Fenofibrate: a novel formulation (Triglide™) in the treatment of lipid disorders: a review

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Abstract: Cardiovascular disease is the major cause of mortality worldwide and accounts for approximately 40% of all deaths. Dyslipidemia is one of the primary causes of atherosclerosis and effective interventions to correct dyslipidemia should form an integral component of any strategy aimed at preventing cardiovascular disease. Fibrates have played a major role in the treatment of hyperlipidemia for more than two decades. Fenofibrate is one of the most commonly used fibrates worldwide. Since fenofibrate was first introduced in clinical practice, a major drawback has been its low bioavailability when taken under fasting conditions. Insoluble Drug Delivery-Microparticle fenofibrate is a new formulation that has an equivalent extent of absorption under fed or fasting conditions. In this review, we will discuss the clinical pharmacology of fenofibrate, with particular emphasis on this novel formulation, as well as its lipid-modulating and pleiotropic actions. We will also analyze the major trial that evaluated fibrates for primary and secondary prevention of cardiovascular disease, the safety and efficacy profile of fibrate–statin combination treatment, and the current recommendations regarding the use of fibrates in clinical practice.

Keywords: fibrates, fenofibrate, combination treatment, dyslipidemia, cardiovascular disease, pleiotropic actions

Introduction

Cardiovascular disease (CVD) is the major cause of mortality worldwide and accounts for approximately 40% of all deaths (AHA 2001). In the US alone, nearly 1 million individuals die of CVD each year whereas 25% of the adult population (62 million) has CVD (AHA 2001). The existing burden of CVD will continue to increase in developed countries as the population ages. Dyslipidemia is one of the primary causes of atherosclerosis and CVD, and effective interventions to correct dyslipidemia should form an integral component of any strategy aimed at preventing CVD (NCEP 2002).

Fibrates have played a major role in the treatment of hyperlipidemia for more than two decades (Miller and Spence 1998). The first member of this class, clofibrate, was identified in 1962 by Thorp and Waring (1962) and became available in the US in 1967. Many other fibrates, including ciprofibrate, bezafibrate, etofibrate, beclofibrate, and pirifibrate, are available in Europe, where the use of such agents is more extensive (Miller and Spence 1998; Guay 1999). The third-generation fibric acid derivative fenofibrate was synthesized in 1975 (Keating and Ormrod 2002) and was introduced into clinical practice in France the same year (Blane 1989; Keating and Ormrod 2002). The original generic name procetofene was changed to fenofibrate to comply with World Health Organization nomenclature guidelines. Fenofibrate is marketed in 86 countries and is one of the most commonly used fibrates worldwide, with more than 6 million patient-years of experience (Brown 1988). More than 80 clinical trials of fenofibrate

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have involved more than 9000 patients and more than 31 000 patient-years of drug exposure (Blane 1989; Keech et al 2005). Its indications include hypercholesterolemia, combined dyslipidemia, remnant hyperlipidemia, endogenous hyperlipemia (hypertriglyceridemia), and mixed hyperlipemia (Frederickson types IIa, IIb, III, IV, and V dyslipidemia, respectively) (Keating and Ormrod 2002).

In this review, we will discuss the clinical pharmacology of fenofibrate, with particular emphasis on its novel formulation (Triglide™), as well as its lipid-modulating and pleiotropic actions. We will also analyze the major trial that evaluated fibrates for primary and secondary prevention of CVD, the safety and efficacy profile of fibrate–statin combination treatment and the current recommendations regarding the use of fibrates in clinical practice.

Clinical pharmacology

Chemically, fenofibrate is 2-(4[4-chlorobenzoyl]phenoxy)-2-methyl-propanoic acid, 1-methylethyl ester. Fenofibrate is a poorly soluble ester of its active derivative, fenofibric acid (Chapman 1987; Adkins and Faulds 1997; Miller and Spence 1998; Munoz et al 1999; Guichard et al 2000; Keating and Ormrod 2002; Ramjattan et al 2002). After oral administration, it is rapidly converted through hydrolysis of its ester bond to fenofibric acid (Adkins and Faulds 1997; Miller and Spence 1998; Munoz et al 1999; Guichard et al 2000; Streel et al 2000; Keating and Ormrod 2002; Ramjattan et al 2002). Hydrolysis is catalyzed by both tissue and plasma esterases and appears to commence concomitantly with absorption (Chapman 1987). No unmodified fenofibrate is found in human plasma (Chapman 1987; Caldwell 1989; Adkins and Faulds 1997; Streel et al 2000). Plasma levels of fenofibric acid peak 6–8 hours after oral administration (Caldwell 1989; Hunninghake 1989; Balfour et al 1990; Adkins and Faulds 1997). Steady-state plasma levels are reached within 5 days of dosing, and no accumulation has been observed in healthy volunteers after administration of multiple doses. Fenofibric acid is extensively protein-bound (99%), primarily to albumin, and has an apparent volume of distribution of 0.89 L/kg (Balfour et al 1990; Adkins and Faulds 1997). Fenofibric acid is metabolized by the hepatic cytochrome P (CYP)-450 3A4 isozyme and has a half-life of 20 hours, which allows once-daily administration (Desager and Harvengt 1978; Miller and Spence 1998). Fenofibric acid is mainly (60%) excreted in urine as metabolites, primarily fenofibric acid and fenofibric acid glucuronide; 25% is eliminated in feces (Desager et al 1982). Fenofibric acid accumulates with chronic use in patients with mild to severe chronic renal disease; the plasma half-life of fenofibric acid is prolonged in these patients, but does not correlate with creatinine clearance (Balfour et al 1990). Hemodialysis does not affect the plasma kinetics of the drug, as fenofibric acid is virtually nondialyzable from plasma (Desager et al 1982).

Since fenofibrate was first introduced in clinical practice, a major drawback has been its low bioavailability when taken under fasting conditions, since it is virtually insoluble in water and highly lipophilic (Desager and Harvengt 1978; Adkins and Faulds 1997; Guay 2002; Keating and Ormrod 2002; Najib 2002; Ramjattan et al 2002). In contrast, its absorption is substantially increased in the presence of food and, particularly, fat (Caldwell 1989; Hunninghake 1989; Balfour et al 1990; Adkins and Faulds 1997; Munoz et al 1999). The bioavailability of the original formulation of fenofibrate was improved through a micronization process, and a micronized capsule formulation has been commercially available in the US since 1998 (Munoz et al 1999; Abbott Laboratories 2000; Guichard et al 2000; Keating and Ormrod 2002; Ramjattan et al 2002). Since July 2001, a new tablet formulation of fenofibrate has been available that combines micronization technology with a microcoating process, allowing more predictable and reliable drug absorption (Guichard et al 2000; Abbott Laboratories 2001). Nevertheless, product labeling of formulations marketed to date has mandated administering the drug with meals, even for these two new formulations (Adkins and Faulds 1997; Abbott Laboratories 2000, 2001; Keating and Ormrod 2002; Ramjattan et al 2002).

In clinical practice, however, patients may confuse the fenofibrate dosage regimen with the traditional regimen for statins and take fenofibrate at bedtime on an empty stomach. Additionally, patients may vary from each other and from day to day in their adherence to the low-fat dietary guidelines for dyslipidemic individuals (NCEP 2002). Even if these guidelines are rigorously followed, they limit the fat content of patients' meals and therefore may compromise the bioavailability of currently marketed fenofibrate products. In the context of these real-world circumstances, the food and fat effects seen with currently marketed products may lead to inconsistent, unpredictable, and suboptimal fenofibrate bioavailability, which, in turn, jeopardizes clinical efficacy (Desager et al 1996).

