The Microvascular and Macrovascular Benefits of Fibrates in Diabetes and the Metabolic Syndrome: A Review

by Pavan Malur, MD, Arthur Menezes, MD, James J. DiNicolantonio, PharmD, James H. O'Keefe, MD & Carl J. Lavie, MD

In pharmacology, the fibrates are a class of amphipathic carboxylic acids. They are used for a range of metabolic disorders, mainly hypercholesterolemia, and are therefore hypolipidemic agents.

Pavan Malur, MD, Arthur Menezes, MD, and Carl J. Lavie, MD, FACC, are in the Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School, the University of Queensland School of Medicine, New Orleans, LA. James J. DiNicolantonio, PharmD, (left), and James H. O'Keefe, MD, (right), MSMA member since 2003, are at Saint Luke's Mid America Heart Institute, Kansas City, MO.
Contact: jjdinicol@gmail.com

Abstract

Background

The purpose of this article is to discuss the evidence regarding potential macrovascular and microvascular benefits of fibrate therapy in general and fenofibrate specifically.

Methods

We performed a literature review summarizing the results of studies testing fibrates on relevant.

Results

Although statins are the first line therapy with an unparalleled amount of evidence for reducing the risk of cardiovascular disease (CVD) in patients with dyslipidemia and the metabolic syndrome (MetS), there are several landmark studies that have focused on the potential benefits of fibrate therapy for reducing CVD risk. Fibrates confer benefits mostly for patients with diabetes mellitus (DM), MetS, and atherogenic dyslipidemia. Recently, many studies have shown that fibrates confer benefits on the vascular system as well as the liver and kidneys. Fibrates also have demonstrable benefits in cohorts of patients with DM and renal disease.

Conclusions

Fibrates appear to provide significant microvascular and macrovascular benefits particularly in patients with DM, MetS, or renal disease.

Introduction

Early fibrate trials used clofibrate as monotherapy, which found that it improved lipid levels in hypercholesterolemic patients. Clofibrate was approved by the Food and Drug Administration (FDA) for hyperlipidemia treatment in the United States (US) in 1967.[1] Since then, additional fibrates were introduced in the late 1970s and early 1980s. During the 1990s and early 2000s, there have been several landmark clinical trials focused on potential clinical benefits of this class of medications.

Metabolic Syndrome and Cardiovascular Disease

Metabolic syndrome (MetS) is characterized by insulin resistance, abdominal or central obesity, hypertension (HTN), impaired glucose tolerance and atherogenic dyslipidemia, is a precursor of type 2 diabetes mellitus (T2DM), and is strongly associated with a high risk of major Cardiovascular Disease (CVD) events, particularly, coronary heart disease (CHD) adverse events.[2]

The Armed Forces Regressive Study (AFREGS) addressed the issue of dyslipidemia in MetS. By definition, two of the components comprising the ATP III definition of MetS are abnormal triglycerides (TGs) and low levels of high-density lipoprotein cholesterol (HDL-C).[3] Although there is an inverse relationship between TGs and HDL-C, elevated TGs are also associated with many other CHD risk factors, such as unhealthy diet, characterized by excess calories and high glycemic load, obesity, diabetes mellitus (DM), HTN, sedentary lifestyle, inflammation and a prothrombotic state.[4, 5]

A study based on the Third National Health and Nutrition Examination Survey data demonstrated that among the components of MetS, elevated serum TGs were strongly related to myocardial infarction (MI) and stroke.[6] Another study showed that among the components of MetS, elevated serum TG levels conferred the highest hazard ratios (HR) to independently predict coronary atheroma progression.[7] The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in MI 22 (PROVE IT-TIMI 22) trial demonstrated that patients with TGs levels less than 150 mg/dL had a lower risk of recurrent CHD events independent of the level of low-density lipoprotein cholesterol (LDL-C).[8] This finding may be secondary to the atherogenicity of TG-rich remnant particles and effects on the relative functionality of circulating LDL-C and HDL-C particles. [7, 9]

Pierre and colleagues published results of their study on the relationship of hypertriglyceridemia (HTG) waist phenotype (waist circumference >35.4 inches in men or >33.5 inches in women) and a plasma TG level >177 mg/dL) and CHD among patients with T2DM or glucose intolerance.[10] Patients who had the hypertriglyceridemic waist phenotype had a significant two-fold increase in risk of CHD (P=0.02) and on average experienced the first symptoms of CHD five years earlier than patients without the phenotype.

