

REVIEW ARTICLE

Belgian expert opinion: how to reduce the residual risk in atherogenic dyslipidaemic patients: place of fibrates**Jean DUCOBU¹, André SCHEEN², Luc VAN GAAL³, Brigitte VELKENIERS⁴, Michel HERMANS⁵**

¹Department of Internal Medicine, Université Libre de Bruxelles, Brussels; ²Department of Diabetes, Nutrition and Metabolic Disorders, University of Liège, CHU Sart Tilman, Liège; ³Department of Diabetology and Metabolism, Faculty of Medicine, University of Antwerp, Antwerp; ⁴Velkeniers Brigitte, Department of Endocrinology, Vrije Universiteit Brussel (UZ-VUB), Brussels; ⁵Department of Diabetology and Nutrition, Université Catholique de Louvain, Woluwe-Saint-Lambert, Brussels, Belgium.

The demographics of dyslipidaemia have changed towards a more complex atherogenic dyslipidaemia involving increased levels of LDL-C, in particular highly atherogenic small dense particles, hypertriglyceridaemia and low HDL, together with increased levels of markers of cardiovascular inflammation, thrombogenesis and endothelial dysfunction. Statins were shown to significantly lower cardiovascular morbidity and mortality, but there still remains a high residual risk in dyslipidaemic patients, in particular with metabolic syndrome, type 2 diabetes, or low HDL levels. Fibrates have been shown to reduce plasma triglycerides and increase HDL-C, while improving inflammation, thrombogenesis and endothelial dysfunction. Clinical trials with fibrates have demonstrated their potential to reduce cardiovascular morbidity and mortality too, often through other mechanisms than these of statins. Combination trials of statins with fibrates have shown a more complete improvement of lipid profile and risk markers than each class separately. In contrast with gemfibrozil, fenofibrate does not interact significantly with the pharmacokinetics of statins, and up until now its combination with statins has been shown to have a low risk of muscular side effects or liver toxicity. The ACCORD outcome trial is exploring the possible benefits of the combination of fenofibrate with statins on morbidity and mortality of patients with atherogenic dyslipidaemia.

Keywords: *atherogenic dyslipidaemia – fibrates – fenofibrate – diabetes – metabolic syndrome – combination therapy.*

Introduction

Over the past 30 years, the demographics of cardiovascular (CV) risk have changed. The stereotypic plain older smoking white male with hypercholesterolaemia and hypertension was steadily substituted by individuals of both sexes and from all socioeconomic strata, being affected by cardiometabolic risk and indeed susceptible to its complications, such as coronary disease or stroke. Obviously, global CV risk includes more than just dyslipidaemia, but several risk factors such as age, sex, hypertension, smoking and diabetes, as taken into account in the European Heart SCORE global risk calculation for individual patients^{1,2}. Despite full avail-

ability of powerful drugs for LDL-cholesterol (LDL-C) lowering, such as statins, coronary care units remain filled with individuals with acute coronary syndromes, yet treated with statins, and whose LDL-C may well have been within the safe zone according to current guidelines. We now face a burden of residual CV risk linked, for instance, to less conventional risk factors such as atherogenic dyslipidaemia, with low HDL-C, high triglycerides and atherogenic small dense LDL particles, with or even without high LDL-C levels, yet associated with significant cardiometabolic risk³.

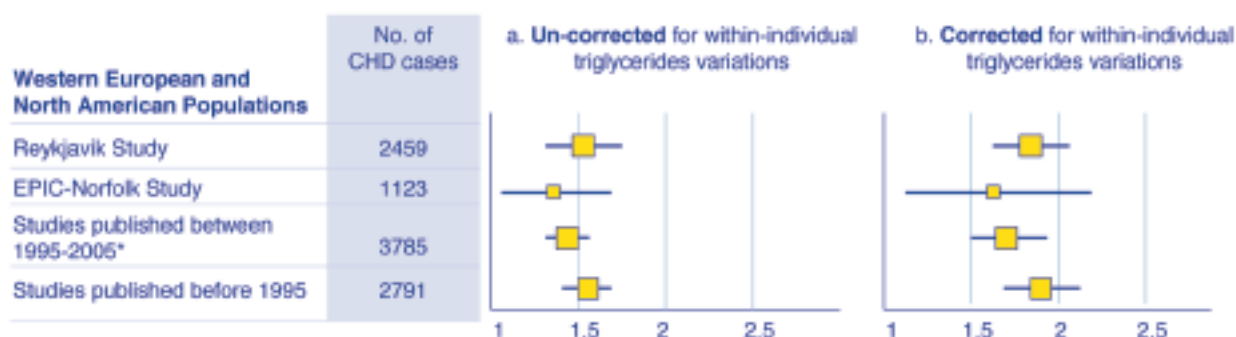
Lipids as a risk factor for cardiovascular disease (CVD)

Many early epidemiological studies have reported significant associations between serum triglycerides and coronary artery disease (CAD)⁴⁻⁶. A meta-analysis⁷ on

Address for correspondence: Jean Ducobu, rue de Beaulieu 101, 7021 Havré, Belgium. E-mail: jducobu@skynet.be

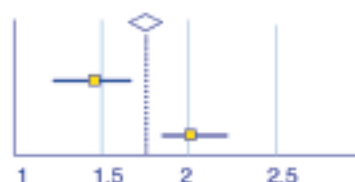
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Risk ratio (95% CIs) (top third vs. bottom third)



Available prospective studies of triglycerides and CHD in essentially general populations. * Includes 3 studies that were published before 1995 but were not included in the previous review.

Location	No. of cases
North America	3388
Europe	6770



Studies of the risk of CHD in individuals in the top vs bottom third of usual log-triglyceride values grouped according to several study characteristics. Pooled estimate presented was calculated using a fixed effects model. Using a random effects model yielded a risk ratio of 1.86 (1.56-2.21)

Fig. 1. – Are triglycerides an independent risk factor?

new primary data on 3582 incident cases of CAD and 6175 controls from the European Reykjavik and EPIC-Norfolk studies showed, after adjustment for baseline values and several established risk factors, odds ratios for coronary heart disease linked to triglycerides of 1.76 (95% CI 1.39-2.21) (Reykjavik) and 1.57 (95% CI 1.10-2.24) (EPIC Norfolk).

