Atherosclerosis xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

Peroxisome proliferator-activated receptor-alpha (PPARα): At the crossroads of obesity, diabetes and cardiovascular disease

Jean-Charles Fruchart*

Laboratoire J & K, Inserm UR 545, Université Lille 2, Faculté de Médecine de Lille, Pôle Recherche, Bd du Prof. Leclerc, 59045 Lille Cedex, France

ARTICLE INFO

Article history:
Received 2 October 2008
Received in revised form 4 March 2009
Accepted 6 March 2009
Available online xxx

Keywords:
Peroxisome proliferator-activated receptor α
Lipoprotein metabolism
Inflammation
Vascular function
Cardiovascular
Microvascular

ABSTRACT

Cardiovascular disease is the leading cause of morbidity and mortality world-wide. The burden of disease is also increasing as a result of the global epidemics of diabetes and obesity. Peroxisome proliferator-activated receptor α (PPARα), a member of this nuclear receptor family, has emerged as an important player in this scenario, with evidence supporting a central co-ordinated role in the regulation of fatty acid oxidation, lipid and lipoprotein metabolism and inflammatory and vascular responses, all of which would be predicted to reduce atherosclerotic risk. Additionally, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study has indicated the possibility of preventive effects in diabetes-related microvascular complications, although the mechanisms of these effects warrant further study. The multimodal pharmacological profile of PPARα has prompted development of selective PPAR modulators (SPPARMs) to maximise therapeutic potential. It is anticipated that PPARα will continue to have important clinical application in addressing the major challenge of cardiometabolic risk associated with type 2 diabetes, obesity and metabolic syndrome.

Contents

1. Introduction

Cardiovascular disease (CVD) is a major public health concern, as it represents the leading cause of morbidity and mortality in the developed world. Within Europe, CVD is responsible for nearly half (49%) of all mortality, over 4 million cases each year [1]. Moreover, the burden of CVD is increasing, attributable to the changing profile of cardiovascular risk, as evident from the global epidemics of obesity, diabetes (predominantly type 2 diabetes) and metabolic syndrome [2,3], the latter characterised by a cluster of metabolic disorders that predispose to type 2 diabetes mellitus and CVD. These trends are projected to substantially increase the cost of managing CVD and highlight the

* Tel.: +33 3 20 97 42 16; fax: +33 3 20 87 73 60.
E-mail addresses: Jean-Charles.Fruchart@pasteur-lille.fr, Jean-Charles.Fruchart@univ-lille2.fr.

0021-9150/$ – see front matter © 2009 Published by Elsevier Ireland Ltd.
doi:10.1016/j.atherosclerosis.2009.03.008

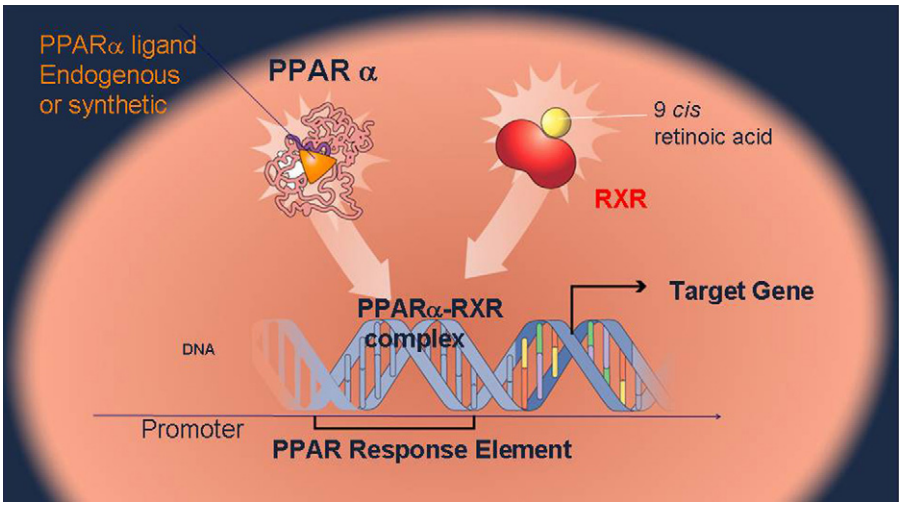

Fig. 1. Schematic representation of PPARα transcriptional activation. Activation of the PPAR is initiated by binding of an agonist to the ligand binding domain of the nuclear receptor. Following ligand activation, the PPARs form heterodimers with retinoid X receptor (RXR), another nuclear receptor activated by its own ligand (purported to be 9 *cis*-retinoic acid). The PPAR–RXR complex subsequently recognises and binds to DNA at sequence-specific regions on target gene promoters, known as PPAR response elements (PPRE), thereby activating their expression.

need for concerted efforts to address this increasing burden of disease.

In the context of this convergence of obesity, diabetes and CVD, the peroxisome proliferator-activated receptor (PPAR) nuclear receptor family has received increasing attention. There are three distinct PPARs – PPARα, PPARδ (also known as PPARβ or PPARβ/δ) and PPARγ – each encoded by a separate gene and with specific tissue distribution. Experimental evidence shows that the PPARs play a central role in the regulation of metabolic homeostasis. Activation of the PPAR is initiated by binding of an agonist, either an endogenous ligand (e.g., fatty acids, eicosanoids, or oxidized phospholipids) or synthetic ligand to the ligand binding domain of the nuclear receptor. This then forms heterodimers with retinoid X receptor (RXR), another nuclear receptor activated by its own ligand (purported to be 9 *cis*-retinoic acid). The PPAR–RXR complex subsequently recognises and binds to DNA at sequence-specific regions on target gene promoters, known as PPAR response elements (PPRE), thereby activating their expression (Fig. 1) [4]. Additionally, activation of the PPAR–RXR complex can repress gene transcription, either by processes independent of DNA-binding via interference with other signalling pathways or down-regulation of membrane receptor expression, or by a DNA-dependent process involving the recruitment of corepressors to PPARα without bound ligand [4]. Thus, PPAR can regulate the expression of multiple gene cassettes, thereby offering the opportunity for a novel integrated co-ordinated response across different organs and cells.

Despite their serendipitous discovery and clinical use in the treatment of dyslipidemia for over three decades, elucidation of the pharmacological profile of activity of the fibrates, PPARα agonists, is more recent. Evidence clearly supports a central role for PPARα in the regulation of lipid and lipoprotein metabolism, inflammation and vascular function, which impacts on the process of atherogenesis. Together, these findings have led to renewed interest in PPARα as a therapeutic target.