Furthermore, the Metabolic, Lifestyle, and Nutrition Assessment in Young Adults (MELANY) study evaluated the effect of variations in TG levels over time on CHD risk. In this trial, men aged between 26 to 45 years (N = 13,953) with baseline fasting TG levels <300 mg/dL had TG measurements taken at two time points over the span of five years; CHD was diagnosed by angiography-proven stenosis > 50% in at least one coronary artery or fatal or nonfatal MI. Men with TG levels (≤ 93 mg/dL) at the first time point experienced a 3.8-fold greater CHD risk if their TG levels increased to intermediate (94-147 mg/dL) or 6.8-fold increased risk if their TG levels increased to high levels (≥ 148 mg/dL) at the second time point, compared with men who maintained low TG levels over the five years. Additionally, men with low TG levels at the second time point had a 3.9-fold and 4.9-fold increased CHD risk if their TG levels were intermediate or high at the first time point compared with men who maintained low TG levels for the duration of the study. Men with high TG levels at both time points had a 8.2-fold greater CHD risk compared to men who maintained low TG levels, whereas men with high TG levels initially, but intermediate or low levels at the second time point, experienced a 6.8-fold or 4.9-fold increased risk as compared to men who continually had low TGs levels.[11] Thus, changes in TG seem to predict CHD risk and thus introducing fibrates to lower elevated TGs may lead to CV risk reduction. This data demonstrated that in addition to being an independent CHD risk factor, TG levels may have a cumulative effect on CHD risk.[11]

The National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) guidelines recommend focusing on LDL-C as the primary target for lipid therapy to prevent development and progression of atherosclerotic vascular disease.[12] However, many CHD events still occur in patients whose LDL-C levels (and other major risk factors) appear to be adequately controlled (suggesting that other factors play an important role in this complex disease).[13,14] This is perhaps why many guidelines have started to shift focus away from LDL-C and towards non-HDL to capture "all atherogenic lipoproteins."

In major trials of patients treated with statins, around 70% of major CHD events and 80% of all-cause mortality events were not prevented.[15] Some of these studies have also shown that low HDL-C may predict CHD events more so than high LDL-C: i.e. for every increase in HDL-C of 1 mg/dL, the risk of major CHD events decreases by 2% to 3% and the risk of CHD mortality decreases by 4% to 5%.[16, 17] The highest risk of CHD occurs when low HDL-C coexists with high LDL-C.[17,18] Thus, in patients with this phenotype, treatment with statins may not provide adequate CV protection and additional therapies might be needed.

The Role of Fibrates on Lipids

Fibric acid compounds are first line therapy in patients who require pharmacologic treatment for low HDL-C associated with HTG, and they are an alternative to niacin in patients with isolated low HDL-C. However, two recently completed large randomized controlled trials (AIM High, HPS-2/THRIVE) found that niacin is a) ineffective at improving CV outcomes and b) poorly tolerated with frequent adverse effects; which has stimulated increased

interest in the fibrate class of medication for individuals with HTG and/or low HDL-C.[19] Fibrates belong to a class of synthetic peroxisome proliferator activated receptor (PPAR) agonists,which are direct or indirect ligand-activated nuclear transcription factors that regulate a wide range of genes, some of which induce synthesis of apo A-I and apo A-II.

Fibrates can provide a greater than 50% reduction in TGs in some patients with very high TG levels and reductions of 25% to 30% are often noted in patients with moderately elevated baseline levels of TGs. Additionally, fibrates can produce an approximate 25% increase in HDL-C in patients with HTG, but increases in HDL-C of 10% are generally obtained in patients without HTG.[20] Although these drugs are very effective in reducing TG levels by up to 60%, they may also raise LDL-C.[21] However, this effect on LDL-C is minimal in those without significant HTG.

Slow-release fibrates, such as fenofibrate, have been found to be more effective than gemfibrozil in raising HDL-C and are effective even among patients who do not respond to gemfibrozil. The main advantage of fenofibrate is the lower risk of drug interactions and myopathy when it is used in combination with statins[5] ,although recently the FDA has removed the official indication for combining fibrates, particularly fenofibric acid, and nicotinic acid with statins.

In 2005, the Effectiveness and Tolerability of Simvastatin Plus Fenofibrate for Combined Hyperlipidemia (the SAFARI trial) demonstrated that combination therapy with simvastatin and fenofibrate among patients with combined hyperlipidemia resulted in additional improvement in all lipoprotein parameters measured compared with simvastatin monotherapy and was well tolerated. Patients (aged 21 to 68 years) with a diagnosis of combined dyslipidemia (fasting TG levels >150 and <500 mg/dL, and LDL-C >130 mg/dL) received simvastatin monotherapy (20 mg/day, n = 207) or simvastatin 20 mg plus fenofibrate (160 mg/day) combination therapy (n = 411) for 12 weeks following a six-week diet and placebo run-in period. From baseline to week 12, median TG levels decreased 43% (combination therapy) and 20% (simvastatin monotherapy treatment difference -24%, p <0.001]). Mean LDL-C levels decreased 31% and 26% (treatment difference -5%, P <0.001), and HDL-C levels increased 19% and 10% (treatment difference 8.8%, P <0.001) in the combination therapy versus monotherapy groups, respectively. No drug-related serious adverse experiences were observed. No patient experienced clinical myopathy or severe abnormalities in liver function.[22]

In late 1980s, Austin and colleagues published their findings on the association of LDL subclass patterns with elevated levels of TGs and low levels of HDL-C, showing that the enhanced CV risk associated with LDL subclass pattern B, characterized by a preponderance of small, dense LDL particles, is associated with a greater risk of MI and is highly influenced by the levels of HDL-C.[23] Given the efficacy of fenofibrate therapy on reducing levels of TG-rich lipoproteins (very low density lipoprotein and intermediate- density lipoprotein) and raising levels of HDL-C, it is not surprising that combination therapy with simvastatin 20 mg/day plus fenofibrate 160 mg/day also improved the LDL subclass pattern compared with statin monotherapy.

