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2.5 ADDENDUM TO THE CLINICAL OVERVIEW

FENOFIBRATE

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LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
ADA	American Diabetes Association
ADR	Adverse Drug Reaction
ARR	Absolute Risk Reduction
CHD	Coronary Heart Disease
HDL-C	High Density Lipoprotein Cholesterol
LDL-C	Low Density Lipoprotein Cholesterol
MAH	Marketing Authorization Holder
NCEP	National Cholesterol Education Programme
NICE	National Institute for Health and Clinical Excellence
PPAR	Peroxisome Proliferator Activated Receptor
PSUR	Periodic Safety Update Report
PVWP	PharmacoVigilance Working Party
RRR	Relative Risk Reduction
SmPC	Summary of Product Characteristics
T2DM	Type 2 Diabetes Mellitus
TC	Total Cholesterol
TG	Triglycerides

This addendum to the fenofibrate clinical overview is supportive of various changes to the current Summary of Product Characteristics (SmPC), submitted as a type II variation, to reflect:

1) The safety information coming from the most recent fenofibrate Periodic Safety Update Report (PSUR) covering the period from May 4, 2006 to November 3, 2007,

2) The overall landscape of treatment options for dyslipidemia and appropriate use of fibrates in this context.

These changes affect several sections of the SmPC, but more especially the therapeutic indications (4.1) and undesirable effects (4.8) sections. Lastly, the proposed variation considers the recommendations of the PharmacoVigilance Working Party (PVWP).

These modifications apply to all fenofibrate formulations and strengths.

2.5.1. Product Development Rationale

2.5.1.1. Pharmacological Class

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of the Peroxisome Proliferator Activated Receptor type alpha (PPARα). After oral administration, fenofibrate is rapidly hydrolysed by esterases to the active metabolite fenofibric acid. No unchanged fenofibrate can be detected in the plasma.

2.5.1.2. Target Indication

Fenofibrate is currently indicated in hypercholesterolaemia and hypertriglyceridaemia alone or combined (types IIa, IIb, IV dyslipidaemias, as well as types III and V dyslipidaemias although only a few patients have been treated during clinical trials) in patients unresponsive to dietary and other non-drug therapeutic measures (e.g. weight reduction or increased physical activity), particularly when there is evidence of associated risk factors.

Some formulations and strengths (160 and 145 mg tablets) of fenofibrate are also indicated for the treatment of secondary hyperlipoproteinaemias, if the hyperlipoproteinaemia persists despite effective treatment of the underlying disease (e.g. dyslipidaemia in diabetes mellitus).

In 2006, the PharmacoVigilance Working Party (PVWP) undertook a benefit/risk assessment of the class of fibrates with the objective of assessing the current place of fibrates in the treatment of cardiovascular and dyslipidemic diseases, and in diabetes mellitus.

The conclusion of the PVWP was that "despite the long presence of fibrates on the market, there is only little evidence of a long term clinical benefit from their use in the primary or secondary prevention of cardiovascular disease. Considering the overwhelming evidence for statins in this area, the use of fibrates as a first line treatment is no longer justified."

The PVWP also considered that "the effects of fibrates, mainly on triglycerides, as well as smaller but overall positive effect on HDL and LDL-C could suggest that some subgroups of patients could still benefit from this therapy."

Consequently, the PVWP proposed to update the SmPC of fibrates to reflect the available evidence and current clinical practice as follows:

Section 4.1 - indications:

"<Name of medicinal product> is indicated as supportive therapy for a diet or other non-medicinal therapy (e.g. sporting activity, weight loss) for the following diseases:

- *severe hypertriglyceridaemia,*
- *mixed hyperlipidaemia where a statin is contraindicated or not tolerated."*

In parallel, PVWP also recommended to add in Section 5.1 "Pharmacodynamic properties" of the SmPC the following text:

"There is evidence that treatment with fibrates reduces the incidence of serious events with coronary heart disease but there are no prove of any positive effect with regard to overall mortality in the primary or secondary prevention of cardiovascular disease."

2.5.1.3. Scientific Rationale for the Drug

Not applicable.

2.5.1.4. Brief Summary of Development Program

Since its first launch in 1975, fenofibrate has been marketed in more than 60 countries for more than 30 years.

Fenofibrate is available either in the form of capsules or tablets. Several formulations and strengths are available in Europe.

Table 1: Formulations of fenofibrate

Standard	**Micronised**		**Nanoparticles**
Capsules	Capsules	Tablets	Tablets
100 mg	67 mg		
300 mg	200 mg	160 mg	145 mg
(250 mg)	267 mg	215 mg	

2.5.2. Overview of Biopharmaceutics

Not applicable.

2.5.3. Overview of Clinical Pharmacology

Not applicable.

2.5.4. Overview of Efficacy

This review of efficacy will be focussed on the co-administration of fenofibrate and HMG-CoA reductase inhibitors or statins through a comprehensive description of clinical studies published in the literature and/or carried out by the Marketing Authorisation Holder and other pharmaceutical companies. Together with current guidelines, the submitted data support the new indications for fenofibrate in monotherapy in patients with mixed dyslipidemia when statins are contra-indicated or not tolerated, as well as the extended claim that fenofibrate is also indicated as an adjunct to statins in these patients or those with high cardiovascular risk who are not appropriately controlled with a statin alone. We also consider that similar to patients with severe hypertriglyceridemia, patients with moderate hypertriglyceridemia associated to low HDL-C levels or high cardiovascular risk should also benefit from fenofibrate treatment.

2.5.4.1. Supportive clinical trials

From 1990 to 2008, a large number of publications or studies have reported the efficacy of fenofibrate and statins taken together in comparison with the use of either agent alone.

This includes a literature search that was carried out at the end of 2007 where most of the results where obtained with the recommended dose of fenofibrate (200 mg micronised capsule or 160 mg micronised tablet) and with moderate doses of several statins (see Appendix 1).

The population evaluated consisted in general of patients with marked lipid anomalies and high cardiovascular risk. However, early studies were of small size, not randomised or with various study designs.

When limited to randomised studies, the characteristics of 22 studies carried out with a total of 3 954 patients receiving combination therapy are given in Table 2. Most of these patients had combined or mixed hyperlipidemia and/or diabetes. With the exception of T2DM patients in UKLDS (stopped after withdrawal of cerivastatin in August 2001), baseline values of total

cholesterol were about 250 mg/dL. Conversely, baseline triglycerides covered a wide range of values from bout 150 mg/dL to 300 mg/dL (Table 3).

Table 2: Description of randomised studies and reports in combination with statins

Ref.	Study, reference	Design	Length mo	Population	Statin in coprescription	Statin in monotherapy	Fenofibrate monotherapy
[1]	Widimsky 1998	Open, 2-arm	6	mixed hyperlipidemia CHD	Fl 20 n=57	Fl 40 n=59	
[2]	Farnier 1999	DB, 3-arm	2	Hypercholesterolemia CHD or ≥ 2 RF for CHD	C0.3 n=115	C0.3 n=115	200M n=112
[3]	Widimsky 1999	Open, 2-arm	18	mixed hyperlipidemia CHD	Fl 20 n=52	Fl 40 n=52	-
[4]	Farnier 2000	DB, 3-arm	4	Hyper cholesterolemia	(Fl 20, Fl 40) n=69	-	200M n=33
[5]	Athyros 2002	Open, 3-arm	6	T2DM, no CHD Combined hyperlipidemia	A20 n=40	A20 n=40	200M n=40
[6]	CCER 9902 2002	DB, 2-arm	3	patients not controlled with a statin	C0.4 n=167	C0.4 n=36	
[7]	CCER 9903 2002	DB, 2-arm	3	patients not controlled with a fibrate	C0.2-0.4 n=175	-	160T n=25
[8]	UKLDS 2003	DB, 4-arm*	24	T2DM no CHD	C0.4 n=1037	C0.4 n= 1038	200M n=1042
[9]	Vega 2003	DB, Cross-over, 3-arm*	3	Combined hyperlipidemia	S10 n=20	S10	
[10]	Derosa 2004	DB,2-arm	12	Combined hyperlipidemia T2DM CHD	Fl 80 n=25	Fl 80 n=23	
[11]	Durrington 2004	Open, 4-arm	6	mixed hyperlipidemia T2DM	R5-10 n=113	R10,20,40 n=51	67Mx1,2,3 n=49
[12]	Athyros 2005	Open, 3-arm	12	MetS	A20 n=100	A20 n=100	200M n=100
[13]	Grundy 2005	DB, 2-arm	3	mixed hyperlipidemia	S20 n=411	S20 n=207	

Ref.	Study, reference	Design	Length mo	Population	Statin in coprescription	Statin in monotherapy	Fenofibrate monotherapy
[14]	Koh 2005	DB, Cross-over, 3-arm	2	mixed hyperlipidemia	A10 n=56	A10	200M
[15]	Ren 2005	Open, 3-arm	3-6	mixed hyperlipidemia CHD or RF	S10 n=81	S10 n=72	200M n=68
[16]	Farnier 2006	DB, 2-arm	3	mixed hyperlipidemia High CHD risk	P40 n=124	P40 n=124	
[17]	Muhlestein 2006	DB, 3-arm	3	mixed hyperlipidemia T2DM	S20 n=100	S20 n=100	160T n=100
[18]	Farnier 2007	DB, 4-arm*	3	Mixed hyperlipidemia	(S20+eze10) n=183	S20 +eze10 n=184	160T n=184
[19]	Shah 2007	Open, 4-arm	3	Acute coronary syndrome	(A10, S20) n=50	A20, S40 n=52	

*: inclusion of a placebo arm; DB double-blind; A atorvastatin; C cerivastatin; Fl fluvastatin; P pravastatin; R rosuvastatin; S; simvastatin; eze ezetimibe; Std, M or T formulation of fenofibrate; FA fenofibric acid; NA not available; CHD coronary heart disease; T2DM type 2 diabetes mellitus; MetS metabolic syndrome; RF risk factors.

As shown in Table 3, combination therapy generally led to superior effects on lipids as compared to therapy with statins or fenofibrate alone. As compared with statin monotherapy, co-administration of a fibrate and a statin adds mostly on TG (about 20 %*) and HDL-cholesterol (about 10%) with less effect on LDL-cholesterol (about 5 %*). Conversely, as compared with fenofibrate monotherapy, a statin adds mostly on LDL-C (about 25 %*) with less effect on triglycerides (about 10 %*) and HDL-C (about 2 %*).

* median changes from all studies/arms where statins were used at the same dose in monotherapy and co-prescription

Table 3: Baseline Total cholesterol and Triglyceride levels and changes in HDL-C and TG with combination therapy fenofibrate-statins versus monotherapies

Ref.	Study, reference	Design	Base-line TC	Base-line TG	% point Δ LDL-C versus		% point Δ HDL-C versus		% point Δ TG versus	
					statin	feno	statin	feno	statin	feno
[1]	Widimsky 1998	0pen, 2-arm	260	260	4	-	14	-	23	
[2]	Farnier 1999	DB, 3-arm	NA	NA	13	20	6	0	27	5
[3]	Widimsky 1999	Open, 2-arm	268	260	-1		16		20	
[4]	Farnier 2000	DB, 3-arm	364	154		Fl20 11 Fl40 20		Fl20 10 Fl40 -1		Fl20 11 Fl40 20
[5]	Athyros 2002	Open, 3-arm	253	279	6	31	13	6	20	9
[6]	CCER 9902 2002	DB, 2-arm	243	232	4		5		16	
[7]	CCER 9903 2002	DB, 2-arm	243	276		25		3		14
[8]	UKLDS 2003	DB, 4-arm*	191	137	5	23	0	-2	24	10
[9]	Vega 2003	DB, Cross-over, 3-arm*	273	321	-3		17		29	
[10]	Derosa 2004	DB,2-arm	263	156	10		20		15	
[11]	Durrington 2004	Open, 4-arm	246	327	R5 -13 R10 -5	R5 35 R10 43	R5 5 R10 6	R5 2 R10 3	R5 11 R10 17	R5 7 R10 13
[12]	Athyros 2005	Open, 3-arm	232	195	4	28	15	4	14	6
[13]	Grundy 2005	DB, 2-arm	257	232	5		9		23	
[14]	Koh 2005	DB, Cross-over, 3-arm	239	320	-10	24	15	-8	32	2
[15]	Ren 2005	Open, 3-arm	275	310	7	23	20	5	51	11
[16]	Farnier 2006	DB, 2-arm	NA	NA	6		5		21	

Ref.	Study, reference	Design	Base-line TC	Base-line TG	% point Δ LDL-C versus		% point Δ HDL-C versus		% point Δ TG versus	
					statin	feno	statin	feno	statin	feno
[17]	Muhlestein 2006	DB, 3-arm	229	283	-2	23	5	2	21	4
[18]	Farnier 2007	DB, 4-arm*	254	228	-1	30	10	1	21	9
[19]	Shah 2007	Open, 4-arm	153	140	-14 -1		24 0		22 8	

*: Percent-point incremental changes in TG, HDL-C and LDL-C with co-administration as compared with monotherapy were determined for each study. The changes were calculated using results obtained in parallel arms on monotherapy. Positive figures are understood as an improvement (decrease in TG or LDL-C or increase in HDL-C), negative figures meaning the opposite.

The lipid levels that would trigger the use of combination therapy remain to be established in a large scale clinical trial; however, insights have been obtained from the FIELD study where the largest absolute (ARR) and relative (RRR) risk reductions of cardiovascular events have been obtained in participants with TG>200 mg/dL and low HDL-C (<40 mg/dL in males and 50 mg/dL in females) (Table 4). Allocation to fenofibrate led to a 4.3% ARR and a 26% RRR in those with moderate hypertriglyceridemia and low HDL-C, independent of whether a statin was added or not.

Table 4: Total cardiovascular events absolute and relative risk reductions with fenofibrate in FIELD

population	5 yr risk in placebo	Absolute risk reduction with fenofibrate	Relative risk reduction	NNT	p
Low HDL-C and TG>200 mg/dL n=2 014	17.8%	4.3%	26%	23	0.007
TG>200 mg/dL n=2 517	17.2%	3.8%	24%	26	0.007
Dyslipidemia * n=3 710	16.3%	2.3%	14%	43	0.06
Low HDL-C N=5 820	15.1%	2.1%	14%	48	0.02
All n=9 795	13.9%	1.4%	11%	70	0.035

*: low HDL-C (<40 mg/dL in males and 50mg/dL in females) and TG >150 mg/dL.

NNT number needed to treat for 5 years to avoid a first cardiovascular event (Cardiovascular death, non fatal MI, non fatal stroke, coronary and carotid revascularisations) [20] - [21].

These results support the use of fenofibrate to reduce cardiovascular events in patients at high cardiovascular risk, such as those with Type 2 diabetes, with moderate hypertriglyceridemia and low HDL-cholesterol, receiving a statin or not or that remain at high residual cardiovascular risk despite being treated with statins.

A similar consideration was included in the letter accompanying the assessment report of the PVWP (see July 1st, 2008 letter from BfArM) as well as in recently published meta-analysis or studies [22] to [25] that re-emphasize the clinical relevance of TG and HDL-C in cardiovascular risk.

The meta-analysis of Sarwar N et al reported the association between risk of coronary heart disease and triglycerides in follow-up of the Reykjavik and EPIC Norfolk studies as well as in 262,525 patients from 27 other studies covering a total of 262,525 participants including 10,158 CHD cases and a mean follow-up of 12 years [22]. After adjustment for age, gender, smoking, lipids and blood pressure, the risk for CHD was 1.7 times higher in the upper tertile (>2 mmol/L 177 mg/dL) as compared with the lower tertile of TG (<1.33 mmol/L 118 mg/dL). It was concluded that there was a consistently moderate and highly significant association between triglyceride levels values whether fasting and non-fasting and risk of coronary heart disease in both genders.

In the Women's Health Study [23] fasting and non-fasting triglyceride levels were associated with incident cardiovascular events in the 11-year follow-up of 26,609 initially healthy US women, after adjustment for age, blood pressure, smoking, use of hormone replacement therapy, total and HDL-C. After further adjustment for presence of diabetes, body mass index and CRP, the hazard of CVD events was 2 times higher in the upper quintile of non fasting TG (>215 mg/dL) as compared to the lower quintile (<85 mg/dL).