2. PPARα and lipid metabolism

The effects of PPARα on lipids and lipoproteins are summarised in Fig. 2. Activation of PPARα leads to increased tissue-specific expression of key genes involved in fatty acid uptake and β-oxidation. This includes acyl-Coenzyme A synthetase, an enzyme which plays a key role in esterification of fatty acids thereby preventing their efflux from cells, in the liver and kidney [5], and carnitine palmitoyltransferase type 1 (CPT-1), a pivotal enzyme involved in fatty acid catabolism within mitochondria in metabolically active tissue such as the heart, skeletal muscle and brown adipose tissue, which contains a PPRE in its promoter region. The net effect of this is reduction in the availability of free fatty acids for synthesis and secretion of very-low-density lipoproteins (VLDL) [4].

2.1. Impact on triglyceride and low-density lipoprotein (LDL) metabolism

PPARα activation decreases triglycerides (TG) by increasing free fatty acid β-oxidation, hepatic lipoprotein lipase expression [6], and expression of apolipoprotein V (apoV) [7], and by decreasing expression of apolipoprotein CIII (apoCIII) [8]. The mechanism by which PPARα activation represses apoCIII transcription has yet to elucidated. In vitro studies imply repression of apoCIII expression via interaction with a PPRE in the Rev-erb-α promoter, given that mice deficient in this protein exhibit increased plasma concentrations of TG and apoCIII [9]. Furthermore, whether apoCIII affects TG metabolism in vivo is contentious. Some studies showed an effect in normolipidemic subjects [10], whereas in other studies apoCIII affected TG metabolism only when associated with lipoproteins at concentrations not found in vivo. Increases in the number and apoC-III content of VLDL particles also have adverse consequences for other lipoprotein subspecies, contributing to an increase in small, dense LDL particles. PPARα activation promotes a change in the distribution profile of LDL particles, decreasing the levels of atherogenic dense LDL-cholesterol, with poor affinity for the LDL receptor, while increasing large buoyant LDL particles, which have a high affinity for this receptor [11].

2.2. PPARα, high-density lipoprotein (HDL) metabolism and reverse cholesterol transport

In addition, PPARα regulates HDL metabolism by (1) stimulating hepatic expression of apoA-I and apoA-II and thus raising HDL production in the liver [12], (2) promoting HDL-mediated cholesterol efflux from macrophages, via enhanced expression of scavenger receptor-BI [13] and the ATP-binding cassette transporter A1 (ABCA1) [14], and (3) inhibiting cellular cholesteryl ester formation activity, thereby limiting accumulation of cholesteryl ester

Please cite this article in press as: Fruchart J-C. Peroxisome proliferator-activated receptor-alpha (PPARα): At the crossroads of obesity, diabetes and cardiovascular disease. Atherosclerosis (2009), doi:10.1016/j.atherosclerosis.2009.03.008

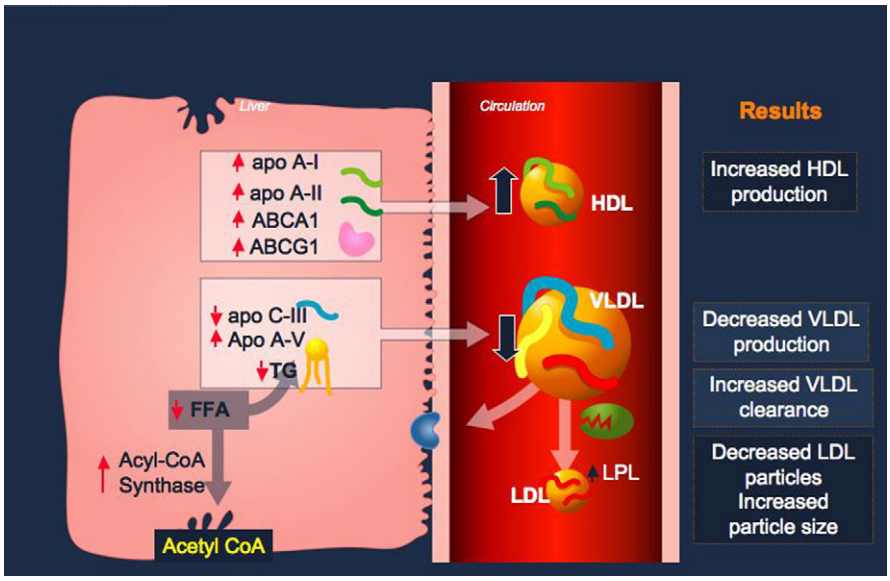

Fig. 2. Fibrates regulate lipid metabolism by controlling the expression of PPARα genes. Activation of PPARα leads to increased expression of genes involved in fatty acid uptake and β-oxidation, as well as those responsible for the expression of hepatic lipoprotein lipase and apolipoprotein V (apoV) and decreased expression of apolipoprotein CIII (apoCIII). The net effects of these actions are increases in high-density lipoprotein (HDL) production, very-low-density lipoprotein (VLDL) clearance and low-density lipoprotein (LDL) particle size and decreases in VLDL production and LDL particle concentration.

in vascular macrophages and preventing foam cell formation [15], as well as contributing to enhanced efflux of free cholesterol to extracellular receptors [14,15]. As well, PPARα activation regulates processes controlling cholesterol mobilisation that are upstream of cholesterol efflux, leading to enhanced availability of plasma membrane cholesterol for cholesterol efflux [16], which together with regulation of ABCA1 and SR-BI expression, stimulate reverse cholesterol transport.

3. PPARα, inflammation and atherosclerosis

Mechanistically, PPARα activation may influence the development of atherosclerosis via indirect effects on glucose and lipid homeostasis in adipose tissue, skeletal muscle and the liver. Additionally, PPARα may have a direct effect on inflammation and atherosclerosis, by modification of the transcription factors nuclear factor-κB (NF-κB) and activator protein-1 (AP-1).

3.1. PPARα and early atherogenesis

PPARα is expressed in inflammatory cells involved in the process of atherogenesis, such as monocytes, macrophages and lymphocytes [17–19] implying a regulatory role in the early stages of atherosclerosis. PPARα activators inhibit cytokine-induced expression of vascular cell-adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), both of which play a critical role in the recruitment of leukocytes and monocytes to the atherosclerotic lesion, by down-regulation at the transcriptional level [18], mediated in part by inhibition of the NF-κB signalling pathway [17,18,20]. The effect of PPARα activation on expression of monocyte chemoattractant protein-1 (MCP-1) is less clear; with studies reporting stimulation of synthesis [21], or reduction in C-reactive protein (CRP)-induced expression [22]. PPARα ligands also repress thrombin-induced expression of endothelin-1 (ET-1), by negatively interfering with the AP-1 signalling pathway [23].

3.2. PPARα and local cellular inflammation

Cytokines such as tumour necrosis factor-α (TNF-α), interleukins and interferon-γ, which are released from T lymphocytes during the initiation of a chronic inflammatory response, play a critical role in cellular immunity, and contribute to the early development of plaque. Therefore, repression of inflammation by decreasing cytokine release could be very important in modulating the cascade of responses in atherosclerosis.