Insoluble Drug Delivery-Microparticle (IDD-P) fenofibrate tablets (TRICOR) are a new formulation developed to provide fenofibrate bioavailability independent of food and its fat content (Mishra et al 2002). The technology used to develop this formulation involves preparing

microparticles of drug and stabilizing them with phospholipid surface-modifying agents that prevent the microparticles from reaggregating (Mishra et al 2002). Thus, this approach preserves the expanded drug surface area that results from microparticularization (Mishra et al 2002). Exposure of the expanded drug surface area to the in vivo dissolution medium upon oral administration thereby increases bioavailability (Mishra et al 2002). IDD-P fenofibrate 160-mg tablets have an equivalent extent of absorption under fed or fasting conditions, suggesting that dosage regimens could include administration of the product without food (Guivarc'h et al 2004). In addition, they have comparable bioavailability regardless of the fat content of the test meal, suggesting that its bioavailability would remain consistent regardless of patients' adherence to low-fat dietary guidelines (Guivarc'h et al 2004). Administering a drug independently of food may provide greater convenience and simplicity for patients and prescribers. Simplicity of administration is particularly relevant given the chronic nature of lipid-lowering therapy, the demands of complying with low-fat dietary recommendations, and the complexity of multiple treatments for associated conditions.

Fenofibrate potentiates the effects of oral anticoagulants, necessitating close monitoring of the international normalized ratio and reduction of the warfarin dose by approximately one third (Lemaire and Tillement; 1982; Adkins and Faulds 1997; Kim and Mancano 2003). The high level of protein binding associated with fenofibrate may cause displacement of warfarin, but the effect is generally small and concentrations of unbound anticoagulant do not change in vivo, leading some investigators to reject this as a significant cause of interaction (Ascah et al 1998; Guay 1999). Fenofibrate also interacts with cyclosporin and there may be a risk of nephrotoxicity, severe myositis, and rhabdomyolysis when the two agents are co-administered (Boissonnat et al 1994). Many sulfonylureas are highly protein bound and may be displaced from albumin by fibrates (Ahmad 1991). Hence, patients receiving agents from both classes must be monitored for signs and symptoms of hypoglycemia. Although there does not appear to be any pharmacokinetic interaction between fenofibrate and bile acid sequestrants, it is recommended that fenofibrate be given more than 1 hour before or 4–6 hours after administration of a bile acid-binding resin (First Horizon Pharmaceutical Corporation 2005).

Fenofibrate is generally well tolerated. Side-effects are primarily gastrointestinal in nature (Keech et al 2005). Abnormal liver function tests and increased creatine kinase (CK) levels are infrequently reported (Adkins and Faulds 1997; Guay 1999; Keating and Ormrod 2002; Barker et al 2003; Kiortsis et al 2003). Only 1 trial reported elevations of CK twice the upper limit of normal in 4 bezafibrate-treated patients versus 1 placebo-treated patient and it is not clear whether these elevations were symptomatic (The BIP study group 2000). Post-marketing surveillance of fenofibrate found only a 2% discontinuation rate due to adverse events (Keating and Ormrod 2002). Fenofibrate has been reported to cause similar changes in biliary lipid composition to those observed with other fibric acid derivatives (Palmer 1987). However, fenofibrate may have a lower propensity to cause gallstones, as it increases phospholipid content and decreases bile acid content, which appears to favor liquid crystal formation (Palmer 1987). A nonsignificant excess in noncardiovascular disease deaths has been reported in some fibrate trials (Heady et al 1992; Keech et al 2005; Studer et al 2005). However, this apparent excess was not attributable to any specific cause of death, nor was it linked to a significant increase in any specific nonfatal noncardiovascular disease event, such as invasive cancers, and so remains consistent with a chance finding (Keech et al 2005). The dose of fenofibrate should be reduced in patients with severe renal impairment (creatinine clearance < 50 mL/min) and increased only after effects on renal function have been evaluated; no dose reduction is required in patients with moderate renal impairment (creatinine clearance 50–90 mL/min). The use of fenofibrate is contraindicated in patients with hypersensitivity to this agent, pre-existing gallbladder disease, hepatic dysfunction, and unexplained persistent abnormality in liver function.

Lipid-modulating actions of fenofibrate

Fenofibrate has a wide range of effects on the synthetic and catabolic pathways of cholesterol and triglycerides (TG) metabolism (Balfour et al 1990; Adkins and Faulds 1997). In the 1990s, it was realized that the lipid-modifying properties of fibrates were attributable to the selective activation of nuclear transcription factor peroxisome proliferator-activated receptor alpha (PPARα) (Gonzalez et al 1998; Knopp 1999). PPARα is expressed mainly in tissues where active free fatty acid (FFA) catabolism occurs (liver, skeletal muscle, heart, and kidney), as well as in vascular endothelium, vascular smooth muscle, and macrophage–foam cells (Kersten et al 2000). Upon activation by ligand binding in the cytoplasm, PPARs migrate to the nucleus where they heterodimerise with the retinoic acid X receptor (RXR); these PPAR-RXR dimers bind to DNA-specific sequences called

peroxisome proliferator–response elements, thus stimulating or dampening the transcription of key genes of the lipid metabolism (Staels et al 1998; Kersten et al 2000).

Fenofibrate substantially reduces TG by about 30% (Keating and Ormrod 2002; Keech et al 2005). TG exert a direct effect on the expansion of the lipid-rich core of the atherosclerotic plaques (Rubins et al 2002). The bulk of the evidence now suggests that an elevated fasting TG level is an independent risk factor for coronary heart disease (CHD) (de Faire et al 1996; Ruotolo et al 1998). Fibrates exert their hypotriglyceridemic action primarily by enhancing hepatic catabolism of FFA, which results in reduced production of TG-rich very low-density lipoprotein cholesterol (VLDL-C), and by inducing hepatic lipoprotein lipase (LPL) expression (Schoonjans, Staels, et al 1996; Staels, Dallongeville, et al 1998; Watts and Dimmitt 1999). Fibrates' hypotriglyceridemic action is further enhanced by PPARα-mediated inhibition of apolipoprotein (apo) CIII gene expression; apoCIII delays the catabolism of TG-rich lipoproteins, since it inhibits their binding to the endothelial surface and lipolysis by LPL and interferes with the clearance of remnant particles from plasma (Staels et al 1995; Schoonjans, Staels, et al 1996; Fruchart et al 2001; Barbier et al 2002). Furthermore, fenofibrate induces apolipoprotein AV, a recently discovered lipoprotein, which results in a significant reduction in serum TG (Pennacchio et al 2001; Vu-Dac et al 2003).