In the Copenhagen City Heart Study [24] 13 981 men and women from the general population were followed for 26 years. The multifactorial hazard ratios for myocardial infarction or all cause mortality for each 1 mmol/L (0.89 g/L) increase in non-fasting TG were significant, 1.20 and 1.18 respectively. In men, the multifactorial hazard ratios for all cause mortality associated with the same increase in nonfasting TG was 1.08 and also statistically significant.

In the MELANY (MEtabolic, Lifestyle, And Nutrition assessment in Young adults) 13 953 apparently healthy young men aged 26 to 45 years in the Israel Defense forces had 2 measurements of TG on inclusion and at 5 years with a subsequent 5-year follow-up [25]. Over 10 years, 158 cases of CHD were identified with coronary angiography. A decrease in initially elevated TG (>148 mg/dL) with life-style therapeutic measures was associated with a decrease in CHD risk compared with stable high levels; however, the risk remains higher than in those with persistently low TG (<90 mg/dL).

Although there is no clear threshold above which elevated triglyceride levels confer an increased cardiovascular risk, such cutpoints are given in the next section about guidelines to define severe (in general 400 mg/dL) and moderate hypertriglyceridemia (in general 150 - 200 to 400 mg/dL).

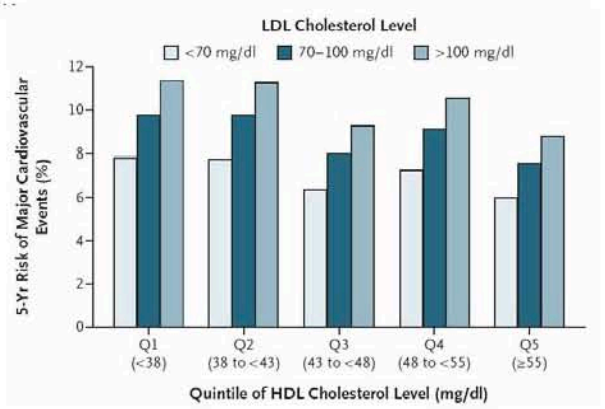
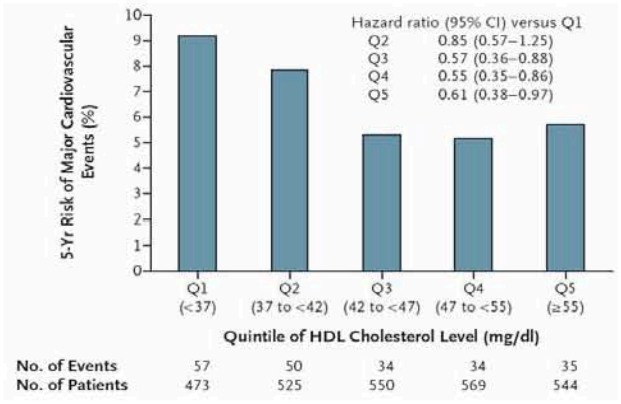
In addition to these epidemiological studies, two recent post hoc analyses from major outcome trials with statins have shed light on the relationship of TG and HDL-C to cardiovascular risk in patients whose LDL-C has been reduced to levels below 100 mg/dL.

The first of these analyses [26] comes from the TNT trial (Treating to New Targets) and examined the relationship between the frequency of major cardiovascular events and HDL cholesterol levels in CHD patients treated with statins and investigated whether any observed relationship was maintained when LDL cholesterol was reduced below 70 mg/dL.

The TNT trial was a randomised, multicenter, double-blind, parallel-group trial conducted in 10,001 patients with clinical CHD and LDL-C levels < 130 mg/dL (3.4 mmol/L) who were randomized to 10 mg or 80 mg of atorvastatin per day and followed for a median of 4.9 years. The primary endpoint was the occurrence of a first major cardiovascular event, defined as death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke. In this post hoc analysis, the 9770 subjects in the TNT trial for whom HDL cholesterol data were available were stratified into quintiles based on their HDL-C levels determined at month 3 of the double-blind treatment phase. The expected 5-year risk of major cardiovascular events was determined for each quintile of HDL-C level using both univariate and multivariate models to adjust for important covariates. It was also determined for specific LDL-C strata, including subjects with LDL-C levels below 70 mg/dL (1.8 mmol/L). The covariates considered in the analyses were sex, age, smoking status, body-mass index, systolic blood pressure, fasting glucose level, LDL-C level, triglyceride level, ratio of apolipoprotein B to apolipoprotein A-I, LDL-C and triglyceride levels at month 3 of the trial, and the presence or absence of a history of diabetes, myocardial infarction, cardiovascular disease, and hypertension.

These analyses yielded the following results:

- After adjustments for covariates, the cardiovascular event rate was reduced by 25% in the highest HDL-C quintile compared with the lowest (HR, 0.75; 95% CI, 0.60 to 0.95), meaning that the quintile of HDL-C level was a significant predictor of major cardiovascular events (p=0.04 across HDL-C quintiles).
- The relationship between HDL-C levels and the frequency of major cardiovascular events was also apparent in each of the two atorvastatin treatment groups (10 mg and 80 mg), as the frequency of major cardiovascular events increased with decreasing levels of HDL-C.

• In a stratified regression analysis to determine the interaction between HDL-C and LDL-C levels in patients receiving statins, **the quintile of HDL-C level remained a significant predictor of major cardiovascular events (P = 0.05),** with no evidence of interaction with the quintile of LDL cholesterol level (P = 0.67).	
In the lowest LDL cholesterol stratum group (<70 mg/dL): • The risk of a major cardiovascular event differed significantly among quintiles of HDL-C levels (P=0.03) • Subjects in the highest HDL-C quintile had a lower risk of major cardiovascular events than subjects in the lowest quintile (hazard ratio, 0.61; 95% CI, 0.38 to 0.97).	

This analysis showed that patients with coronary heart disease treated with statins remain at risk for subsequent CV events even when LDL-C is at target and that HDL-C levels are a significant predictor of major cardiovascular events in statin-treated patients, even when LDL-C is very low (< 70 mg/dL).

The second analysis comes from the PROVE-IT trial and looked at the impact of on-treatment TG on CHD risk following Acute Coronary Syndrome. 4,162 patients were enrolled in the PROVE IT-TIMI 22 (Pravastin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction) trial. Patients hospitalised for ACS were randomised to receive intensive therapy (atorvastatin 80 mg/d) or standard therapy (pravastatin 40 mg/d). The composite primary endpoint was death, MI or recurrent ACS. Of the 4,162 patients initially enrolled in the PROVE IT-TIMI 22 trial, the present analysis focuses on the incidence of death, MI, or rehospitalization for ACS

occurring after an interval of 30 days following the initial ACS event, with follow-up through 2 years. A number of 3,718 patients were thus considered in this analysis.

This analysis yielded the following results:

- Low on-treatment TG (<150 mg/dl) was associated with reduced CHD risk compared with higher TG (hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.62 to 0.87; $p < 0.001$),
- For each 10-mg/dl decrement in on-treatment TG, the incidence of death, MI, and recurrent ACS was lower by 1.6% ($p < 0.001$),
- Lower CHD risk was observed with TG < 150 mg/dl and LDL-C < 70 mg/dl (HR 0.72, 95% CI 0.54 to 0.94; $p = 0.017$) compared with higher levels of each variable,
- Lower CHD risk was observed with low on-treatment TG, LDL-C, and C-reactive protein (< 2 mg/l) (HR 0.59, 95% CI 0.41 to 0.83; $p = 0.002$) compared with higher levels of each variable.

Similar to the TNT trial, patients treated with statins after ACS were found to be at residual risk for CHD even when LDL-C was at target. TG play a significant role in CHD and clinical studies suggest that TG is a predictor of risk of future CHD events.

Taken together, the results from these two major statin trials provide a strong clinical rationale to consider treating residual risk due to low HDL-C levels and/or elevated TG levels with drugs that address these components of atherogenic dyslipidemia such as fenofibrate.

2.5.4.2. Existing guidelines and new proposed indication

Several existing guidelines are useful documents to guide prescription of lipid lowering drugs as they define the populations, the choice of treatment, when to intervene and the goals of therapy (reference).

The **European guidelines on cardiovascular disease prevention** do not recommend specific intervention values or treatment goals for TG and HDL-C, but HDL-C <1 mmol/L (40 mg/dL) in men and <1.2 mmol/L (45 mg/dL) in women, and, similarly, fasting TG >1.7 mmol/L (150 mg/dL) serve as markers of increased cardiovascular risk [28]. Values of HDL cholesterol and triglycerides should also be used to guide the choice of drug therapy.

We report below the relevant sections of the NCEP and French guidelines for treatment of general lipid disorders as well as the ADA and the recent NICE guidelines for the treatment of diabetes.

The **NCEP guidelines** [29] recommend the following:

In all persons with low HDL-C, the primary target is LDL-C and ATPIII guidelines should be followed to achieve the LDL-C goal. After the LDL-C goal has been reached, emphasis shifts to weight reduction and increase physical activity. When a low HDL-C is associated with high TG (200 - 499 mg/dL), secondary priority goes to achieving the non-HDL-C goal. If TG are < 200 mg/dL (isolated low HDL-C), fibrates or nicotinic acid can be considered, however such treatment should be reserved for persons with CHD and CHD risk equivalents.

In diabetic dyslipidemia, when LDL-C are in the range of 100 - 129 mg/dL at baseline or on treatment, several therapeutic options are available: increasing intensity of LDL-lowering therapy, adding a drug to modify atherogenic dyslipidemia such as a fibrate or nicotinic acid, or intensifying control of other risk factors including hyperglycemia.

The **French Authorities (AFSSAPS 2005) guidelines** [30] recommend that:

In primary or mixed hypercholesterolemia, inhibitors of cholesterol absorption, fibrates or nicotinic acid can be used.

The prescription of a fibrate can be justified in secondary prevention when diet measures are insufficient in patients with elevated TG, LDL-C <1g/L (2.6 mmol/L) and HDL <0.4 g/L (1.03 mmol/L).

The treatment of some high-risk patients can necessitate the combination of lipid lowering drugs. The choice of the combination depends upon the residual lipid abnormalities on monotherapy. To act on TG and HDL-C, the association of statin and nicotinic acid is possible. The association of a statin and fenofibrate, although classically not recommended, can be discussed after advice of a specialist. It necessitates regular and rigorous clinical and biological monitoring.

The **French Society of Atherosclerosis guidelines** [31] further describes the conditions to associate fibrates and statins when monotherapy with a lipid agent is insufficient to reach the recommended therapeutic targets:

- In patients not at goal on statin therapy:
  - with normalized LDL-C ,but TG and/or HDL-C not at goal: 1) reinforce life style therapeutic measures, 2) if TG >2.5 g/L and HDL-C <0.35 g/L in men and 0.40 g/L in women, associate statin plus a fibrate to the exclusion of gemfibrozil or statin plus nicotinic acid;
  - with LDL-C, TG and HDL-C not at goal: priority is to be given to LDL-C goal: 1) moderate TG elevation, use statin plus ezetimibe, 2) marked TG elevation with LDL-C close to therapeutic goal, use statin plus a fibrate or statin plus nicotinic acid if LDL-C exceed the goal

by more than 10%, 3) in very severe mixed hyperlipidemia high-risk patients and after specialist advice, consider tritherapy statin plus ezetimibe plus fibrate or nicotinic acid;

- In patients not at goal on fibrate or nicotinic acid:
  - Fibrate and statin co-prescription, which gives marked LDL-C reduction as compared to fibrate monotherapy, is especially interesting in subjects with elevated LDL-C and high cardiovascular risk;
  - Fibrate and ezetimibe as a second option to reduce LDL-C but without additional effect on TG and HDL-C.

The **ADA guidelines** recommend in people with diabetes [32]:

- lowering triglycerides and increasing HDL-C with a fibrate is associated with a reduction in cardiovascular events in patients with clinical CVD, low HDL- and near normal levels of LDL-cholesterol;
- combination therapy employing statin and fibrates or niacin may be necessary to achieve lipid targets but has not been evaluated in outcomes studies for either CVD event reduction or safety.

The **NICE guidelines** for the treatment of diabetes (NICE 2008) [33] include in Section 1.10.2 a recommendation on the use of fibrates.

- If there is a history of elevated serum triglycerides, perform a full fasting lipid profile (including HDL cholesterol and triglyceride estimations) when assessing cardiovascular risk annually.
- Assess possible secondary causes of high serum triglyceride levels, including poor blood glucose control (others include hypothyroidism, renal impairment and liver inflammation, particularly from alcohol). If a secondary cause is identified, manage according to need.
- Prescribe a fibrate (fenofibrate as first-line) if triglyceride levels remain above 4.5 mmol/L despite attention to other causes. In some circumstances, this will be before a statin has been started because of acute need (that is, risk of pancreatitis) and because of the undesirability of initiating two drugs at the same time.
- If cardiovascular risk is high (as is usual in people with type 2 diabetes), consider adding a fibrate to statin therapy if triglyceride levels remain in the range 2.3 - 4.5 mmol/L despite statin therapy.

When considering the recent clinical study results and existing guidelines presented previously, we propose the following indications for fenofibrate:

<Name of medicinal product> is indicated as supportive therapy for a diet or other non-medicinal therapy (e.g. sporting activity, weight loss) for the following diseases:

- severe hypertriglyceridaemia, ***or moderate hypertriglyceridemia when associated with low HDL cholesterol and high cardiovascular risk***.
- mixed hyperlipidaemia where a statin is contraindicated or not tolerated, ***or for patients at high cardiovascular risk who are not appropriately controlled with a statin alone***.

2.5.5. Overview of Safety

2.5.5.1. Safety of clinical trials

This review of safety of fenofibrate in clinical trials in support of the requested indications includes:

- The description of muscle and liver safety in clinical studies with combination of fenofibrate published in the literature and/or carried out by the MAH and other pharmaceutical companies.
- A summary of selected clinical and biological safety findings in FIELD over 5 years, where by the end of treatment 34% of placebo-allocated patients and 18% of fenofibrate-allocated patients were taking a statin.

In the fenofibrate and statin co-administration studies published in the literature, the frequency of adverse events and more particularly of clinical or laboratory muscular adverse events was reported as low (Table 5) and does not appear to be modified as compared with monotherapies.

Even, in the UKLDS where 1 037 patients received the co-administration of fenofibrate and cerivastatin for an average duration of 12 months, no cases of myositis or rhabdomyolysis were reported. The frequency of muscle pain did not differ between the 4 groups. Only one patient had elevated CK levels > 10 x UNL once [8]. In the SAFARI study [13], of the 411 patients receiving the fenofibrate-simvastatin co-administration, two cases of CK > 5-10 x UNL without symptoms and one case of CK >10 x UNL occurred.

Table 5: CK and transaminase elevations reported in the 45 studies* reporting safety data of fenofibrate-statin co-administration (3 626 subjects)

N [95% Confidence Interval]	Fenofibrate + Statins N=3 626	Statins N=2 964	Fenofibrate N=2 363
Significant CK elevation (>5 UNL)	14 [0.2%; 0.6%]	3 [<0.1%; 0.2%]	9 [0.1%; 0.7%]
– leading to withdrawal	1	-	-
Significant myalgia	82 [1.8%; 2.7%]	110 [3.0%; 4.4%]	55 [1.7%; 2.9%]
– leading to withdrawal	8	4	-
Significant transaminase ALT elevation (>3 UNL)	37 [0.7%; 1.3%]	5 [<0.1%; 0.4%]	9 [0.1%; 0.7%]
– leading to withdrawal	5	-	-

*: No safety data in Reiber 1997, Ellen 1998 and Stefanutti 2004.

As shown in Table 6, the distribution of events of interest in the FIELD study between placebo- and fenofibrate-allocated subjects did not differ between those who eventually received a statin and those who did not. Indeed as all events occurring from randomization to close-out were considered and subjects received statins for an average of 2 years, these percentages do not reflect what would have been these events with combination therapy over 5 years. Conversely, the 2 events reported as rhabdomyolysis occurred prior to introduction of a statin. Even if current practice now recommends initiating statin therapy first, the FIELD results provide reassurance on the safety on fenofibrate-statin combination.