Cytokine imbalance associated with the metabolic syndrome is thought to be the mechanism driving the development of non-alcoholic fatty liver disease (NAFLD) (Fig. 3). TNF-α promotes insulin resistance and liver inflammation and suppresses the expression and secretion of adiponectin in adipocytes, although the underlying mechanism is poorly elucidated. TNF-α polymorphisms have been associated with increased susceptibility genotype for insulin resistance, NAFLD, and steatohepatitis [24].

Activation of PPARα inhibits the expression of genes coding for a range of acute-phase proteins and inflammatory cytokines, such as interleukin-6 (IL-6), C-reactive protein (a complement activator and inducer of MCP-1 expression), fibrinogen and TNF-α [25], which implies an anti-inflammatory role for PPARα. Control of the expression of these inflammatory cytokines is exerted by interference with the NF-κB and AP-1 inflammatory pathways at the transcriptional level [20,26]. The clinical relevance of these findings is supported by studies showing that fenofibrate treatment decreased plasma concentrations of IL-6 and TNF-α in patients with dyslipidemia [27]. Additionally, given that hepatic PPARα activation suppresses expression of hepatic inflammatory mediators including TNF-α and reduces hepatic fat accumulation in the liver during the development of fatty liver disease [28], suggests a potential role in preventing steatosis and subsequent progression to NAFLD. In support of this, preliminary data show that fenofibrate treatment improved metabolic syndrome and liver function tests in patients with NAFLD [29].

3.3. PPARα, plaque stability and thrombosis

Advanced atherosclerotic plaques are characterised by a core of extracellular lipid droplets, cellular debris and foam cells, surrounded by a fibrous cap of smooth muscle cells and a collagen-rich matrix. Progression from a stable to unstable plaque is dependent largely on the balance between production and degradation of the extracellular matrix in the fibrous cap. Experimental evidence

Please cite this article in press as: Fruchart J-C. Peroxisome proliferator-activated receptor-alpha (PPARα): At the crossroads of obesity, diabetes and cardiovascular disease. Atherosclerosis (2009), doi:10.1016/j.atherosclerosis.2009.03.008

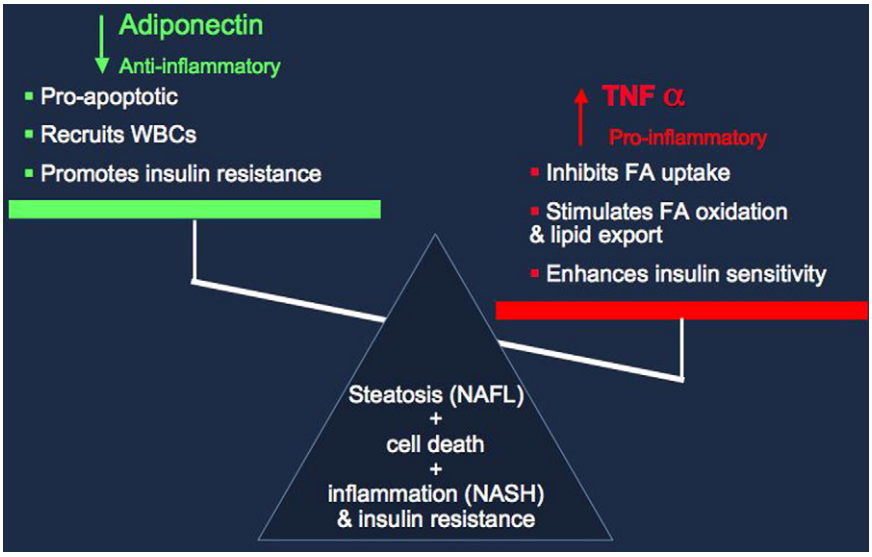

Fig. 3. Cytokine imbalance associated with the metabolic syndrome resulting in underlies the development of non-alcoholic fatty liver disease. The development of non-alcoholic fatty liver disease (NAFLD) is associated with imbalance between the pro-inflammatory actions resulting in increased expression of tumour necrosis factor-α (TNF-α) and anti-inflammatory actions resulting in reduced adiponectin expression. This in turn promotes insulin resistance, inflammation (non-alcoholic steatohepatitis, NASH) and subsequently steatosis and cell death (NAFLD).

suggests that PPARα ligands may modulate this balance by down-regulation of LPS-induced secretion of matrix metalloproteinase-9 (MMP-9) [30]. PPARα ligands also enhance macrophage apoptosis, probably by negative interference with the anti-apoptotic NF-κB pathway [31], although the clinical relevance of this effect is not certain.

Additionally, PPARα activation may impact on the processes involved in atherothrombosis subsequent to plaque rupture. Experimental studies show that expression of tissue factor in human monocytes and macrophages is down-regulated by activation of PPARα ligands, suggesting a potential mechanism whereby fibrates may influence atherothrombosis in patients with vascular disease [32]. PPARα activation may also modulate the expression of plasminogen activator inhibitor type 1 (PAI-1), a member of the serine protease inhibitor family which limits fibrinolysis and promotes thrombosis, although results are conflicting, with studies showing increased PAI-1 expression with clofibrate or bezafibrate [33], but a decrease with fenofibrate or gemfibrozil [34].

4. PPARα and vascular function

While the role of PPARα in the regulation of lipid metabolism and inflammation is now well recognized (Table 1), recent evidence also indicates that PPARα is important in controlling vascular smooth muscle cell proliferation. Activation of smooth muscle cell proliferation is a key event in the development of atherosclerotic complications. In response to vascular injury, smooth muscle cells migrate into the intima of the arterial wall, where they subsequently proliferate and synthesize extracellular matrix, resulting in intimal hyperplasia. During this process, smooth muscle cells undergo phenotypic changes from a differentiated, contractile quiescent state (G_0 phase of the cell cycle), to a synthetic, embryonic, proliferative state (S phase).

In vitro studies using both human and mouse primary aortic smooth muscle cells show that PPARα inhibits smooth muscle cell-cycle progression at the G_1/S transition, an effect attributed to induction of the cyclin-dependent kinase inhibitor and tumour suppressor gene $p16^{INK4a}$ (p16). This in turn results in the sequestration of cyclin-dependent kinase 4 (CDK4) and subsequent decrease in CDK4-mediated phosphorylation, thereby providing a molecular mechanism whereby PPARα directly interferes with cell-cycle progression [35]. In an in vivo mouse model of mechanical carotid artery injury, p16 deficiency was associated with enhanced smooth muscle cell proliferation underlying intimal hyperplasia, and this effect was markedly enhanced in PPARα deficient mice compared with wild type ($PPAR\alpha^{+/+}$) mice. Moreover, treatment of PPARα wild type mice with fenofibrate substantially reduced intimal hyperplasia (Fig. 4) [35]. Together these findings suggest potential therapeutic application for PPARα in preventing restenosis either via systemic administration or in coated stents.