Fenofibrate consistently raises high-density lipoprotein cholesterol (HDL-C) in the range of 5%–50%, depending on lipid phenotype and baseline concentration, with the greatest elevations being observed when baseline HDL-C is less than 1.03 mmol/L (Shepherd et al 1985; Schonfeld 1994; Guerin et al 1996; Adkins and Faulds 1997; Kirschgassler et al 1998; Poulter 1999; le Roux et al 2002; Keech et al 2005). HDL-C protects against atherosclerosis primarily by carrying cholesterol away from blood vessel walls to the liver, where it is metabolized (reverse cholesterol transport). In addition, HDL-C displays antioxidant, anti-inflammatory, and plaque-stabilizing properties (Von Eckardstein et al 2001; Sacks 2002, 2003). Decreased HDL-C is a potent and independent risk factor for CHD; both observational studies and controlled clinical trials suggest that each 1% increase in HDL-C is associated with a 2%–3% reduction in risk of CHD (Miller et al 1977; Goldbourt et al 1979; Wilson et al 1988; Gordon et al 1989; Gordon and Rifkind 1989; Jacobs et al 1990; Assmann et al 1996; Fruchart et al 1998; Boden 2000; Sacks et al 2000; NCEP 2002; Sacks 2002, 2003; Athyros et al 2004a). Fibrates increase HDL-C by decreasing VLDL-C concentrations, which causes a decreased transfer of cholesterol from HDL-C to VLDL-C (Grundy and Vega 1987; Hunninghake and Peters 1987). HDL levels are equally increased with fibrates via promotion of the synthesis and production of apoA-I and apoA-II, which are the major protein constituents of HDL-C and are integral to the process of reverse cholesterol transport (Knopp et al 1987; Hunninghake 1989; Adkins and Faulds 1997; Staels, Dallongeville, et al 1998; Watts and Dimmitt 1999; Chinetti et al 2001).

In hypertriglyceridemic dyslipidemias, lipid-poor, small HDL-C particles with attenuated antiatherogenic activities are preferentially formed (Lamarche et al 1999). Fibrates shift this HDL-C profile towards large, cholesteryl ester-rich particles, which are more potent in withdrawing cholesterol from peripheral tissues. The underlying mechanism is the fibrate-mediated reduction in the numbers of acceptor particles (VLDL-C, intermediate-density lipoprotein cholesterol [IDL-C], low-density lipoprotein cholesterol [LDL-C]) for cholesteryl ester transfer from HDL, which results in increased retention of cholesteryl ester in HDL, whose particle size increases (Guerin et al 1996; Durrington et al 1998; Staels, Dallongeville, et al 1998; Watts and Dimmitt 1999; Sasaki et al 2002).

The effects of fibrates on LDL-C are much smaller, and somewhat varied – in 2 major fibrate trials, no fall in LDL-C was reported with gemfibrozil (Rubins et al 2002) or with bezafibrate (The BIP Study Group 2000). An average increase of 15% is also not unexpected in patients with baseline TG values >3.4 mmol/L, since fibrates increase conversion of VLDL-C to LDL-C through enhanced delipidation (Staels, Dallongeville, et al 1998; Westphal et al 2003; Ikewaki et al 2004). With fenofibrate, a fall of 13% in LDL-C cholesterol was noted in a recent landmark study (Keech et al 2005). Epidemiological surveys in many populations throughout the world have shown a log-linear relationship between LDL-C levels and CHD risk over a broad range of cholesterol values (Law and Wald 1994; Law et al 1994, 2003). Fenofibrate may inhibit hydroxymethyl-glutaryl coenzyme A reductase activity, thus reducing cholesterol synthesis, and might also increase the clearance of circulating LDL-C via the high-affinity receptor system (Haubenwallner et al 1995; Schoonjans, Peinado-Onsurbe, et al 1996). Fenofibrate has also been reported to increase cholesterol excretion into the bile, contributing to lower intracellular cholesterol levels and providing added stimulus to the generation of LDL-C receptors in the liver (Brown 1988).

Fibrates modify the subgroup pattern of LDL-C from small, dense particles to large, buoyant particles; this effect is more pronounced with fenofibrate, involving up to 50%

reduction in dense LDL-C particles levels (Shepherd et al 1985; Schonfeld 1994; Auwerx et al 1996; Guerin et al 1996; Anber et al 1997; Ruotolo et al 1998; Staels, Dallongeville, et al 1998; Feher et al 1999). Dense LDL-C particles are of elevated atherogenic potential (de Graaf et al 1991; Tribble et al 1992; Chait et al 1993 ; Griffin et al 1994; Anber et al 1996; Lamarche et al 1997). They possess a lower binding affinity for the LDL receptor than light particles, and thus a longer residence time in plasma in vivo (Packard and Shepherd 1977; Chapman et al 1998). Dense LDL-C particles also exhibit high affinity for binding to arterial proteoglycans, leading to their preferential retention at sites in the arterial wall of high endothelial permeability, as at bifurcations in the arterial tree (Williams and Tabas 1995; Anber et al 1997). They are, therefore, exposed to biological modifications (Chapman et al 1998), which may lead to their catabolism by atherogenic pathways, such as the macrophage pathway (Young and Parthasarathy 1994). Dense LDL-C particles also exhibit diminished resistance to oxidative stress in vitro. Oxidized LDL-C particles are avidly bound, internalized, and degraded by macrophages, leading to their transformation into foam cells, the latter representing a key cellular component of atheromatous lesions (Young and Parthasarathy 1994). LDL-C particle size has been shown to be an independent predictor of the degree of CHD progression (Vakkilainen et al 2003).

Fibrates also reduce VLDL-C, VLDL-C remnants, and IDL-C in both fasting and postprandial states (Schonfeld 1994; Rubins et al 1995; Anber et al 1997; Chapman et al 1998). Fenofibrate mediates marked decreases, up to 60%, in the area under the postprandial curve for these lipoproteins (Simpson et al 1990; Staels, Dallongeville, et al 1998; Cavallero et al 2003; Westphal et al 2003; Ooi et al 2004). The postprandial phase is of considerable relevance to atherogenesis in dyslipidemic subjects and is intimately associated with endothelial dysfunction and oxidative stress (Simpson et al 1990; Karpe et al 1993; Cohn 1994; Evans et al 1999; Kugiyama et al 1999; Kolovou et al 2005). Extensive evidence substantiates the atherogenicity and cytotoxicity to endothelial cells of VLDL-C and their remnants, which represent major risk factors for premature atherosclerotic disease (Simpson et al 1990; Karpe et al 1993; Cohn 1994; Alaupovic et al 1997; Evans et al 1999; Gianturco and Bradley 1999; Kugiyama et al 1999). Following transendothelial transport, these lipoprotein particles are retained in the arterial intima, where they undergo structural modification, including oxidation, resulting in macrophage uptake (Williams and Tabas 1995). Equally, native VLDL-C subfractions may directly induce lipid accumulation in monocyte-macrophages via LPL-mediated mechanisms involving lipolysis and/or ligand binding; macrophage lipid accumulation is a key factor in the transformation of these cells to a proinflammatory and prothrombogenic phenotype (Milosavljevic et al 2001).

Fenofibrate reduces levels of apoB, a major component of LDL-C and TG-rich lipoproteins (Gami et al 2003). Few studies have reported on the influence of fenofibrate therapy on lipoprotein (a) and both an absence of effect (Adkins and Faulds 1997; Guay 2002) and a significant decrease (Bairaktari et al 1999) have been reported.

