

## Do Fibrates Have a Role in Reducing Cardiovascular Disease in Diabetes?

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Cardiovascular disease (CVD) remains the leading cause of death among individuals with diabetes mellitus (DM) and, as a result, there continues to be a strong focus on therapies to further reduce CV outcomes. The peroxisome proliferator-activated receptor (PPAR) family of ligand-activated transcription factors has been a popular therapeutic target for many years because of its multiple roles in lipid and glucose metabolism and vascular biology.<sup>1</sup> Pharmacologic and endogenous PPAR ligands exist and, upon binding, activation, or repression of their targets, gene expression occurs.<sup>1</sup> Three forms of PPAR have been identified (alpha, gamma, and beta/delta), which exist in different tissues in varying quantities with different effects (Table 1). The most well-known PPAR to date is PPAR-gamma, which has received a lot of attention because of its role in insulin resistance and glucose metabolism and as the primary target of the thiazolidinediones (TZDs). PPAR-alpha has also been demonstrated to have important effects on lipid/glucose metabolism and atherosclerosis development and is, therefore, receiving therapeutic attention. The proposed consequences of PPAR-alpha activation would be expected to be beneficial in reducing CVD risk. In fact, fibrates, synthetic ligands for PPAR-alpha, have been demonstrated to have beneficial CV effects in some clinical trials and are known to reduce triglycerides (TGs), modestly raise high-density lipoprotein cholesterol (HDL-C), and may favour less atherogenic low-density lipoprotein cholesterol (LDL-C). Therefore, fibrates appear to be an ideal therapy to combat the typical dyslipidemia of type 2 DM. However, recent clinical trial data has sparked some controversy over the role of fibrates and has led to a number of reviews on this topic.<sup>2,3</sup> This issue of *Endocrinology Rounds* focuses on PPAR-alpha and discusses its roles in lipid/glucose metabolism and atherosclerosis and, most importantly, the clinical outcome data pertaining to fibrate use in DM.

### Effects of PPAR-alpha

#### Lipid metabolism

**TG and LDL-C:** PPAR-alpha is expressed in tissues that have high levels of fat metabolism, such as liver, skeletal muscle, heart, brown fat, kidney, endothelial cells, macrophages, and smooth muscles cells.<sup>4</sup> Activation of PPAR-alpha triggers a cascade of events that result in lower TG levels and favours large, less atherogenic LDL particles over small, dense, more atherogenic LDL particles. Intracellular fatty acid and very low-density lipoprotein (VLDL) production by the liver is reduced through beta-oxidation of fatty acids.<sup>4</sup> Lipoprotein lipase (LPL) transcription is upregulated, resulting in an increase in the activity of this critical enzyme for the hydrolysis of the TG chylomicrons and VLDL and catabolism of TG-rich particles.<sup>5</sup> In addition, expression of apo-CIII, an inhibitor of LPL activity, is decreased.<sup>6</sup> Therefore, treatment with fibrates results in a reduction in TGs, with variable effects on LDL. In some situations, LDL may fall but, in others, the LDL level may paradoxically rise if there is an additional abnormality that causes an inability to clear the increased LDL particles resulting from improved catabolism of VLDL particles.

**Effects on HDL metabolism:** The HDL pathway allows the movement of cholesterol from peripheral tissues to the liver for possible excretion through bile, thereby serving a very important role in lipid metabolism. Activation of PPAR-alpha has several positive effects on HDL metabolism, potentially increasing both HDL levels and activity.<sup>7</sup> Expression of the gene for



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Table 1: Distribution and actions of the peroxisome proliferator-activated receptors ( $\alpha$ , $\beta/\delta$ , $\gamma$ )		
Subtype	Distribution	Physiological Involvement
PPAR $\alpha$	Liver, kidney, heart, gut, skeletal muscle, adipose tissue	Lipid catabolism and oxidation gluconeogenesis
PPAR $\beta/\delta$	ubiquitous	Adipocyte differentiation (minor) continued to be fully elucidated
PPAR $\gamma$	Adipose tissue Large intestine Hematopoietic cells Kidney, liver Intestinal mucosa	Glucose and fatty acid uptake Gluconeogenesis Lipogenesis Glycogenesis Adipocyte differentiation Macrophage maturation Modulation of inflammation