Table 1
Summary of effects of PPARα activation in improving vascular function.

Response	Mediators
↓ Cell recruitment and activation	↓MCP-1, VCAM-1, ICAM-1 and chemokines
↓ Inflammatory response	↓TNF-α, interleukins, CRP, VCAM-1, tissue factor, fibrinogen
↑Cholesterol efflux, ↓ foam cell formation	↑ABCA1, SR-BI, CD36, ↓SR-A
↓ Vasoconstriction and cell migration	↓ET-1, MMP, thromboxane
↓ Thrombosis, ↑ plaque stability	↓MMP-9, PAF, tissue factor

ABCA1 ATP-binding cassette transporter A1; CRP C-reactive protein; CD36 cluster of differentiation 36; ET-1 endothelin-1; ICAM-1 intercellular adhesion molecule-1; MCP-1 monocyte chemoattractant protein-1; MMP matrix metalloproteinase; SR-A scavenger receptor A; SR-BI scavenger receptor-BI, TNF-α tumour necrosis factor-α; VCAM-1 vascular cell-adhesion molecule-1.

5. The role of PPARα in obesity

Increasing evidence suggests that PPARα may have a role in the management of obesity, especially central obesity associated with insulin resistance syndromes, given its involvement in the regulation of fatty acid oxidation, lipid metabolism and inflammation. Stimulation of β-oxidation by PPARα activation (see Section 2), implies a mechanism for decreasing tissue lipid content, thereby preventing lipid accumulation. Experimental studies also indicate the involvement of PPARα in the transcriptional response to fasting, as evident by the development of steatotic liver and heart and marked increases in free fatty acid levels, indicative of inhibition of fatty acid uptake and oxidation, in mice deficient in PPARα [36]. PPARα activation may also have a beneficial effect on insulin sensitivity, by reducing plasma TG levels and adiposity [37].

Please cite this article in press as: Fruchart J-C. Peroxisome proliferator-activated receptor-alpha (PPARα): At the crossroads of obesity, diabetes and cardiovascular disease. Atherosclerosis (2009), doi:10.1016/j.atherosclerosis.2009.03.008

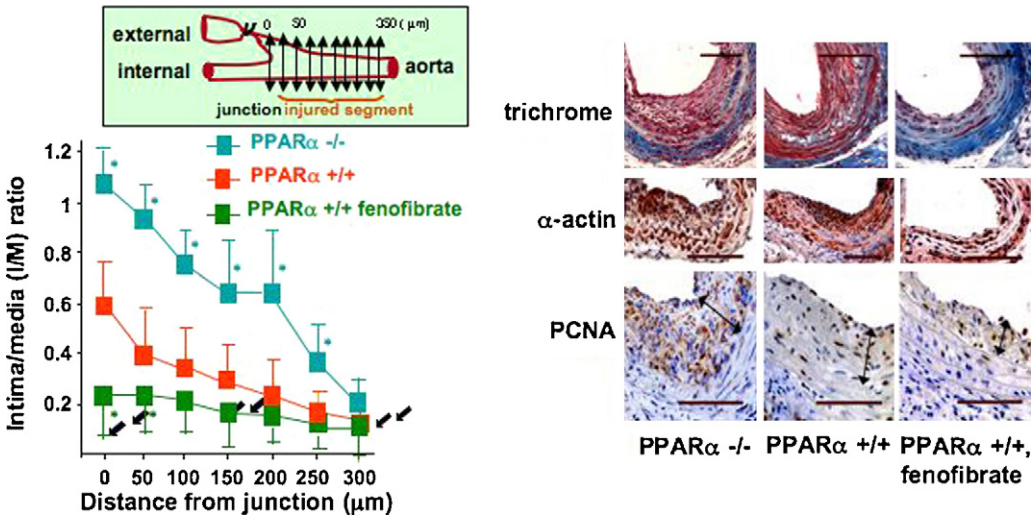

Fig. 4. Animal studies using a mouse model show that treatment with fenofibrate inhibits neointima formation after mechanical carotid injury. Data from Gizard et al. [35]. Left carotid artery injury was performed on PPARα−/− ($n = 6$) or PPARα+/+ Sv/129 mice treated ($n = 5$) or not ($n = 8$) with fenofibrate. The topographic pattern of intima–media (I/M) area ratio 3 weeks after injury was markedly enhanced in PPARα−/− mice but reduced in PPARα+/+ mice treated with fenofibrate ($^*p \leq 0.05$ versus PPARα+/+ wild type mice not treated with fenofibrate for each comparison). Values were reported as mean ± S.E.M. of the I/M ratios measured on Masson's trichrome-stained sections at the indicated distances from the junction between the external and internal branches of the left carotid artery. Consistent with this, representative carotid sections of uninjured right and injured left carotids at 50 μm from the junction stained with Masson's trichrome (top panel), immunostained for SMC (α-actin staining, middle panel) or for proliferation marking (proliferating PCNA immunostaining to identify cells in S phase, bottom panel) also showed marked reduction in PPARα+/+ mice treated with fenofibrate. Scale bars: 100 μM. SMC smooth muscle cells.

Additionally, PPARα activation may protect against chronic inflammation associated with obesity, by down-regulation of gene expression of inflammatory markers and attenuating inflammation in adipose tissue, supported by results in a mouse model [38]. In PPARα deficient mice, which exhibit high adiposity together with an inflammatory state, there was evidence of down-regulation of mRNA expression of insulin gene transcription factors, reduction of pancreatic function, together with down-regulation of adipocyte mRNA of pro-inflammatory mediators including MCP-1, TNF-α and IL-6 [39]. Furthermore, PPARα activation may play a role in amelioration of obesity-induced insulin resistance in obese diabetic mice via novel mechanisms including suppression of adipose hypertrophy and macrophage infiltration in white adipose tissue and increasing the action of adiponectin by upregulation of adiponectin receptor expression [40]. Further work is needed to define whether the anti-inflammatory effects of PPARα in white adipose tissue are caused by direct or indirect mechanisms.