An updated meta-analysis in the same paper on 10 158 incident coronary cases from 262 525 participants in 29 studies (figure 1) found a similar odds ratio of 1.72 (95% CI 1.56-1.90) when comparing the population in the upper triglyceride levels tertile with that in the lower tertile. This largest and most comprehensive epidemiological assessment on available prospective studies in Western populations therefore consistently shows moderately strong but highly significant associations between triglyceridaemia and CAD risk. The impact was similar for men and women, in contrast to previous observations. As can be expected from the link between triglyceride and HDL-cholesterol pathways, adjustment for HDL cholesterol decreased the magnitude of the association, as evidenced by heterogeneity test $\chi^2 = 6.4$ with $P = 0.01$. As can also be derived from these pooled data, the impact of triglycerides seems even more pronounced in European than in US populations. The German PROCAM study⁸ including 4559 participants followed during 6 years showed similar correlations between triglycerides and coronary artery disease.

The imbalance between circulating levels of atherogenic lipoproteins such as LDL, VLDL or IDL,

relative to those of HDL is associated with induction of endothelial dysfunction, intimately related to inflammation and oxidative stress, and closely related to the development of atherosclerosis⁹.

HDL particles possess multiple antiatherogenic activities, including reverse cholesterol transport from arterial wall to liver for catabolism/excretion, as well as antioxidant, anti-inflammatory, anti-apoptotic, antithrombotic, vasodilatory, and even anti-infectious properties¹⁰. The antioxidant effect of HDL typically inhibits LDL oxidation, a major physiological target¹¹, with apolipoprotein A1 (apo-A1) being a major component of antioxidative activity¹¹. Among HDL subfractions, the small and dense HDL₃ is the most potent protector of LDL against oxidation¹², through capture and inactivation of the oxidized lipids in LDL, ensuring their elimination by transfer to the liver^{13,14}.

Triglyceride enrichment is the most frequent abnormality of HDL lipid composition, as occurs in mixed hyperlipidaemia (also known as atherogenic dyslipidaemia) observed in patients with metabolic syndrome or type 2 diabetes¹⁵. CETP-mediated replacement of cholesteryl esters with triglycerides in the HDL core results in decreased plasma HDL-cholesterol levels¹⁵. It could even be a critical factor that lowers both HDL particle stability and plasma residence time¹⁵. From a functional viewpoint, the capacity of triglyceride-enriched HDL to deliver cholesteryl esters to hepatic cells is impaired¹⁶ and shifted towards macrophages¹⁷, thus redirecting cholesterol to the inflammatory atherosclerotic plaque. It is obvious that in this context, a

therapy able to lower triglycerides while improving or restoring HDL functionality is intuitively worth considering. Fibrates lower triglyceridaemia by an average 36%¹⁸ and selectively raise small HDL particles levels¹⁹ which are vasculoprotective. In the Veterans Affairs HDL Intervention trial (VA-HIT), plasma levels of HDL₃ were a powerful predictor of cardiovascular risk, suggesting that fibrates are useful in correcting the functionality of small dense HDL^{14,19}.

Prospective studies in several countries provide compelling evidence for an inverse relationship between HDL-C levels and cardiovascular risk. This relationship was quantified in an analysis of cohorts from 4 prospective North American studies²⁰. Two of the cohorts were derived from observational studies, i.e. the Framingham Heart Study²¹ and the Lipid Clinics Follow-up Study²², and two from control groups of randomized clinical trials in high-risk middle-aged men, the Multiple Risk Factor Intervention Trial²³ and the Coronary Primary Prevention Trial²⁴. The results from each cohort were consistent with a decrease of 2-3% in CHD risk for each 1 mg/dL increase in HDL-C level²⁰. Another study examined the prevalence of risk factors in 321 men with angiographically documented coronary disease²⁵. Nearly half of the patients did not have elevated total cholesterol levels. However, 75% of patients with total cholesterol < 200 mg/dl were found to have low HDL-C (< 35 mg/dL). Apparently, low HDL-C seemed to be the second commonest CHD risk factor after smoking. For Europe, the European Consensus Panel on HDL-C²⁶ also concluded to a 2% increase in CHD for men and 3% for women for each 1 mg/dl decrease in HDL-C. A post-hoc analysis of the Treatment to New Targets (TNT) study²⁷ showed HDL-C in patients receiving statins to be predictive of major cardiovascular events. Even among subjects with LDL-C below 70 mg/dL, those in the highest quintile of HDL-C were at less risk than those in the lowest quintile.

The inverse relationship between HDL-C and CHD risk also prevails for cerebrovascular accidents. A large scale survey²⁸ on 7735 men from 24 British towns showed a significant inverse relationship between HDL-C levels and risk of stroke (adjusted relative risk 0.68; 95% CI 0.46-0.99), especially for nonfatal strokes (RR 0.59; 95% CI 0.39-0.90).

Recently, outcome trials²⁹ with the CETP inhibitor torcetrapib could not confirm the classical inverse relationship between HDL-C and cardiovascular events. Possible explanations for this lack of efficacy on morbidity and mortality could be the generation by CETP inhibition of HDL particles of enlarged size, known to be less effective in reverse cholesterol transport³⁰. CETP inhibition also decreases fractional clearance of apo A-1, increasing the susceptibility of these large HDL particles to oxidation. Moreover, larger particles fail to activate endothelial NO synthase through the

Scavenger Receptor class B type 1 (SR-BI) for NO dependent vasorelaxation³¹. These changes could induce thrombogenesis and atherogenesis in some patients instead of inhibiting it, with neutral or negative outcome as a result³².

Epidemiology of dyslipidaemia

An epidemiological study (Odyssee) in France³³ on 22 323 patients followed by 4000 GPs and 527 cardiologists showed that among dyslipidaemic patients the prevalence of mixed hyperlipidaemia was 50% and therefore higher than that of single hypercholesterolaemia (42%). Drug-based regimens based solely on LDL-C lowering may just prove insufficient in this respect, taking into consideration the abovementioned links between triglycerides, HDL-C and cardiovascular risk. Mixed hyperlipidaemia is also becoming increasingly common, as is the prevalence of the metabolic syndrome (MetS) phenotype, itself associated with abdominal obesity, insulin resistance, and risk of developing abnormal glucose homeostasis, including the common form of type 2 diabetes mellitus³⁴. A survey on 62 254 individuals in France³⁵ showed an increase from 11% to 13% in the prevalence of metabolic syndrome in men, according to ATP III criteria, and from 7% to 9% in women over a mere 3 years of follow-up.