The lipid-modulating actions of fibrates are to some degree phenotype-dependent, but this question has not been systematically addressed (Schonfeld 1994). For example, TG lowering is of greatest magnitude in hypertriglyceridemic phenotypes and may exceed 50%, but is lower, and typically less than 30%, in type IIa hypercholesterolemia (Shepherd et al 1985; Schonfeld 1994; Guerin et al 1996; Adkins and Faulds 1997; Kirschgassler et al 1998; Rubins et al 1999). Equally, the potency of fibrates to lower LDL-C is influenced by the initial concentration; in the type IIa phenotype for example, LDL-C and apoB reduction typically range up to 25% (Shepherd et al 1985; Schonfeld 1994; Guerin et al 1996; Adkins and Faulds 1997; Kirschgassler et al 1998). In the IIb phenotype, LDL-C lowering is comparable with that in type IIa, whereas plasma TG and VLDL-C reductions tend to be superior (30%–50%) (Shepherd et al 1985; Schonfeld 1994; Guerin et al 1996; Adkins and Faulds 1997; Kirschgassler et al 1998).

The relative potency of fibrates in lowering levels of lipoproteins has not been compared in large, randomized, placebo-controlled, crossover trials. The activity of fenofibrate in a cell-based transactivation assay for PPARα is 40% greater than that of either bezafibrate or clofibrate (Willson et al 2000; Chapman 2003). The lipid-lowering effects of fenofibrate are 6-fold greater than those achieved with an equivalent dose of clofibrate (Blane 1989). It is also generally recognized that fenofibrate tends to be more efficacious in lowering LDL-C than gemfibrozil in both the IIa and IIb phenotypes (Schonfeld 1994). In major clinical trials, gemfibrozil induced small decreases in LDL-C levels or did not affect them at all (Frick et al 1987, 1997; Rubins et al 1999); in fact, in people who have very high TG-rich lipoproteins, treatment with gemfibrozil may result in an increase in LDL-C (Steiner 2005). Bezafibrate can also reduce LDL-C in a range of 10%–20% depending on the lipoprotein abnormality, although in the major clinical

trials with bezafibrate, no effect on LDL-C concentrations was observed (de Faire et al 1996; Elkeles et al 1998; The BIP Study Group 2000; Steiner 2005). Finally, ciprofibrate, similar to fenofibrate, has been shown to mediate marked reduction (up to 60%) in the area under the postprandial curve for TG and TG-rich lipoproteins (Evans et al 1999).

Pleiotropic actions of fenofibrate

Results from clinical trials have suggested that the cardioprotective effects of fibrate treatment cannot be explained solely by changes in the traditional lipid profile, suggesting that fibrate-induced modifications of emerging risk factors may contribute to their beneficial effects on cardiovascular endpoints (Manninen et al 1992; Staels, Dallongeville, et al 1998; NICE 2002; Rubins et al 2002; Robins et al 2003; Vakkilainen et al 2003; Despres et al 2004; Ikewaki et al 2004; Tsimihodimos et al 2005). The activation of PPARα by fenofibrate regulates the expression of key genes involved in all stages of atherogenesis, including vascular inflammation, plaque instability, and thrombosis and exerts direct antiatherogenic actions in the vascular wall (Barbier et al 2002).

Atherosclerosis is a chronic inflammatory disorder with an inflammation component in all stages of atherogenic plaque formation and growth (Ross 1999). A growing number of studies confirms that fibrates act pleiotropically on inflammatory processes, and that their efficacy in this field is comparable with that of statins (Wang et al 2003). Fibrates exert anti-inflammatory action by inhibiting the production of inflammatory cytokines, including interleukin (IL) IL-1α, IL-1β, IL-2, IL-6, interferon-γ, and tumor necrosis factor-α; this action results from repression of nuclear factor κb transcriptional activity (Staels et al 1995; Madej et al 1998; Staels, Koenig, et al 1998; Kleemann et al 2003; Wang et al 2003; Okopien et al 2004, 2005; Koh, Ahn, Han, et al 2004). Fenofibrate therapy significantly lowers C-reactive protein (CRP) (Staels, Koenig, et al 1998; Marx et al 1999; Barbier et al 2002; Wang et al 2003; Ikewaki et al 2004; Tsimihodimos et al 2004; Gervois et al 2004; Athyros et al 2005; Koh, Ahn, Han, et al 2005; Undas et al 2005), even more than atorvastatin (Malik et al 2001). Prospective epidemiological studies have found increased vascular risk in association with increased levels of CRP (Kuller et al 1996; Haverkate et al 1997; Ridker et al 1997, 1998, 2000; Tracy et al 1997; Koenig et al 1999). It also lowers the CD40 ligand, which plays an important role in a cascade of inflammatory and proatherothrombotic functions (Libby and Simon 2001; Schönbeck and Libby 2001; Wang et al 2003; Undas et al 2005). Fenofibrate can also reduce the expression of monocyte chemoattractant protein-1, which controls chemotaxis of mononuclear cells into the vascular wall (Pasceri et al 2001; Kowalski et al 2003; Undas et al 2005), as well as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 levels (Marx et al 1999; Marchesi et al 2003). These anti-inflammatory actions of fenofibrate have been reported to occur as early as after 3 days of therapy and are independent of changes in lipid profiles (Undas et al 2005). Fenofibrate also lowers serum amyloid A (Marx et al 1999; Gervois et al 2004). Fenofibrate may also exhibit antioxidant activity (Inoue et al 2001), decrease the production of reactive oxygen species (Iglarz et al 2003), and reduce the concentration of lipid peroxidation products (Beltowski et al 2002).

In dyslipidemic patients, a procoagulant state is observed, with elevated levels of fibrinogen and plasminogen activator inhibitor-1 (PAI-1) (Okopien et al 2001, 2005). Many prospective studies have shown that fibrinogen is an independent risk factor for CVD (Wilhelmsen et al 1984; Stone and Thorp 1985; Meade et al 1986; Kannel et al 1987; Yarnell et al 1991; Ernst and Koenig 1997). Fenofibrate lowers plasma fibrinogen levels by up to 20%, independently of lipid changes (Stokhler et al 1989; Branchi et al 1993; Durrington et al 1998; Staels, Koenig, et al 1998; Kockx et al 1999; Marx et al 1999; Barbier et al 2002; Guay 2002; Maison et al 2002; Gervois et al 2004; Koh, Ahn, Han, et al 2004; Koh, Han, Quon, 2005; Saklamaz et al 2005), in contrast to gemfibrozil, which may induce elevations (Branchi et al 1993; Durrington et al 1998; Mussoni et al 2000). This decrease in fibrinogen levels is associated with a decrease in plasma viscosity and an improvement in red cell aggregation and microcirculation (Haak et al 1998; Frost et al 2001). Different hypotheses may explain the nonlipid effect of fenofibrate on fibrinogen, including the direct suppression of fibrinogen gene expression (Kockx et al 1999), the inhibition of IL-6, which promotes fibrinogen synthesis in the liver (Green and Humphries 1989; Di Minno and Mancini. 1992), or a direct action on fibrin gel and thrombus structure (Kockx et al 1997, 1998). Fenofibrate also significantly lowers plasma concentrations of thrombin-antithrombin complexes (Undas et al 2005) and PAI-1 (Durrington et al 1998; Okopien et al 2001, 2005), and suppresses the upregulation of tissue factor expression on stimulated monocytes and macrophages (Marx et al 2001; Neve et al 2001).