6. PPARα in the setting of increased cardiometabolic risk

Given that PPARα is a central target influencing vascular function via effects on cholesterol homeostasis and inflammation control in macrophages, ET-1 signalling in endothelial cells and vascular remodelling in smooth muscle cells, highlights a cardioprotective role for PPARα activators, especially in patients at increased cardiometabolic risk,

Among people with type 2 diabetes and/or metabolic syndrome, an atherogenic lipid profile characterized by elevated TG and low plasma levels of HDL cholesterol, usually with a preponderance of small, dense LDL particles, is common. Lowering LDL-cholesterol with statins is the primary focus of lipid management for prevention CVD in patients at increased cardiometabolic risk, supported by an extensive evidence base of large prospective trials [41]. However, despite intensive LDL-lowering (from 100 mg/dL to 70 mg/dL) there remains substantial residual risk of cardiovascular events, associated with low HDL cholesterol (<37 mg/dL) [42] or elevated TG (>200 mg/dL) [43]. These data highlight a potential need for additional therapeutic intervention.

7. Macrovascular benefits of PPARα agonists

In this setting, PPARα agonists represent a logical therapeutic choice, supported by clinical trial evidence showing improvement in lipid profiles and clinical outcome benefits associated with fibrate treatment (Table 2) [44–51]. Cardiovascular risk reduction with fibrate therapy appeared to be further enhanced in patients at increased cardiometabolic risk due to diabetes, as evident by 32% reduction in major cardiovascular events, a composite of CHD death, nonfatal MI and stroke versus 22% in all study patients with gemfibrozil treatment in the Veterans Affairs HDL Intervention Trial (VA-HIT) [44,45]. As well as those with hypertriglyceridemia or metabolic syndrome had risk reductions of 39.5% and 25%, respectively, in fatal or nonfatal MI or sudden death versus 9.4% in all patients with bezafibrate treatment in the Bezafibrate Infarction Prevention study (Table 2) [46,47].

In the primary prevention setting, post hoc analysis of the Helsinki Heart study showed enhanced clinical benefit with gemfibrozil treatment in patients with features of the metabolic syndrome (baseline TG >200 mg/dL, HDL cholesterol <40 mg/dL and BMI >26 kg/m^2) with 78% reduction in coronary risk versus 34% reduction in all patients (Table 2) [48,49]. Furthermore, in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study in 9795 patients with well-controlled, type 2 diabetes and mainly without prior CVD (78%), the presence of markedly elevated TG (>200 mg/dL) together with low HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women), was associated with enhanced reduction in risk for total cardiovascular events (27%, $p = 0.005$, versus 11%, $p = 0.035$ in all patients) [50,51]. It should be noted that fenofibrate treatment did not have a significant effect on the primary end point (nonfatal MI or CHD death, −11%, $p = 0.16$), although this may have been attributable to the confounding influence of an excess of drop-in non-study lipid-modifying therapy, predominantly statins, in the placebo group (17% versus 8%, averaged over the study) [50]. Coronary angiographic trials generally support these findings of the fibrate outcome studies with significant reduction in atheroma progression in coronary or carotid arteries associated with fibrate treatment [52].

Please cite this article in press as: Fruchart J-C. Peroxisome proliferator-activated receptor-alpha (PPARα): At the crossroads of obesity, diabetes and cardiovascular disease. Atherosclerosis (2009), doi:10.1016/j.atherosclerosis.2009.03.008

Table 2
Effects of fibrates on macrovascular outcomes in patients at increased cardiometabolic risk.

Trial	End point	Patients	Absolute event rate (%)		Reduction in relative risk (%)	*p*-value
			Control	Fibrate		
HHS [48,49]	Fatal + nonfatal MI and CHD death	(a) All patients (4081 men without CHD + non-HDL-C ≥200 mg/dL)	4.1	2.7	34	<0.02
			NR	NR	78	0.002
		(b) Met Syn (TG ≥204 mg/dL HDL-C <40 mg/dL, BMI > 26 kg/m^2)	NR	NR		
VA-HIT [44,45]	Nonfatal MI + CHD death + stroke	(a) All patients (2531 men with CHD and low HDL-C (<40 mg/dL)	26.0	20.4	24	<0.001
			36.1	24.5	32	0.004
		(b) Diabetes				
		(c) Elevated TG (≥150 mg/dL)	27.0	20.0	27	0.01
BIP [46,47]	Fatal or nonfatal MI or sudden death	(a) All patients (3090 men and women with previous MI or angina)	15.0	13.6	7.3	0.24
			19.7	12.0	39.5	0.02
		(b) Elevated TG (>200 mg/dL)				
		(c) Met Syn[a]	18.4	14.1	25.0	0.03
FIELD [50]	Nonfatal MI + CHD death	(a) All patients (9795 men and women with type 2 diabetes)	5.9	5.2	11	0.16
	Total CVD events		13.9	12.5	11	0.035
	Total CVD events	(b) Met Syn[b]	17.8	13.5	26	0.01

CHD, coronary heart disease; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; Met Syn, metabolic syndrome; NR, not reported; BIP, Bezafibrate Infarction Prevention study; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes study; HHS, Helsinki Heart study; VA-HIT, Veterans Affairs HDL Intervention Trial.

[a] Defined by least three of the following: fasting glucose ≥110 mg/dL or current use of oral hypoglycemic treatment, TG ≥150 mg/dL, HDL-C <40 mg/dL in men and <50 mg/dL in women, systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or body mass index ≥28.0 mg/kg^2.

[b] Defined as HDL cholesterol <40 mg/dL in men and <50 mg/dL in women and TG ≥ 200 mg/dL.

However, changes in the lipoprotein–lipid profile only partially explain the clinical outcome benefits of fibrates. The VA-HIT investigators demonstrated reduction in CRP, a marker of inflammation, in men with high fasting insulin levels in whom CVD risk was reduced by 34% [53]. This finding is also supported by evidence of 74% reduction in high-sensitivity CRP levels in dyslipidemic obese subjects [54]. These data imply that clinical outcomes benefits associated with fibrate treatment result not only from improvement in the plasma lipoprotein and lipid profile, but also the chronic low-grade inflammatory state associated with increased cardiometabolic risk.

7.1. Combination therapy: which PPARα agonist?

Thus, these data provide a rationale supporting the use of fibrates as add-on therapy to statins in patients at increased metabolic risk, characterised by marked dyslipidemia (elevated TG and low HDL cholesterol), supported by clinical studies such as SAFARI (Simvastatin plus Fenofibrate for combined hyperlipidemia) [55]. Of the available fibrates, fenofibrate is probably the most appropriate PPARα agonist for combination with a statin, supported by analysis of safety surveillance data from the US Food and Drug Administration's Adverse Events Reporting System (AERS) database (1998–2002), which reported a 15-fold increase in the incidence of cases of rhabdomyolysis and 33-fold increase in the incidence of cases of myopathy (without rhabdomyolysis) associated with prescription of gemfibrozil and a statin (excluding cerivastatin, now discontinued) compared with fenofibrate plus statin [56]. This may be explained on the basis of in vitro experimental studies which report that gemfibrozil competes with the statin for metabolism by UDP-glucuronyl transferases, in turn increasing plasma levels of the statin, whereas fenofibrate is metabolized by a different family of glucuronyl transferases and is therefore much less likely to increase statin plasma concentrations in vivo [57]. Supportive data from the FIELD study show that none of 890 patients who received the combination of fenofibrate plus statin developed rhabdomyolysis during the study [50]. Clearly, this strategy warrants evaluation, currently being addressed by the lipid treatment protocol of the ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, which is studying the combination of simvastatin plus fenofibrate in about 5500 patients with type 2 diabetes and existing or at risk for clinical CVD. Data are anticipated in 2009.