A systematic review and meta-analysis of 37 longitudinal studies³⁶ including 43 cohorts and 172 573 individuals, showed a relative risk of MetS for cardiovascular events and death of 1.78 (95% CI 1.58-2.00). The significant association remained after adjusting for traditional cardiovascular risk factors. When MetS was split into its various discrete components and their relative risks for myocardial infarction calculated³⁷, it appears that the sole two variables having significant odds ratios for that endpoint were high triglyceride levels (OR 1.51; 95% CI 1.04-2.20) and low HDL-C (OR 1.41; 95% CI 1.03-1.95). Diabetes mellitus, another common discrete component of the MetS is a standard risk factor for CVD, and its presence increases such risk twofold in men and fourfold in women^{1,38,39}.

Have statins solved all problems? Is everything under control?

There is strong evidence from several mega-trials that statins effectively lower LDL-C and hence reduce cardiovascular morbidity and mortality. Although much emphasis was put on a maximal lowering of LDL-C, albeit without taking into account other lipid parameters, mortality was typically decreased by 25-35%, but not further, as shown in figure 2. PROVE-IT/TIMI-22⁴⁰

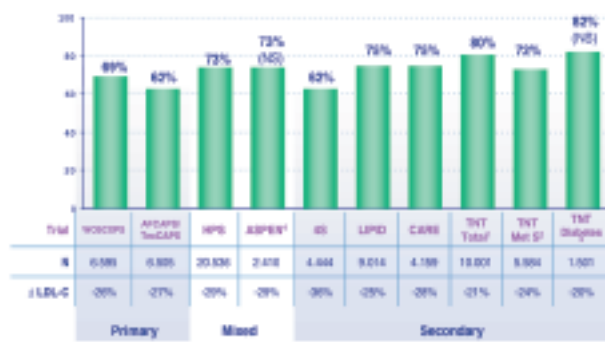


Fig. 2. – Residual risk in statin trials.

has revealed that lowering of LDL-C < 70 mg/dL further reduced cardiovascular endpoints, but could not eliminate residual cardiovascular risk. At the same time, up-titration of statins ended up with a flattening of their dose-response curve, making the therapeutic benefit of such dose increases limited, and the risk of adverse events, such as myopathy, higher⁴¹.

Even under maximal therapy with statins, patients are left with a major residual relative risk of 62%-82%. When the effects of statins are split into subgroups of patients with high or with low HDL-C, discrepancies in absolute risk reduction do appear, as shown in figure 3.

Thus, although the overall magnitude of risk reduction with statins appears to be similar for both subgroups, the baseline risk of the low HDL-C subgroup is higher, and the treated group ends up at the risk level of control groups with high HDL-C. This clearly invites to consider a therapeutic intervention to bring HDL-C to higher levels.

In diabetic patients the Collaborative Atorvastatin Diabetes Study (CARDS)⁴² showed statin therapy to significantly reduce cardiovascular events by 37% in patients without high LDL-C (117 mg/dL). LDL-C was lowered 40% in the statin arm, supporting the concept for LDL-C of “the lower the better”. In the ASCOT-LLA study^{43,44}, statin efficacy appeared to be lower in type 2 diabetes patients and even lower in patients with MetS than in the normal population, albeit non significantly. Again, both types of patients have the typical atherogenic triad of low HDL-C, high triglycerides and small dense LDL particles, where statins preferably lowers the latter of the three lipid parameters. The question that arises is therefore whether fibrates can be of further benefit in such a setting.

Mode of action of fibrates

Fibrates are synthetic carboxylic acids that behave as peroxisome proliferator activating receptor α ligands (PPAR α), forming heterodimers with another nuclear receptor partner, the retinoid X receptor, and subsequently binding to specific PPAR response



Fig. 3. – Statins: limited coronary risk reduction when HDL-C level is low.

elements (PPREs) in the promoter region of target genes, thereby regulating gene function. PPAR α are found in tissues where fatty acid catabolism is important, such as liver, heart, kidney and muscle, and regulate genes involved in lipid and lipoprotein metabolism⁴⁵. PPAR α is markedly expressed in the liver, where it enhances fatty acids uptake, activation and oxidation. It also does so in other non-white adipose tissue (non-WAT) organs. PPAR α expression is correlated with elevated mitochondrial and peroxisomal β -oxidation activities in tissues which primarily use fatty acids for ATP production. It functions in a complementary and tissue-specific manner with PPAR β/δ in skeletal muscle.

With respect to lipid physiology, the expression of lipoprotein lipase is enhanced and hepatic apolipoprotein CIII expression is decreased. The effects on lipids and lipoproteins can be globally summarized as follows⁴⁶ (figure 4):

- 1) induction of lipoprotein lipolysis,
- 2) induction of hepatic cellular fatty acid uptake (through, for instance, induction of FATP1 and CPTI) and β -oxidation,
- 3) reduction of hepatic triglyceride and VLDL production,
- 4) increased removal of LDL particles,
- 5) reduction in cholesterol and triglyceride exchange between VLDL and HDL,
- 6) increase in HDL production and stimulation of reverse cholesterol transport. HDL-cholesterol is increased through transcriptional induction of the synthesis of the major HDL apolipoproteins apoA-I and apoA-II, as well as ATP-binding cassette A1 (ABCA1),
- 7) fibrates lower the levels of small dense LDL, but not that of the light, buoyant, LDL fraction, which is less susceptible to oxidation⁴⁶ and could be considered as the most vascular-friendly fraction of LDLs.