Table 6: Selected Clinical and Biological Adverse Events Observed with Combination Therapy Reported during the Randomized Period (FIELD report Table 65 p 253) [34-FIELD]

	Placebo N=4 900 a		Fenofibrate N=4 895 b	
Statins	N=**1 649**	**%**	N=**884**	**%**
CK<=5xULN	258	15.6	169	19.1
5<CK<=10xULN	2	0.1	1	0.1
CK>10xULN	1	<0.1	2	0.2
myositis	0	0	1	0.1
rhabdomyolysis	1	<0.1	1	0.1
ALT>3xULN	8	0.2	7	0.8
Hepatitis	2	0.1	0	0
pancreatitis	9	0.5	13	1.5
Creatinine >200 µmol/L	26	1.6	21	2.4
Need for dialysis	9	0.5	4	0.3
Study medication only	N = **3 099**	**%**	N = **3917**	**%**
CK<=5xULN	442	14.3	694	17.7
5<CK<=10xULN	5	0.2	10	0.3
CK>10xULN	1	<0.1	2	<0.1
myositis	1	<0.1	1	<0.1
rhabdomyolysis	0	0	2	<0.1
ALT>3xULN	29	0.6	15	0.3
Hepatitis	6	0.2	7	0.2
pancreatitis	12	0.4	26	0.7
Creatinine >200 µmol/L	20	0.6	52	1.3
Need for dialysis	11	0.4	13	0.3

a: 33 missing data for CK, 31 missing data for ALT and creatinine; b: 42 missing data for CK, 39 missing data for ALT and creatinine.

Despite the satisfactory safety of fenofibrate-statin combination therapy shown in clinical trials and in accordance with most recent analyses of databases of health authorities [35] or managed care organisations [36], [37], the general warnings on safety of fibrates or fenofibrate when given together with statins should continue to be included in the labelling to caution prescribers and patients (see Section 4.4 **"Special warnings and special precautions for use"**).

"The risk of muscle toxicity may be increased if the drug is administered with another fibrate or an HMG-CoA reductase inhibitor, especially in cases of pre-existing muscular disease. Consequently, the co-prescription of fenofibrate with a statin should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease. This

combination therapy should be used with caution and patients should be monitored closely for signs of muscle toxicity."

As very few data are available on the safety of combination with the highest registered doses of statins e.g. atorvastatin or simvastatin 80 mg/day, such combinations should then be used with extreme caution and restricted to specialists [38].

2.5.5.2. Other safety information

The data presented in the most recent fenofibrate PSUR (May 2006 to November 2007) led to the conclusion that some changes in the characteristics of listed Adverse Drug Reactions and warnings were necessary. The Core Company Safety Information (CCSI) was therefore amended accordingly.

In addition, some editorial adaptations, changes for consistent wording and enhanced readability as well as revisions to meet the requirements of the first revision of the guideline on Summary of Product Characteristics issued in October 2005 by the European Commission were implemented in the CCSI.

In order to reflect the current safety knowledge on fenofibrate we propose to modify, in parallel to the CCSI, the fenofibrate SmPC:

2.5.5.2.1. Contra-indications

Under contra-indications, the following changes are proposed (changes in ***bold italics***):

- Hepatic insufficiency (including biliary cirrhosis ***and unexplained persistent liver function abnormality***).
- Hypersensitivity to ~~fenofibrate~~ **the active substance or to any** ~~component of this medication~~ **of the excipients**.

Regarding use during pregnancy and lactation and to comply with the guideline on Summary of Product Characteristics, we propose to delete the reference to the Section 4.6 from the contra-indication section.

2.5.5.2.2. Special warnings and precautions for use

In this section, we propose the following changes:

Liver function

It is recommended that transaminase levels ~~be~~ ***are*** monitored every 3 months during the first 12 months of treatment ***and thereafter periodically***. Attention should be paid to patients who develop increase in transaminase levels and therapy should be discontinued if ASAT (SGOT) ***and ALAT (SGPT) levels increase to more than 3 times the upper limit of the normal range. When symptoms indicative of hepatitis occur (e.g. jaundice, pruritus), laboratory tests are to be conducted for verification and discontinuation of fenofibrate therapy may be considered.***

Renal function

Treatment should be interrupted in case of an increase in creatinine levels > 50% of UNL (upper limit of normal). It is recommended that creatinine ***is*** measure~~dment may be considered~~ during the first 3 months after initiation of treatment ***and thereafter periodically (for dose recommendations see 4.2 Posology and method of administration).***

2.5.5.2.3. Interactions

In this section some more details have been added to the section relative to Cytochrom P450 enzymes.

Cytochrome P450 enzymes: *In vitro* studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Patients co-administered fenofibrate and CYP2C19 and CYP2A6, and especially CYP2C9 metabolised drugs with a narrow therapeutic index should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

2.5.5.2.4. Undesirable effects

Section 4.8 was checked for concise and specific wording including MedDRA coding. The frequency categories were derived from the integrated safety database with overall 3 273 patients participating in placebo-controlled studies (fenofibrate n = 2 344; placebo n = 929). To follow recommendation from the guidance, the format was modified.

Additional amendment concerns the conclusion drawn from the signal evaluation on hypersensitivity.

Hypersensitivity

Further to the identification of a number of effects reported as a variety of terms associated with hypersensitivity, the CCSI section undesirable effects was amended as follows:

Skin and subcutaneous tissue disorders: Cutaneous hypersensitivity (e.g. rashes, pruritus, and urticaria).

Immune system disorders: hypersensitivity.

To follow this recommendation, we propose to modify the SmPC in Section 4.8 (undesirable effects) accordingly.

Tabulated summary of adverse reactions

In this section, the following changes are proposed (changes in ***bold italics***):

The most commonly reported ADRs during <Tradename> therapy are digestive, gastric or intestinal disorders.

The following undesirable effects have been observed during placebo-controlled clinical trials (n=2 344) with the below indicated frequencies:

MedDRA system organ class	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000, <1/1,000	Very rare <1/10,000 incl. isolated reports
Blood and lymphatic system disorders			~~Decrease in~~ Haemoglobin ~~and leukocytes~~ decreased ***White blood cell count decreased***	
Immune system disorder			***Hypersensitivity***	
Nervous system disorders		***Headache***	~~Sexual asthenia~~ ~~Headache~~	
Vascular disorders		Thromboembolism (pulmonary embolism, deep vein thrombosis)*		
~~Respiratory, thoracic and mediatinal disorders~~				~~Interstitial pneumopathies~~
Gastrointestinal disorders	~~Digestive, gastric or intestinal disorders~~ ***Gastrointestinal signs and symptoms*** (abdominal pain, nausea, vomiting, diarrhoea, flatulence)	Pancreatitis*		
Hepatobiliary disorders	~~Moderately elevated levels of~~ Transaminases ***increased***	~~Development of gallstones~~ ***Cholelithiasis***	***Hepatitis***	~~Episodes of hepatitis~~
Skin and subcutaneous tissue disorders		***Cutaneous hypersensitivity (e.g.*** Rashes, pruritus, urticaria, ~~photosensitivity reactions)~~	Alopecia ***Photosensitivity reactions***	~~Cutaneous photosensitivity with erythema, vesiculation or nodulation~~
Musculoskeletal, connective tissue and bone disorders		***Muscle disorder (e.g. myalgia, myositis, muscular spasms and weakness)***	~~Diffuse Myalgia, myositis, muscular cramps and weakness~~ ~~Rhabdomyolysis~~	
Reproductive system and breast disorders		***Sexual dysfunction***		
Investigations		~~Increases in serum creatinine and urea~~ ***Blood creatinine increased***	***Blood urea increased***	

*: In the FIELD-study, a randomized placebo-controlled trial performed in 9 795 patients with type 2 diabetes mellitus, a statistically significant increase in pancreatitis cases was observed in patients receiving fenofibrate versus patients receiving placebo (0.8% versus 0.5%; p = 0.031). In the same study, a statistically significant increase was reported in the incidence of pulmonary embolism (0.7% in the placebo group versus 1.1% in the fenofibrate group; p = 0.022) and a statistically non-significant increase in deep vein thromboses (placebo: 1.0% [48/4 900 patients] versus fenofibrate 1.4% [67/4 895 patients]; p = 0.074).

In addition to those events reported during clinical trials, the following side effects have been reported spontaneously during postmarketing use of <Tradename>. A precise frequency cannot be estimated from the available data and is therefore classified as "not known".

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease.

Musculoskeletal, connective tissue and bone disorders: Rhabdomyolysis.

Indeed, from the analysis of the literature and newly completed clinical studies (Table 5 and Table 6), the frequency of rhabdomyolysis should be considered as rare (>1/10,000, <1/1,000) with fenofibrate in monotherapy and in combination with statins.

2.5.5.2.5. Overdose

We propose to rephrase the overdose section as follow after re-evaluation of all-time data:

~~No case of overdosage has been reported~~. ***Only anecdotal cases of fenofibrate overdosage have been received. In the majority of cases no overdose symptoms were reported.***

No specific antidote is known. If an overdose is suspected, treat symptomatically and institute appropriate supportive measures as required. Fenofibrate can not be eliminated by haemodialysis.

2.5.6. Benefits and Risks Conclusions

Cumulative experience with fenofibrate confirms that fenofibrate is generally well tolerated. Among several signals identified and monitored by drug safety, only hypersensitivity was considered relevant and added to the undesirable effect section of the SmPC. Editorial adaptations, changes for consistent wording and enhanced readability as well as MedDRA coding are proposed to be implemented in the fenofibrate SmPC to align with the most recent PSUR.

In conclusion, the benefit/risk ratio of fenofibrate remains positive. The fenofibrate SmPC, as proposed, with amendments in Sections 4.1, 4.8 and 5.1, reflects the available evidence and current clinical practice.

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Appendix 1

Analysis of clinical trials with co-administration of fenofibrate and statins (1990 - 2008)

ANALYSIS OF CLINICAL TRIALS WITH CO-ADMINISTRATION OF FENOFIBRATE AND STATINS

1990-2008

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1. INTRODUCTION

Intervention studies using statins have shown a consistent reduction of cardiovascular events mostly attributed to LDL-C reduction. Conversely, intervention studies with fibrates induced a reduction in cardiovascular events by other mechanisms such as those described in Table 1. Moreover, the relative risk reduction with HMG-CoA reductase inhibitors (statins) or fibrates in monotherapy is 25-35% which leaves a significant residual risk in treated patients. A post-hoc analysis from 4S (Scandinavian Simvastatin Survival Study) suggested that patients with elevated LDL-C, low HDL-C and elevated TG derived a greater benefit with drug therapy, similarly to what is observed in trials of fibrates in patients with low HDL-C and elevated TG. Thus, authors questioned whether optimal therapy for these high-risk patients should consist of high dose monotherapy with fibrate or statin or combination therapy with statin plus fibrate [1].

Table 1: Lipid altering effects of fenofibrate and/or HMG-CoA reductase inhibitors

Lipid-altering effect	HMG-CoA reductase inhibitors	Fenofibrate	HMG-CoA reductase inhibitors+ fenofibrate
LDL-C decrease	+++	+	+++
TG-rich lipoprotein decrease	+	+++	+++
HDL-C increase	+	++	++
Improvement in LDL size profile	±	++	++
Post-prandial lipemia decrease	±	+++	Not evaluated

Adapted from Farnier M. Am J Cardiovasc Drugs 2003;3:169-178 [2]

Currently, the therapeutic interest of the co-administration is based on improvement of standard lipid profile and non lipid effects in comparison to monotherapy. Clinical endpoint studies with co-administration of fibrates and statins (ACCORD with fenofibrate 160 mg tablet and simvastatin 20 mg) are underway (see www.accordtrial.org). The objective of ACCORD is to verify whether or not the increase in HDL-C and the reduction in TG with fenofibrate is able to reduce cardiovascular events beyond what is provided by LDL-C reduction with simvastatin 20 or 40 mg alone. ACCORD plans to recruit 10000 patients in USA and Canada with type 2 diabetes of whom about 29% should receive fenofibrate and simvastatin. As of November 2005, the ACCORD study was fully recruited with a total of 10,261 patients been randomised since January 2001, including about 5500 included in the lipid study.

The effects induced by the concomitant use of fibrate and statin have been evaluated in many clinical studies carried out in the last 15 years, soon after introduction of statins in small patient groups and more recently in large randomised trials.

We conducted an analysis of the literature of these clinical studies and unpublished reports using co-administration of fenofibrate and statins to assess both the efficacy on lipid parameters and muscular safety.

2. SEARCH METHODS FOR IDENTIFICATION OF STUDIES

We used the following sources for the identification of trial:

- MEDLINE® – Datastar server (until October 2007);
- MEDLINE®– Datastar server (until October 2007);
- Internal database (Fulcrum®).

Search was performed using specific key words for each database as well as the words in title and abstract. The specific key words were:

- For MEDLINE: atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, simvastatin, rosuvastatin, hydroxymethylglutaryl-coA-reductase-inhibitors, fenofibrate, procetofen, drug-combinations, drug-therapy-combination, combined, combination, concomitant;
- For EXERPTA MEDICA: atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, simvastatin, rosuvastatin, hydroxymethylglutaryl-coenzyme-A-reductase-inhibitor, fenofibrate, drug-combination, combined, combination, concomitant.

The duplicates between the 2 databases were dropped.

The search was performed from January 1990 until October 2007, without any language limitation.

All studies with data regarding effect of a fenofibrate/statin combination treatment on lipids were selected.

3. DESCRIPTION OF THE STUDIES

Forty-eight studies (publications from 1990 to 2007 and internal reports), including in total more than 4,000 patients treated with fenofibrate in co-administration with statins, dealt with lipid management in patients with combined hyperlipidaemia and/or in patients presenting with a particularly high risk for atherosclerosis such as those with type 2 diabetes (see Table 2 which gives average baseline total cholesterol and triglycerides and Appendix 1). The co-administration of fenofibrate and pravastatin or rosuvastatin was also studied to improve dyslipidemia in HIV patients [3]. These studies essentially looked for superior efficacy of the co-administration either in patients that were defined as having severe hyperlipidemia and that were randomized to combination or monotherapy or in patients receiving the combination in case of insufficient response to monotherapy.

Fenofibrate was co-administered with simvastatin in 20 studies (1,236 treated patients), with fluvastatin in six studies (303 patients), with cerivastatin in four studies (1,494 patients), with pravastatin in four studies (326 patients) and atorvastatin in six studies (244 patients), and titrated with rosuvastatin in two studies (156 patients). In six studies (335 patients), fenofibrate was co-administered with different statins.

Fenofibrate was given as the usual dose (250-300 mg non-micronised or 200 mg micronised capsules or 160 mg tablet) in all but three studies where either a dose of 200 mg non-micronised capsule was given as monotherapy or titration with 80-160 mg tablets or 67 mg capsules were used in combination with cerivastatin or rosuvastatin.

Out of 23 randomised studies, three studies used co-administration after initial randomization to either fenofibrate or a statin, 9 studies randomized patients to either the co-administration, statin or fibrate monotherapy. Eight studies randomized patients to co-administration or statin monotherapy, Two studies randomised patients to co-administration or fibrate monotherapy and one study to two schemes of coadministration.

Co-administration of fenofibrate plus a statin was studied over a wide range of doses for atorvastatin: 5 to 40 mg, fluvastatin: 20 to 80 mg, and simvastatin: 10 to 40 mg, or with the starting doses of pravastatin 20-40 mg or rosuvastatin 5-10 mg.

Finally, comparative arms with statins in monotherapy mainly received the same dose or a doubled dose or the highest dose registered e.g. atorvastatin 80 mg or rosuvastatin 40 mg when compared to the co-administration arm.

Of note, baseline values of TC tended to decrease over time from around 400 mg/dL in the 90s to about 250 mg/dL nowadays. Conversely, baseline TG remained stable covering a wide range of values from below 150 mg/dL to 400 mg/dL and above (see Figures in Appendix 4).