8. Microvascular benefits of PPARα

As type 2 diabetes prevalence has increased, so too has the burden of diabetes-related microvascular complications, including diabetic retinopathy, nephropathy and neuropathy. While the STENO-2 study showed the benefits of intensive multifactorial treatment (targeting blood pressure, blood glucose and lipids in addition to treatment with an angiotensin converting enzyme inhibitor, low-dose aspirin and lifestyle modification) over conventional treatment in reducing the risk of both macrovascular and microvascular complications, there remains a residual microvascular risk; 34% of these patients developed retinopathy, 20% developed nephropathy and peripheral neuropathy progressed in 50% of patients over the study period [58].

Findings from the FIELD study suggest that fenofibrate may have a preventive role in reducing the risk of diabetes-related microvascular complications, specifically first laser treatment for diabetic retinopathy (−31%, $p = 0.0002$) [59], progression of albuminuria (−15%, $p = 0.002$) [50] and non-traumatic lower-extremity amputation (−38%, $p = 0.04$), predominantly microvascular amputation (−47%, $p = 0.025$) [67]. The preventive effects of fenofibrate treatment on retinopathy applied similarly to both maculopathy (−31%, $p = 0.002$) and proliferative retinopathy (−30%, $p = 0.015$). Patients without retinopathy history derived greater benefit (−39%, $p = 0.0008$ reduction in first laser therapy) than those with (−23%, $p = 0.06$) Placing these data in a clinical context, 17 patients with pre-existing retinopathy and 90 without known prior eye disease, would need to be treated with fenofibrate for 5 years to avoid first laser therapy in one patient [59]. Additionally, the FIELD Ophthalmology substudy ($n = 1012$) which used serial fundus photography to assess retinopathy progression, showed that fenofibrate treatment led to significant reduction in the progression of disease in patients with pre-existing retinopathy (−79%, $p = 0.004$), although

Please cite this article in press as: Fruchart J-C. Peroxisome proliferator-activated receptor-alpha (PPARα): At the crossroads of obesity, diabetes and cardiovascular disease. Atherosclerosis (2009), doi:10.1016/j.atherosclerosis.2009.03.008

findings were not statistically significant when all patients included in the substudy were evaluated. The effects of fenofibrate did not, however, appear to be related to the degree of glycemic or lipid control, or concomitant medication [59].

Experimental evidence implies that PPARα activation may play a role in the aetiology of these microvascular effects by inhibiting angiogenesis via effects on expression of vascular endothelial growth factor (VEGF)-receptor 2 and VEGF-receptor signalling [60], as well as proliferation of capillary endothelial cells induced by VEGF and fibroblast growth factor [61]. Additionally, reduction of plasma levels of insulin-like growth factor-1 (IGF-1) associated with PPARα activation may reduce neovascularisation associated with proliferative retinopathy, stimulated by protein kinase B and the NF-κB and AP-1 pathways [62]. In vitro evidence also suggests that fenofibrate may regulate retinal endothelial cell survival via a novel mechanism dependent on adenine monophosphate-activated protein kinase (AMPK) activity [63]. The mechanism(s) of fenofibrate's effect in improving albuminuria progression is still under investigation, although reduction in mesangial cell hypertrophy and matrix expansion, together with renal inflammation and glomerular cell apoptosis associated with PPARα activation may be implicated [64].

9. Future directions

To maximise therapeutic potential, future developments in the area of PPARα are aimed at developing selective agents with tissue-selective and targeted gene-selective activities, i.e. selective PPAR modulators (SPPARMs). The validity of this concept is supported by demonstration of differential PPARα-dependent effects of gemfibrozil and fenofibrate on hepatic apoA-I expression. Whereas both fenofibrate and gemfibrozil increase HDL cholesterol levels, fenofibrate also efficiently increases apoA-I levels, whereas gemfibrozil has little or no effect in man. In vitro pharmacological profiling shows that fenofibrate acts as a full agonist of PPARα, whereas gemfibrozil acts as a partial agonist due to differential recruitment of coactivators to the promoter region [65].

The SPPARM concept has been used to select and develop new PPARα activators, based on pharmacological profiling assays, gene profiling and microarray and in vivo assays to evaluate effects on lipid and glucose metabolism, anti-inflammatory and vascular effects, as well as potential side effects. A promising SPPARM developed using this process is GFT505, a potent partial PPARα agonist with SPPARM characteristics. Compared with fenofibrate, GFT505 behaves as a PPARα-selective SPPARM modulator with improved lipid-modifying activity (lowering TG and cholesterol and raising HDL cholesterol and apoA-I to a greater extent than comparable doses of fenofibrate). This lipid-modifying activity translated to 50% reduction in atherosclerotic plaque in an in vivo animal model. Ongoing clinical trials are investigating the potential of GFT505 for management of dyslipidemia associated with abdominal obesity [66]. These findings highlight the potential of these novel PPARα agonists in the management of cardiometabolic risk.

10. Conclusion

Experimental evidence supports the mechanistic view that PPARα represents a central target regulating fatty acid oxidation, lipid and lipoprotein metabolism and inflammatory and vascular responses, all of which would be predicted to decrease atherosclerotic risk. Anti-inflammatory activities demonstrated for PPARα also suggest potential therapeutic application for the management of NAFLD. The use of PPARα activators such as fibrates therefore offers the possibility of co-ordinated modification to repress inflammatory mechanisms and limit the development of atherosclerosis in individuals with insulin-resistant conditions, supported by clinical outcomes studies. Moreover, findings from the FIELD study also indicate a preventive role for the use of fenofibrate for attenuation of residual diabetes-mediated microvascular risk.

Elucidation of the effects of PPARα has prompted further evolution to novel selective PPARα agonists using the SPPARM concept. It is anticipated that PPARα will continue to have important therapeutic application in the management of cardiometabolic risk associated with type 2 diabetes and metabolic syndrome, in particular in addressing the major challenge of residual vascular risk.