$\alpha$  = alpha;  $\beta/\delta$  = beta/delta;  $\gamma$  = gamma

the main HDL apolipoproteins, apo-AI and apo-AII, is increased.<sup>7,8</sup> There is also an increase in ABC transporter A1 (ABCA1) and scavenger receptor Class BI (SR-BI) receptor transcription, resulting in enhanced cholesterol movement from peripheral tissues to HDL as part of reverse cholesterol transport (Figure 1).<sup>4</sup>

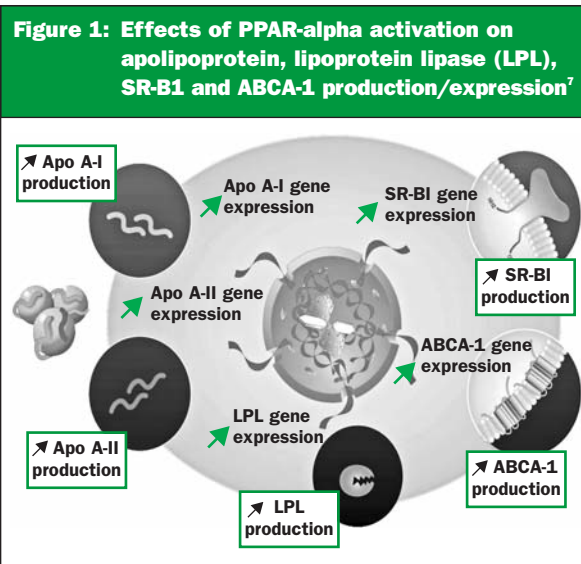
### Glucose metabolism

PPAR-alpha agonists have been shown to decrease insulin resistance and reduce blood glucose levels in animal models of insulin resistance,<sup>9-11</sup> however, this has not been demonstrated in humans. Another potential explanation for this finding in animals is that PPAR-alpha activation promotes fatty acid oxidation in pancreatic beta-cells, thereby reducing pancreatic lipotoxicity and, potentially, improving insulin secretion.<sup>12</sup>

### Atherosclerosis

Endothelial cells, smooth muscle cells, and macrophages also express PPAR-alpha.<sup>1</sup> There are many steps involved in the formation of an atherosclerotic plaque. To begin with, there is monocyte recruitment into the arterial intima mediated by adhesion molecules (eg, vascular cell adhesion molecule [VCAM]-1 and chemokines (eg, monocyte chemoattractant protein-1 [MCP-1])). The recruited monocytes then differentiate into macrophages that produce other proinflammatory substances. The macrophages internalize oxidized LDL and form foam cells. Smooth muscle cells migrate into this proinflammatory environment and proliferate, resulting in intimal hyperplasia. More proinflammatory and procoagulant substances are released. Ultimately, disruption of the plaque surface or necrosis of the plaque core triggers a procoagulant cascade and an acute thrombus develops, resulting in CV clinical syndromes.

Both *in vitro* and *in vivo* studies have suggested that activation of PPAR-alpha may positively impact some of these steps. VCAM-1 and MCP-1 expression is reduced in



the face of inflammation.<sup>13</sup> Interestingly, expression of these substances can actually be increased by PPAR-alpha activation in the absence of inflammation, suggesting that the antiatherogenic effects may be inflammation-dependent.<sup>14</sup> Within macrophages, expression of ABCA1 and SR-BI is increased, allowing for more cholesterol efflux from the macrophage, thereby reducing the foam cell burden.<sup>15</sup> In vascular smooth muscle cells, there is a reduction in proinflammatory substances such as interleukin-1, interleukin-6, and prostaglandins.<sup>16</sup> In addition, vascular tone is improved by enhancing nitric oxide synthase activity and reducing endothelin-1 expression and production.<sup>17,18</sup>

Given all of the above effects on the mediators of lipid and glucose metabolism and atherosclerosis, one would expect that with the activation of PPAR-alpha by fibrates, its synthetic ligand would have beneficial effects on CV events. In the next section, differences between the fibrates and clinical outcome data associated with the fibrates are reviewed to determine if this holds true.