Macrovascular Benefits

Diabetic dyslipidemia (generally characterized as small and dense LDL-C, low HDL-C, and high TGs) can be substantially improved with fibrates. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was designed to evaluate this hypothesis. This study included 9,795 patients with T2DM, aged 50–75 years, with a total cholesterol concentration between 3.0–6.5 mmol/L and a total cholesterol/HDL-C ratio of 4.0 or greater or a plasma TG concentration between 1.0–5.0 mmol/L. The population was composed of 2,131 patients with previous CVD and 7,664 without. Patients were not taking statin therapy at baseline and were randomly assigned to either micronized fenofibrate 200 mg/day or placebo.[24] Fenofibrate therapy was associated with a non-significant 11% reduction in the primary endpoint (CHD death, nonfatal MI) (P=0.16), corresponding to a significant 24% reduction in nonfatal MI (P=0.010) and a non-significant 19% increase in all-cause mortality (P=0.22). Furthermore, there was a significant 11% reduction in total CVD events (P=0.035) among patients allocated to fenofibrate. Finally, subgroup analysis demonstrated that reduction in total CVD events was significant only among patients in primary prevention and in those aged less than 65 years.[25]

Before the FIELD study, several important clinical outcome trials with fibrates were performed: the primary prevention Helsinki Heart Study[26] and the secondary prevention study Veterans Affairs HDL Intervention Trial (VAHIT)[27] with gemfibrozil and the secondary prevention study Bezafibrate Infarction Prevention (BIP) with bezafibrate.[28] Among the 4,081 males included in

the Helsinki Heart study, 135 had type T2DM; among these patients, gemfibrozil reduced CVD risk by 68%, but the difference was not statistically significant due to the small number of T2DM patients included in the study. VAHIT demonstrated that gemfibrozil provided a significant 24% reduction in the incidence of acute CVD events ($P < 0.001$). And in the subgroup of 769 patients with T2DM, gemfibrozil induced a 32% reduction in the incidence of acute CVD events ($P = 0.004$) and a 41% reduction in CVD mortality risk ($P = 0.02$).[29]

In the BIP Study, bezafibrate treatment was associated with a non-significant 10% reduction in the incidence of CVD events in the entire population.[28] Among patients treated with bezafibrate, a significant reduction in fatal and nonfatal MI was noted in the subgroup of patients with MetS,[30] but not in the subgroup of patients with T2DM.[31]

Lee and colleagues conducted a systematic review and meta-analysis to investigate the influence of fibrates on vascular risk reduction among individuals with atherogenic dyslipidemia – HDL-C <40 mg/dL or TG >200 mg/dL. Their analysis of six trials that met selection criteria demonstrated that compared to placebo, the greatest benefit with fibrate treatment was seen among subjects with high TG, as well as high TG and low HDL-C (RR 0.75, 95% CI 0.65 to 0.86, and RR 0.71, 95% CI 0.62 to 0.82, respectively, $P < 0.001$ for both). Less benefit (though still significant) was noted among the 15,303 subjects selected for low HDL-C (RR 0.84, 95% CI 0.77 to 0.91, $P < 0.001$). Among 9,872 subjects with neither high TG nor low HDL-C, fibrate therapy did not reduce subsequent vascular events ($P = 0.53$).[32] The authors concluded, "Fibrate treatment directed at markers of atherogenic dyslipidemia substantially reduced subsequent vascular event risk."[32]

Microvascular Benefits

In the FIELD study, fenofibrate therapy was associated with a significant improvement in DM microvascular disease with a 2.6% reduction in the grade of albuminuria ($P = 0.002$) and a 1.6% reduction in laser treatment for retinopathy ($P = 0.0003$).[25] These results demonstrate the beneficial effect of fenofibrate on the progression of albuminuria as reported in Diabetes Atherosclerosis Intervention Study (DAIS).[33] Additionally, there was a 38% reduction in the number of non-traumatic amputations among individuals on fenofibrate therapy ($P = 0.011$), indicative of the microvascular benefits of fenofibrate.[24]

The mechanism behind an improvement on microvascular endpoints are unknown and cannot be explained by changes in A1C or by the minor reduction in blood pressure (BP) noted in the fenofibrate group according to Verges and colleagues.[25] Furthermore, this microvascular benefit of fenofibrate appeared to be at least partially due to its effect on the lipid profile. Statins have been shown to slow the progression of both nephropathy and retinopathy.[25] The vascular and/or anti-inflammatory effects of fenofibrate, mediated through the activation of PPAR receptors, could contribute to the microvascular benefits.[34]

Effect of Fenofibrates on the Liver

As mentioned previously, fibrates are potent PPARα agonists. Liver fat metabolism depends on PPARα activity and there has been interest in its role in non-alcoholic fatty liver disease (NAFLD) development, which is a spectrum of liver disease ranging from steatosis to non-alcoholic steatohepatitis (NASH). This spectrum of disease is associated with an increased risk of CV disease, DM and liver-related complications.[35]