References

[1] Petersen S, Peto V, Rayner M, et al. European cardiovascular disease statistics. London: British Heart Foundation; 2005.
[2] Diabetes prevalence. Available from International Diabetes Federation, www.idf.org. Accessed September 29, 2008.
[3] U.S. Obesity trends 1985–2007. Available from Centers for Disease Control and Prevention, www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/index.htm. Accessed September 29, 2008.
[4] Chinetti-Gbaguidi G, Fruchart JC, Staels B. Role of the PPAR family of nuclear receptors in the regulation of metabolic and cardiovascular homeostasis: new approaches to therapy. Curr Opin Pharmacol 2005;5:177–83.
[5] Martin G, Schoonjans K, Lefebvre AM, Staels B, Auwerx J. Coordinate regulation of the expression of the fatty acid transport protein and acyl-CoA synthetase genes by PPARalpha and PPARgamma activators. J Biol Chem 1997;272:28210–7.
[6] Schoonjans K, Peinado-Onsurbe J, Lefebvre AM, et al. PPARalpha and PPARgamma activators direct a distinct tissue-specific transcriptional response via a PPRE in the lipoprotein lipase gene. EMBO J 1996;15:5336–48.
[7] Prieur X, Coste H, Rodriguez JC. The human apolipoprotein AV gene is regulated by PPARα and contains a novel FXR response element. J Biol Chem 2003;278:25468–80.
[8] Staels B, Vu-Dac N, Kosykh V, et al. Fibrates down-regulate apolipoprotein C-III expression independent of induction of peroxisomal acyl co-enzyme A oxidase. J Clin Invest 1995;95:705–12.
[9] Raspé E, Duez H, Mansén A, et al. Identification of Rev-erbalpha as a physiological repressor of apoC-III gene transcription. J Lipid Res 2002;43:2172–9.
[10] Tomiyasu K, Walsh BW, Ikewaki K, et al. Differential metabolism of human VLDL according to content of ApoE and ApoC-III. Arterioscler Thromb Vasc Biol 2001;21:1494–500.
[11] Hiukka A, Fruchart-Najib J, Fruchart JC, et al. Alterations of lipids and apolipoprotein CIII in very low density lipoprotein species in type 2 diabetes. Diabetologia 2005;48:1207–15.
[12] Staels B, Dallongeville J, Auwerx J, et al. Mechanism of action of fibrates on lipid and lipoprotein metabolism. Circulation 1998;98:2088–93.
[13] Chinetti G, Gbaguidi GF, Griglio S, et al. CLA-SR-BI is expressed in atherosclerotic lesion macrophages and regulated by activators of peroxisome proliferator-activated receptors. Circulation 2000;101:2411–7.
[14] Chinetti G, Lestavel S, Bocher V, et al. PPAR-alpha and PPAR-gamma activators induce cholesterol removal from human macrophage foam cells through stimulation of the ABCA1 pathway. Nat Med 2001;7:53–8.
[15] Chinetti G, Lestavel S, Fruchart JC, Clavey V, Staels B. Peroxisome proliferator-activated receptor alpha reduces cholesterol esterification in macrophages. Circ Res 2003;92:212–7.
[16] Chinetti-Gbaguidi G, Rigamonti E, Helin L, et al. Peroxisome proliferator-activated receptor α controls cellular cholesterol trafficking in macrophages. J Lipid Res 2005;46:2717–25.
[17] Staels B, Koenig W, Habib A, et al. Activation of human aortic smooth-muscle cells is inhibited by PPARalpha but not PPARgamma activators. Nature 1998;393:790–3.
[18] Marx N, Sukhova G, Collins T, Libby P, Plutzky J. PPARα activators inhibit cytokine-induced vascular cell adhesion molecule 1 expression in human endothelial cells. Circulation 1999;99:3125–31.
[19] Neve BP, Corseaux D, Chinetti G, et al. PPARα agonists inhibit tissue factor expression in human THP-1 cells, monocytes and macrophages. Circulation 2001;103:207–12.
[20] Delerive P, De Bosscher K, Besnard S, et al. PPARα negatively regulates the vascular inflammatory gene response by negative cross-talk with transcription factors NF-κB and AP-1. J Biol Chem 1999;274:32048–54.
[21] Lee H, Shi W, Tontonoz P, et al. Role for peroxisome proliferator-activated receptor alpha in oxidized phospholipid-induced synthesis of monocyte chemotactic protein-1 and interleukin-8 by endothelial cells. Circ Res 2000;87:516–21.
[22] Pasceri V, Cheng JS, Willerson JT, Yeh ET. Modulation of C-reactive protein-mediated monocyte chemoattractant protein-1 induction in human endothelial cells by anti-atherosclerosis drugs. Circulation 2001;103:2531–4 [Erratum in: Circulation 2001;104(October(16)):1992. Chang J [corrected to Cheng JS]].
[23] Delerive P, Martin-Nizard F, Chinetti G, et al. Peroxisome proliferator-activated receptor activators inhibit thrombin-induced endothelin-1 production in human vascular endothelial cells by inhibiting the activator protein-1 signaling pathway. Circ Res 1999;85:394–402.

Please cite this article in press as: Fruchart J-C. Peroxisome proliferator-activated receptor-alpha (PPARα): At the crossroads of obesity, diabetes and cardiovascular disease. Atherosclerosis (2009), doi:10.1016/j.atherosclerosis.2009.03.008