### Differences between the fibrates

All fibrates are ligands of PPAR-alpha. However, there are some clinically-relevant differences among the commercially-available fibrates that may or may not account for some of the differences in the clinical outcome data associated with the different fibrates.

A study comparing the effects of gemfibrozil to bezafibrate demonstrated that gemfibrozil reduced intermediate-density lipoprotein (IDL) to a greater degree than bezafibrate; however, bezafibrate increased apo-AI and decreased cholesterol ester transfer activity more than gemfibrozil.<sup>19</sup> Gemfibrozil also raised fibrinogen levels, whereas bezafibrate decreased fibrinogen levels.<sup>19</sup> Gemfibrozil has also been shown to have more drug interactions than fenofibrate or bezafibrate. Of importance, there is a 2- to 6-fold increase in statin concentration when they are combined with gemfibrozil – an increase that is not seen with fenofibrate.<sup>20</sup> LDL is also reduced to a lesser degree

with gemfibrozil than with the other fibrates.<sup>21</sup> However, use of fenofibrate and bezafibrate is associated with a 20%-40% increase in homocysteine and creatinine, while gemfibrozil is not.<sup>21,22</sup> Bezafibrate also appears to be different in that it not only acts upon PPAR-alpha, but also on the other PPAR receptors (gamma and delta).<sup>23</sup> Therefore, although all fibrates are known to have similar effects on TGs and HDL, there are distinct differences amongst them that may or may not account for some of the observed differences in the clinical outcome studies.

### Clinical outcomes – Primary prevention

**The Helsinki Heart Study (HHS)**<sup>24</sup> was a primary prevention study that investigated the effects of gemfibrozil on CV outcomes. This Finnish study was a 5-year, randomized, placebo-controlled, double-blind study of 4081 asymptomatic men with dyslipidemia (either high LDL-C, high TGs, or both), aged 40-55 years. They were randomized to receive either gemfibrozil (n=2046) or placebo (n=2035). The primary endpoint consisted of fatal and nonfatal myocardial infarction (MI) and cardiac death which, at 5 years, was reduced by 34% (95% CI, 8.2-52.6%, p<0.02). Compared to baseline, the gemfibrozil-treated group had lower total cholesterol, TG, non-HDL, and LDL levels, and higher HDL levels. Further analysis demonstrated that the greatest benefit was seen in the subgroup with high TGs (>2.3 mmol/L) and either low HDL (<1.10 mmol/L) or high LDL/HDL ratio (>5.0 mmol/L).<sup>25</sup> Among the small number of patients with DM (N=135), there was a statistically nonsignificant 68% risk reduction in CV disease in the group receiving gemfibrozil.<sup>26</sup> Presumably, the non-significance was due to the small number of DM subjects. As one of the earlier large lipid outcome trials, the HHS played an important role in establishing the link between fibrate use, lipid-lowering, and a reduction in CV disease.

### Clinical outcomes – Secondary prevention

**The Veterans Affairs HDL Intervention Trial (VA-HIT)** was a secondary prevention study examining the effects of gemfibrozil in men primarily with low HDL ( $\leq 1.0$  mmol/L) and LDL <3.60 mmol/L.<sup>27</sup> In a double-blind fashion, 2531 men with coronary heart disease (CHD) were randomly allocated to receive either gemfibrozil (1200 mg per day) or placebo. The primary outcome was nonfatal MI or CHD death. After a median of 5.1 years, there was a 22% relative risk reduction in the primary outcome (95% CI, 7-35; p=0.006). The gemfibrozil group had HDL levels that were approximately 6% higher than those in the placebo group. A nuclear magnetic resonance spectrography study of the VA-HIT population demonstrated that the number and size of the LDL and HDL particles were independent predictors of new coronary events.<sup>28</sup> Gemfibrozil altered these parameters favourably by reducing the number and increasing the size of LDL particles. In addition, there were more HDL particles that were smaller.<sup>28</sup> In a subsequent analysis, the population was divided into one of the following groups: known DM (n=627), undiagnosed DM (n=142), impaired fasting glucose (n=323), and