PPAR α agonism with fibrates also shows “pleiotropic” effects. Fibrates have vascular effects and counteract many components of the atherosclerotic cascade. They improve exercise-induced flow-mediated dilation, as shown in coronary patients with bezafibrate⁴⁷, and with fenofibrate⁴⁸ and ciprofibrate⁴⁹, but

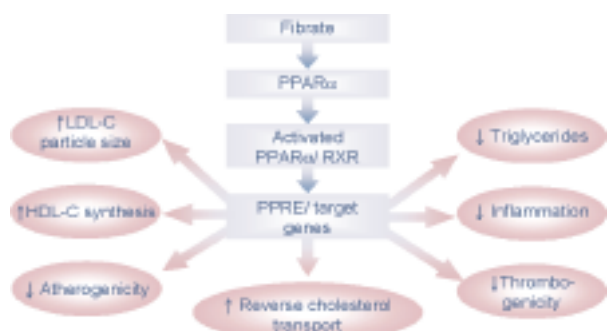


Figure. Mechanism of action of fibrates. HDL = high-density lipoprotein; LDL = low-density lipoprotein; PPARα = peroxisome proliferator-activated receptor; PPRE = peroxisome proliferator response element; RXR = retinoid receptor; ↑ = increase; ↓ = decrease.

Fig. 4. – Fibrates: effects on lipids and other actions.

less with gemfibrozil^{50,51}. This could be a consequence of increased endothelial NO synthase expression, with an inhibition of inducible NO synthase, providing antioxidant effects. Fenofibrate also reduces collagen deposition, preventing cardiac fibrosis in experimental models⁵². They reduce the expression of cell adhesion molecules ICAM-1 and VCAM-1 by modulating the nuclear transcription factor NF-κB, lowering at the same time chemoattractant factors, such as MCP-1, and inflammation. As a consequence, fenofibrate decreases several inflammatory factors, such as CRP, TNFα, CD40, IL-6 and IL-1β⁵³, the latter two being also strong procoagulant cytokines. This implies an inhibitory effect of fenofibrate on haemostasis. Fenofibrate also decreases PAI-1, and –in contrast to statins– also decreases fibrinogen⁵⁴.

If one considers the various metabolic pathways that are found to be disturbed in metabolic syndrome and type 2 diabetes (table 1), it appears that fenofibrate has beneficial effects on many of those factors involved.

Overall, the atherogenic lipid profile of low HDL-C, high triglycerides and high small dense LDL levels is improved. Fenofibrate slightly increases insulin sensitivity, increases adiponectin, decreases thrombogenic factors, lowers inflammatory markers and improves endothelial function.

Evidence-based medicine for fibrates

GEMFIBROZIL

In the VA-HIT⁵⁵ trial on 2531 male coronary patients with low HDL and LDL cholesterol levels, gemfibrozil (1200 mg/day) decreased mean plasma triglycerides by a significant 31% ($P < 0.001$) and increased HDL-C by 6% ($P < 0.001$), while having no effect on LDL-C and only a minor effect on total cholesterol (–4%) (figure 5). This lipid profile change was linked to a reduction of the combined endpoint of [non-fatal MI - cardiovascular mortality - stroke] by a significant 24% ($P < 0.001$) versus placebo. Non-fatal MI decreased by 23% ($P = 0.02$), stroke decreased by

Table 1. – Cardiovascular risks of metabolic syndrome and type 2 diabetes

Lipids: HDL-C ↓ - TG ↑ - small dense LDL-C ↑
 Glucose metabolism: Insulin ↑ - glucose ↑
 Adipose hormones: leptin ↑ - adiponectin ↓
 Thrombogenicity: fibrinogen ↑ - PAI-1 ↑
 Inflammation: CRP ↑ - IL6 ↑ - TNFα
 Endothelial dysfunction

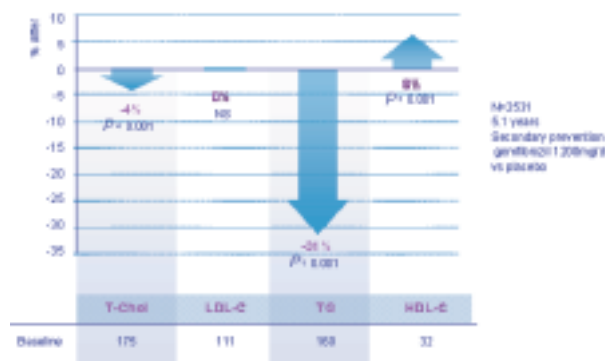


Fig. 5. – VA-HIT lipid changes.

Table 2. – VA-HIT clinical results.

Clinical results	Active N = 1264	Placebo N = 1267	% Risk Reduction	P-value
Nonfatal MCHC+	219 (17.3%)	275 (21.7%)	-22%	0.006
Nonfatal MI / CHF+ / Stroke	256 (20.4%)	330 (26.0%)	-24%	< 0.001
Nonfatal MI	146 (11.6%)	184 (14.5%)	-23%	0.02
Stroke	64 (5.1%)	88 (6.9%)	-29%	0.04
TIA	22 (1.7%)	53 (4.2%)	-59%	< 0.001
Carotid endarterect	16 (1.3%)	44 (3.5%)	-55%	< 0.001
Hospitalization CHF	134 (10.6%)	168 (13.3%)	-22%	0.04

29% ($P = 0.04$), among which transient ischaemic attacks (TIA) were lowered by 59% ($P < 0.001$) (table 2). This study shows that without any therapeutic change of LDL-C, CV morbidity and mortality of coronary patients can be decreased by changing the lipid profile towards higher levels of HDL-C and lower triglyceridaemia, with a magnitude of protection comparable to that of major statin trials. The level of benefit was greatest at the highest tertile of baseline triglycerides⁵⁶.

In the Helsinki Heart Study⁵⁷ (HHS), treatment with 1200 mg gemfibrozil in 4081 asymptomatic men with dyslipidaemia resulted in an 11% decrease in LDL-C, a 35% decrease in triglycerides and an 11% increase in HDL-C versus placebo. All cardiac events were lowered by 34% ($P = 0.02$), and non-fatal MI by 37% ($P < 0.05$), an achievement comparable to what would be expected from LDL-C lowering with statins. An 18-year mortality follow-up⁵⁸ including the 5-year double-blind period and a 13-year open-label phase showed a further separation of coronary mortality curves over time. Adjusted CHD mortality risk was

0.76 (95% CI 0.59-0.99). As in the double-blind phase, the effect of gemfibrozil on mortality at 18 years was most striking in overweight patients with baseline high triglyceride (RR 0.30; 95% CI 0.15-0.58) or low HDL-C levels. In both trials, multivariate analysis showed a good correlation between HDL-C increase and therapeutic benefit, but a lesser correlation with triglyceride reduction. The presence or absence of insulin resistance seems even more important for fibrate benefit, as shown in the VA-HIT trial⁵⁹. It should be noted that gemfibrozil is not available in Belgium.