An experimental study in laboratory animals suggested that fenofibrate might have a beneficial effect on apoptosis induced by bile duct obstruction as well as on hepatocellular damage. Fenofibrate improved cholestasis-induced histopathologic parameters, such as portal inflammation, hepatic necrosis and apoptosis while lowering the concentrations of total bilirubin, total bile acid, alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyltranspeptidase (GGT), tumor necrosis factor-alpha and interleukin-1 beta in rats with experimental cholestasis.[36] To further test this in humans, a pilot trial was conducted with 16 patients with biopsy-confirmed NAFLD. They were treated with fenofibrate 200 mg/day for 48 weeks and a liver biopsy was performed at the end of the therapy. This study showed that there was significant decrease in TG, glucose, ALT, and GGT along with a decrease in insulin levels and an improvement in insulin resistance. Furthermore, the proportion of patients with abnormal aspartate transaminase and ALT decreased significantly, from 50% to 19% ($P = 0.02$) and from 94% to 63% ($P = 0.02$, respectively). Biopsy at the end of treatment revealed a decrease in the grade of hepatocellular ballooning degeneration ($P = 0.03$), but the grade of steatosis, lobular inflammation, fibrosis or NAFLD activity score did not change significantly.[37]

Effect of Fibrates on the Kidney

There is additional literature that supports the use of fibrates for renovascular protection apart from the FIELD

study. It has been suggested that dyslipidemia can damage the kidney in a manner similar to atherosclerosis.[38] Lipid deposition in the kidney may trigger glomerular mesangial cell activation and proliferation, which ultimately causes diffuse inflammation resulted in renal fibrosis.[38, 39] Furthermore, these activated mesangial cells, foam cells and macrophages produce reactive oxygen species , which in turn produce oxidized LDL (oLDL), which advances monocyte recruitment, mesangial cell proliferation and cytotoxicity as well as endothelial dysfunction.[38-40]

Diabetic nephropathy or nodular diabetic glomerulosclerosis and intercapillary glomerulonephritis, is a progressive kidney disease caused by angiopathy of capillaries in the kidney glomeruli.[41] Metabolic abnormalities play a key role in the development of DM nephropathy. Hyperglycemia triggers mesangial expansion through increased matrix production and/or glycosylation of matrix proteins.[42] Diabetic dyslipidemia also adversely affects renal function through lipotoxicity. PPARα is implicated in metabolic pathways in T2DM.[43] Reduced or dysfunctional PPAR-α can impair glycemic control and raise free fatty acids and TG levels in DM.[43]

Bishnoi and colleagues explained that PPARα agonism by fenofibrate can prevent early pathological and clinical changes of diabetic nephropathy.[44] A recent experimental study by Kadian and colleagues suggested a protective effect of low-dose fenofibrate pre-treatment against biochemical (raised serum creatinine [SCr] levels, blood urea nitrogen and microalbuminuria) and histological changes (glomerular-capsular wall distortion, mesangial expansion and tubular damage) of diabetic nephropathy in streptozocin-induced DM rats.[45]

Fenofibrate may also protect against diabetic nephropathy abnormalities via vasoactive pathways. It is known that cyclooxygenase-2 and prostaglandins are overproduced by mesangial cells and glomeruli of diabetic kidneys in vivo. These are associated with hyperfiltration in the early stages of DM nephropathy. Hyperglycemia-related enhanced oxidative stress may be the stimulus for this abnormality in DM kidneys.[46]

An ACCORD substudy included 5,518 simvastatin-treated patients. These patients were randomized to fenofibrate or placebo. Mean SCr levels were increased (from 82 μmol/L [0.93 mg/dL] to 97 μmol /L [1.10 mg/dL]) in the first year in the fenofibrate group and remained stable throughout the study (mean 4.7 years). However, no difference between groups was noted in the incidence of end stage renal disease or hemodialysis. Despite adverse effects on estimate glomerular filtration rate a lower incidence of both micro- and macro-albuminuria was noted in the fenofibrate group compared with the placebo group (38.2 vs. 41.6% [P =0.01] and 10.5 vs. 12.3% [P=0.04], respectively).[47]

The anti-inflammatory and antioxidant effects of fenofibrate may also be relevant in hypertensive nephrosclerosis. An experimental study conducted in salt-loaded spontaneously hypertensive stroke-prone rats (this animal model develops systemic inflammation, HTN and proteinuria leading to renal and cerebral injury) indicated that fenofibrate significantly increased survival by delaying both the occurrence of brain lesions (monitored by magnetic resonance imaging) and proteinuria.[48] Moreover, fenofibrate significantly reduced proteinuria, inflammatory cell recruitment and extracellular matrix protein deposition in the kidney of spontaneously hypertensive rats without affecting BP.[49]

Kostapanos and colleagues emphasize that beyond theories on pathophysiology 1] increases in SCr levels are transient and reversible even without treatment discontinuation, 2] fenofibrate can limit proteinuria, which is an independent risk factor for both CVD events and chronic kidney disease, and, 3] fenofibrate was associated with long-term benefits on renal function. However, a close monitoring of SCr levels is relevant especially in high-risk patients. Increases in SCr levels greater than 30% can impose treatment discontinuation.[41]