Evidence exists that fenofibrate can improve nitric oxide (NO) bioavailability (Koh, Ahn, Jin, et al 2004) and endothelial function, during both the fasting and postprandial

phase, and independently of changes in plasma lipids (Liang et al 2000; Malik et al 2001; Sebestjen et al 2002; Capell et al 2003; Marchesi et al 2003; Playford et al 2003; Wang et al 2003; Koh, Ahn, Han, et al 2004; Koh, Han, Quon, et al 2005). Fenofibrate may also prevent the development of angiotensin II-dependent hypertension (Diep et al 2002; Vera et al 2005), as well as myocardial inflammation and fibrosis (Diep et al 2004; Ogata et al 2004). Some, but not all, studies suggest that the fibrate-induced improvement in serum lipids is followed by a decrease in blood pressure (Walus-Idzior et al 2000; Keech et al 2005).

Among fibrates, only fenofibrate significantly decreases serum uric acid (Elisaf et al 1999; Elisaf 2002; Liamis et al 1999; Kiortsis and Elisaf 2001; Achimastos et al 2002). Uric acid levels are probably related to adverse outcomes in patients with CHD (Fang and Alderman 2000; Bickel et al 2002; Athyros, Elisaf, et al 2004). Furthermore, a recent prospective cohort study of 1423 middle-aged men without CVD or type 2 diabetes mellitus (DM) at baseline, found uric acid to be an independent and strong predictor of CVD mortality (Niskanen et al 2004). In a recent study, fenofibrate significantly reduced uric acid levels by 27.9% (from 408 ± 72 μmol/L to 294 ± 84 μmol/L, $p < 0.001$) by inducing a profound increase in the fractional excretion of uric acid (from $8\% \pm 3\%$ to $13\% \pm 4\%$, $p < 0.01$), independently of any change in lipid parameters (Liamis et al 1999; Elisaf et al 2002).

In some, but not all studies, fenofibrate has been found to improve insulin sensitivity and carbohydrate metabolism in patients with DM or impaired glucose tolerance (Guerre-Millo et al 2000; Walus-Idzior et al 2000; Malik et al 2001; Elisaf 2002; Nagai et al 2002; Wysocki et al 2004; Koh, Han, Quon, et al 2005). It is possible that hypertriglyceridemia contributes to the induction of glucose intolerance and fibrates enhance insulin action by lowering TG (Steiner 1991; Avogaro et al 1995; Marcus 2001; Elisaf 2002). Another possible explanation for this improvement in insulin sensitivity could be the induction of FFA-binding protein as well as the stimulation of β-oxidation in skeletal muscles (Furuhashi et al 2002). Interestingly, an important effect of treatment with fenofibrate on the progression of albuminuria has been recently reported in patients with DM (Ansquer et al 2005; Keech et al 2005), along with a favorable effect on the need for retinal laser therapy (Keech et al 2005). Fenofibrate also significantly increased plasma adiponectin levels in patients with primary hypertriglyceridemia or with combined hyperlipidemia (Koh, Han, Quon, et al 2005; Koh, Quo, Han, et al 2005).

A reduction in serum alkaline phosphatase (ALP) and gamma glutamyltranspeptidase (gGT) activity is a well-documented effect of treatment with fenofibrate (Steinmetz et al 1981; Mikhailidis et al 1998; Genest et al 2004). Fenofibrate has been shown to reduce ALP activity by 14% ($p < 0.00001$), significantly more than gemfibrozil ($p < 0.0001$) (Ganotakis et al 2002). Interestingly, this decrease in serum ALP has been used to monitor compliance to fibrate treatment (Mikhailidis et al 1998; Genest et al 2004). Even though the underlying mechanisms explaining these results remain undefined, it has been speculated that changes in hepatic fat deposition may be involved; more specifically, the fenofibrate-induced, PPARα-mediated stimulation of oxidative metabolism of FFA in the liver might reduce the potential for lipid deposition in the liver cells (Mikhailidis et al 1998). This mechanism could also account for the smaller decrease in ALP with gemfibrozil, which does not activate PPARα (Post et al 2001). Alternatively, the decreased liver ALP release might result from a reduction in the rate of hepatic bile acid secretion (Day et al 1993). Fibrates suppress bile acid biosynthesis in rodents via PPARα-activation; among fibrates, gemfibrozil had the smallest effect (Post et al 2001; Roglans et al 2004).

Fenofibrate increases homocysteine in both the fasting and fed state (Dierkes et al 2001; Giral et al 2001; Stule et al 2001; Westphal et al 2001; Mayer et al 2003; Melenovsky et al 2003); gemfibrozil does not increase homocysteine, possibly due to different interaction with PPARα (Westphal et al 2001; Syvanne et al 2004). The addition of vitamin supplementation (folic acid and vitamins B6 and B12) can markedly reduce the homocysteine elevation induced by fenofibrate (Dierkes et al 2001; Stule et al 2001; Mayer et al 2003; Melenovsky et al 2003). Recently, an increase of the median plasma homocysteine concentration by about 4 μmol/L has been reported with fenofibrate (Keech et al 2005). Epidemiological data suggest an increase in risk of 10%–20% in cardiovascular events could be associated with this difference (HSC 2002), but whether changes in homocysteine are causal for cardiovascular disease or an epiphenomenon is unknown, and to date there is no randomized evidence that lowering homocysteine levels reduces cardiovascular disease events. Furthermore, fenofibrate induced a selective increase of protein-bound homocysteine in rodents, whereas the atherogenic reduced fraction of homocysteine remained unchanged (Legendre et al 2002). In addition, a recent analysis revealed that the fenofibrate-induced increase in homocysteine levels did not attenuate the beneficial effects of the drug on CHD progression or clinical events (Papadakis et al 1999).

Fenofibrate increases creatinine plasma levels (Levin et al 2000; Keech et al 2005), which is fully reversed within 6–8 weeks of stopping fenofibrate (Keech et al 2005); however, permanent increases in serum creatinine levels have been rarely reported in renal transplant recipients (Broeders et al 2000). Gemfibrozil does not appear to increase creatinine levels (Tsimihodimos et al 2001; Westphal et al 2001). One possible explanation for this effect is that activation of PPARα by fenofibrate downregulates the renal cyclooxygenase-2 enzyme system and may impair the synthesis of vasodilating prostaglandins (de la Serna and Cadarso 1999). In contrast, gemfibrozil does not activate PPARs, which may account for the observed absence of an increase in serum creatinine (Yoshinari et al 1998). It has been proposed that fenofibrate increases the metabolic production rate of creatinine (Hottelart et al 2002). The fenofibrate-induced increase in creatinine plasma levels does not appear to be related to alterations in renal hemodynamics (Hottelart et al 1999, 2002) or in tubular creatinine secretion (Hottelart et al 2002); accelerated muscular cell lysis has also been ruled out (Hottelart et al 2002). It must be pointed out that this increase in creatinine plasma levels is not associated with reductions in glomerular filtration rate (Hottelart et al 1999, 2002; Deighan et al 2001), and therefore seems unlikely to be clinically significant.