BEZAFIBRATE

The Bezafibrate Infarction Prevention (BIP) study⁶⁰ explored during 6 years the effects of bezafibrate (400 mg) versus placebo in 3090 patients with coronary disease and HDL-C < 45 mg/dL. The most pronounced effects were a 17.9% increase of HDL-C versus baseline, and a 20% decrease of triglycerides, with only minor effects on total or LDL-C. Figure 6 shows those changes versus placebo. At 6 years, the primary endpoint rate was decreased by 9.4% (NS) and non-fatal MI by 12.8% (NS). However, it should be noted that two-thirds of patients randomized to placebo received open-label lipid-lowering drugs with ability for improving outcome, making a real comparison of bezafibrate with “placebo” invalid. When patients were selected according to triglyceridaemia > 200 mg/dL, the primary endpoint was lowered by 39.5% ($P = 0.02$), despite the bias of added lipid-lowering therapy in the placebo group. A further post-hoc analysis of 1470 patients with MetS in the BIP trial⁶¹ showed for bezafibrate a significant 25% reduction in the primary endpoint, a 29% reduction in any MI and a 26% lowering of cardiac death (figure 7). In patients with augmented features of MetS (4/5 or 5/5 scores), cardiac mortality was dramatically lowered by 56% ($P = 0.005$).

FENOFIBRATE

Comparative trials of fenofibrate versus statins in primary dyslipidaemia⁶² show, as expected, a 17 to 36% decrease in LDL-C with statins, and for fenofibrate a 30 to 50% decrease of triglycerides and a 1 to 25% increase in HDL-C. Interestingly, when patient groups were split up according to initial HDL-C values⁶³, the effect of fenofibrate on both HDL-C and triglycerides increase with decreasing baseline levels of HDL-C. By contrast, the effect of the statin was not only modest on these lipid fractions, but independent of initial HDL-C. This confirms earlier findings with other fibrates and stresses the potential benefit of adding fenofibrate to patients with low baseline or residual HDL-C, as, for instance, in MetS and type 2 diabetes.

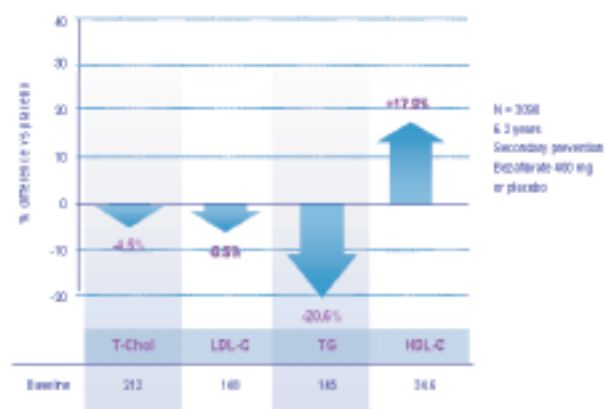


Fig. 6. – BIP lipid changes.

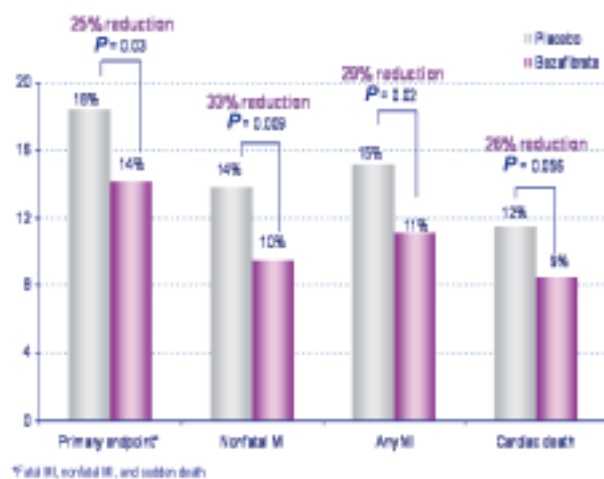


Fig. 7. – BIP clinical results.

Clinical trials exploring the combination of fenofibrate with statins^{62,64-66} reported a lowering of LDL-C by 30 to 41%, a decrease of triglycerides by 39 to 57%, and an increase of HDL-C by 3 to 19%.

Triple therapy with fenofibrate, simvastatin and ezetimibe, as investigated in 611 patients⁶⁷ with mixed hyperlipidaemia (figures 8, 9), decreased LDL-C 45%, triglycerides 50%, and increased HDL-C 19%. Interestingly, the powerful and beneficial effect on small dense LDL particles was mainly driven by fenofibrate, as their proportion decreased from 61% at baseline to 17% after 12 weeks of treatment.

Fibrates studies in diabetic patients

GEMFIBROZIL

Subgroup analysis of the VA-HIT trial⁶⁸ for diabetes ($n = 769$) showed, as expected, a higher cumulative incidence of major cardiovascular events in the diabetic group (36.5%) versus the normal fasting glucose group (21%). In patients with diabetes, gemfibrozil induced a lesser increase of HDL-C (+5% vs. +8%, $P = 0.02$) and a lesser decrease in triglycerides

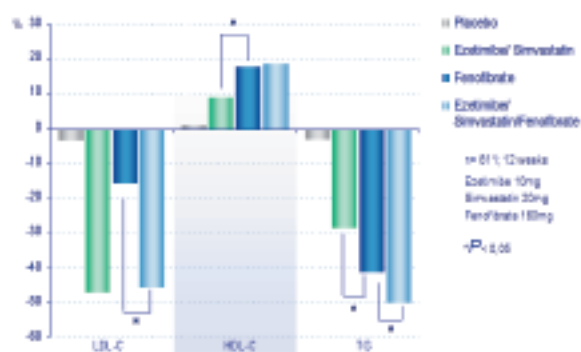


Fig. 8. – Combination fenofibrate + simvastatin + ezetimibe in mixed dyslipidaemia: effects on lipids.

