerides.

The patient can be started on a once daily dose of fenofibrate or bezafibrate, or a twice daily dose of gemfibrozil. Fibrates should be taken with the main meal(s) of the day to reduce the risk of gastrointestinal side effects, such as dyspepsia, which has an incidence of 5% to 10%.[4] Both fenofibrate and bezafibrate come in once-a-day sustained release formulations, including a micronized formulation of fenofibrate (Lipidil Micro®), which allows use of a lower drug dose to achieve therapeutic blood levels.

What to watch for

Fibrates, particularly clofibrate and gemfibrozil, have been associated with an increased incidence of gallstones, as well as asymptomatic transaminase rise (about 5% incidence), which is dose-related.[4] Patients should be advised of these potential symptoms and of the need for regular monitoring of liver enzymes.

Because they are metabolised via the hepatic cytochrome P450 CYP3A4 system, fibrates may interact with other drugs using this system.

Case Discussion

Answer: 4 - All of the above

This gentleman has abdominal obesity, hypertension, low HDL-C, and a high triglyceride level. These findings are typical in someone with the so-called "metabolic syndrome" of insulin resistance. He should be tested for diabetes.

It is reasonable to start this patient on a fibrate to try to increase his HDL-C in view of the results of the VA-HIT study.[11] Alternatively, a statin may also be reasonable in view of the recent results of the Heart Protection Study.[12]

Drug therapy can be started immediately if he is shown to be diabetic.[1]

These include statins, warfarin, grapefruit juice (enhances levels and toxicity), cyclosporin (reduces levels), oral hypoglycemic agents, and metformin and the sulphonylureas (increases hypoglycemia). Fibrates are renally excreted and doses should be reduced in the elderly and in patients with renal insufficiency or renal failure.

The main precaution with fibrates concerns their use in combination with statins. This combination therapy increases the risk for myopathy and subsequent rhabdomyolysis. In patients who have not responded adequately to either drug alone (commonly a statin is used first), a decision has to be made regarding the risk versus benefit of combination therapy. Combination therapy may be clearly indicated in patients with severe coronary artery disease and dyslipidemia who have not responded adequately to optimal statin treatment. Its use, however,

Table 3

Examples for monitoring combination therapy in a patient

1. Recall the patient at four to six weeks after initiation of combination therapy. Look for symptoms of side effects, especially myopathy, and check CPK and transaminase levels.
2. If the patient remains well, repeat every three months to a year, and every four to six months thereafter (depending on the dose of drugs employed) if the patient continues to be well.
3. Monitoring should be increased every time a dose of either statin or fibrate is increased, or if other drugs that may interact with these lipid-lowering drugs are added to the patient's medications.
4. If there is no response to combination therapy in four to eight weeks, combination therapy should be discontinued.

may be less clear in asymptomatic patients with mild mixed dyslipidemia not reaching lipid treatment goals, but who have few other risk factors. One should also consider the type of patient one is dealing with. A patient who is sensible, compliant, and able to recognise and take prompt action if symptoms of myopathy occur, and who fills the necessary medical requirements, would be a better candidate for combination therapy.

Because myopathy has been reported more with gemfibrozil in combination therapy, some lipidologists prefer to use fenofibrate and bezafibrate with statins. Also, because pravastatin and fluvastatin are not extensively metabolised by the CYP3A4 system, some clinicians prefer to use these statins in combination therapy. The patient should be advised of the increased risks and the need for regular followups, which include monitoring for symptoms of, and laboratory tests for, myopathy [checking the creatine phosphokinase (CPK) levels, if necessary] and hepatic dysfunction (checking hepatic transaminases). An example of a monitoring regimen is shown in Table 3.

Are fibrates effective?

Fibrates have been the "poor cousins" to the statins for evidence-based benefit in reducing cardiovascular disease. Published clinical trials of the role of fibrates in reducing cardiovascular disease have shown positive benefit (or a trend towards positive benefit) for surrogate or clinical endpoints. The number of patients enrolled, as well as the end results, however, are generally felt to be less dramatic compared to those of the statin trials (Table 4).

Clinical trials

Results of primary prevention studies using fibrates have generally not been dramatic.[5,6]

Studies using gemfibrozil, bezafibrate, and fenofibrate have demonstrated reduction in progression of coronary stenosis as a surrogate endpoint in patients after myocardial infarction (MI).[7-9] These studies were not powered to demonstrate differences in clinical events.