normal fasting glucose (n=1425).<sup>29</sup> Among the 769 subjects with DM, gemfibrozil reduced the composite endpoint of CHD death, stroke, or MI by 32% (p=0.004) and the reduction in CHD death was 41% (HR 0.52; 95% CI, 0.39-0.91; p=0.02).

**The bezafibrate infarction prevention (BIP) trial:** In BIP, 3090 subjects with prior MI or stable angina were randomized to receive either bezafibrate 400 mg/day (n=1548) or placebo (n=1546) for a mean of 6.2 years.<sup>30</sup> All had HDL levels of  $\leq 1.16$  mmol/L, TGs  $\leq 3.4$  mmol/L, and total cholesterol between 4.5 and 6.7 mmol/L. Unlike HHS or VA-HIT, women were included in this trial, albeit comprising only a small proportion of the overall population (8.8%). Bezafibrate therapy resulted in an 18% increase in HDL, a 21% decrease in TGs, and a 6% reduction in LDL. However, the primary endpoint of fatal and nonfatal MI and cardiac death was not statistically different between the bezafibrate and placebo groups (13.6% vs 15%). In a post hoc analysis of the data by baseline HDL and TG levels, statistically-significant benefit was seen among subjects whose baseline TG was  $\geq 2.3$  mmol/L (relative risk reduction [RRR] 39.5%, p=0.02). A further analysis suggested that bezafibrate was particularly beneficial among subjects with metabolic syndrome,<sup>31</sup> demonstrating an RRR of 29% (95% CI, 5-46) for any MI and 33% (95% CI, 9-51) for nonfatal MI. When comparing VA-HIT and BIP, the subjects in VA-HIT were older, had more DM, lower HDL, lower LDL, and higher baseline TG levels than the subjects in BIP. These differences have been proposed as a potential explanation for the differences in outcome between the two studies.

**The Diabetes Atherosclerosis Intervention Study (DAIS):** Analyses of the diabetic subgroups in the previous studies suggested that there was a CV benefit with the use of fibrates in this population. One of the first fibrate studies to exclusively enroll subjects with DM was the DAIS.<sup>32</sup> In DAIS, 418 people with type 2 DM and angiographic evidence of atherosclerosis were randomized to receive either micronized fenofibrate 200 mg/day (n=207) or placebo (n=211) for at least 3 years. The original primary endpoint of the study was mean segment diameter. There were no differences between the groups; however, there were differences in the percentage of diameter stenosis and minimal lumen diameter, all in favour of fenofibrate. The benefit is theorized to have resulted from enlargement of LDL particle size generated by the use of fenofibrate.<sup>33</sup> As for clinical outcomes, the study was not powered to demonstrate a difference. However, 50 participants in the placebo group experienced a CV event compared to only 38 participants in the fenofibrate group.

**Fenofibrate Intervention and Event Lowering in Diabetes (FIELD):** Prior to the completion of the FIELD trial,<sup>34</sup> subgroup analyses of diabetic subjects and angiographic evidence from DAIS appeared to support the use of fibrates in DM patients to reduce CV disease. The FIELD trial was the first fibrate clinical outcomes trial to enroll diabetic subjects exclusively. FIELD, a randomized