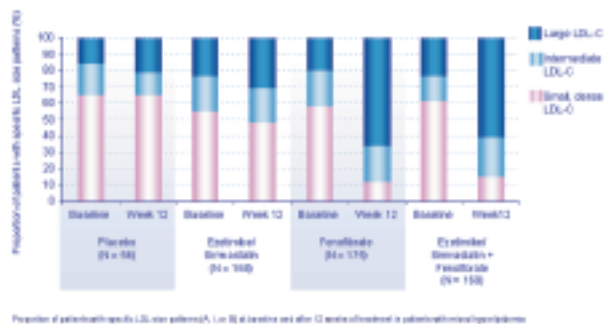


Fig. 9. – Combination fenofibrate + simvastatin + ezetimibe in mixed dyslipidaemia: effect on small dense LDL.

(–20 vs. –29, $P < 0.001$) than in normal fasting glucose patients. As in the main trial, LDL-C was not affected. Diabetic patients showed a greater benefit of gemfibrozil treatment with a 32% risk reduction (HR 0.68; 95% CI 0.53–0.88; $P = 0.004$) than those without diabetes (–18%; HR 0.82; 95% CI 0.67–1.02; $P = 0.07$). Diabetic individuals had a 41% reduction in CHD death (HR 0.59; 95% CI 0.39–0.91; $P = 0.02$) and a 40% reduction in stroke risk (HR 0.60; 95% CI 0.37–0.99; $P = 0.046$).

In the HHS study, the subgroup of type 2 diabetes ($n = 135$) was too small to draw conclusions⁶⁹, although a similar trend of benefit for diabetic patients from gemfibrozil treatment could be seen as in VA-HIT.

BEZAFIBRATE

For bezafibrate no large-scale outcome studies in diabetes are available. A small study⁷⁰ in 164 type 2 diabetic patients followed during 5 years showed a significant reduction in the combined incidence of Minnesota-coded probable ischaemic change on resting ECG and of documented myocardial infarction.

FENOFIBRATE

In patients with diabetes, fenofibrate was shown to improve the atherogenic lipid profile and certain

thrombogenic factors. Fenofibrate alone decreased triglyceride levels by 25 to 28% and increased HDL-C by 3 to 7% in the two available major studies^{71,72}. In type 2 diabetes, the combination of fenofibrate with statins lowered LDL-C by 29 to 46%, triglycerides by 32 to 50% and increased HDL-C by 11 to 34%, making this combination very attractive for this type of patients⁶². For patients with MetS, the combination of fenofibrate and simvastatin lowered triglycerides by 52% and increased HDL-C by 23%. VLDL and IDL cholesterol were lowered more than with statin monotherapy⁷³.

When comparing atorvastatin with fenofibrate in type 2 diabetic patients regarding their effects upon LDL-particles according to size⁷⁴, it appeared that atorvastatin did not change LDL subtype distribution. The statin had the strongest and significant effect on the naturally occurring large, buoyant particles (–31%) and a somewhat less pronounced but still significant effect on the most atherogenic small dense particles (–25%). In contrast, fenofibrate lowered the small dense particles significantly by 32%, while increasing the intermediate sized particles and lowering the buoyant size ones by 24%.

The effect of fenofibrate on atheroma progression was measured with computer-assisted quantitative analysis of paired angiograms in the DAIS trial (Diabetes Atherosclerosis Intervention Study)⁷¹, exploring 418 patients with type 2 diabetes during 3 years. Fenofibrate decreased LDL-C 7% and triglycerides 28%, while increasing HDL-C 8%. As shown in table 3, there was a significant 40% lesser progression in minimum lumen diameter and 42% for percentage diameter of stenotic lesions, reflecting a significant effect on focal coronary disease. There was also 25% lesser progression in mean segment diameter, indicating a therapeutic effect on diffuse disease. Although the study was not designed for hard clinical endpoints (the latter requiring massive study populations), there was a trend for lowering morbidity, mortality and invasive interventions. This study also confirmed the corrective effect of fenofibrate on LDL particle size⁷⁵, and the link between small dense particles and CAD progression. Regression analysis showed an additive effect of small LDL to the effect of LDL-C and apo-B on lesion progression. This study also confirmed the importance of HDL increase by fenofibrate in stabilisation of atheroma progression, as demonstrated in multivariate correlation analyses⁷⁶ of four major statin atheroma regression studies (ACTIVATE⁷⁷, ASTEROID⁷⁸, CAMELOT⁷⁹ and REVERSAL⁸⁰; β coefficient –0.26, CI –0.41 to –0.10, $P < 0.001$).

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study⁷² investigated the effects of fenofibrate in 9795 patients with type 2 diabetes during 5 years. More than 75% of patients were in primary prevention. Total cholesterol and LDL-C

Table 3. – DAIS: effects of fenofibrate on atherosclerotic plaque.

Results – clinical	Active N = 207	Placebo N = 211	% Risk reduction	P value
Deaths	6	9	ca. -33	NS
MI	9	12	ca. -25	NS
Angioplasty	5	13	ca. -62	NS
CABG	14	18	ca. -22	NS
All cardiac	38	50	-23	NS
Results – Angiogram	Active N = 207	Placebo N = 211	% Risk reduction	P value
Minimum lumen diameter	-0.06	-0.10	-40	0.029
% diameter	2.11	3.65	-42	0.020
Mean segment diameter	-0.06	-0.08	-25	0.171

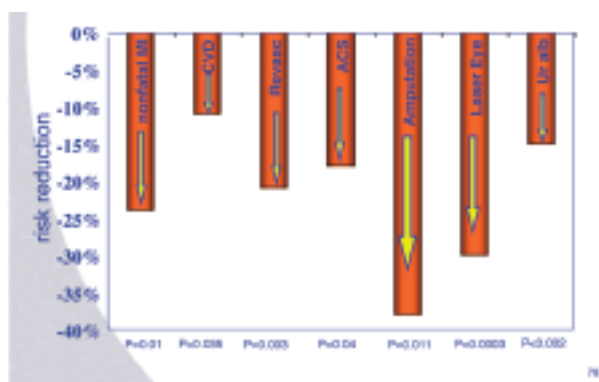


Fig. 10. – FIELD trial: clinical effects of fenofibrate.