[24] Valenti L, Fracanzani AL, Dongiovanni P, et al. Tumor necrosis factor alpha promoter polymorphisms and insulin resistance in nonalcoholic fatty liver disease. Gastroenterology 2002;122:274–80.
[25] Marx N, Kehrle B, Kohlhammer K, et al. PPAR activators as anti-inflammatory mediators in human T lymphocytes, implications for atherosclerosis and transplantation-associated arteriosclerosis. Circ Res 2002;90:703–10.
[26] Delerive P, Gervois P, Fruchart JC, Staels B. Induction of IκBα expression as a mechanism contributing to the anti-inflammatory activities of PPARα activators. J Biol Chem 2000;275:36703–7.
[27] Madej A, Okopien B, Kowalski J, et al. Effects of fenofibrate on plasma cytokine concentrations in patients with atherosclerosis and hyperlipoproteinemia IIb. Int J Clin Pharmacol Ther 1998;36:345–9.
[28] Ip E, Farrell C, Robertson G, et al. Central role of PPARα-dependent hepatic lipid turnover in dietary steatohepatitis in mice. Hepatology 2003;38:123–32.
[29] Fernández-Miranda C, Pérez-Carreras M, Colina F, et al. A pilot trial of fenofibrate for the treatment of non-alcoholic fatty liver disease. Dig Liver Dis 2008;40:200–5.
[30] Shu H, Wong B, Zhou G, et al. Activation of PPARalpha or gamma reduces secretion of matrix metalloproteinase 9 but not interleukin 8 from human monocyte THP-1 cells. Biochem Biophys Res Commun 2000;267:345–9.
[31] Chinetti G, Griglio S, Antonucci M, et al. Activation of peroxisome proliferator-activated receptors α and γ induces apoptosis of human monocyte-derived macrophages. J Biol Chem 1998;273:25573–80.
[32] Neve BP, Corseaux D, Chinetti G, et al. PPARα agonists inhibit tissue factor expression in human monocytes and macrophages. Circulation 2001;103:207–12.
[33] Nilsson B, Banfi C, Diczfalusy U, et al. Unsaturated fatty acids increase plasminogen activator inhibitor-1 expression in endothelial cells. Arterioscler Thromb Vasc Biol 1998;18:1679–85.
[34] Durrington PN, Mackness MI, Bhatnagar D, et al. Effects of two different fibric acid derivatives on lipoproteins, cholesteryl ester transfer, fibrinogen, plasminogen activator inhibitor and paraoxonase activity in type IIb hyperlipoproteinaemia. Atherosclerosis 1998;138:217–25.
[35] Gizard F, Amant C, Barbier O, et al. PPARα inhibits vascular smooth muscle cell proliferation underlying intimal hyperplasia by inducing the tumor suppressor $p16^{INK4a}$. J Clin Invest 2005;115:3228–38.
[36] Kersten S, Seydoux J, Peters JM, et al. Peroxisome proliferator-activated receptor alpha mediates the adaptive response to fasting. J Clin Invest 1999;103:1489–98.
[37] Guerre-Millo M, Gervois P, Raspé E, et al. Peroxisome proliferator-activated receptor alpha activators improve insulin sensitivity and reduce adiposity. J Biol Chem 2000;275:16638–42.
[38] Stienstra R, Mandard S, Patsouris D, et al. Peroxisome proliferator-activated receptor alpha protects against obesity-induced hepatic inflammation. Endocrinology 2007;148:2753–63.
[39] Yessoufou A, Atègbo JM, Attakpa E, et al. Peroxisome proliferator-activated receptor-alpha modulates insulin gene transcription factors and inflammation in adipose tissues in mice. Mol Cell Biochem 2008;(November) [Epub ahead of print].
[40] Tsuchida A, Yamauchi T, Takekawa S, et al. Peroxisome proliferator-activated receptor (PPAR)alpha activation increases adiponectin receptors and reduces obesity-related inflammation in adipose tissue: comparison of activation of PPARalpha, PPARgamma, and their combination. Diabetes 2005;54:3358–70.
[41] Cholesterol Treatment Trialists' (CTT) CollaboratorsKearney PM, Blackwell PM, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;371:117–25.
[42] Barter PJ, Gotto AM, LaRosa JC, et al. Treating to New Targets Investigators. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med 2007;357:1301–10.
[43] Miller M, Cannon CP, Murphy SA, et al. PROVE-IT TIMI 22 Investigators. 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;51:724–30.
[44] 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. N Engl J Med 1999;341:410–8.
[45] Rubins HB, Robins SJ, Collins D, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). Arch Intern Med 2002;162:2597–604.
[46] 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;102:21–7.
[47] Tenenbaum A, Motro M, Fisman EZ, et al. Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome. Arch Intern Med 2005;165:1154–60.
[48] Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. N Engl J Med 1987;317:1237–45.
[49] Tenkanen L, Mantarri M, Manninen V. Some coronary risk factors related to the insulin resistance syndrome and treatment with gemfibrozil: experience from the Helsinki Heart Study. Circulation 1995;92:1779–85.
[50] Keech A, Simes RJ, Barter P, et al. The FIELD study investigators. Effect of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849–61.
[51] Scott R, O'Brien R, Fulcher G, et al. The effects of fenofibrate treatment on cardiovascular disease risk in 9795 people with type 2 diabetes and various components of the metabolic syndrome: the FIELD study. Diabetes Care 2008, doi:10.2337/dc08-1543, published on-line November 4, 2008.
[52] DAIS Investigators. DAIS: effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: The Diabetes Atherosclerosis Intervention Study, a randomised study. Lancet 2001;357:905–10.
[53] Bloomgarden ZT. Second world congress on the insulin resistance syndrome. Diabetes Care 2005;28:2073–80.
[54] Coban E, Sari R. The effect of fenofibrate on the levels of high sensitivity C-reactive protein in dyslipidemic obese patients. Endocr Res 2004;30:343–9.
[55] Grundy SM, Vega GL, Yuan Z, et al. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). Am J Cardiol 2005;95:462–8.
[56] Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. Am J Cardiol 2005;95:120–2.
[57] Prueksaritanont T, Tang C, Qiu Y, et al. Effects of fibrates on metabolism of statins in human hepatocytes. Drug Metab Dispos 2002;30:1280–7.
[58] Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383–93.
[59] Keech AC, Mitchell P, Summanen PA, et al. FIELD Study Investigators, effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Lancet 2007;370:1687–97.
[60] Sato M. Peroxisome proliferator activated receptor ligands and angiogenesis. Nippon Rinsho 2005;63:603–8.
[61] Panigrahy D, Kaipainen A, Huang S, et al. PPARalpha agonist fenofibrate suppresses tumor growth through direct and indirect angiogenesis inhibition. Proc Natl Acad Sci USA 2008;105:985–90.
[62] Wilkinson-Berka JL, Wraight C, Werther G. The role of growth hormone, insulin-like growth factor and somatostatin in diabetic retinopathy. Curr Med Chem 2006;13:3307–17.
[63] Kim J, Ahn JH, Yu YS, et al. Fenofibrate regulates retinal endothelial cell survival through the AMPK signal transduction pathway. Exp Eye Res 2007;84:886–93.
[64] Kamijo Y, Hora K, Tanaka N, et al. Identification of functions of peroxisome proliferator-activated receptor alpha in proximal tubules. J Am Soc Nephrol 2002;13:1691–702.
[65] Duez H, Lefebvre B, Poulain P, et al. Regulation of human apoA-I by gemfibrozil and fenofibrate through selective peroxisome proliferator-activated receptor α modulation. Arterioscler Thromb Vasc Biol 2005;25:585–91.
[66] Fruchart JC. Novel peroxisome proliferator activated-receptor-α agonists. Am J Cardiol 2007;100(suppl):41N–6N.
[67] Colman P, Rajamani K, Li L-P et al. Benefits of long-term fenofibrate therapy on amputations in type 2 diabetes mellitus in the FIELD trial. Presented at the European Association for the study of Diabetes (EASD), Rome, September 2008.

Please cite this article in press as: Fruchart J-C. Peroxisome proliferator-activated receptor-alpha (PPARα): At the crossroads of obesity, diabetes and cardiovascular disease. Atherosclerosis (2009), doi:10.1016/j.atherosclerosis.2009.03.008