Table 2: Description of published studies and reports

No.	Study, reference	Baseline TC, mg/dl	Baseline TG, mg/dl	CV risk	Statin in coprescription*	Statin in monotherapy	Fenofibrate monotherapy
[45]	Weisweiler 1990 **	412	213	Not Available	S40 n=6	S40 baseline	-
[13]	Farnier 1991 **	500	226	NA	S20 n=10	S20 baseline	-
[39]	Schlienger 1991**	NA	NA	NA	S40 n=12	S40 baseline	-
[8]	Chanu 1994	NA	NA	NA	S20 or P20-40 n=7	S60-80	-
[14]	Farnier 1994	335	184	NA	S20-40 n=30	S20-40 baseline (n=27)	
[34]	Reiber 1994	353	477	NA	S40 n=24	-	-
[29]	Lyakishev 1996 **	NA	NA	NA	Fl 40 n=18	Fl 40 baseline	300Std baseline
[20]	Garrido 1997	305	390	CHD or risk factors	S10-20 n=17	-	-
[35]	Reiber 1997	352	477	NA	Fl 20-40, L20-40, S10-20 n=22	-	-
[38]	Schaper 1997	330	615	CHD or risk factors	S10-40 n=12	-	-
[48]	Wierzbicki 1997	406	220	NA	S40 n=29	S40 (+cholestyramine) baseline n=29	-
[12]	Ellen 1998 **	275	191	CHD or>=3 RF	S10, P20 n=80	S10, P20 n=80 baseline	200M-300Std baseline
[46]	Widimsky 1998	268	260	CHD	Fl 20 n=57	Fl 40 n=59	-
[49]	Wierzbicki 1998	406	220	NA	S40 n=36	A80 n=54	-
[15]	Farnier 1999 **	NA	NA	-	C0.3 n=115	C0.3 n=115	200M n=112
[23]	Kayikçioglu 1999	299	372	CHD, T2DM	S10 n=69	-	-
[33]	Pella 1999	291	363	CHD	P20 n=20	-	-
[47]	Widimsky 1999	268	260	CHD	Fl 20 n=52	Fl 40 n=52	-
[16]	Farnier 2000	364	154	-	(Fl 20, Fl 40) n=69	-	200M n=33
[24]	Kiortsis 2000 **	340	380	>=3 Risk Factors	A40 n=12 period 3	A40 period 2	200M period 1
[52]	Zoppo 2000	NA	NA	NA	S n=8	-	-
[4]	Athyros 2002 **	253	279	T2DM, no CHD	A20 n=40	A20 n=40	200M n=40
[6]	CCER 9902 2002 **	243	232	-	C0.4 n=167	C0.4	-
[7]	CCER 9903 2002	243	276	-	C0.2-0.4 n=175	-	160T
[28]	Liamis 2002	299	317	-	A5 n=11	-	200M baseline

*n= treated with co-administration ** Data taken into account in figures in Appendix 4

Table 2: Description of published studies and reports (end)

No.	Study, reference	Baseline TC, mg/dl	Baseline TG, mg/dl	CV risk	Statin in coprescription*	Statin in monotherapy	Fenofibrate monotherapy
[25]	Klosiewicz 2003 **	320	369	CHD, T2DM or RF	(A10, Fl 40, L20, S20) n=129	A10, Fl 40, L20, S20	200M
[32]	Neil 2003		135	CHD, T2DM	C0.4 n=462	C0.4 n=497	200 n=496
[42]	UKLDS 2003 **	191	137	T2DM	C0.4 n=1037	C0.4	200M
[19]	Fegan 2005***	179	197	T2DM	C0.4 n=11	C0.4 n=20	200M n=10
[37]	Sarano 2003 **	299	278	CHD, T2DM +/-	Fl 40 n=82	Fl 40 baseline	200M baseline
[43]	Vega 2003 **	273	321	MetS.	S10 n=20	S10	-
[50]	Zeman 2003	294	493	CHD, T2DM	P20 n=46	-	-
[10]	Derosa 2004 **	263	156	CHD, T2DM	Fl 80 n=25	Fl 80 n=23	-
[11]	Durrington 2004	246	327	T2DM	R5-10 n=113	R10,20,40	67Mx1,2,3
[26]	Klosiewicz 2004 **	314	383	-	S20 n=116	S20 n=93	200M n=327
[41]	Stefanutti 2004	306	339	-	S10-30 n=45	-	-
[3]	Aberg 2005 **	270	326	HIV	P40 n=136	P40 baseline n=67	200M baseline n=69
[5]	Athyros 2005**	232	195	MetS	A20 n=100	A20 n=100	200M n=100
[21]	Grundy 2005 **	257	232	-	S20 n=411	S20 n=207	-
[27]	Koh 2005 **	239	320	-	A10 n=56	A10	200M
[30]	McIvor 2005	NA	NA	MetS.	Statin n=34	Statin baseline n=48	-
[36]	Ren 2005 **	275	310	CHD or risk factors	S10 n=81	S10 n=72	200M n=68
[17]	Farnier 2006 **	NA*	NA*	Combined hyperlipidemia High risk	P40 n=124	P40 n=124	-
[31]	Muhlenstein 2006 **	229	283	T2DM	S20 n=100	S20 n=100	160T n=100
[44]	Vega 2006 **	NA*	NA*	T2DM	S20 n=20	S20	-
[51]	Zeman 2006 **	270	341	Primary hyperlipidemia	(A20, S40) n=20	A20, S40 n=46	-
[9]	Chatley 2007	247	315	-	A5 n=25	A10-40 n=45	160T-200 n=25
[18]	Farnier 2007 **	254	228	MetS (62%), T2DM (9%)	(S20+eze10) n=183	S20 +eze10 n=184	160T n=184
[22]	Johns 2007 **	253	466	MetS HIV+	(R5-40) n=42	R5-40 n=70	-
[40]	Shah 2007	153	140	Acute coronary syndrome	(A10, S20) n=50	A20, S40 n=52	-

*n= treated with co-administration ** Data taken into account in figures in Appendix 4 *** substudy from UKLDS

4. EFFICACY ANALYSIS

Table 3 provides percent-point additional changes of LDL-C, HDL-C and TG with co-administration as compared with monotherapy in 37 studies (either randomised or when the same number of patients was treated with both monotherapy and combination). These differences are calculated using results obtained in parallel arms or successive periods, when appropriate or, falling this, in reference to baseline period on monotherapy. Positive figures are understood as an improvement (decrease in LDL-C or TG or increase in HDL-C), negative figures meaning the opposite.

Appendix 2 provides relative changes of lipids versus baseline for monotherapy and for the co-administration. As the studies have different designs (parallel, cross-over, successive periods of monotherapy and co-administration on a systematic basis or for non-responders), results obtained with the co-administration are listed first, before results obtained with fenofibrate and/or statin monotherapy. Results with combinations not including fenofibrate are not given.

In general, co-administration led to superior effects on lipids as compared to monotherapy with statins or fenofibrate alone.

When the same dose of statin was used in monotherapy or co-administered with fenofibrate in 27 studies, the effect of adding fenofibrate decreased LDL-C by 11-20% in five cases (19%), by 6-10% in seven cases (26%), by 0-5% in seven cases (26%) and increased LDL-C in eight cases (30%). The percent change in HDL-C when fenofibrate was added was between 11 and 20% in 14 cases (52%), between 6 and 10% in six cases (22%), between 0 and 5% in seven cases (26%). Similarly, additional TG reduction was over 30% in eight cases (30%), between 21% and 30% in 13 cases (48%), between 11% and 20% in five cases (19%) and below 10% in only one case (4%).

Conversely, when a statin was added to the usual dose of fenofibrate in 21 studies:

- improvement in LDL-C was as follows: over 30% in four cases (19%), 21-30% in 12 cases (57%) and 11-20% in five cases (24%);
- improvement in HDL-C was between 6% and 10% in four cases (19%), between 0% and 5% in 14 cases (67%) and HDL-C was worsened in 3 cases (14%);
- with associated changes in TG between 11% and 20% in 4 cases (19%), below 10% in 16 cases (76%) and negative in 1 case (5%).

Additional effects on LDL-C, HDL-C and TG of combination versus statin and fenofibrate monotherapies at the same doses observed in 27 and 22 studies, respectively, is represented in

Figure 1, Figure 2 and Figure 3.

Table 3: Description of additional lipid changes with co-administration as compared with monotherapy with fenofibrate or a statin

No.	Study reference	Statin in combo	Statin in mono	Feno in mono	% point Δ LDL-C vs statin	% point Δ LDL-C vs feno	% point Δ HDL-C vs statin	% point Δ HDL-C vs feno	% point Δ TG vs statin	% point Δ TG vs feno
[45]	Weisweiler 1990 [a]	S40	S40		-5	-	12	-	49	-
[13]	Farnier 1991 [a]	S20	S20		12	-	0	-	29	-
[39]	Schlienger 1991 [a]	S40	S40		6	-	12	-	46	-
[8]	Chanu 1994	S20 or P20-40	S60-80							
[14]	Farnier 1994	S20-40	S20-40							
[34]	Reiber 1994	S40	-							
[29]	Lyakishev 1996 [a b]	F40	Fl40	300Std	12	15	10	6	26	-2
[20]	Garrido 1997	S10-20	-							
[35]	Reiber 1997	F20-40, L20-40, S10-20	-							
[38]	Schaper 1997	S10-40	-							
[48]	Wierzbicki 1997	S40	S40 (+cholestyramine)		4		15		5	
[12]	Ellen 1998 [a b]	S,P	S10, P20	200M-300Std	-3	28	7	8	32	0
[46]	Widimsky 1998	F20	Fl40		4	-	14	-	23	
[49]	Wierzbicki 1998	S40	A80		-4		23		1	
[15]	Farnier 1999 [a b]	C0.3	C0.3	200M	13	20	6	0	27	5
[23]	Kayikçioglu 1999	S10	-							
[33]	Pella 1999	P20	-							
[47]	Widimsky 1999	Fl 20	Fl40		-1		16		20	
[16]	Farnier 2000 [b]	Fl 20 Fl 40	-	200M		11/20		10/-1		10/11
[24]	Kiortsis 2000 [a b]	A40	A40	200M	5	33	15	4	18	7
[52]	Zoppo 2000	S	-							
[4]	Athyros 2002 [a b]	A20	A20	200M	6	31	13	6	20	9
[6]	CCER 9902 2002 [a]	C0.4	C0.4		4		5		16	
[7]	CCER 9903 2002 [b]	C0.2-0.4	-	x		25		3		14
[28]	Liamis 2002 [b]	A5	-	200M		21		3		5

[a] Data taken into account in Figures 1 to 3 (vs. statin) [b] Data taken into account in Figures 1 to 3 (vs. fenofibrate)

Table 3: Description of additional lipid changes with co-administration as compared with monotherapy with fenofibrate or a statin

No.	Study reference	Statin in combo	Statin in mono	Feno in mono	% point Δ LDL-C vs statin	vs feno	% point Δ HDL-C vs statin	vs feno	% point Δ TG vs statin	vs feno
[25]	Klosiewicz 2003 [a b]	A, Fl, L, S	A10, Fl40, L20, S20	200M	16	26	8	0	23	10
[32]	Neil 2003	C0.4	C0.4	200	5	23	0	-2	24	10
[42]	UKLDS 2003 [a b]									
[37]	Sarano 2003 [a b]	F40	F40-DM+	200-DM+	8	21	15	5	35	9
			DM-	DM-	6	28	13	3	34	7
[43]	Vega 2003 [a]	S10	S10		-3		17		29	
[50]	Zeman 2003	P20	P20	-		-		-		-
[10]	Derosa 2004 [a]	F80	F80	-	10		20		15	
[11]	Durrington 2004 [b]	R5/10	R10,20,40	67Mx1,2,3	-13/-5	35/43	5/6	2/3	11/17	7/13
[26]	Klosiewicz 2004 [a b]	S20	S20	200M	11	17	11	1	35	9
[41]	Stefanutti 2004	S10-30	-							
[3]	Aberg 2005 [a b]	P40	P40	200M	-12	16	11	0	22	0
[5]	Athyros 2005 [a b]	A20	A20	200M	4	28	15	4	14	6
[19]	Fegan 2005*	C0.4	C0.4	200M	1	19	-4	-4	17	8
[21]	Grundy 2005 [a]	S20	S20	-	5		9		23	
[27]	Koh 2005 [a b]	A10	A10	200M	-10	24	15	-8	32	2
[30]	McIvor 2005	Statin	Statin	-	4		2		39	
[36]	Ren 2005 [a b]	S10	S10	200	7	23	20	5	51	11
[17]	Farnier 2006 [a]	P40	P40	-	6	-	5	-	21	-
[31]	Muhlenstein 2006 [a b]	S20	S20	160T	-2	23	5	2	21	4
[44]	Vega 2006 [a]	S20	S20	-	1	-	5	-	25	-
[51]	Zeman 2006 [a]	A20, S40	A20, S40	-	3	-	5	-	4	-
[9]	Chatley 2007 [b]	A5	A10-40	160T-200	13	41	15	7	18	9
[18]	Farnier 2007 [a b]	S20 (+eze10)	S20 (+eze10)	160T	-1	30	10	1	21	9
[22]	Johns 2007 [a]	R5-40	R5-40	-	-4	-	12	-	24	-
[40]	Shah 2007	A10	A20	-	-14	-	24	-	22	-
		S20	S40	-	-1	-	0	-	8	-

[a] Data taken into account in Figures 1 to 3 (vs. statin) [b] Data taken into account in Figures 1 to 3 (vs. fenofibrate)

*substudy of UKLDS; Positive changes are improvement and vice versa for negative changes

Figure 1: Additional effects on LDL-C of combination versus statin and fenofibrate monotherapies at the same doses observed in 27 and 22 studies, respectively

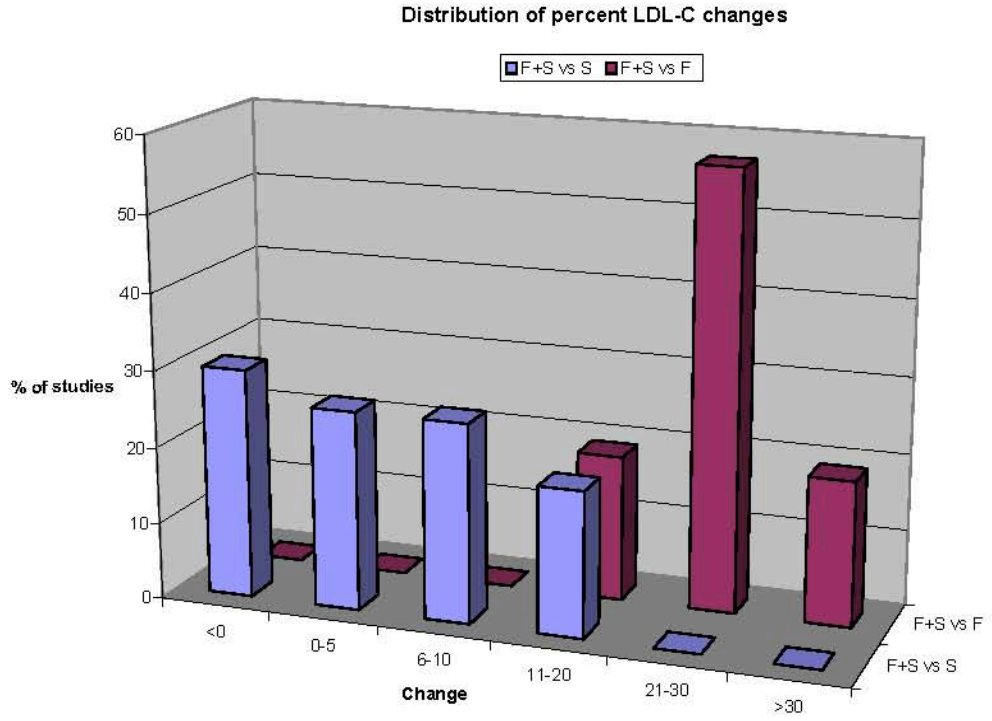


Figure 2: Additional effects on HDL-C of combination versus statin and fenofibrate monotherapies at the same doses observed in 27 and 22 studies, respectively