decreased by 12%, triglycerides by 30% and HDL-C increased by 4% at 12 months. By the end of the study, the differences were 7%, 6%, 22% and 1.2% respectively, partly because of discontinuation of active treatment. These lipid changes resulted in an 11% reduction in primary endpoint ($P = 0.16$), inappropriately obscured by a 17% statin use in the placebo group versus 8% in the treatment arm. When corrected for this (not randomised) use in a time-dependent pre-specified Cox regression analysis, fenofibrate reduced the risk of coronary disease events by 19% ($P = 0.01$). For the 7664 primary prevention patients, cardiac endpoints were reduced by 25% ($P = 0.014$). There was a 24% reduction in non-fatal myocardial infarction ($P = 0.01$), with a non-significant trend in coronary mortality increase, 15% lesser albuminuria progression ($P = 0.002$), 30% lesser laser treatment for retinopathy ($P = 0.0003$) and 38% lesser non-traumatic lower limb amputations ($P = 0.04$), indicating an effective, clinical relevant and statistical significant protection against diabetic macrovascular and microvascular complications (figure 10). In the smaller group of patients in secondary prevention, no change in risk profile could be detected, suggesting that fenofibrate could be of

Table 4. – Combination fibrates + statin: incidence of rhabdomyolysis.

Number of reports of rhabdomyolysis for fibrate/statin therapies (1998-2002)			
Medication	Cases reported*	Prescriptions dispensed**	Number of cases reported per million prescriptions
Fenofibrate			
With cerivastatin	14	190,800	140
With other statins	2	3,418,080	8.58
Fenofibrate total	16	3,518,080	4.5
Gemfibrozil			
With cerivastatin	533	116,800	4808
With other statins	57	6,841,080	8.3
Gemfibrozil total	590	6,957,080	87

particular benefit in patients with early type 2 diabetes without CVD.

Further analysis of the effects of fenofibrate on VLDL and HDL subspecies in a substudy of FIELD⁸¹ showed mainly an increase in small dense more vasculoprotective HDL₃-C (+13.0% vs. placebo; 95% CI 7.5-18.3; $P < 0.001$) and HDL₃-C particle mass (+12.5% vs. placebo; 95% CI 7.2-17.9; $P < 0.001$) at 5 years versus baseline and versus placebo, together with a decrease in HDL₂-C (-27.5%; 95% CI 18.3-37.3; $P < 0.001$) and HDL₂ particle mass (-23.1; 95% CI 13.6-32.2; $P < 0.001$). For triglycerides, fenofibrate decreased mostly the large buoyant VLDL₁-TG (-46.5%; 95% CI 31.3-63.2; $P < 0.001$), but also VLDL₂-TG (-33.3%; 95% CI 20.6-45.8; $P < 0.001$) and the particle mass of VLDL₁ (-43.5%; 95% CI 29.5-59.4; $P < 0.001$), VLDL₂ (-32.5%; 95% CI 20.0-45.3; $P < 0.001$) and IDL (-12.0%; 95% CI 2.0-21.5; $P = 0.019$).

Interactions with food

Fibrates do counteract the deleterious effects of high-fat diet as shown in various animal models⁸². Combination of a fibrate with a Mediterranean diet decreased significantly Lp(a) median values from 36.5 to 8.4 mg/dL, and total cholesterol as well, showing a positive interaction with hypolipaeamic diets^{83,84}. In a study in 45 subjects no significant interaction appeared between food and fenofibrate nano tablets^{85,86}.

Combination of fibrates and statins – safety aspects

Combinations of fibrates and statins have shown in multiple trials to be effective not only on atherogenic lipid profile⁶⁴⁻⁶⁶, but both classes have also demonstrated an effect on atheroma progression (e.g. ASTEROID⁷⁸, REVERSAL⁸⁰, DAIS⁷¹). Are all statins and fibrates equivalent on safety? The answer is no, and the reason is linked to different metabolism and pharmacokinetic interactions.

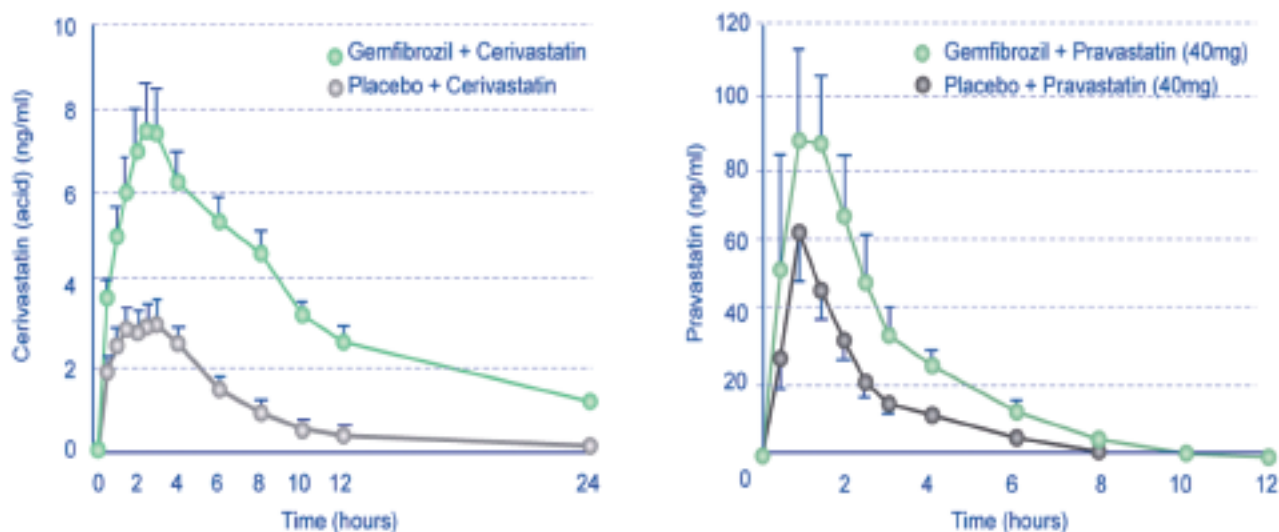


Fig. 11. – Combination gemfibrozil + statins: kinetics.