Other fibrates also display pleiotropic effects. Ciprofibrate has been shown to decrease CRP and fibrinogen and to increase fibrinolysis and attenuate platelet hyperaggregability (Simpson et al 1989; Rizos, Bairaktari, et al 2002; Rizos, Kostoula, et al 2002). Ciprofibrate also improves fasting and postprandial endothelial function and reduces postprandial oxidative stress in patients with DM (Evans et al 2000). Bezafibrate decreases CRP (Gomez-Gerique et al 2002), reverses insulin resistance (Taniguchi et al 2001), and increases exercise-induced coronary artery dilation in patients with CHD (Seiler et al 1995). It should be noted that bezafibrate is an unusual member of the fibrate class in that although it acts primarily as a PPARα agonist, it also has some effect on PPARδ (Peters et al 2003). Gemfibrozil reduces CRP (Despres et al 2003), lowers the factor VII–phospholipid complex, reduces plasma levels of PAI-1, improves fibrinolytic activity (Mussoni et al 2000) and, in patients with DM, improves insulin sensitivity and flow-mediated vasodilation (Steiner 1991; Avogaro et al 2001). All fibrates significantly reduced serum ALP activity, with bezafibrate inducing the greatest changes and gemfibrozil the smallest (Ganotakis et al 2002). All fibrates, except gemfibrozil, reduce fibrinogen and increase homocysteine levels (Branchi et al 1993; Schonfeld 1994; Durrington et al 1998; Chan and Chow 2001; Westphal et al 2001; Young and Woodside 2001; Maison et al 2002). On the other hand, all fibrates, with the possible exception of gemfibrozil, increase serum creatinine levels (Broeders et al 2000; Rizos, Kostoula, et al 2002).

Major clinical trials of fibrates

Fibrate treatment has been shown to slow the rate of atherosclerotic disease progression and reduced cardiovascular events in both primary and secondary prevention trials (NICE 2002). The Helsinki Heart Study (HHS) tested gemfibrozil 600 mg twice daily in 4081 men, aged 40–55 years, with primary dyslipidemia (nonHDL-C > 5.17 mmol/L) and without previous coronary disease, and demonstrated a significant 34% reduction in combined fatal and nonfatal myocardial infarction (MI) associated with gemfibrozil therapy ($p < 0.02$) (Frick et al 1987). The overall reduction in coronary events was greater than would have been expected on the basis of lowering of LDL-C alone and was 44% when baseline HDL-C was < 1.08 mmol/L and 58% when baseline TG levels were > 2.3 mmol/L (Manninen et al 1992; Koskinen et al 1992). Gemfibrozil lowered coronary events more in people with DM than in those without in a post-hoc analysis (3.4% vs 10.5%, respectively), though the difference was not significant due to the low number of diabetic patients in this study (n = 135) (Koskinen et al 1992).

The Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT) (de Faire et al 1996) was a 5-year, placebo-controlled study of bezafibrate 200 mg 3 times daily and dietary intervention in male survivors of MI below 45 years of age with dyslipidemia (predominantly hypertriglyceridemia). The angiographic analysis included 81 patients who underwent baseline and at least 1 post-treatment angiogram, at 2 and 5 years. Changes in mean minimum lumen diameter indicated that there was significantly less disease progression in focal lesions in the bezafibrate group than in the placebo group ($p = 0.049$). Parallel, but not significant, treatment effects were observed for mean segment diameter and percent stenosis. Three patients treated with bezafibrate and 11 patients in the placebo group suffered coronary events during the course of the trial ($p = 0.02$).

The Lopid Coronary Angiography Trial (LOCAT) randomly assigned 395 postcoronary bypass men, who had a low HDL cholesterol (≤ 1.1 mmol/L) as their main lipid abnormality and LDL cholesterol ≤ 4.5 mmol/L, to receive gemfibrozil 1200 mg/day or placebo (Frick et al 1997). Coronary angiography was performed at baseline and after,

on average, 32 months of therapy. The gemfibrozil group showed significantly smaller changes in per-patient means of average diameters of native coronary segments ($p = 0.009$) and in minimum luminal diameters of stenosis ($p = 0.002$) compared with the placebo group. In aortocoronary bypass grafts, fewer patients assigned to gemfibrozil had new lesions in the follow-up angiogram compared with subjects assigned to placebo ($p < 0.001$).

The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention trial (VA-HIT) was designed specifically to look at patients with low HDL-C (< 1.03 mmol/L) and included 2531 men with CHD. LDL-C levels, which were considered low in this population (mean, 2.87 mmol/L), did not change (Rubins et al 1999). After an average of 5.1 years, gemfibrozil 1200 mg daily provided a significant 24% reduction in the composite end point of CHD death, nonfatal MI, or stroke, and reduced cardiovascular events, stroke, and CHD death by 24%, 25%, and 22% respectively (Rubins et al 1999). Subgroup analysis from this study highlighted the particular benefit of gemfibrozil among patients with concomitant DM ($n = 769$), in whom it reduced the risk of the composite end point by 32% and cardiovascular events, stroke, and CHD death by 32%, 40%, and 41% respectively (Rubins et al 2002). Interestingly, despite the greater efficacy of gemfibrozil in reducing the risk of CVD recurrence in patients with DM, the increase in HDL-C levels and the reduction in TG levels were less pronounced among these patients (Rubins et al 2002).

The Bezafibrate Infarct Prevention (BIP) trial tested the effect of bezafibrate 400 mg daily in 3090 patients with CHD, low HDL-C levels, and moderately elevated LDL-C levels (mean, 3.88 mmol/L) (The BIP study group 2000). Although the CHD event reduction was small (7%) and not significant in this trial (The BIP study group 2000), posthoc analyses suggested a preferential benefit of CHD risk reduction of 39% ($p = 0.02$) in the subgroup of patients with TG levels ≥ 2.25 mmol/L or with the metabolic syndrome (MetS) (Tenenbaum et al 2005).

In the Saint Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) study (Elkeles et al 1998), 164 patients with DM and without previous cardiovascular disease were randomized to bezafibrate or placebo. Although there was no significant difference between groups in the progression of ultrasonically measured arterial disease in carotids and femoral arteries at 3 years, those treated with bezafibrate experienced a significant reduction in the combined incidence of probable ischemic change on resting electrocardiogram and documented MI.

In the Diabetes Atherosclerosis Intervention Study (DAIS) (DAIS Investigators 2001), of 418 patients with DM and good glycemic control, mild lipoprotein abnormalities typical of DM, and with angiographically documented CHD (half patients had no previous clinical CHD), fenofibrate 200 mg/day was associated with a significantly smaller increase in percentage diameter stenosis than the placebo group ($p = 0.02$), a significantly smaller decrease in minimum lumen diameter ($p = 0.029$), and a nonsignificantly smaller decrease in mean segment diameter ($p = 0.171$) over 3 years. There were also fewer clinical events with treatment (38 in the fenofibrate group vs 50 in the placebo group, 23% risk reduction), but this finding was not significant and the study was not designed to examine clinical outcomes.

The Lower Extremity Arterial Disease Event Reduction (LEADER) study looked at the effect of bezafibrate 400 mg daily in 1568 men, with a mean age of 68 years, with lower extremity arterial disease (Meade et al 2002). Although this study showed no benefit on CHD events or stroke, there was a 19% reduction in MI over 4.6 years and a 62% reduction in CHD in the subgroup of men aged < 65 years. An improvement in patients' symptoms was also noted.