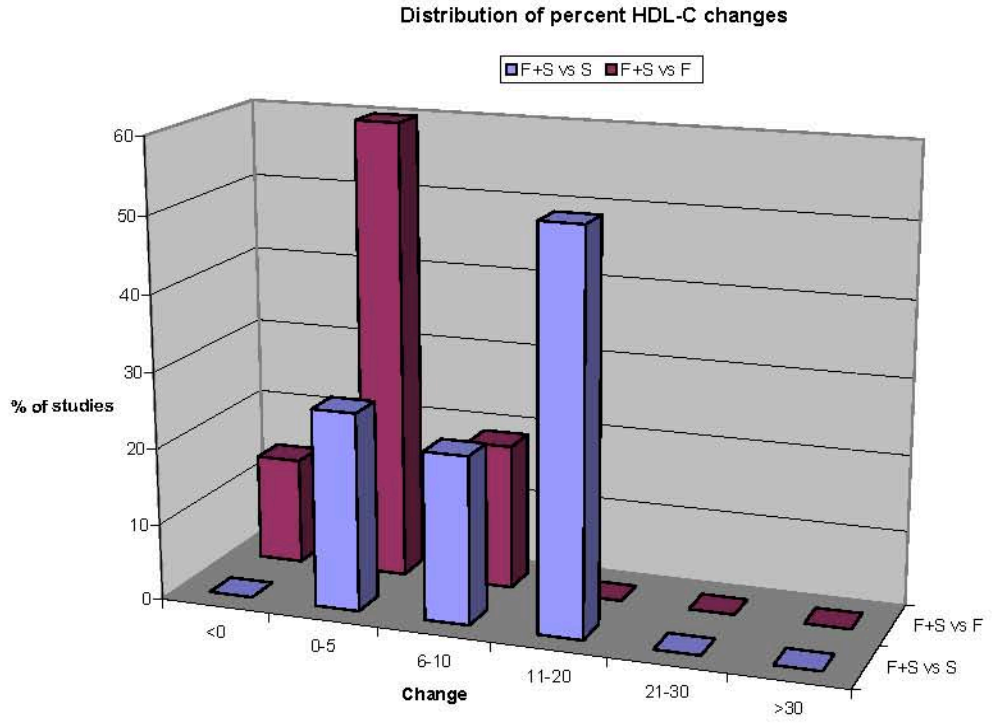
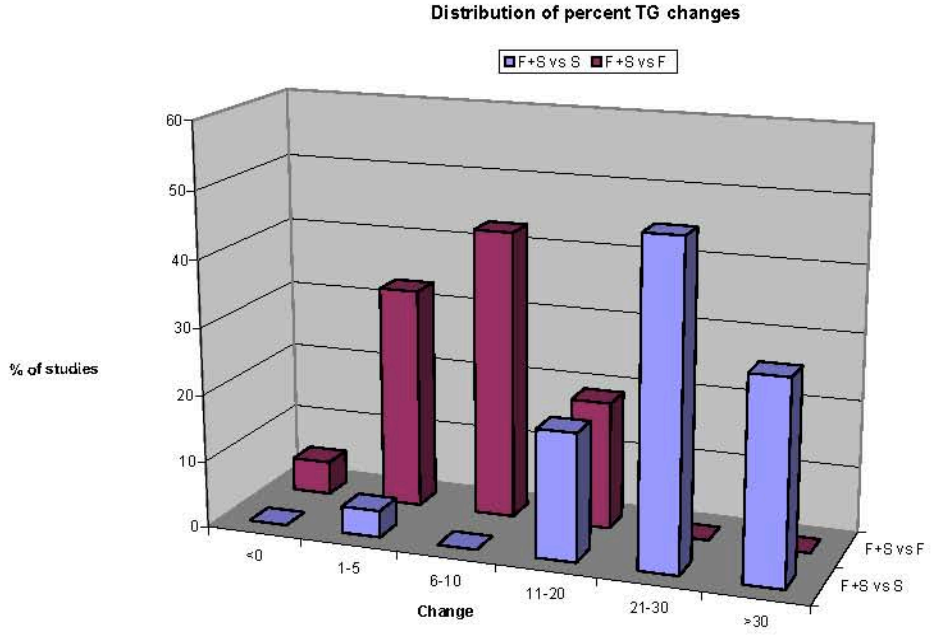


Figure 3: Additional effects on TG of combination versus statin and fenofibrate monotherapies at the same doses observed in 27 and 22 studies, respectively,



4.1. STUDIES IN COMBINED DYSLIPIDEMIA

Several randomised, double-blind studies have been conducted in patients with combined hyperlipidemia, often labelled by the authors as severe or with additional risk factors such as presence of coronary heart disease. Two multicentre, randomised, double–blind, placebo–controlled, parallel-group studies (unpublished reports), investigated the efficacy and safety of cerivastatin associated to fenofibrate in dyslipidaemic patients incompletely controlled with any statin alone [6] or fibrate alone [7]. In the first study, approximately 40% of the patients incompletely controlled with a statin alone, were controlled with the co-administration of cerivastatin 0.4 mg plus fenofibrate 80 mg. An additional dose of 80 mg fenofibrate in patients not adequately controlled with the co-administration was effective in a further 18% of cases. In parallel, approximately 40% of the patients incompletely controlled with a fibrate alone, were controlled with the co-administration of fenofibrate 160 mg plus cerivastatin 0.2 mg. The additional dose of 0.2 mg cerivastatin in patient not adequately controlled with the co-administration was effective in a further 30% of cases. In another randomised study, the decrease in TG and LDL-C levels were about 40% with cerivastatin 0.3 mg plus fenofibrate 200 mg [15].

Among the published studies with simvastatin, the largest one (The SAFARI trial) included in total 619 patients, with combined hyperlipidemia. After 12 weeks of treatment, the combination of simvastatin 20 mg plus fenofibrate 160 mg induced a 31% decrease in LDL-C, a 43% decrease in TG and a 19% increase in HDL-C versus baseline [21]. In a smaller study in which 32 patients with mixed dyslipidemia were treated for a 6-month duration, fenofibrate 250 mg plus simvastatin 10 mg led to a 36% decrease in LDL-C, a 54% decrease in TG and a 15% increase in HDL-C versus baseline [23]. In a randomized, placebo-controlled trial with a cross-over design, 20 patients with combined hyperlipidemia and the metabolic syndrome according to NCEP/ATPIII definition were treated for 3 months with fenofibrate 200 mg and simvastatin 10 mg. When fenofibrate was added to simvastatin therapy, HDL-C increased significantly by 23% and TG decreased by 52% as compared with placebo [43]. In this study, co-administration caused a marked increase in the ratio of large-to-small LDL particles.

When patients with severe combined hyperlipidemia were treated with fenofibrate 200 mg plus fluvastatin 20 mg and 40 mg, LDL-C levels were reduced by 32% with fenofibrate plus fluvastatin 20 mg and by 41% with fenofibrate plus fluvastatin 40 mg. In both cases, TG were reduced by about 40% [16].

In four studies, different combinations of fenofibrate and statins were studied [35], [12], [25], [51]. These were generally retrospective studies. In the study of Ellen [12], 80 patients received fenofibrate 200 mg or equivalent plus simvastatin 10 mg or fenofibrate 200 mg plus pravastatin 20 mg. The benefit of the complementary effects were observed in both groups, there was a 28% decrease in LDL-C levels, a 41% reduction in TG and a 22% rise in HDL-C. In the second study [25], 129 patients were treated with fenofibrate 200 mg plus a statin for 6 to 9 months. Ninety-two patients received fenofibrate plus simvastatin 20 mg, 17 received fenofibrate plus fluvastatin 40 mg, 11 received fenofibrate plus lovastatin 20 mg and 9 fenofibrate plus atorvastatin 10 mg. The observed decrease in LDL-C and TG levels were 42% and 55%, respectively. HDL-C levels increased by 8%.

From these data it is difficult to identify one statin among others for preferential co-administration with fenofibrate, as far as efficacy is concerned. The association of fenofibrate with any of the available statins contributes to a better lipid control in patients presenting with combined dyslipidemia and associated with risk factors.

4.2. STUDIES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

The combined use of statins and fenofibrate could be particularly interesting in patients with type 2 diabetes, whose typical dyslipidemia associates low HDL-C and high TG to moderately elevated LDL-C, because these patients are also considered at high cardiovascular risk. Five studies have been conducted that assess the use of combination therapy with fenofibrate and a statin in these patients. In 40 patients with type 2 diabetes treated with fenofibrate 200 mg and atorvastatin 20 mg, Athyros et al observed a 46% decrease in LDL-C levels, a 50% reduction in TG levels and a 22% increase in HDL-C levels [4]. In another study, rosuvastatin 5 or 10 mg combined with fenofibrate 67 mg three times daily induced a 34% and 42% reduction in LDL-C levels, respectively, and a 41% and 47% decrease in TG levels, respectively [11]. More recently, fenofibrate was co-administered with fluvastatin in two different studies performed in patients with T2DM. In a 12-week study including 52 patients treated with the co-administration, Sarano et al [37] found that 200 mg fenofibrate combined with 40 mg fluvastatin induced a decrease of 38% in LDL-C, 46% in TG and an increase of 23% in HDL-C, similar figures as in the non-diabetic patients treated in parallel. In a second study where 25 patients were treated during 12 months with 200 mg fenofibrate combined with 80 mg fluvastatin, it was observed a 35% decrease in LDL-C levels, a 32% reduction in TG levels and a 34% increase in HDL-C levels [10].

The UK-Lipids in Diabetes Study (UKLDS) was planned to evaluate in patients with type 2 diabetes the effects of micronised fenofibrate 200 mg, cerivastatin 0.4 mg and their combination on cardiovascular events [32]. The study was terminated in August 2001, after the worldwide withdrawal of cerivastatin. This study recruited 4191 patients of which 4156 received at least one dose of medication and were treated on average over one year. The lipid changes with fenofibrate and cerivastatin in co-administration were partially additive on LDL-C (-35%) and TG (-42%), while there was only a minor effect on HDL-C (+1%) as the baseline levels were in the normal range. Monotherapy with cerivastatin alone led to a decrease of LDL-C and TG by 30% and 18%, respectively and to an increase of HDL-C by 1%. With fenofibrate alone, LDL-C were decreased by 12%, TG by 32% and HDL-C increased only by 3%, as baseline levels were in the normal range.

More recently, in another randomised study conducted by Muhlenstein et al [31]in 300 patients with type 2 diabetes, simvastatin 20 mg combined with fenofibrate 160 mg daily induced a 34% and 42% reduction in LDL-C levels, respectively, and a 41% and 47% decrease in TG levels, respectively.

5. SAFETY ANALYSIS

In the fenofibrate and statin co-administration studies (Appendix 3) published in the literature or available as internal reports, the frequency of adverse events and more particularly of clinical or biological muscular adverse events was reported as low.

When considering all the fenofibrate statin studies where 4,094 subjects received co-administation, CPK elevations were reported in 24 cases (0.7%), of which 4 with CPK>10 times the upper normal limit, transaninase ALT elevation in 28 cases (0.7%). No cases of rhaddomyolysis was reported whereas significant myalgia occurred in 42 cases (1.0%).

In the UKLDS where 1037 patients received the combination of fenofibrate and cerivastatin for an average duration of 12 months, no myositis or rhabdomyolysis were reported. The frequency of muscle pain did not differ between the 4 groups. Only one patient had elevated CPK levels > 10 x UNL once [32]. In another study [21], of the 411 patients receiving the co-administration of fenofibrate and simvastatin, two cases of CPK > 5-10 x UNL without symptoms and one case of CPK > 10 x UNL occurred.

The three most serious muscular adverse events reported in fenofibrate/statins studies and listed as “rhabdomyolysis” were observed with fenofibrate in co-administration with pravastatin 40 mg [12], simvastatin 20 mg [15] and fluvastatin 20 mg. This analysis can not identify among the available statins which one(s) to co-prescribe with fenofibrate. Indeed these frequencies do not differ from what is reported for monotherapy with statins (to the exception of cerivastatin) and fibrates.

6. CONCLUSION

Overall, the results of these studies with more than 4,000 patients receiving fenofibrate and a statin show (as compared with monotherapy) a partially additive effect on the reduction in total cholesterol, LDL-C and triglycerides, as well as on the increase in HDL cholesterol, whatever the statin associated with fenofibrate. Compared with monotherapy with a statin, this results in an additional decrease in LDL-C about 5-6%. This additional LDL-C reduction generally corresponds to what would occur when doubling the statin dose used in co-administration.

A further reduction of triglycerides, usually between 20 to 30%, is obtained when fenofibrate is added to any statin, an effect which is not observed when statins are added to fenofibrate.

The additional increase in HDL cholesterol may reach 10% to 20% when compared with the most efficient statins in tems of LDL-C reduction (atorvastatin 40-80 mg and rosuvastatin up to 40 mg).

The frequency of muscular adverse events and significant ALT or CPK elevations observed with co-administration of fenofibrate and a statin was very low and does not appear to be modified as compared with monotherapy.

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8. APPENDICES

Appendix 1: Description of studies and conditions for the co-administration of fenofibrate with a statin

Appendix 2: Efficacy of the co-administration of fenofibrate and statins on lipid parameters

Appendix 3: Safety of the co-administration of fenofibrate and statins

Appendix 4: Baseline TC and TG in 27 studies where combination and statin monotherapies are given at the same doses

List of abbreviations

Std: standard, non micronised fenofibrate

M: micronised fenofibrate

T: micronised tablet

FA: fenofibric acid

A: atorvastatin

C: cerivastatin

Fl: fluvastatin

L: lovastatin

P: pravastatin

S: simvastatin

TC: total cholesterol

TG: triglycerides

CHD: coronary heart disease

CV: cardiovascular

FH: familial hyperlipidemia

HIV: human immunodeficiency virus

T2DM: type 2 diabetes mellitus

RF: risk factor

DB : double-blind

CO: cross-over

PG: parallel-group

Appendix 1: Description of studies and conditions for the co-administration of fenofibrate with a statin

No.	Reference	Treatment (months) Study design	Dyslipidemia type CHD/RF T2DM	No of patients	Fenofibrate dosage (mg)	Statin dosage (mg)	Conditions to use coprescription (Units are mg/dl - NA not available)				
							none	failure of monotherapy	other	Baseline TC	baseline TG
[45]	Weisweiler 1990	3 sequential	Severe IIa	6	250 Std -	S40 S40		LDL-C>155 with S40		412 422	213 135
[13]	Farnier 1991	3 prospective	Severe IIa/IIb	10	300 Std -	S20 S20			not described	500	226
[39]	Schlienger 1991	≥ 8 prospective	IIa	12	300 Std	S40		LDL-C>210 with S40 + cholestyramine		NA	NA
[8]	Chanu 1994	6 prospective	Severe IIa/IIb	7 5	200Std -	S20 or P20-40 S60-80		TC>350 with S40 or F400			
[14]	Farnier 1994	3 to 39 prospective	Severe IIa/IIb	30	300 Std /200M	S20/S40		not normalized after S20 (n=27) or feno (n=3)		335	184
[34]	Reiber 1994	3 to 40 retrospective	IIb	24	250 Std	S40			not described	353	477
[29]	Lyakishev 1996	1+1 rando to monotherapy prior to combination	IIa/IIb	18	300Std 300Std -	F140 - F140	TC>300 TG<400			NA	NA

No.	Reference	Treatment (months) Study design	Dyslipidemia type CHD/RF T2DM	No of patients	Fenofibrate dosage (mg)	Statin dosage (mg)	Conditions to use coprescription (Units are mg/dl - NA not available)				
							none	failure of monotherapy	other	Baseline TC	baseline TG
[20]	Garrido 1997	2 to >24 retrospective	IIb, CHD or CV risk factor	17	250 Std	S10/S20		x		305	390
[35]	Reiber 1997	6 to 15 retrospective	IIb	22 8 10 4	200M 200M 200M 200M	Any statin Fl20/Fl40 L20/L40 S10/S20	x			352	477
[38]	Schaper 1997	8 to 20 retrospective	IIb, CHD or CV risk factor	12	250 Std	S10/S40		x		330	615
[48]	Wierzbicki 1997	6 prospective	Severe FH	29	200M	S40		TC>270 LDL-C > 135		414	228
[12]	Ellen 1998	25 on average prospective	IIb, CHD (80%) or >=3 RF	80 41 39	200M/300 Std 200M/300Std -	S10/P20 - S10/P20	LDL-C≥130, TG≥270 and/or HDL-C<35			275 - -	438 - -
[46]	Widimsky 1998	6 rando, open, PG	IIb, CHD	57 59	200 Std -	Fl20 Fl40	LDL-C>160 TG 200-400			267 270	256 262
[49]	Wierzbicki 1998 extension	2 to 6 prospective	Severe FH	36	200M -	S40 A80		TC>270 LDL-C > 135		406	220

No.	Reference	Treatment (months) Study design	Dyslipidemia type CHD/RF T2DM	No of patients	Fenofibrate dosage (mg)	Statin dosage (mg)	Conditions to use coprescription (Units are mg/dl - NA not available)				
							none	failure of monotherapy	other	Baseline TC	baseline TG
[15]	Farnier 1999	2 rando, DB, PG (3 arms)	IIa/IIb CHD or ≥ 2 risk factors for CHD	115 112 115	200M 200M -	C0.3 - C0.3	LDL-C>130 TG<353			NA	NA
[23]	Kayikçioglu 1999	6 rando, open, PG	IIb, CHD (60%) T2DM (32%)	32 37	250 Std 250 Std (1/2d)	S10 S10 (1/2d)		x		299 294	372 367
[33]	Pella 1999	3	IIb, CHD	20	200M	P20	x			291	363
[47]	Widimsky 1999 extension	18 rando, open, PG (2 arms)	IIb, CHD	52 52	200M -	Fl20 Fl40	LDL-C>160 TG 200-400			268 268	258 261
[16]	Farnier 2000	4 rando, DB, PG (3 arms)	IIa/IIb	35 34 33	200M 200M 200M	Fl20 Fl40 -	LDL-C ≥ 190 TG ≤ 350			375 356 351	157 142 158
[24]	Kiortsis 2000	4.5 Open sequential design	Severe mixed hyperlipidemia at high risk for CHD	12	200M 200M -	A40 - A40	LDL-C>160 TG>320			340	380
[52]	Zoppo 2000	1 sequential	IIb	8	F F (1/2d)	S S (1/2d)				NA	NA