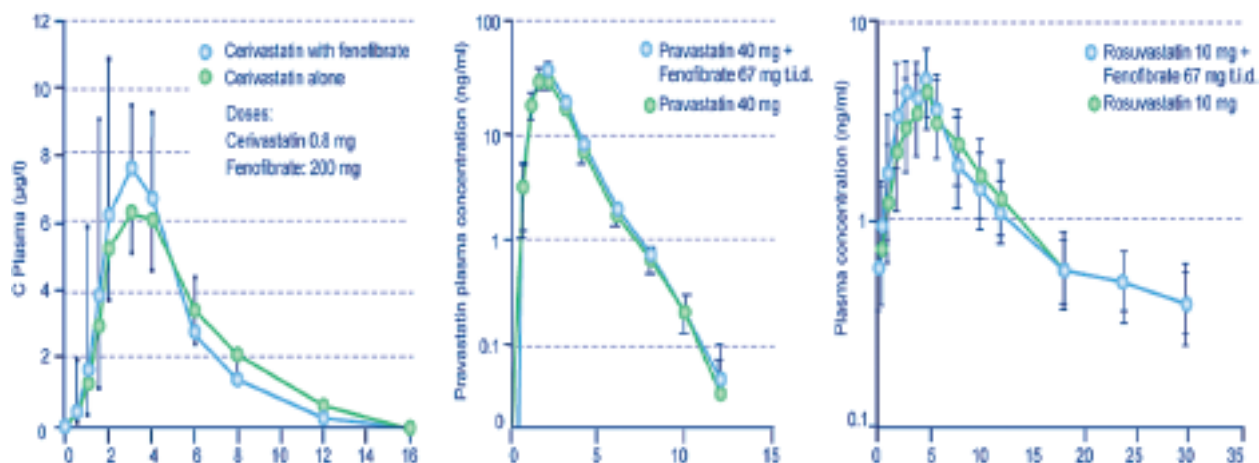


Fig. 12. – Combination fenofibrate + statins: kinetics.

Cerivastatin is well known to increase the risk of rhabdomyolysis, and was withdrawn from the market for that reason. Table 4 shows the number of reports of rhabdomyolysis to the American FDA⁸⁷ between 1998 and 2002. It appeared that the combination of gemfibrozil and cerivastatin was linked to 533 reports, corresponding to an incidence of 4600 cases per million prescriptions. On the other hand, the combination of fenofibrate with cerivastatin was associated with 14 reports, with an incidence of 140 cases per million prescriptions. The combination of fenofibrate with other statins generated only 2 reports over this 4-year period, corresponding to an incidence of 0.58 cases of rhabdomyolysis per million prescriptions. Why such a difference?

Gemfibrozil increases the plasma levels of statins, with the most pronounced effect for cerivastatin. This can be explained by inhibition of the cytochrome P450 (CYP) 2C8 and of the glucuronidation pathway of statins^{87,88}, reducing their metabolism and increasing

as a consequence their plasma levels and area under the concentration-time curve (AUC), i.e. the amount of drug available for target tissues (figure 11).

In contrast, fenofibrate does not significantly interact with the kinetic inactivation pathways of statins, and is therefore much less likely to increase their plasma concentrations and AUC^{87,89}. This is shown in figure 12 for cerivastatin⁸⁷, pravastatin⁹⁰ and rosuvastatin⁹¹, and has also been investigated for simvastatin^{92,93} and atorvastatin^{88,93}. This lack of pharmacokinetic interactions between statins and fenofibrate has relaxed the recommendations in package leaflets and allows all statin doses to be used in combination with fenofibrate⁸⁸. The recent NCEP guideline update also supports a lessening of concern regarding this combination⁹⁴. Therefore, in patients with mixed hyperlipidaemia (such as in type 2 diabetes or metabolic syndrome), fenofibrate appears to be the most appropriate fibrate choice in addition to a statin⁸⁸. The AHA/NHLBI Scientific Statement on diagnosis and

management of the metabolic syndrome⁹⁵ specifically recommends, as secondary target in treating atherogenic dyslipidaemia, non-HDL-C, and, as tertiary target, reduced HDL-C. For the former, once LDL-lowering therapy is intensified, addition of a fibrate (preferably fenofibrate) or nicotinic acid is recommended in high-risk patients, and in all patients when triglycerides > 500 mg/dL (in the latter case, even before LDL-lowering therapy). For the latter, addition of a fibrate or nicotinic acid is to be considered, following maximization of lifestyle therapies, weight reduction and increased physical activity.

Future perspectives

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial⁹⁶ is a randomized, multicentre, double 2 × 2 factorial design study involving 10 251 high-risk type 2 diabetic patients. It explores the benefits and risk of intensive glucose control, intensive blood pressure control, and the combination of fenofibrate with a statin in the management of dyslipidaemia. Its completion is expected in 2009. In the lipid trial involving 5518 patients, fenofibrate is compared with placebo on top of statin therapy. Moreover, the results of the ACCORD trial could provide substantial direction regarding the appropriate targets and techniques of risk factor management for diabetic patients.

Conclusions

- The prevalence of atherogenic dyslipidaemia is steadily increasing, and each item of the atherogenic lipid triad (low HDL-C, high triglyceridaemia and small dense LDL particle number) was shown to increase the risk of CV morbidity and mortality.

- In patients with such mixed hyperlipidaemia, statins alone were shown to decrease primarily LDL-C levels, while having little impact on the atherogenic triad. As a consequence, the residual risk in patients with low HDL-C remains high. Although they have proven to lower significantly CV morbidity and mortality for patients with cardiovascular risk, statins still leave them with a high residual risk for coronary events of more than 60%.

- Fenofibrate acts primarily on the components of the atherogenic lipid triad, and on the various dysfunctional markers associated with a metabolic syndrome and type 2 diabetes.

- Fenofibrate was shown to slow down the progression of atheromatous lesions, and to lower CV endpoints and macrovascular and microvascular complications of type 2 diabetes.

- The combination of fenofibrate with statins has proven to be safe and highly potent in lowering LDL-

C, triglycerides, small dense LDL particle numbers, and in increasing HDL-C in patients with mixed hyperlipidaemia.

- It seems therefore logical to consider combining statins and fenofibrate for patients with mixed hyperlipidaemia, metabolic syndrome and/or type 2 diabetes, with a potential rationale to use fenofibrate for intervening at the level of decreasing residual risk while on statin therapy. The ACCORD trial will provide further clinical prospective evidence for this combination.

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