controlled trial of 9795 patients with type 2 DM, compared the effects of fenofibrate and placebo on the primary endpoint of the first occurrence of coronary events (CHD death or nonfatal MI). Of the 9795 subjects, 7664 had no prior clinical history of CHD. Baseline entry total cholesterol was <6.5 mmol/L and the mean LDL-C was 3.1 mmol/L. All subjects were statin-free at the time of enrollment. During the course of the study, lipid-lowering therapy could be modified by the participants' primary care physician at his/her own discretion. As a result, at the study end, 17% of the subjects in the placebo arm and 8% in the fenofibrate arm were also receiving other lipid-lowering therapy, 93% of which were statins. After a median follow-up of 5 years, there were no significant differences in the primary outcome. Although nonfatal MI was significantly reduced by 24% (HR=0.76; 95% CI, 0.62-0.94; p=0.01), CHD mortality was increased by a non-significant 19% (HR=1.19; 95% CI, 0.90-1.57; p=0.22) (Figure 2). Other secondary outcomes that achieved statistical significance included total CV disease (CHD events, stroke, CV death, coronary and carotid revascularization) (HR=0.89; 95% CI, 0.80-0.99; p=0.035). There were no differences in total mortality. In a prespecified subgroup analysis, a statistically-significant difference was seen in the primary endpoint in patients with no prior CV disease (ie, primary prevention), but not in those with pre-existing CV disease (ie, secondary prevention). Interestingly, some positive tertiary outcome benefits were associated with fenofibrate including reduced progression of albuminuria (p=0.002) and retinopathy requiring laser treatment (p=0.0003). Adverse event rates were low overall, but there were more cases of pancreatitis and pulmonary embolism in the fenofibrate group, although the number of cases was quite small. In addition, plasma homocysteine levels were found to be an average of 3.7 µmol/L higher in the fenofibrate group compared

to the placebo group. Creatinine was also found to be slightly higher (10-12 µmol/L) in the fenofibrate group compared with placebo (p<0.001).

## Interpretation

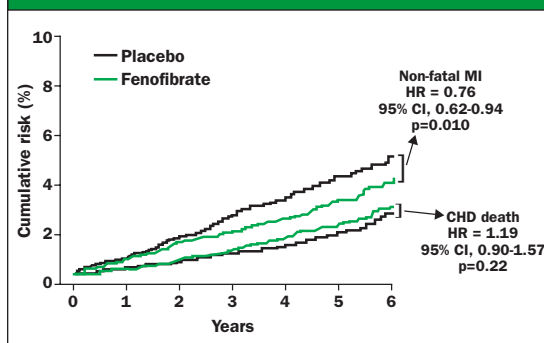
Prior to FIELD, there were post hoc analyses in diabetic subgroups and angiographic evidence from DAIS that suggested a benefit of fibrate use in patients with DM. However, the FIELD study – the first large-scale fibrate study with clinical outcomes that exclusively assessed subjects with DM – has provided mixed results that call into question the role of fibrates in reducing CV disease in DM. There has been much discussion about the results of FIELD and various hypotheses have been generated in an attempt to explain the mixed results.<sup>34,35</sup>

First, there was a high use of statins in the placebo arm. By the end of the study, 34% of subjects in the placebo arm and 18% in the fenofibrate arm were on statins. The role of statins in reducing CV risk in primary prevention,<sup>36</sup> secondary prevention,<sup>37</sup> and exclusively in patients with diabetes,<sup>38</sup> is certainly well-established.<sup>39-41</sup> Therefore, the differential use of statins in the two study arms may have been meaningful. On the other hand, the study was designed with the expectation that there would be a 23% drop in statin therapy. In addition, a prespecified analysis of the data, adjusting for new lipid-lowering therapy, still demonstrated a benefit with the use of fenofibrate, with a 19% (p=0.01) risk reduction in CHD events and a 15% (p=0.004) risk reduction in total CV disease events.<sup>34</sup> Yet, this possibly does not fully explain the mixed results.

Beyond the statin issue, another hypothesis is that the difference in HDL between the 2 groups in FIELD was not as great as the differences observed in the other fibrate studies. Furthermore, the HDL-raising benefits of fenofibrate were attenuated over the course of the study, dropping from 5% at 4 months to 2% at study end. The reasons for this are unclear. In addition, an increase in homocysteine was observed in the fenofibrate group, the clinical significance of which is uncertain. Although epidemiologic studies have shown a positive correlation between homocysteine levels and CV disease risk,<sup>42</sup> no randomized controlled studies have yet demonstrated a reduction in CV disease risk by lowering homocysteine levels and, therefore, the hypothesis that homocysteine is causally related to CV risk remains unproven.