Pleiotropic Effect of Fibrates

There have been numerous studies published on fibrates that elicit the pleiotropic effects of these medications. In addition to its pivotal role in treating dyslipidemia, many authors suggest that fibrates should also be evaluated in patients with cancer, heart failure, diabetic retinopathy, and nephropathy.[50]

Data from recent studies show that fenofibrate improves vascular endothelial function in healthy normolipidemic middle-aged and older adults by reducing oxidative stress and inducing an increase endothelial nitric oxide synthase.[51] Plasma oLDL, a systemic marker of oxidative stress, also decreased with fenofibrate treatment.[51]

Another study observed a significant improvement in endothelium-dependent vascular reactivity with fenofibrate compared to atorvastatin. This was trial was performed over 10 weeks and compared fenofibrate 200 mg/day to atorvastatin 10 mg/day. There was a significant decrease in indirect markers of chronic vessel wall inflammation such as c-reactive peptide and insulin, as well as in peak blood

flow, an index that measures endothelial-dependent post-ischemic change.[52]

PPARα may mediate fibrinogen gene expression, which if activated reduces plasma viscosity and red blood cell aggregation.[53, 54] There have been many studies that resulted in significant reduction of plasma fibrinogen levels in patients with primary dyslipidemia and impaired glucose tolerance when treated with fenofibrate.[55, 56] Additionally, studies show that fenofibrate reduced activity of factor VII, concentration of thrombin activatable fibrinolysis inhibitor, and the total amount of thrombin generated at the site of microvascular injury.[57-60] Fenofibrate also decreases tissue factor (TF) expression in human monocytes and macrophage. TF, a protein present in subendothelial tissue and leukocytes, is necessary for the initiation of thrombin formation in the clotting cascade.[61, 62] Fenofibrate also upregulates the expression of thrombomodulin (an anticoagulant protein) as shown from studies using carotid atheroma biopsies.[63] High levels of plasminogen activator inhibitor-1 (PAI-1), an inhibitor of plasma fibrinolytic activity, is another important risk factor for thrombotic disease and atherosclerosis.[64] And in patients with T2DM who have increased levels of PAI-1 and fibrinogen, fenofibrate significantly decreased levels of fibrinogen and PAI-1 after just 1-month of therapy compared to the controls.[65]

Studies have shown that serum uric acid is directly associated with CVD, independent of classic CVD risk factors. In their recent publication based on data from the Established Populations for Epidemiologic Studies of the Elderly, Iowa (Iowa-EPESE) and the Third National Health and Nutritional Examination Survey (NHANES III), Dutta and colleagues concluded that individuals age 70 and older without overt CVD, renal dysfunction, or diuretic use, serum uric acid greater than 7.0 mg/dL was associated with greater CVD mortality.[66] Hyperuricemia is also frequently present in patients with the MetS, so this is another measure which clinicians should pay attention in order to reduce risk for CVD.[67]

Li and colleagues studied 116 patients with HTG and hyperuricemia and treated them with 200 mg micronized fenofibrate for four weeks to investigate any changes in lipid profiles, serum uric acid and 24-hour uric acid levels. Not surprisingly, serum TG decreased 51%, HDL-C increased by 24%, total cholesterol and LDL-C decreased by 10% and 12%, respectively. Serum uric acid levels were significantly reduced by 28% and urine uric acid levels were increased by 36%. Fenofibrate was thought to exert its anti-hyperuricemic effect by increasing the urinary excertion of uric acid.[68] This increased urinary excretion of uric acid seems most likely through the inhibition of urate transporter 1 by fenofibric acid, a fenofibrate metabolite.[69]

Researchers have investigated fenofibrate in certain patients with gout. One study evaluated the relationship between urine pH and MetS. Their results suggested that insulin resistance plays an important role in the development of low urinary pH in patients with gout and that PPARα agonists are preferable for raising urinary pH of gout patients with HTG.[70] Another study in patients with gout compared fenofibrate plus anti-hyperuricemic agents, benzbromarone (50 mg once daily) or allopurinol (200 mg twice a day), vs. losartan plus benzbromarone. Additionally, both fenofibrate and losartan combined with benzbromarone was studied to measure the combined hypouricemic effect. The study revealed that a combination of fenofibrate or losartan combined with benzbromarone is a good option for the treatment of gout in patients with HTG and/or HTN, but the additional hypouricemic effect may be modest.[71]

Adverse Effects

A slight, but significant, increase in pancreatitis (0.5 with placebo compared with 0.8% with fenofibrate, P=0.031) was observed in FIELD. This excess in pancreatitis has been noted in many fibrate trials. Another important side effect is an increase in homocysteine plasma levels and venous thrombotic events. In FIELD, a 39% increase in homocysteine was observed in the fenofibrate-treated patients. As increased plasma homocysteine level is a risk factor for thrombosis, and Verges pointed out that the significant increase in plasma homocysteine induced by fenofibrate could account for the augmented number of venous thrombotic events.[25] The risk of myopathy is increased with statin-fibrate combinations.