No.	Reference	Treatment (months) Study design	Dyslipidemia type CHD/RF T2DM	No of patients	Fenofibrate dosage (mg)	Statin dosage (mg)	Conditions to use coprescription (Units are mg/dl - NA not available)				
							none	failure of monotherapy	other	Baseline TC	baseline TG
[4]	Athyros 2002	6 rando, open, PG (3 arms)	T2DM + Combined hyperlipidemia, no CHD	40 40 40	200M 200M -	A20 - A20	TC>220 LDL-C>130 TG200-400 HDL-C<40 ApoB>150			255 253 252	279
[6]	CCER 9902 2002	3 rando, DB, PG (2 arms)	patients not controlled with a statin	203 of which 49 (160+0.4) 118 (80+ 0.4) 36 (C0.4)	80/160T - -	C0.4 - C0.4		LDL-C>100 (CHD),130 (2+RF) or 160 (<2RF) and/or TG>170		243	232
[7]	CCER 9903 2002	3 rando, DB, PG (2 arms)	patients not controlled with a fibrate	200 of which 46 (160+0.4) 129 (160+0.2) 25 (160T)	160T - 160T	C0.2-0.4 - -		LDL-C>100 (CHD), 130 (2+RF) or 160 (<2RF) and/or TG>170		243	276
[28]	Liamis 2002	3 + 3 open sequential	Mixed hyperlipidemia	11	200M 200M	A5 -		Failure of 3 months fenofibrate LDL-C>130		299	317

No.	Reference	Treatment (months) Study design	Dyslipidemia type CHD/RF T2DM	No of patients	Fenofibrate dosage (mg)	Statin dosage (mg)	Conditions to use coprescription (Units are mg/dl - NA not available)				
							none	failure of monotherapy	other	Baseline TC	baseline TG
[25]	Klosiewicz 2003	6 to 9 retrospective	Severe mixed dyslipidemia CHD (32%) T2DM (19%) or multiple RF	129	200M - 200M	Any statin Any statin -		x		321	337
[32]	Neil 2003	12 rando, DB, PG vs placebo	T2DM and LDL-C<4.1 mmo/L	462 496 497 494	200M 200M - -	C0.4 - C0.4 -					
[42]	UKLDS 2003	Up to 27 rando, DB 2x2 factorial	T2DM CHD-	1037 1042 1038 1039	200M 200M - -	C0.4 - C0.4 -	LDL-C<160 TG<400			191	137
[37]	Sarano 2003	1+3 rando to monotherapy (1	CHD and combined hyperlipidemia with T2DM	52 27 25	200M 200M -	Fl40 - Fl40	LDL-C>160 TG>200			299 290 305	275 274 278

No.	Reference	Treatment (months) Study design	Dyslipidemia type CHD/RF T2DM	No of patients	Fenofibrate dosage (mg)	Statin dosage (mg)	Conditions to use coprescription (Units are mg/dl - NA not available)				
							none	failure of monotherapy	other	Baseline TC	baseline TG
		month) prior to combination (3 months)	CHD and combined hyperlipidemia without T2DM	30	200M	Fl40	LDL-C>160			300	282
				15	200M	-	TG>200			294	285
				15	-	Fl40				305	277

No.	Reference	Treatment (months) Study design	Dyslipidemia type CHD/RF T2DM	No of patients	Fenofibrate dosage (mg)	Statin dosage (mg)	Conditions to use coprescription (Units are mg/dl - NA not available)				
							none	failure of monotherapy	other	Baseline TC	baseline TG
[43]	Vega 2003	3 rando, DB, CO vs placebo	Combined hyperlipidemia and MetS	20 -	200M -	S10 S10	LDL-C>160 TG 200-800 MetS NCEP			273	321
[50]	Zeman 2003	36 (mean) non rando open, PG	Severe mixed dyslipidemia CHD (39%) T2DM (24%)	46	200M	P20		x		299	463
[10]	Derosa 2004	12 rando, DB, PG	Combined hyperlipidemia+ T2DM + CHD	25 23	200M -	Fl80 Fl80	TC>200 TG>150 LDL>100			265 260	161 150
[11]	Durrington 2004	6 rando, open, PG (4 arms)	IIb + T2DM	60 53 49 51	1-3X67M 1-3X67M 1-3X67M -	R5 R10 - R10-40	TC>=200 TG 200-800			251 247 244 240	310 310 372 319
[26]	Klosiewicz 2004	12+12 open sequential	Mixed hyperlipidemia	116 327 93	200M 200M -	S20 - S20		LDL-C>100 (CHD, T2DM) or> 130 and/or TG>150		310 305 321	411 437.5 280

No.	Reference	Treatment (months) Study design	Dyslipidemia type CHD/RF T2DM	No of patients	Fenofibrate dosage (mg)	Statin dosage (mg)	Conditions to use coprescription (Units are mg/dl - NA not available)				
							none	failure of monotherapy	other	Baseline TC	baseline TG
[41]	Stefanutti 2004	12 after simvastatin run-in open	Mixed hyperlipidemia	5 26 11 3	200M 200M 300 Std 200M	S10 S20 S20 S30		LDL-C>130 Elevated TG after 2-4 weeks simvastatin run-in TG<500		291 314 281 352	328 353 301 374
[3]	ACTG5087 Aberg 2005	3+9 rando, open to monotherapy, then combination	HIV+ dyslipidemia	136 88 86	200M 200M -	P40 - P40		Not at LDL-C, HDL-C and TG composite goal at 3 months *		270	326
[5]	Athyros 2005	12 rando, open PG (3 arms)	MetS	100 100 100	200M 200M -	A20 - A20	>=3 components of MetS ATPIII			232 228 232	195 186 195
[19]	Fegan 2005	3 rando, DB, 2x2 factorial	T2DM	11 10 20 12	200M 200M - -	0.4C - 0.4C -	LDL<160 TG<400			174 186 178 182	186 177 204 213

* LDL-C ≤ 100 (≥2RF) or <130 (<2RF)
HDL-C ≥ 35
TG<200 (if 200-800 on entry) or <400 (if >800 on entry)

No.	Reference	Treatment (months) Study design	Dyslipidemia type CHD/RF T2DM	No of patients	Fenofibrate dosage (mg)	Statin dosage (mg)	Conditions to use coprescription (Units are mg/dl - NA not available)				
							none	failure of monotherapy	other	Baseline TC	baseline TG
[21]	Grundy 2005	3 rando 2/1, DB, PG	Combined hyperlipidemia	411 207	160T -	S20 S20	LDL-C>130 TG 150-500			257 256	234 227
[27]	Koh 2005	2 rando, DB, CO	Combined hyperlipidemia	56	200M 200M -	A10 - A10	TC>200 TG 200-800			240 234 243	322 337 301
[30]	McIvor 2005	4 Prospective, open, sequential	MetS	34	160T -	Statin Statin (=baseline)	Fasting glucose 110–129 on statin				
[36]	Ren 2005	3 to 6 rando, open	Combined hyperlipidemia CHD or RF	81 68 72	200M 200M -	S10 - S10	LDL-C>140 TG> 150			282 267 275	301 310 319
[17]	Farnier 2006	3 rando, DB, PG (2 arms)	Combined hyperlipidemia High CHD risk	248	160T -	P40 P40	LDL-C≥ 100 TG 150-400 on P40	x		-	-
[31]	Muhlestein 2006	3 rando, DB, PG (3 arms)	T2DM with mixed dyslipidemia	100 100 100	160T 160T -	S20 - S20	2 of LDL-C >100, TG> 200 or HDL-C<40			231 226 229	284 271 230

No.	Reference	Treatment (months) Study design	Dyslipidemia type CHD/RF T2DM	No of patients	Fenofibrate dosage (mg)	Statin dosage (mg)	Conditions to use coprescription (Units are mg/dl - NA not available)				
							none	failure of monotherapy	other	Baseline TC	baseline TG
[44]	Vega 2006	4 prospective, open, sequential	T2DM.	20 -	160T -	S20 S20	TG 150-800 LDL-C > 100 HDL-C < 40 on S20	x			
[51]	Zeman 2006	12 non rando, open, PG	Primary hyperlipidemia	20 46	200M -	A20, S40 A20, S40	LDL-C>160 TG > 310 TG<310			295 259	610 224
[9]	Chatley 2007	4 non-rando, open, PG (3 arms)	Mixed hyperlipidemia	25 20 45	160T-200 160T-200 -	A5 - A10-40	NA			258 236 246	372 350 267
[18]	Farnier 2007	3 rando, DB, PG (4 arms) vs placebo	Mixed hyperlipidemia	183 184 184 60	160T 160T - -	S20 (+eze) - S20 (+eze) -	LDL-C 130-220 TG 150-300			248 256 259 255	230 231 223 231

No.	Reference	Treatment (months) Study design	Dyslipidemia type CHD/RF T2DM	No of patients	Fenofibrate dosage (mg)	Statin dosage (mg)	Conditions to use coprescription (Units are mg/dl - NA not available)				
							none	failure of monotherapy	other	Baseline TC	baseline TG
[22]	Johns 2007	~5 Retrospective	HIV+ MetS	43 70	F -	R5-40 R5-40	x			253	466
[40]	Shah 2007	3 rando, open, PG (4 arms)	Acute coronary syndrome	25 25 25 27	200M 200M - -	A10 S20 A20 S40	x		Patients with PTCA	152 150 157 151	141 135 151 133

Appendix 2: Efficacy on the co-administration of fenofibrate with a statin on lipid parameters

No.	Reference	Treatment (months) Study design	Dyslipidemia type (mg/dl)	No of patients	Fenofibrate dosage (mg)	Statin (mg)	Modification of lipid levels (%) compared to baseline without treatment except otherwise indicated					
							TC	LDL-C	HDL-C	TG	LDL/HDL	Apo B
[45]	Weisweiler 1990	3 sequential	Severe IIa	6 6	250 Std -	S40 S40	-34 -34	-38 -43	+12 0	-47 +2		-36 -31
[13]	Farnier 1991	3 prospective	Severe IIa/IIb	10	300 Std -	S20 S20	-41 -27	-41 -29	+16 +16	-48 -19		-44 -26
[39]	Schlienger 1991	8 prospective	IIa, LDL-C>210	12	300 Std	S40	-6 vs S40	-9 vs S40	+12 vs S40	-46 vs S40		-8 vs S40
[8]	Chanu 1994	6 prospective	Severe IIa/IIb	7 5	200Std -	S20 or P20-40 S60-80						
[14]	Farnier 1994	3 to 39	IIa/IIb severe	30	300 Std /200M	S20/S40						
[34]	Reiber 1994	3 to 40 retrospective	IIb	24	250 Std	S40	-31	-33	+23	-43		-29
[29]	Lyakishev 1996	2 prospective	TC>300 TG<400	18 9 9	300Std 300Std -	Fl40 - F40	-36 -25 -24	-44 -29 -32	+16 +10 +6	-35 -37 -9		
[20]	Garrido 1997	2 to >24 retrospective	IIb, CHD or CV risk factor	17	250 Std	S10/S20	-25	-26	+7	-30		

No.	Reference	Treatment (months) Study design	Dyslipidemia type (mg/dl)	No of patients	Fenofibrate dosage (mg)	Statin (mg)	Modification of lipid levels (%) compared to baseline without treatment except otherwise indicated					
							TC	LDL-C	HDL-C	TG	LDL/HDL	Apo B
[35]	Reiber 1997	6 to 15	IIb	22	200M	Any statin	-29		+32	-55		
		retrospective		8	200M	Fl20/Fl40						
				10	200M	L20/L40						
				4	200M	S10/S20						
[38]	Schaper 1997	8 to 20	IIb	12	250 Std	S10/S20	-28		+25	-62		-32
		retrospective										
[48]	Wierzbicki 1997	6	Severe FH	29	200M	S40	-35	-41	+20	-17	-53	-27
		prospective	TC>270									
[12]	Ellen 1998	25	IIb, TG≥270	80	200M/300 Std	S10/P20	-26	-28	+22	-41	-42	
		prospective	LDL-C≥130 CHD	41	200M/300Std	-	-9	0	+14	-41	-19	
			(80%) or ≥ RF	39	-	S10/P20	-25	-30	+15	-9	-38	
[46]	Widimsky 1998	6	CHD, IIb	57	200 Std	Fl20	-23	-30	+20	-39		
		rando, open, PG	LDL-C>160	59	-	Fl40	-17	-26	+6	-16		
			200<TG<400									
[49]	Wierzbicki 1998	2 to 6	Severe FH	36	200M	S40	-34	-42	+25	-35	-48	-29
		prospective	TC>270	54	-	A80	-41	-46	+2	-34	-48	-40
[15]	Farnier 1999	2	IIa/IIb	115	200M	C0.3	-30	-41	+12	-37		
		rando, DB, PG (3 arms)	CHD≥ 2 risk factors for CHD	112	200M	-	-16	-21	+12	-32		
				115	-	C0.3	-20	-28	+6	-10		

No.	Reference	Treatment (months) Study design	Dyslipidemia type (mg/dl)	No of patients	Fenofibrate dosage (mg)	Statin (mg)	Modification of lipid levels (%) compared to baseline without treatment					
							TC	LDL-C	HDL-C	TG	LDL/HDL	Apo B
[23]	Kayikçioglu 1999	6 rando, PG	IIb, CHD in 60% of cases T2DM (32%)	32 37	250 Std 250 Std (1/2d)	S10 S10 (1/2d)	-31 -31	-36 -34	+15 +18	-54 -55		-18 -20
[33]	Pella 1999	3	IIb, CHD	20	200M	P20	-34			-46		
[47]	Widimsky 1999 extension	18 rando, open, PG	IIb, CHD	52 52	200M -	Fl20 Fl40	-22 -19	-29 -30	+26 +10	-40 -20		
[16]	Farnier 2000	4 rando, DB, PG (3 arms)	LDL-C ≥ 190 TG ≤ 350	35 34 33	200M 200M 200M	F20 F40 -	-27 -35 -19	-32 -41 -21	+14 +3 +4	-39 -40 -29		-28 -34 -15
[24]	Kiortsis 2000	4.5 Open sequential design	Severe mixed hyperlipidemia at high risk for CHD	12	200M 200M -	A40 - A40	-42 -15 -35	-42 -9 -37	+29 +25 +14	-46 -39 -28		-28 -8 -24
[52]	Zoppo 2000	1 sequential	IIb	8	F F (1/2d)	S S (1/2d)	-18 -29	-39 -36	+22 +32	-33 -41		
[4]	Athyros 2002	6 rando, open, PG (3 arms)	Combined hyperlipidemia + T2DM no CHD	40 40 40	200M 200M -	A20 - A20	-37 -16 -31	-46 -15 -40	+22 +16 +9	-50 -41 -30		-41 -14 -31

No.	Reference	Treatment (months) Study design	Dyslipidemia type (mg/dl)	No of patients	Fenofibrate dosage (mg)	Statin (mg)	Modification of lipid levels (%) compared to baseline without treatment					
							TC	LDL-C	HDL-C	TG	LDL/HDL	Apo B
[6]	CCER 9902 2002	3 rando, DB, PG	patients not controlled with a statin	203 in which 49 (160T+0.4) 118 (80T+0.4)	80/160T	C0.4		-31*	+8*	-27*	* results at 4 weeks	
				36 (C0.4)	-	C0.4		-27	+3	-11		
[7]	CCER 9903 2002	3 rando, DB, PG	patients not controlled with a fibrate	200 in which 46 (160T+0.4) 129 (160+0.2)	160T	C0.2/0.4	-22*	-29*	+7*	-28*		-22
				25 (160T)	160T	-	-6	-4	+4	-14		-7
[28]	Liamis 2002	3 + 3	Mixed hyperlipidemia. Failure of fenofibrate after 3 months	11	200M	A5	-27	-29	+22	-48		
				11	200M	-	-12	-8	+19	-43		
[25]	Klosewitz 2003	6 to 9 retrospective	Severe mixed dyslipidemia	129	200M	Any statin*	-35	-42	+8	-55		
					200M		-14	-16	+8	-45		
					-	Any statin	-22	-26	0	-32		