Finally, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a multinational, randomized, controlled trial that enrolled 9795 participants with DM, aged 50–75 years; 2131 patients had previous cardiovascular disease and 7664 did not (Keech et al 2005). Patients received fenofibrate daily or matching placebo and were followed up for a median of 5 years. 5.9% ($n = 288$) of patients on placebo and 5.2% ($n = 256$) of those on fenofibrate had a coronary event (relative reduction of 11%, $p = 0.16$). This finding corresponds to a significant 24% reduction in nonfatal MI ($p = 0.01$) and a nonsignificant increase in CHD mortality. Total cardiovascular disease events were significantly reduced by 11% ($p = 0.035$). This finding included a 21% reduction in coronary revascularization ($p = 0.003$). Total mortality was 6.6% in the placebo group and 7.3% in the fenofibrate group ($p = 0.18$). The effects of fenofibrate on cardiovascular events were less than planned for in the study design. Of note, more patients allocated placebo (17%) than fenofibrate (8%; $p < 0.0001$) commenced other lipid treatments, predominantly statins, and this might have masked a moderately larger treatment benefit. A second possible explanation for the small effect of fenofibrate on cardiovascular events in the FIELD study relates to the unexpectedly small difference in HDL-C concentrations between the two groups (1.2% increase in the fenofibrate group compared to the placebo group). It is well known that treatment with fibrates in patients with diabetes,

as those in the FIELD study, results in smaller increases in HDL-C levels than in the nondiabetic population (DAIS Investigators 2001; Rubins et al 2002). In addition, the initiation of other lipid-lowering medications during the study further decreased the differences in HDL-C levels between study groups (0.5% increase in patients who started other lipid treatments vs 2.1% in those who did not). However, the initial increase in HDL-C levels (5.1% at 4 months) also decreased (to 2.1% at study end) in patients who did not start other lipid treatments, while the effect of fenofibrate on other lipid fractions remained stable; the explanation for this finding is unclear.

Even though the results of VA-HIT and BIP studies appear to be contradictory, it must be mentioned that the mean LDL-C value in VA-HIT was lower than that in BIP (2.89 vs 3.82 mmol/L) (Rubins et al 1999; The BIP study group 2000). Furthermore, it has already been mentioned that a subgroup of patients in BIP, with HDL-C and TG levels similar to the VA-HIT population, had a statistically significant reduction in cardiovascular risk (Tenenbaum et al 2005). This comparative analysis of the VA-HIT and BIP studies shows that treatment with fibrates might be more beneficial in reducing the risk of vascular events in patients with elevated TG levels and low HDL-C levels, but with LDL-C levels close to the target levels for secondary prevention of CVD (< 2.6 mmol/L) (Rizos and Mikhailidis 2002).

Finally, the evidence from HHS (Koskinen et al 1992), VA-HIT (Rubins et al 2002), and BIP (Tenenbaum et al 2005) suggests possible larger-than-average benefits of fibrate therapy in patients with DM or the MetS than in those without; in contrast, this was not observed in the FIELD study (Keech et al 2005). Moreover, the reduction in CHD events noted in the latter study was less than that reported in other randomized trials of fibrate therapy, particularly in patients with diabetes and low HDL-C in the VA-HIT trial (Rubins et al 2002) or with MetS in a post-hoc analysis of the BIP trial (Tenenbaum et al 2005). However, VA-HIT and BIP were both secondary prevention studies with different patients' characteristics and lipid profiles, limiting direct comparisons.

Fibrate–statin combination therapy

The different mechanisms of action of fibrates and statins provide a rationale for combination drug therapy in high-risk patients with combined hyperlipidemia refractory to monotherapy. However, fibrate–statin combination is associated with a 1%–5% risk of myopathy, which may occasionally be accompanied by rhabdomyolysis and renal failure (Miller and Spence 1998; Guay 1999; Mantel-Teeuwisse et al 2002; NCEP 2002; Pasternak et al 2002; Taher et al 2002; Thompson et al 2003). Risk factors include underlying renal or hepatic insufficiency, age greater than 70 years, debilitation, high doses of statins, and multiple medications (Guay 1999). Gemfibrozil appears to account for most cases of severe myopathy and rhabdomyolysis; during a survey in 1998–2002 on total reports of rhabdomyolysis in patients on fibrate–statin combination therapy, gemfibrozil–cerivastatin accounted for most reports (88%), whereas fenofibrate–cerivastatin was associated with a small proportion of cases (2.3%) (Jones and Davidson 2005). Indeed, no significant side-effects were observed when fenofibrate was co-administered with a variety of statins (Athyros et al 2002a, 2002b; Taher et al 2002; Vega et al 2003; Keech et al 2005; Koh, Ahn, Jin, et al 2005; Grundy et al 2005). The exact mechanism of this interaction and the subsequent myotoxicity is unknown; statins may cause muscle toxicity on their own (NCEP 2002; Pasternak et al 2002; Thompson et al 2003). In vitro studies have highlighted that gemfibrozil may increase the myotoxic effects of statins (Prueksaritanont, Tang, 2002; Prueksaritanont, Zhao, et al 2002). In addition, coadministration of gemfibrozil led to significant increases in systemic exposure to several statins, including pravastatin (increased by 202%) (Kyrklund et al 2003), simvastatin (by 185%) (Backman et al 2000), lovastatin (by 280%) (Kyrklund et al 2001), and cerivastatin (by 559%) (Backman et al 2002). Recent in vitro microsomal studies suggest that the observed statin–gemfibrozil interaction is due to inhibition of statin acid glucuronidation by gemfibrozil (Prueksaritanont, Tang, et al 2002; Prueksaritanont, Zhao, et al 2002). Moreover, gemfibrozil reduces the renal clearance of pravastatin and, possibly, inhibits an organic anion-transporting polypeptide or some other transporter of pravastatin (Kyrklund et al 2003). In contrast, fenofibrate does not have any significant effects on the pharmacokinetics of pravastatin (Gustavson et al 2005) or simvastatin (Bergman et al 2004). Furthermore, in vivo data suggest that fenofibric acid does not undergo significant oxidative metabolism by cytochrome P450 and does not inhibit most cytochrome P450 isoforms (Keating and Ormrod 2002; Telford and Elisaf 2003).

Fibrate–statin combination treatment has been shown to lead to greater changes in lipid levels compared with monotherapy (Athyros et al 1997, 2002a, 2002b; Ellen and McPherson 1998; Kiortsis et al 2000; Taher et al 2002; Vega et al 2003; Grundy et al 2005; Keech et al 2005;