Conclusion

There are many aspects of fibrates that make them an appealing adjunctive therapy to reduce the risk of CVD. As the PROVE IT-TIMI 22 trial highlighted, the role of TGs and risk of CVD events, independent of LDL-C, highlights the potential role of fibrates in the face of recurrent cardiac events in patients on statins. Several additional trials, such as SAFARI, FIELD, VAHIT, and BIP showed the beneficial effects of fibrates, especially in patients with certain conditions (most notably DM, MetS and atherogenic dyslipidemia). Fibrates function as PPARa agonists, which may be at the center of their pleiotropic effects. There have been many studies indicating benefits

of fibrates on the liver, kidney, and the vascular system. There are also potential benefits of using fibrates in patients with gout and further studies should be conducted in other patient populations. Larger randomized trials are required to ascertain these possible benefits, however, fibrates seem to have a plethora of evidence for providing both microvascular, especially in DM, and macrovascular benefits, especially in those with both HTG and low HDL-C.

References

1. Lalloyer F, Staels B. Fibrates, glitazones, and peroxisome proliferator-activated receptors. Arterioscler Thromb Vasc Biol. May 2010;30(5):894-899.
2. Lavie CJ, Milani RV, O'Keefe JH. Dyslipidemia intervention in metabolic syndrome: emphasis on improving lipids and clinical event reduction. Am J Med Sci. 2011 May; 341(5):388-393.
3. Krasuski RA, Devendra GP, Cater G, Whitney EJ. The effect of gemfibrozil, niacin and cholestyramine combination therapy on metabolic syndrome in the Armed Forces Regression Study. Am J Med Sci. 2011 May;341(5):378-382.
4. Lavie CJ, Milani RV. Shedding light on high-density lipoprotein cholesterol: the post-ILLUMINATE era. J Am Coll Cardiol. 2008 Jan 1;51(1):56-58.
5. Cardenas GA, Lavie CJ, Cardenas V, Milani RV, McCullough PA. The importance of recognizing and treating low levels of high-density lipoprotein cholesterol: a new era in atherosclerosis management. Rev Cardiovasc Med. 2008 Fall;9(4):239-258.
6. Ninomiya JK, L'Italien G, Criqui MH, Whyte JL, Gamst A, Chen RS. Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. Circulation. 2004 Jan 6;109(1):42-46.
7. Bayturan O, Tuzcu EM, Lavoie A, et al. The metabolic syndrome, its component risk factors, and progression of coronary atherosclerosis. Arch Intern Med. 2010 Mar 8;170(5):478-484.
8. Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. J Am Coll Cardiol. 2008 Feb 19;51(7):724-730.
9. Imke C, Rodriguez BL, Grove JS, et al. Are remnant-like particles independent predictors of coronary heart disease incidence? The Honolulu Heart study. Arterioscler Thromb Vasc Biol. 2005 Aug;25(8):1718-1722.
10. St-Pierre J, Lemieux I, Perron P, et al. Relation of the "hypertriglyceridemic waist" phenotype to earlier manifestations of coronary artery disease in patients with glucose intolerance and type 2 diabetes mellitus. Am J Cardiol. 2007 Feb 1;99(3):369-373.
11. Tirosh A, Rudich A, Shochat T, et al. Changes in triglyceride levels and risk for coronary heart disease in young men. Ann Intern Med. 2007 Sep 18;147(6):377-385.
12. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002 Dec 17;106(25):3143-3421.
13. Greenland P, Knoll MD, Stamler J, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA. 2003 Aug 20;290(7):891-897.
14. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA. 2003 Aug 20;290(7):898-904.
15. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA. 1999 Dec 22-29;282(24):2340-2346.
16. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. Am J Med. 1977 May;62(5):707-714.
17. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation. 1989 Jan; 79(1):8-15.
18. Ballantyne CM, Olsson AG, Cook TJ, Mercuri MF, Pedersen TR, Kjekshus J. Influence of low high-density lipoprotein cholesterol and elevated triglyceride on coronary heart disease events and response to simvastatin therapy in 4S. Circulation. 2001 Dec 18; 104(25):3046-3051.
19. Lavie CJ, Dinicolantonio JJ, Milani RV, O'Keefe JH. Niacin therapy lives for another day-maybe? J Am Coll Cardiol. 2013 May 28;61(21):2197-2198.
20. Menuet R, Lavie CJ, Milani RV. Importance and management of dyslipidemia in the metabolic syndrome. Am J Med Sci. 2005 Dec; 330(6):295-302.
21. Vega GL, Grundy SM. Lipoprotein responses to treatment with lovastatin, gemfibrozil, and nicotinic acid in normolipidemic patients with hypoalphalipoproteinemia. Arch Intern Med. 1994 Jan 10;154(1):73-82.
22. Grundy SM, Vega GL, Yuan Z, Battisti WP, Brady WE, Palmisano J. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). Am J Cardiol. 2005 Feb 15;95(4):462-468.
23. Austin MA, Breslow JL, Hennekens CH, Buring JE, Willett WC, Krauss RM. Low-density lipoprotein subclass patterns and risk of myocardial infarction. JAMA. 1988 Oct 7;260(13):1917-1921.
24. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005 Nov 26;366(9500):1849-1861.
25. Verges B. Fenofibrate therapy and cardiovascular protection in diabetes: recommendations after FIELD. Curr Opin Lipidol. 2006 Dec;17(6):653-658.
26. 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 Nov 12; 317(20):1237-1245.
27. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med. 1999 Aug 5;341(6):410-418.
28. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. Circulation. 2000 Jul 4;102(1):21-27.
29. Robins SJ, Collins D, Wittes JT, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. JAMA. 2001 Mar 28;285(12):1585-1591.
30. Tenenbaum A, Motro M, Fisman EZ, Tanne D, Boyko V, Behar S. Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome. Arch Intern Med. 2005 May 23;165(10):1154-1160.
31. Arcavi L, Behar S, Caspi A, Reshef N, Boyko V, Knobler H. High fasting glucose levels as a predictor of worse clinical outcome in patients with coronary artery disease: results from the Bezafibrate Infarction Prevention (BIP) study. Am Heart J. 2004 Feb;147(2): 239-245.
32. Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. Atherosclerosis. 2011 Aug;217(2):492-498.
33. Vakkilainen J, Steiner G, Ansquer JC, et al. Relationships between low-density lipoprotein particle size, plasma lipoproteins, and progression of coronary artery disease: the Diabetes Atherosclerosis Intervention Study (DAIS). Circulation. 2003 Apr 8; 107(13):1733-1737.
34. Verges B. Clinical interest of PPARs ligands. Diabetes Metab. 2004 Feb;30(1):7-12.
35. Chhabra R, O'Keefe JH, Patil H, et al. Association of coronary artery