* results at 4 weeks

No.	Reference	Treatment (months) Study design	Dyslipidemia type (mg/dl)	No of patients	Fenofibrate dosage (mg)	Statin (mg)	Modification of lipid levels (%) compared to baseline without treatment					
							TC	LDL-C	HDL-C	TG	LDL/HDL	Apo B
[32]	Neil 2003	12 rando, DB, CO vs placebo	T2DM and LDL-C<4.1 mmo/L	462	200M	C0.4						
				496	200M	-						
				497	-	C0.4						
				494	-	-						
[42]	UKLDS 2003	1 year analysis rando, DB 2x2 factorial	T2DM	1037	200M	C0.4		-35	+1	-42		
				1042	200M	-		-12	+3	-32		
				1038	-	C0.4		-30	+1	-18		
				1039	-	-		-2	-0	+2		
[37]	Sarano 2003	3 rando to monotherapy (4 weeks) prior to combination (12 weeks)	CHD and combined hyperlipidemia with T2DM	52	200M	F40	-31	-38	+23	-46		-30
				27	200M	-	-16	-17	+18	-37		-11
				25	-	F40	-22	-30	+8	-11		-26
			CHD and combined hyperlipidemia without T2DM	30	200M	F40	-31	-40	+19	-47		-30
				15	200M	-	-13	-12	+16	-40		-9
				15	-	F40	-25	-34	+6	-13		-28
[43]	Vega 2003	3 rando, DB, CO vs placebo	Combined hyperlipidemia and MetS	20	200M	S10	-29	-25	+23	-53		
					-	S10	-27	-28	+6	-24		
[50]	Zeman 2003	36 (mean) non-rando	Severe mixed dyslipidemia	46	200M	P20	-22	-36	+17	-44		-36

No.	Reference	Treatment (months) Study design	Dyslipidemia type (mg/dl)	No of patients	Fenofibrate dosage (mg)	Statin (mg)	Modification of lipid levels (%) compared to baseline without treatment					
							TC	LDL-C	HDL-C	TG	LDL/HDL	Apo B
		open, PG										

No.	Reference	Treatment (months) Study design	Dyslipidemia type (mg/dl)	No of patients	Fenofibrate dosage (mg)	Statin (mg)	Modification of lipid levels (%) compared to baseline without treatment					
							TC	LDL-C	HDL-C	TG	LDL/HDL	Apo B
[10]	Derosa 2004	12	Combined	25	200M	Fl80	-26	-35	+34	-32		
		rando	hyperlipidemia+	23	-	Fl80	-20	-25	+14	-17		
		DB, PG (2 arms)	CHD + T2DM									
[11]	Durrington 2004	6	IIb + T2DM	60	1-3X67M	R5	-31	-34	+11	-41	-39	-35
		rando, open,	TC>=200	53	1-3X67M	R10	-36	-42	+12	-47	-47	-40
		PG (4 arms)	TG 200-800	49	1-3X67M	-	-8	+1	+9	-34	-6	-8
				51	-	R10-40	-37	-47	+6	-30	-49	-41
[26]	Klosiewicz 2004	12+12	Mixed	116	200M	S20	-36	-44	+12	-58	-49	
		open	hyperlipidemia	327	200M	-	-28	-28	+15	-58	-32	
		sequential		93	-	S20	-34	-43	+3	-38	-30	
[41]	Stefanutti 2004	12	Mixed	5	200M	S10	-18	-21	+30	-39		
		after	hyperlipidemia	26	200M	S20	-31	-32	+8	-56		
		simvastatin		11	300 Std	S20	-24	-25	+21	-35		
		run-in		3	200M	S30	-39	-39	+28	-46		
		open										
[3]	ACTG5087	9	HIV +	123	200M	P40	-14	-8	+11	-35		

No.	Reference	Treatment (months) Study design	Dyslipidemia type (mg/dl)	No of patients	Fenofibrate dosage (mg)	Statin (mg)	Modification of lipid levels (%) compared to baseline without treatment					
							TC	LDL-C	HDL-C	TG	LDL/HDL	Apo B
	Aberg 2005	open rando to monotherapy, then combination	dyslipidemia	88 86	200M -	- P40	-5 -16	+8 -20	+11 0	-35 -13		

No.	Reference	Treatment (months) Study design	Dyslipidemia type (mg/dl)	No of patients	Fenofibrate dosage (mg)	Statin (mg)	Modification of lipid levels (%) compared to baseline without treatment					
							TC	LDL-C	HDL-C	TG	LDL/HDL	Apo B
[5]	Athyros 2005	12	MetS	100	200M	A20	-32	-39	+24	-46		
		rando, open		100	200M	-	-12	-11	+20	-40		
		PG (3 arms)		100	-	A20	-30	-35	+9	-32		
[19]	Fegan	3	T2DM	11	200	0.4C	-26	-37	+2	-35		
	2005	rando, DB,		10	200	-	-10	-18	+6	-27		
		2x2 factorial		20	-	0.4C	-27	-36	+6	-18		
				12	-	-						
[21]	Grundy 2005	3	Combined hyperlipidemia	411	160T	S20	-26	-31	+19	-43		-33
		rando 2/1, DB, PG		207	-	S20	-20	-26	+10	-20		-23
[27]	Koh	2	Combined hyperlipidemia	56	200M	A10	-29	-30	+15	-57		-30
	2005	rando, DB,			200M	-	-13	-6	+23	-55		-21
		CO			-	A10	-29	-40	0	-25		-30
[30]	McIvor 2005	4	MetS.	34	160T	Statin	-11	-4	+2	-39		
		Prospective, open, sequential			-	Statin (=baseline)						
[36]	Ren 2005	3 to 6	Combined hyperlipidemia	81	200M	S10	-30	-37	+24	-56		
		rando, open, PG		68	200M	-	-13	-14	+19	-45		
				72	-	S10	-23	-30	+4	-5		

No.	Reference	Treatment (months) Study design	Dyslipidemia type (mg/dl)	No of patients	Fenofibrate dosage (mg)	Statin (mg)	Modification of lipid levels (%) compared to baseline without treatment					
							TC	LDL-C	HDL-C	TG	LDL/HDL	Apo B
[17]	Farnier 2006	3 rando, DB, PG (2 arms)	Combined hyperlipidemia High risk	248	160T	P40	-10	-12	+7	-23		
					-	P40		-6	+2	-2		
[31]	Muhlestein 2006	3 rando, DB, PG (3 arms)	Type 2 diabetes with mixed dyslipidemia	100	160T	S20	-28	-33	+11	-45		
				100	160T	-	-13	-10	+13	-41		
				100	-	S20	-26	-35	+6	-24		
[44]	Vega 2006	4 prospective, open, sequential	T2DM	20	160T	S20						
					-	S20						
[51]	Zeman 2006	12 nn rando, open, PG	Primary hyperlipidemia	20	200M	A20, S40	-15	-25	-1	-30		-7
				46	-	A20, S40	-25	-22	-6	-26		-21
[9]	Chatley 2007	4 non-rando, open, PG (3 arms)	Mixed hyperlipidemia	25	160T-200	A5	-41	-54	+24	-56		
				20	160T-200	-	-19	-13	+17	-47		
				45	-	A10-40	-35	-41	+9	-38		
[18]	Farnier 2007	3 rando, DB, PG (4 arms) vs placebo	Mixed hyperlipidemia	180	160T	S20 (+eze)	-39	-46	+19	-50	-53	-45
				180	160T	-	-15	-16	+18	-41	-26	-20
				179	-	S20 (+eze)	-35	-47	+9	-29	-51	-39
				60	-	-	-1	-4	+1	-3	-2	0

No.	Reference	Treatment (months) Study design	Dyslipidemia type (mg/dl)	No of patients	Fenofibrate dosage (mg)	Statin (mg)	Modification of lipid levels (%) compared to baseline without treatment					
							TC	LDL-C	HDL-C	TG	LDL/HDL	Apo B
[22]	Johns 2007	~5	HIV+ MetS	42	?	R5-40	-25	-28	+8	-45		-24
		Retrospective		70	-	R5-40	-29	-22	-4	-21		-23
[40]	Shah	3	Acute coronary	25	200M	A10	+3	-5	+34	-30	-28	
	2007	rando, open,	syndrome	25	200M	S20	-6	-17	+24	-19	-39	
		PG (4 arms)		25	-	A20	-4	-19	+9	-8	-28	
				27	-	S40	-3	-18	+24	-11	-34	

Appendix 3: Safety of the co-administration of fenofibrate with a statin

No.	Reference	Sex/age	Duration of treatment (months)	Dyslipidemia type	No of patients	Fenofibrate dosage (mg)	Statin* dosage (mg)	Safety
[45]	Weisweiler 1990	6M 45 ± 10	3 sequential	Severe IIa	6 6	250 Std -	S40 S40	No clinically relevant adverse experience.
[13]	Farnier 1991	-	3	Severe FH	10	300 Std -	S20 S20	One case of transient CPK increased. Absence of muscular pain; no significant changes in transaminases.
[39]	Schlienger 1991	-	8	IIa, LDL-C>210	12	300 Std	S40	Increase of CPK and gamma GT within normal limits; mild transaminases elevations in 2 cases.
[8]	Chanu 1994	-	6	IIa/IIb	7 5	200Std -	S20 or P20-40 S60-80	3 withdrawals because of myalgia n=1, palpitation n=1 and increase of CPK n=1 .
[14]	Farnier 1994	52.8	3 to 39	Severe IIa/IIb	30	300 Std/200M	S20/S40	One transient CPK increase > 5 x UNL. No significant changes in transaminases and creatinine. One patient withdrawn for skin rash attributed to fenofibrate.
[34]	Reiber 1994	20M/4F 56 ± 7	3 to 40	IIb	24	250 Std	S40	No increase of CPK >2N or transaminases >3 x ULN. Absence of muscular pain.
[29]	Lyakishev 1996	-	2	TC>300 TG<400	18 9 9	300Std 300Std -	Fl40 - Fl40	No reported modification. Absence of muscular pain.
[20]	Garrido 1997	14M/3F 51 ± 9	Up to 24	IIb, CHD or CV risk factors	17	250 Std	S10/S20	No significant increase of CPK or transaminases. Absence of muscular pain. One patient withdrawn for GI disturbances.

No.	Reference	Sex/age	Duration of treatment (months)	Dyslipidemia type	No of patients	Fenofibrate dosage (mg)	Statin* dosage (mg)	Safety
[35]	Reiber 1997	8M/14F 57 ± 9	6 to 15	IIb	22 8 10 4	200M 200M 200M 200M	Any statin Fl20/Fl40 L20/L40 S10/S20	No reported modification Absence of muscular pain
[38]	Schaper 1997	10M/2F 56 ± 4	8 to 20	IIb	12	250 Std	S10/S20	No significant increase of CPK or transaminases Absence of muscular pain
[48]	Wierzbicki 1997		6	Severe FH TC>270	29	200M -	S40 A80	No significant increase of CPK or transaminases 4 cases of myalgia
[12]	Ellen 1998	64M/16F 58	25	IIb, TG<270 LDL-C>130	80 41 39	200M/300Std 200M/300Std -	S10/P20 - S10/P20	2 cases of isolated and transient increase of CPK <6 x ULN. 2 cases of CPK > 10N (feno + S60 et feno + P40) without myalgia 2 cases of myalgias 8 cases of isolated and transitory increases in transaminases <3 x ULN
[46]	Widimsky 1998	46%/54% 57 ± 8	6	CHD, LDL-C>160 200<TG<400	57 59	200 Std -	Fl20 Fl40	2 patients with transaminases >3 x ULN No increases in CPK >5 x ULN Absence of muscular pain Four patients withdrawn for AE (1 acute myocardial infarction, 1 aorta aneurysm, 1 eczema, 1 nausea).
[49]	Wierzbicki 1998	-	2 to 6	Severe FH TC>270	36 54	200M -	S40 A80	No additional findings. 6 cases of myalgia with A80.

No.	Reference	Sex/age	Duration of treatment (months)	Dyslipidemia type	No of patients	Fenofibrate dosage (mg)	Statin* dosage (mg)	Safety
[15]	Farnier 1999		2	IIa/IIb CHD ≥ 2 risk factors for CHD	115 112 115	200M 200M -	C0.3 - CO.3	Moderate increase in transaminase elevations with combination. No change in muscular safety. No change in myoglobin
[23]	Kayikçioglu 1999	- 56 ± 7	6	IIb	32 37	250 Std 250Std (1/2d)	S10 S10 (1/2d)	4 cases of CPK increase (3 cases>3 x ULN); 5 cases with ALT>3 x ULN concomitant from alcohol intake Absence of muscular pain. No increase in CPK or transaminases with alternate day regimen
[33]	Pella 1999	-	3	IIb	20	200M	P20	No adverse events were observed.
[47]	Widimsky 1999	44%/56% 59 ± 8	18	IIb	52 52	200M -	Fl20 Fl40	1 patient withdrawn (200M+F20) for increase liver enzymes. 1 patient (200M+F20) with elevated CPK between 3 x UNL and 5 x UNL. 10% increase in creatinine. No sign of myopathy.
[16]	Farnier 2000	61M/41F 49	4	LDL-C ≥ 190 TG ≤ 350	35/34 33	200M 200M	Fl20/Fl40 -	One patient withdrawn for AST/ALT > 3N (200M+F40). 4 cases of myalgia (n=2 200M+F40, 1 200M+F20, 1 200M) No report of CPK increase > 5 x ULN
[24]	Kiortsis 2000	8M/4F 51	4.5	Mixed dyslipidemia severe	12	200M 200M -	A40 - A40	No significant increase of muscle and liver enzymes. Absence of muscular pain.
[52]	Zoppo 2000	-	1	IIb	8	F F (1/2d)	S S (1/2d)	No elevations of liver or muscle enzymes

No.	Reference	Sex/age	Duration of treatment (months)	Dyslipidemia type	No of patients	Fenofibrate dosage (mg)	Statin* dosage (mg)	Safety
[4]	Athyros 2002	68M/52F 58	6	Mixed hyperlipidemia + T2DM	40 40 40	200M 200M -	A20 - A20	No cases of myalgia and no increase of CPK> 10x ULN No significant increase in transaminases > 3x ULN
[6]	CCER 9902 2002	118M/85F 58	3	Patients not controlled with a statin	118/49 36	80/160T -	C0.4 C0.4	1 case of CPK increase <4N (F+C) 3 cases of myalgias (1 F+C, 2 C) 1 case of ALT increase <4N
[7]	CCER 9903 2002	147M/53F 53	3	Patients not controlled with a fibrate	200	160T 160T	C0.2/0.4 -	3 cases of CPK increase (F+C) 3 cases of myalgias (2F+C, 1 F) 2 cases of transaminase increase
[28]	Liamis 2002		3 + 3	Mixed hyperlipidemia. Not controlled with fenofibrate after 3 months	11 11	200M 200M	A5 -	No significant increase of CPK and transaminases Absence of muscular pain. No episode of myopathy
[25]	Klosiewicz 2003	63%/37% [35-70]	6 to 9	Severe mixed dyslipidemia	129 129 129	200M 200M -	Any statin - Any statin	No myopathy or CPK > 10x UNL Increase of CPK to less than 3 x UNL in 27 cases on combo No increase in transaminases levels > 3x UNL Increase of ALT to less than 3x UNL in 7 cases
[32]	Neil 2003	65%M/35%F 61 ± 9	12	T2DM and LDL-C<4.1 mmo/L	462 496 497 494	200M 200M - -	C0.4 - C0.4 -	No myositis or rhabdomyolysis. CK increase > 10 x ULN in 4 patients and CK increase > 5 x ULN in 2 patients (2 cerivastatin, 3 fenofibrate, 1 combination)