Koh, Ahn, Jin, et al 2005). In one of these studies, 120 consecutive patients were randomly assigned to atorvastatin 20 mg/day (n = 40), fenofibrate 200 mg/day (n = 40), or a combination of both (n = 40) (Athyros et al 2002a). After 24 weeks, the atorvastatin–fenofibrate combination reduced total cholesterol (TC) by 37%, LDL-C by 46%, and TG by 50%, whereas it increased HDL-C by 22% ($p < 0.0001$ for all), significantly better than those of both monotherapies. Of the patients on drug combination, 97.5% reached the LDL-C treatment goal of < 2.59 mmol/L, 100% reached the desirable TG levels of < 2.25 mmol/L, and 60% reached the optimal HDL-C levels of > 1.16 mmol/L; these rates were also significantly higher than those of both monotherapies. No significant adverse events were recorded. All patients remained under the 3-fold level of the upper normal limit of serum transaminase values and no patient presented myalgia or creatine kinase levels > 10-fold from pretreatment values. In another prospective, randomized trial, 300 nondiabetic patients with MetS were randomly allocated to atorvastatin 20 mg/day (n = 100), fenofibrate 200 mg/day (n = 100), or both drugs (n = 100) (Athyros et al 2005). After 12 months, the combined treatment group attained lipid targets to a greater extent than those in the monotherapy groups. In the most recent study, combination therapy with simvastatin 20 mg/day plus fenofibrate 160 mg/day (n = 411) was compared with monotherapy with simvastatin 20 mg/day (n = 207) in patients with combined hyperlipidemia (Grundy et al 2005). From baseline to week 12, median TG levels decreased 43.0% and 20.1% (treatment difference −23.6%, $p < 0.001$), mean LDL-C levels decreased 31.2% and 25.8% (treatment difference −5.4%, $p < 0.001$), and HDL-C levels increased 18.6% and 9.7% (treatment difference 8.8%, $p < 0.001$) in the combination therapy versus monotherapy groups, respectively. No patient experienced clinical myopathy or severe abnormalities in liver function. Despite these emerging data, there are still no currently published trials of surrogate atherosclerosis end points or hard outcomes using a statin–fibrate combination compared with either a statin alone or a fibrate alone (NCEP 2002; ADA 2004). Short-term studies suggest that the combination of a statin and fibrate can reduce CHD risk status significantly more than each drug alone in patients with DM (Athyros et al 2002a). Long-term follow-up data from 525 patients with combined hyperlipidemia who were treated with 4 different statin–fibrate combinations showed that total and CHD mortality, as well as morbidity and need for revascularization, were much better than those of the landmark studies with statins in patients with hypercholesterolemia, both in secondary and primary CHD prevention; however, this was not a placebo-controlled trial and its size lacked the statistical power of a survival study (Athyros et al 2001). A 6-year prospective primary intervention study, the Lipids in Diabetes Study (LDS), involving 5000 patients with DM was underway comparing the effects of cerivastatin or fenofibrate monotherapy or combination therapy on CVD mortality and morbidity (Neil et al 2003). However, the study ended prematurely when cerivastatin was withdrawn in August 2001. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study began in 2003 and is investigating the use of statin monotherapy or combination therapy with a fibrate as part of a wider intensive strategy to improve cardiovascular outcomes that also involves tight glycemic control and antihypertensive treatment (ACCORD 2005). It is expected to involve a total of 10 000 patients and is due to be completed by 2009. The American Heart Association and the American College of Cardiology recently released a joint clinical advisory reinforcing the benefits of combination therapy when used in selected cases in conjunction with careful patient monitoring, but suggested caution in groups of patients at higher risk of myopathy (Pasternak et al 2002). In addition, both the American Diabetes Association (ADA 2003) and the National Institute of Clinical Excellence of Great Britain (NICE 2002) guidelines recommend the appropriate use of statin–fibrate combination therapy.

Ezetimibe prevents the absorption of dietary and biliary cholesterol and reduces LDL-C by 15%–25% with modest favorable effects on TG and HDL-C in patients with primary hypercholesterolemia (van Heek et al 1997; Bays et al 2001; Dujovne et al 2002; Knopp et al 2003). In a recent multicenter, randomized, double-blind, placebo-controlled, parallel-arm trial, 625 patients with mixed hyperlipidemia were randomized in a 1:3:3:3 ratio to 1 of 4 daily treatments: placebo; ezetimibe 10 mg; fenofibrate 160 mg; fenofibrate 160 mg plus ezetimibe 10 mg (Farnier et al 2005). After 12 weeks, combination therapy reduced LDL-C and nonHDL-C significantly more than both monotherapies ($p < 0.001$) and was well tolerated. Thus, concomitant treatment with fibrates and ezetimibe may provide a complementary and alternative treatment for mixed hyperlipidemia without the safety concerns associated with co-administration of fibrates and statins.

Finally, in patients with mixed hyperlipidemia, the addition of colesevelam (a specifically engineered bile acid sequestrant) 3.75 g/day to fenofibrate 160 mg/day significantly reduced LDL-C, nonHDL-C, TC, and apoB levels compared with fenofibrate monotherapy (McKenney et al

2005). Fenofibrate–colesevelam combination therapy might also represent a safe, useful alternative for the treatment of mixed hyperlipidemia.

Fenofibrate in human immunodeficiency virus infection-associated dyslipidemia

Fenofibrate has been assessed in patients with human immunodeficiency virus (HIV) infection-associated dyslipidemia, which is characterized by elevated concentrations of TG, decreased levels of HDL-C, and altered distribution of LDL-C subfractions towards smaller particles (Grunfeld et al 1992; Stein et al 2001; Badiou et al 2003). This disorder is mainly attributed to the use of protease inhibitors (Carr et al 1998), even though several studies indicate that disturbances in lipoprotein metabolism in HIV-infected patients exist even before the initiation of antiretroviral therapy (Grunfeld et al 1992). Fenofibrate represents a safe and effective therapeutic option in these patients (Calza et al 2002, 2003; Badiou et al 2004; and may act synergistically with antiretroviral therapy, since it was shown that activation of PPARα receptors may result in inhibition of HIV replication (Skolnik et al 2002).

Guidelines

The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) recognized that a substantial proportion of patients have mixed dyslipidemia, which is characterized by increased levels of TG, TG-rich lipoprotein remnants and apoB, small dense LDL particles, low HDL-C levels, and is associated with substantial elevation in cardiovascular event risk (NCEP 2002). Mixed dyslipidemia is closely related to insulin resistance and patients with DM, as well as those with the MetS, often demonstrate this lipid profile (Wilson et al 1985; Assmann and Schulte 1988; Feingold et al 1992; Guerin et al 2001; Farnier and Picard 2001; Haffner 2002; Taskinen 2003). The MetS represents a cluster of metabolic abnormalities driven by abdominal obesity and insulin resistance, leading to the development of high blood pressure, mixed dyslipidemia, as well as impairment of glucose tolerance (NCEP 2002). In an analysis of 8814 US adults from the Third National Health and Nutrition Examination Survey, the prevalence of the MetS was estimated to be 24% (Ford et al 2002); the European Group for the Study of Insulin Resistance suggests a similar prevalence in Europe (Balkau et al 2002). MetS confers an increased risk of CVD-related morbidity and mortality (Isomaa et al 2001; Lakka et al 2002; Girman et al 2004; Athyros et al 2004b) and all-cause mortality (Lakka et al 2002; Grundy, Brewer, et al 2004). The effect of clustering of MetS components on the risk of CHD morbidity in individuals with the MetS appears greater than the relative risk associated with its individual components (Isomaa et al 2001; Athyros et al 2004b).

The ATP III guidelines currently recommend a stepped-care approach to patients with mixed dyslipidemia (NCEP 2002). LDL-C levels remain the primary target of therapy and statins are the mainstay of therapy in patients with high levels of LDL-C. Once the LDL-C target has been reached, if the TG level is >2.25 mmol/L, the secondary target is the nonHDL-C level. Goals for nonHDL-C are 0.77 mmol/L higher than goals for LDL-C. To this end, combination therapy is frequently required for mixed dyslipidemia.

Conclusions

Although the evidence base to support fibrate therapy is not as strong as that for statins, fibrates may have an adjunctive role in the treatment of patients with low HDL-C and high TG, especially in combination with statins (Grundy, Cleeman, et al 2004). Treatment with fibrates also appears to be particularly appropriate in patients with a high risk of CHD but no or little increase in LDL-C levels (Sacks 2002). A HDL-C treatment target of >1.0mmol/L is recommended in patients with low HDL-C who are currently receiving statins according to clinical guidelines, as well as those who are not (Sacks 2002).

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