calcification with hepatic steatosis in asymptomatic individuals. Mayo Clin Proc. 2013 Nov;88(11):1259-1265.
36. Cindoruk M, Kerem M, Karakan T, et al. Peroxisome proliferators-activated alpha agonist treatment ameliorates hepatic damage in rats with obstructive jaundice: an experimental study. BMC Gastroenterol. 2007;7:44.
37. Fernandez-Miranda C, Perez-Carreras M, Colina F, Lopez-Alonso G, Vargas C, Solis-Herruzo JA. A pilot trial of fenofibrate for the treatment of non-alcoholic fatty liver disease. Dig Liver Dis. 2008 Mar;40(3):200-205.
38. Gyebi L, Soltani Z, Reisin E. Lipid nephrotoxicity: new concept for an old disease. Curr Hypertens Rep. 2012 Apr;14(2):177-181.
39. Kostapanos MS, Liberopoulos EN, Elisaf MS. Statin pleiotropy against renal injury. J Cardiometab Syndr. 2009 Winter;4(1):E4-9.
40. Rutledge JC, Ng KF, Aung HH, Wilson DW. Role of triglyceride-rich lipoproteins in diabetic nephropathy. Nat Rev Nephrol. 2010 Jun;6(6):361-370.
41. Berkman J, Rifkin H. Unilateral nodular diabetic glomerulosclerosis (Kimmelstiel-Wilson): report of a case. Metabolism. 1973 May;22(5):715-722.
42. Dronavalli S, Duka I, Bakris GL. The pathogenesis of diabetic nephropathy. Nat Clin Pract Endocrinol Metab. 2008 Aug;4(8):444-452.
43. Park CW, Kim HW, Ko SH, et al. Accelerated diabetic nephropathy in mice lacking the peroxisome proliferator-activated receptor alpha. Diabetes. 2006 Apr;55(4):885-893.
44. Bishnoi HK, Mahadevan N, Balakumar P. The combined strategy with PPARalpha agonism and AT(1) receptor antagonism is not superior relative to their individual treatment approach in preventing the induction of nephropathy in the diabetic rat. Pharmacol Res. 2012 Oct;66(4):349-356.
45. Kadian S, Mahadevan N, Balakumar P. Differential effects of low-dose fenofibrate treatment in diabetic rats with early onset nephropathy and established nephropathy. Eur J Pharmacol. 2013 Jan 5;698(1-3):388-396.
46. Chen YJ, Quilley J. Fenofibrate treatment of diabetic rats reduces nitrosative stress, renal cyclooxygenase-2 expression, and enhanced renal prostaglandin release. J Pharmacol Exp Ther. 2008 Feb;324(2):658-663.
47. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010 Apr 29;362(17):1563-1574.
48. Gelosa P, Banfi C, Gianella A, et al. Peroxisome proliferator-activated receptor {alpha} agonism prevents renal damage and the oxidative stress and inflammatory processes affecting the brains of stroke-prone rats. J Pharmacol Exp Ther. 2010 Nov;335(2):324-331.
49. Hou X, Shen YH, Li C, et al. PPARalpha agonist fenofibrate protects the kidney from hypertensive injury in spontaneously hypertensive rats via inhibition of oxidative stress and MAPK activity. Biochem Biophys Res Commun. 2010 Apr 9;394(3):653-659.
50. Tsimihodimos V, Liberopoulos E, Elisaf M. Pleiotropic effects of fenofibrate. Curr Pharm Des. 2009;15(5):517-528.
51. Walker AE, Kaplon RE, Lucking SM, Russell-Nowlan MJ, Eckel RH, Seals DR. Fenofibrate improves vascular endothelial function by reducing oxidative stress while increasing endothelial nitric oxide synthase in healthy normolipidemic older adults. Hypertension. 2012 Dec;60(6):1517-1523.
52. Malik J, Melenovsky V, Wichterle D, et al. Both fenofibrate and atorvastatin improve vascular reactivity in combined hyperlipidaemia (fenofibrate versus atorvastatin trial--FAT). Cardiovasc Res. 2001 Nov;52(2):290-298.
53. Kockx M, Gervois PP, Poulain P, et al. Fibrates suppress fibrinogen gene expression in rodents via activation of the peroxisome proliferator-activated receptor-alpha. Blood. 1999 May 1;93(9):2991-2998.
54. Frost RJ, Otto C, Geiss HC, Schwandt P, Parhofer KG. Effects of atorvastatin versus fenofibrate on lipoprotein profiles, low-density lipoprotein subfraction distribution, and hemorheologic parameters in type 2 diabetes mellitus with mixed hyperlipoproteinemia. Am J Cardiol. 2001 Jan 1;87(1):44-48.