Another potential explanation for the discrepancy in results between the fibrate trials is that perhaps not all fibrates have similar CV benefits. For example, as mentioned above, gemfibrozil, the drug associated with improved outcomes both in the HHS and the VA-HIT, is known to raise homocysteine levels to a lesser degree<sup>43</sup> and drug interactions are known to occur less frequently with fenofibrate compared with gemfibrozil. Therefore, perhaps the

**Figure 2: Cumulative risk curves of time to non-fatal MI and CHD death in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study<sup>34</sup>**



MI = myocardial infarction

differences among the fibrates may account for the differences observed in the fibrate outcome studies.

As a point of interest, some of the microvascular complications of DM appeared to be reduced by fenofibrate treatment. This is in keeping with animal, as well as some limited human data, suggesting that improvements in the lipid profile may be associated with a reduction in the microvascular complications of DM.<sup>44</sup> This observation needs to be studied in greater detail before any firm conclusions can be drawn; however, these potential benefits are certainly intriguing.

When compiling all of the information, taking into account all the potential explanations for the mixed results of FIELD, one could conclude that fibrates do not have a role as monotherapy in reducing CV disease in DM. Although their role in the treatment of marked hypertriglyceridemia to prevent the complications of hypertriglyceridemia remains, the role of the fibrates as monotherapy for CV risk reduction in diabetes has not been proven. As emphasized in multiple guidelines around the world,<sup>39-41</sup> this role generally belongs to statins. However, the FIELD study does suggest that combining statin and fibrate therapy is relatively safe, given the fact that 2720 patients received the combination and no apparent increased toxicity was observed. Therefore, it is possible that the predominant role of fibrates in patients with DM will be in combination with statins. This important question will be answered by the ongoing National Institutes of Health (NIH)-sponsored Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,<sup>45</sup> which includes a comparison of simvastatin monotherapy vs. simvastatin plus fenofibrate on CV outcomes in approximately 5800 subjects with type 2 DM.

## Conclusions

PPAR-alpha has been shown to play an important role in lipid and glucose metabolism and in the pathophysiology of atherosclerosis. Therefore, it would seem appropriate to target PPAR-alpha with fibrates to reduce CV disease, particularly among patients with DM who have the typical dyslipidemia targeted by fibrates. In fact, the HHS demonstrated the benefit of fibrates for primary prevention, while the VA-HIT (and, to some extent, the BIP) trials demonstrated the benefit of fibrates for secondary prevention. All of these studies included small subgroups of subjects with DM. The DAIS trial provided angiographic evidence that fenofibrate therapy can reduce some of the markers of atherosclerosis progression in patients with DM. However, clinical outcome trials can sometimes demonstrate unexpected or mixed results that call into question the effectiveness of certain therapies. This was the case for the FIELD study that studied the use of fibrates

as monotherapy for CV disease reduction in DM. FIELD was the first large outcome study to exclusively study patients with DM and the results were disappointing and mixed. Therefore, in the treatment of the dyslipidemia associated with type 2 DM, fibrates maintain their role for the treatment of marked hypertriglyceridemia, but should no longer be used as monotherapy for CV risk reduction. Statins remain the first-line therapy for CV risk reduction; however, whether fibrates may play a role in combination with statins in reducing CV risk is a question that will be answered in ongoing trials.

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## Upcoming Scientific Meetings

3-7 November 2007

### American Heart Association 2007

Orlando, Florida

Orange County Convention Center

CONTACT: <http://aha.orlandomeetinginfo.com>

1-3 February 2008

### 55<sup>th</sup> Annual Advanced Postgraduate Course

American Diabetes Association

San Francisco, California

CONTACT: <http://professional.diabetes.org/>

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