No.	Reference	Sex/age	Duration of treatment (months)	Dyslipidemia type	No of patients	Fenofibrate dosage (mg)	Statin* dosage (mg)	Safety
[37]	Sarano 2003	44M/38F 55	1(monother) 3 (combo)	CHD and combined hyperlipidemia with/without T2DM	82 42 40	200M 200M -	Fl40 - Fl40	No safety changes reported
[43]	Vega 2003	16M/4F 53 ± 9	3	Combined hyperlipidemia and MetS	20	200M -	S10 S10	No change in muscular safety No significant changes in transaminases or CPK
[42]	UKLDS 2003	65%/35% 61 ± 9	12 (mean)	T2DM	1037 1042 1038 1039	200M 200M - -	C0.4 - C0.4 -	CPK > 10 x UNL : 1 (F+C), 2 [C], 1 (F) CPK > 5 x UNL (twice) : 2 (F) Muscle pain F+C 51/1037 4.9% F 42/1042 4.0% C 47/1038 4.5% P 41/1039 3.9%
[50]	Zeman 2003	31M/15F 57	36 (mean)	Severe mixed dyslipidemia	46	200M	P20	Slight rise in CPK (16%) No significant changes in liver enzymes No myopathy
[10]	Derosa 2004	24M/24F 61 ± 5	12	IIa/IIb+ T2DM + CHD	25 23	200M -	Fl80 Fl80	3 withdrawals for myalgia (2 in combination therapy and 1 with fluvastatin monotherapy) No significant changes in CPK and transaminases

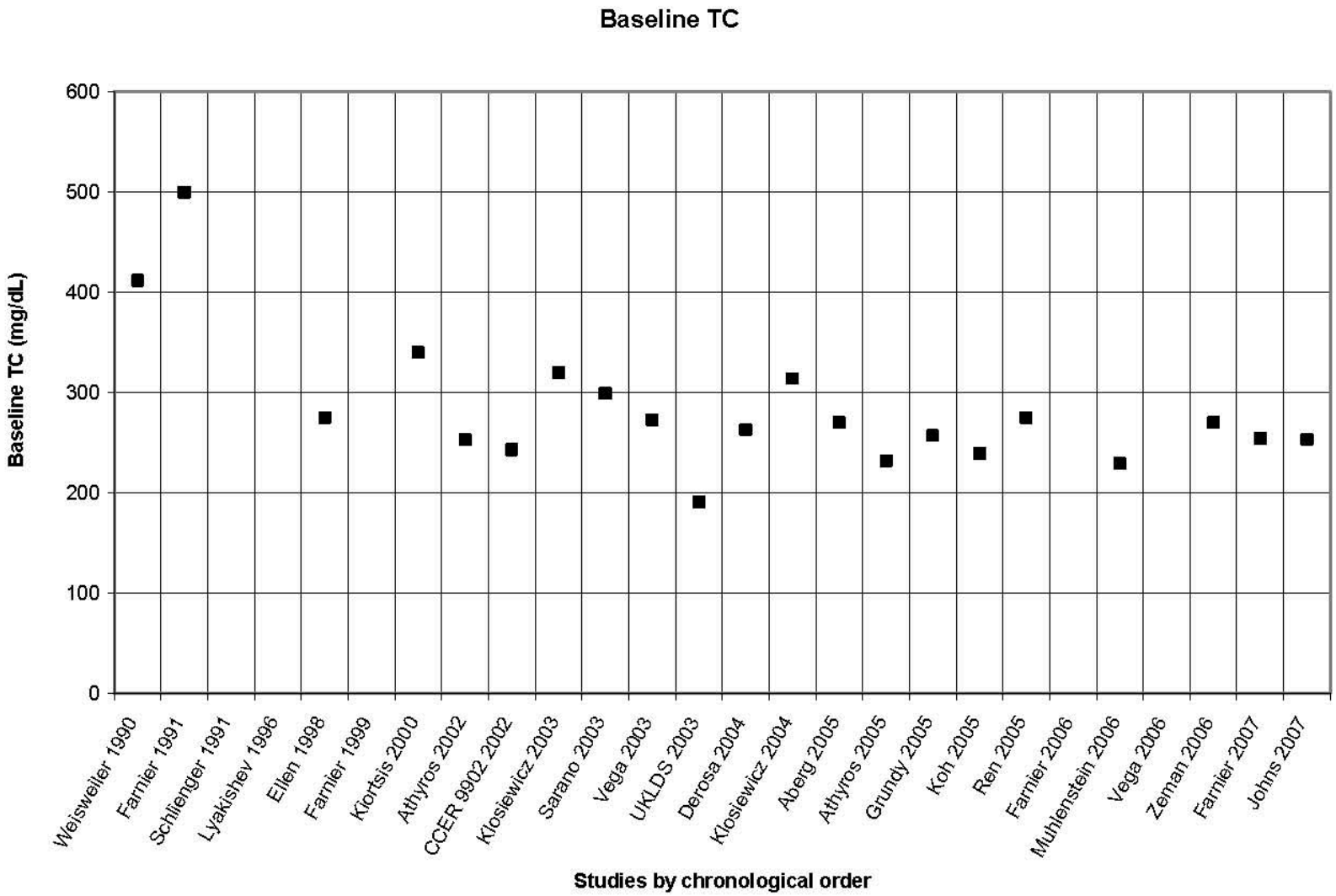
No.	Reference	Sex/age	Duration of treatment (months)	Dyslipidemia type	No of patients	Fenofibrate dosage (mg)	Statin* dosage (mg)	Safety
[11]	Durrington 2004	41% to 53% F Means: 58 to 61	6	IIb + T2DM	60 53 49 51	1-3X67M 1-3X67M 1-3X67M -	R5 R10 - R10-40	2 deaths: 1 for CABG (R), 1 for septicaemic shock after intestinal obstruction (F+R5) 5 withdrawals for treatment-related AE: 1 for myositis, 1 for peripheral edema, 1 for nausea in R10-40, 1 for myalgia,1 for diarrhea/vomiting in F+R5 5 cases of myalgias (2F+R5, 1F+R10, 1F, 1R10-40) 6 patients with single ALT > 3N (4F+R5, 2F+R10) 2 patients with clinically relevant ALT > 3N (1F+R5, 1F) 5 cases of CPK increase>3UNL (2F+R5, 2F+R10, 1F) none above 10 UNL
[26]	Klosiewicz 2004	220M/200F 56	12 (monother) 12 (combo)	Mixed hyperlipidemia	116 327 93	200M 200M -	S20 - S20	CPK 1-3xUNL 6% ALT 1-3xUNL 4% CPK 1-3xUNL 9% ALT 1-3xUNL 2% CPK 1-3xUNL 10% ALT 1-3xUNL 1%
[41]	Stefanutti 2004	27M/18F 59 ± 11	12	Mixed hyperlipidemia	5 26 11 3	200M 200M 300 Std 200M	S10 S20 S20 S30	No change in CPK or ALT; No reports of muscle symptoms

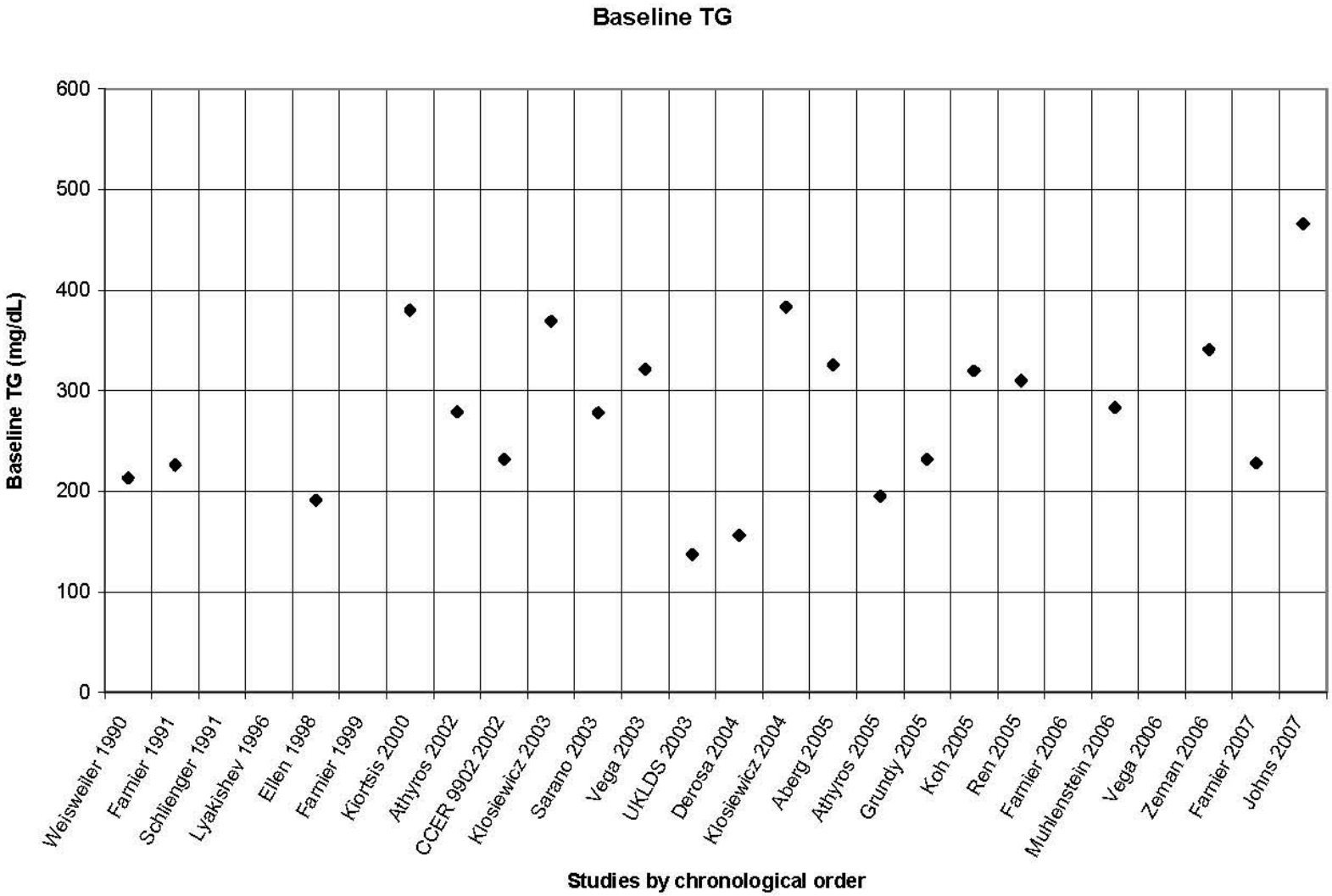
No.	Reference	Sex/age	Duration of treatment (months)	Dyslipidemia type	No of patients	Fenofibrate dosage (mg)	Statin* dosage (mg)	Safety
[3]	ACTG5087 Aberg 2003	159M/15F	9	HIV + dyslipidemia	123 88 86	200M 200M -	P40 - P40	4 withdrawals during monotherapy (3F;1P) for: myalgia and CPK elevation; asymptomatic CPK elevation; pancreatitis; asymptomatic lipase elevation. 3 withdrawals during combined Rx: 2 for asymptomatic lipase elevation; 1 for thrombocytopenia No report of rhabdomyolysis or hepatitis
[5]	Athyros 2005	189M/111F 59	12	Metabolic syndrome	100 100 100	200M 200M -	A20 - A20	3 withdrawals for myalgia without CPK increase (1F+A, 2A) 1 case of ALT elevation > 3 x UNL (A20) Creatinine % changes (-3% F+A, +8% F, -12% A) No case of myopathy.
[19]	Fegan 2005	37M/16F 63	3	T2DM	11 10 20 12	200 200 - -	0.4C - 0.4C -	Not reported

No.	Reference	Sex/age	Duration of treatment (months)	Dyslipidemia type	No of patients	Fenofibrate dosage (mg)	Statin* dosage (mg)	Safety
[21]	Grundy 2005	315M/303F 53 ± 9	3	Combined hyperlipidemia	411 207	160T -	S20 S20	No case of myopathy - 2 cases of CPK 5-10 x UNL and 1 case of CPK > 10 x UNL, all without symptoms. 3 withdrawals for muscle AEs (2F+S, 1S) 13 cases of myalgia (8 F+S, 5S) 9 cases of ALT>3N of which 8 with 2 consecutive elevations (8F+S, 2%) (8 F+S (2%))leading to withdrawal in 4 cases
[27]	Koh 2005	23M/33F 56 ± 1	2	Combined hyperlipidemia	56	200M 200M -	A10 - A10	CPK 1-3xUNL 7% ALT 1-3xUNL 14% CPK 1-3xUNL 4% ALT 1-3xUNL 7% CPK 1-3xUNL 2% ALT 1-3xUNL 7%
[30]	McIvor 2005	- 63 ± 2	4	MetS.	34	160T	Statin	Not reported
[36]	Ren 2005	118M/103F 54	3 to 6	Combined hyperlipidemia	81 68 72	200M 200M -	S10 - S10	One case of isolated muscle pain (S10) without CK elevation 2 cases of CPK elevation 1-3xUNL (1 F+S, 1 S) 5 cases of ALT or AST elevation 1-3xUNL (2 F+S, 1F, 2S)
[17]	Farnier 2006	-	3	Combined hyperlipidemia High risk	248	160T -	P40 P40	No safety issue.
[31]	Muhlestein 2006	165M/135F 61	3	Type 2 diabetes with mixed dyslipidemia	100 100 100	160T 160T -	S20 - S20	Not reported

No.	Reference	Sex/age	Duration of treatment (months)	Dyslipidemia type	No of patients	Fenofibrate dosage (mg)	Statin* dosage (mg)	Safety
[44]	Vega 2006	18M/2F 59 ± 7	4	T2DM	20 -	160T -	S20 S20	No changes in transaminase and CK levels
[51]	Zeman 2006	- 51	12	Primary hyperlipidemia	20 46	200M -	A20, S40 A20, S40	Not reported
[9]	Chatley 2007	57M/33F [30-70]	4	Mixed hyperlipidemia	25 20 45	160T-200 160T-200 -	A5 - A10-40	Significant increase in average transaminase and CK levels in the 3 treatment groups. Muscle pain reported in 16% patients on atorvastatin, 15% patients on fenofibrate and 16% patients on combination.
[18]	Farnier 2007	319M/292F 55	3	Mixed hyperlipidemia	183 184 184 60	160T 160T - -	S20 (+eze10) - S20 (+eze10) -	19 withdrawal for AEs (7F+S°E, 6F, 6S+E, 1P).11 cases of transaminase elevations ≥ 3 x ULN (6F and 5F+S+E). Myalgia reported in 21 patients (7S+E, 6F and 8F+S+E). 2 cases of CK ≥ 10 x ULN without muscle symptoms (2F).No report of pancreatitis
[22]	Johns 2007	128M/2F 53 ± 8	5	HIV+ MetS	42 70	? -	R5-40 R5-40	5 withdrawals for AES: 3 for elevated liver enzymes, 2 for complaints of muscle soreness.
[40]	Shah 2007	91M/11F 58	3	Acute coronary syndrome after PTCA	25 25 25 27	200M 200M - -	A10 S20 A20 S40	No significant elevations in bilirubin, transaminase levels. 2 cases of mild muscle pain (in the simvastatin group). No report of myopathy.

Appendix 4: Baseline TC and TG in 27 studies where combination and statin monotherapies are given at the same doses


Baseline TC
Baseline TC (mg/dL)
600
500
400
300
200
100
0
Weisweiler 1990
Farnier 1991
Schlienger 1991
Lyakishev 1996
Ellen 1998
Farnier 1999
Kiortsis 2000
Athyros 2002
CCER 9902 2002
Klosiewicz 2003
Sarano 2003
Vega 2003
UKLDS 2003
Derosa 2004
Klosiewicz 2004
Aberg 2005
Athyros 2005
Grundy 2005
Koh 2005
Ren 2005
Farnier 2006
Muhlenstein 2006
Vega 2006
Zeman 2006
Farnier 2007
Johns 2007
Studies by chronological order


Baseline TG
Baseline TG (mg/dL)
600
500
400
300
200
100
0
Weisweiler 1990
Farnier 1991
Schlienger 1991
Lyakishev 1996
Ellen 1998
Farnier 1999
Kiortsis 2000
Athyros 2002
CCER 9902 2002
Klosiewicz 2003
Sarano 2003
Vega 2003
UKLDS 2003
Derosa 2004
Klosiewicz 2004
Aberg 2005
Athyros 2005
Grundy 2005
Koh 2005
Ren 2005
Farnier 2006
Muhlenstein 2006
Vega 2006
Zeman 2006
Farnier 2007
Johns 2007
Studies by chronological order