55. Athyros VG, Papageorgiou AA, Athyrou VV, Demitriadis DS, Kontopoulos AG. Atorvastatin and micronized fenofibrate alone and in combination in type 2 diabetes with combined hyperlipidemia. Diabetes Care. 2002 Jul;25(7):1198-1202.
56. Branchi A, Rovellini A, Sommariva D, Gugliandolo AG, Fasoli A. Effect of three fibrate derivatives and of two HMG-CoA reductase inhibitors on plasma fibrinogen level in patients with primary hypercholesterolemia. Thromb Haemost. 1993 Aug 2;70(2):241-243.
57. Okopien B, Krysiak R, Herman ZS. Effects of short-term fenofibrate treatment on circulating markers of inflammation and hemostasis in patients with impaired glucose tolerance. J Clin Endocrinol Metab. 2006 May;91(5):1770-1778.
58. Okopien B, Haberka M, Madej A, et al. Extralipid effects of micronized fenofibrate in dyslipidemic patients. Pharmacol Rep. 2006 Sep-Oct;58(5):729-735.
59. Kilicarslan A, Yavuz B, Guven GS, et al. Fenofibrate improves endothelial function and decreases thrombin-activatable fibrinolysis inhibitor concentration in metabolic syndrome. Blood Coagul Fibrinolysis. 2008 Jun;19(4):310-314.
60. Undas A, Celinska-Lowenhoff M, Domagala TB, et al. Early antithrombotic and anti-inflammatory effects of simvastatin versus fenofibrate in patients with hypercholesterolemia. Thromb Haemost. 2005 Jul;94(1):193-199.
61. Neve BP, Corseaux D, Chinetti G, et al. PPARalpha agonists inhibit tissue factor expression in human monocytes and macrophages. Circulation. 2001 Jan 16;103(2):207-212.
62. Marx N, Mackman N, Schonbeck U, et al. PPARalpha activators inhibit tissue factor expression and activity in human monocytes. Circulation. 2001 Jan 16;103(2):213-219.
63. Mangan S, Clancy P, Golledge J. Modulation of endothelial cell thrombomodulin by PPAR ligands--variation according to environment. Thromb Res. 2008;121(6):827-834.
64. Vaughan DE. PAI-1 and atherothrombosis. J Thromb Haemost. 2005 Aug;3(8):1879-1883.
65. Okopien B, Cwalina L, Lebek M, et al. Effects of fibrates on plasma prothrombotic activity in patients with type IIb dyslipidemia. Int J Clin Pharmacol Ther. 2001 Dec; 39(12):551-557.
66. Dutta A, Henley W, Pilling LC, Wallace RB, Melzer D. Uric acid measurement improves prediction of cardiovascular mortality in later life. J Am Geriatr Soc. 2013 Mar;61(3): 319-326.
67. Puig JG, Martinez MA. Hyperuricemia, gout and the metabolic syndrome. Curr Opin Rheumatol. 2008 Mar;20(2):187-191.
68. Li LJ, Chen H, Ren JY, Wang L, Luo Y. [Effects of micronized fenofibrate on lipid and uric acid metabolism in patients with hyperlipidemia]. Beijing Da Xue Xue Bao. 2009 Oct 18;41(5):541-544.
69. Uetake D, Ohno I, Ichida K, et al. Effect of fenofibrate on uric acid metabolism and urate transporter 1. Intern Med. 2010;49(2):89-94.
70. Takahashi S, Inokuchi T, Kobayashi T, et al. Relationship between insulin resistance and low urinary pH in patients with gout, and effects of PPARalpha agonists on urine pH. Horm Metab Res. 2007 Jul;39(7):511-514.
71. Takahashi S, Moriwaki Y, Yamamoto T, Tsutsumi Z, Ka T, Fukuchi M. Effects of combination treatment using anti-hyperuricaemic agents with fenofibrate and/or losartan on uric acid metabolism. Ann Rheum Dis. 2003 Jun;62(6):572-575.

Disclosure

JHO has served as a speaker for many lipid companies, most recently for Amgen and Sanofi/Regeneron for the PCSK9 Inhibitors, but nothing recently on fibrates or statins; CJL has served as a Consultant and Speaker for many lipid companies, most recently Amarin for Vascepa and Amgen and Sanofi/Regeneron for the PCSK9 Inhibitors and Upsher-Smith, but not recently on fibrates or statins. **MM**