The Bezafibrate Infarction Prevention (BIP) study involved 3,090 patients with coronary heart disease, low HDL-C, and high triglyceride levels over 6.2 years

Table 4

Clinical trials using fibrates

Primary prevention

1. WHO Study (clofibrate): Showed increase in cholelithiasis, and excess deaths (non-cardiac) in the clofibrate-treated patients during treatment period; generally not used anymore.[5]
2. Helsinki Heart Study (gemfibrozil): Showed reduced risk of coronary artery disease in patients with mixed hyperlipidemia, without significant differences in coronary or all-cause mortality.[6]

Secondary prevention (see text for details)

1. LOCAT (gemfibrozil; surrogate outcome)[7]
2. BCAIT (bezafibrate; surrogate outcome)[8]
3. DAIS (fenofibrate; surrogate outcome)[9]
4. BIP (bezafibrate)[10]
5. VA-HIT (gemfibrozil)[11]

Pending

1. FIELD (results due 2004): Micronized fenifibrate versus placebo in 8,000 dyslipidemic diabetics.

(mean).[10] The overall result demonstrated a trend to benefit in reducing fatal/nonfatal MI and sudden death (-9%, P = not significant) in the bezafibrate treated patients.

The Veterans Affairs High-Density Lipoprotein Cholesterol Interventional Trial (VA-HIT) treated 2,531 male patients, age 64 (±7), with gemfibrozil or placebo for 5.1 years (mean). These patients also had coronary artery disease, low HDL-C (0.8 ±0.1 mmol/L), and modestly elevated triglyceride (1.8 ±0.8 mmol/L) and LDL-C (2.9 ±0.6 mmol/L) levels. Again, this dyslipidemia pattern is characteristic of the obese patients with the metabolic syndrome, and indeed 25% of these patients were diabetic and 57% had hypertension. Patients treated with gemfibrozil showed a 6% increase of their HDL-C levels, a 31% decrease of triglyceride levels, and negligible change in LDL-C levels compared with placebo. Coronary heart disease death (-23%, P = 0.006) and nonfatal MI (-22%, P = 0.07) were significantly reduced with gemfibrozil, but total mortality was not.[11]

Although VA-HIT showed significant benefit in clinical cardiovascular endpoints that seem unrelated to LDL-C lowering, as seen in statin trials, discussion continues as to whether the results reflect the benefit of HDL-C elevation, that of qualitative change to LDL-C particles, or both.

It should also be noted that although diabetics showing lipid profiles, such as those in VA-HIT, likely benefit from fibrates, many statin trials have demonstrated benefit in diabetics as well. In the recently published Heart Protection Study, which involved a large number of diabetics, simvastatin was shown to be of benefit even at low LDL-C levels.[12] Whether fibrates parallel this

Take-home message

Although statins continue to be the mainstay of treatment of hypercholesterolemic patients, with increasing evidence of benefit in many types of patients, fibrates can also be useful for the patient with low HDL-C or high triglyceride levels alone, or (in certain cases) in combination with statins for cardiovascular risk reduction. However, more clinical trials with fibrates, especially involving their combination with statins, are needed.

benefit or increase it further when combined to a statin, remains to be determined. PCard

References

1. Fodor J.G, Frohlich JJ, Genest JJ Jr, et al: Recommendations for the management and treatment of dyslipidemia: Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. CMAJ 2000; 162(10):1441-7.
2. Despres J-P, Lemieux I, Prud'homme D, et al: Treatment for obesity: need to focus on high-risk abdominally obese patients. BMJ 2001; 322(7288):716-20.
3. Lemieux I, Pascot A, Couillard C, et al: Hypertriglyceridemic waist: A marker of the atherogenic metabolic triad (hyperinsulinemia, Hyperapolipoproteinemia B; Small Dense LDL) in men? Circulation 2000; 102(2):179-84.
4. Drug Information Handbook:1978-present. Lexi-Comp Inc.
5. WHO cooperative trial on primary prevention of ischemic heart disease with clofibrate to lower serum cholesterol: Final mortality follow-up. Report of the Committee of Principal Investigators. Lancet 1984; 2(8403):600-4.
6. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: primary prevention trial with gemfibrozil in middle aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987; 317(20):1237-45.
7. Syvanne M, Nieminen MS, Frick MH, et al: Associations between lipoproteins and the progression of coronary and vein-graft atherosclerosis in a controlled trial with gemfibrozil in men with low baseline levels of HDL cholesterol. Circulation 1998; 98(19):1993-9.
8. Ruotolo G, Ericsson CG, Tettamanti C, et al: Treatment effects on serum lipoprotein lipids, apolipoproeins and low density lipoproteins in particle size and relationship of lipoprotein variables to progression of coronary artery disease in the Bezafibrate Coronary Atherosclerosis Intervention Trial [BECAIT]; J Am Coll Cardiol 1998; 32(6):1648-56.
9. The DAIS Investigators: Effect of Fenofibrate on Progression of Coronary-Artery Disease in Type 2 Diabetes: The Diabetes Atherosclerosis Intervention Study, A Randomised Study. Lancet 2001; 357(9260):905-10.
10. The BIP Study Group: Secondary Prevention by Raising HDL Cholesterol and Reducing Triglycerides in Patients With Coronary Artery Disease: The Bezafibrate Infarction Prevention (BIP) Study. Circulation 2000; 102(1):21-7.
11. Rubins HB, Robbins SJ, Collins D, et al: For the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. N Engl J Med 1999; 341(6):410-8.
12. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360:7-22.