

Fenofibrate therapy and cardiovascular protection in diabetes: recommendations after FIELD

Bruno Vergès^{a,b}

Purpose of review

The aim of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was to provide valuable information on the ability of fibrates to reduce cardiovascular risk in type 2 diabetes. The purpose of this review is to analyse results from FIELD and to see whether they may lead to modify the recommendations for treatment of diabetic dyslipidemia.

Recent findings

In FIELD, fenofibrate therapy was associated with a nonsignificant 11% reduction in the primary endpoint (coronary heart disease death, nonfatal myocardial infarction), corresponding to a significant 24% reduction in nonfatal myocardial infarction ($P=0.010$) and a nonsignificant 19% increase in CHD mortality. Fenofibrate reduced CHD events only in patients in primary prevention, but not in secondary prevention. Fenofibrate treatment was associated with less albuminuria progression and less retinopathy needing laser treatment.

Summary

FIELD's results are somewhat disappointing. The relatively low cardiovascular risk population from FIELD and the 'pollution' by statin therapy may not totally explain the weak results of fenofibrate in the reduction in CHD events. The significant increase in plasma homocysteine observed with fenofibrate could partly explain not only the higher number of venous thrombotic events, but also the poor effect of fenofibrate in reducing clinical outcomes, more particularly in patients with previous cardiovascular disease.

Keywords

coronary heart disease, diabetes, fenofibrate, fibrates, lipids

Abbreviations

| | |
|--------------|---|
| CHD | coronary heart disease |
| FIELD | Fenofibrate Intervention and Event Lowering in Diabetes study |
| HDL | high-density lipoprotein |
| LDL | low-density lipoprotein |

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Introduction

The abnormalities of lipid metabolism observed in type 2 diabetes are among the major factors contributing to vascular risk [1,2]. Diabetic dyslipidaemia involves quantitative (e.g. hypertriglyceridaemia and low high-density lipoprotein (HDL)-cholesterol level) and qualitative lipid abnormalities, which are potentially atherogenic [e.g. increased prevalence of small, dense low-density lipoprotein (LDL) particles] [3]. Fibrates are known to be effective in increasing plasma HDL-cholesterol, and in reducing plasma triglyceride levels and the number of small, dense LDL particles [4]. Thus, they appear to be appropriate drugs to treat diabetic dyslipidaemia and potentially to reduce cardiovascular risk in patients with type 2 diabetes. Before the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, data on the effect of fibrate therapy on the reduction in cardiovascular risk in patients with diabetes were limited to subgroup analyses from VAHIT and BIP, which were not sufficient to draw firm conclusions [5,6]. A few months ago, the results of FIELD [7^{*}] were published; it was an intervention study with fenofibrate conducted in a large population of patients with type 2 diabetes, and its aim was to provide valuable information and robust data on the ability of fibrates to reduce cardiovascular risk in patients with diabetes. As we will discuss below, the results from FIELD are somewhat disappointing and raise some questions. In comparison with clinical trials performed with statins in patients with diabetes, FIELD has not been able to show a robust effect of fenofibrate in reducing cardiovascular risk in type 2 diabetes.

FIELD: main results

FIELD was performed in 9795 patients with type 2 diabetes, aged 50–75 years, with a total cholesterol concentration of 3.0–6.5 mmol/l and a total cholesterol/HDL-cholesterol ratio of 4.0 or more or a plasma triglyceride concentration of 1.0–5.0 mmol/l [7^{*}]. Patients were not taking statin therapy at baseline and were randomly assigned to micronized fenofibrate 200 mg/day

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^aService Endocrinologie, Diabétologie et Maladies Métaboliques, Centre Hospitalier Universitaire de Dijon and ^bINSERM U 498, Faculté de Médecine, Dijon, France

Correspondence to Prof. Bruno Vergès, Service Endocrinologie, Diabétologie et Maladies Métaboliques, Hôpital du Bocage, 21000 Dijon, France
Tel: +33 3 80 29 34 53; fax: +33 3 80 29 35 19;
e-mail: bruno.verges@chu-dijon.fr

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or placebo. The studied population was composed of 2131 patients (22%) with previous cardiovascular disease and 7664 (78%) without. During the 5-years study duration, similar proportions in each group discontinued study medication (10% placebo, 11% fenofibrate) and more patients on placebo (17%) than on fenofibrate (8%, $P < 0.0001$) commenced other hypolipidaemic treatments, predominantly statins. Fenofibrate therapy was associated with a nonsignificant 11% reduction in the primary endpoint (coronary heart disease [CHD] death, nonfatal myocardial infarction) ($P = 0.16$), corresponding to a significant 24% reduction in nonfatal myocardial infarction ($P = 0.010$) and a nonsignificant 19% increase in CHD mortality ($P = 0.22$). A significant 11% reduction in total cardiovascular disease events ($P = 0.035$) in patients allocated to fenofibrate was observed. Subgroup analysis showed that reduction in total cardiovascular disease events was significant only in patients in primary prevention and in those aged under 65 years. Fenofibrate treatment was associated with less albuminuria progression ($P = 0.002$) and less retinopathy needing laser treatment ($P = 0.0003$). Fenofibrate was associated with a slight increase in pancreatitis (0.5 compared with 0.8%, $P = 0.031$) and pulmonary embolism (0.7 compared with 1.1%, $P = 0.022$).

Population from FIELD

The main differences between the population from FIELD and those from the three major cardiovascular prevention trials including patients with diabetes – CARDS, PROactive and the diabetic subgroup from HPS – are shown in Table 1 [7*,8–10]. Since the publication of FIELD, it has been largely discussed that patients included in FIELD were low cardiovascular risk patients. This is true in comparison with the PROactive study. We have to acknowledge, however, that when taking into account concomitant cardiovascular risk factors and prior coronary disease, cardiovascular risk in patients from FIELD was not so different from the

one in patients from HPS or CARDS. Patients from FIELD had similar plasma triglyceride, LDL-cholesterol and HDL-cholesterol levels to patients from the other cardiovascular clinical trials. The only exception is the presence of higher HDL-cholesterol levels in CARDS, which have been attributed to the measurement method used in that study [9].

As compared with diabetic patients from CARDS, HPS and PROactive, patients from FIELD showed a shorter duration of diabetes, a lower mean HbA1c and a reduced prevalence of retinopathy at baseline, and fewer patients were treated with insulin (Table 1). All these data clearly indicate that diabetes was less severe in FIELD than in the other cardiovascular prevention trials. This is, here, the main difference.

FIELD: 'pollution' by statins

In FIELD, patients were not taking statin therapy at baseline. Initiation of statin therapy during the study, however, was not forbidden and at the discretion of the patient's primary care doctor or specialist physician. During the study, there was a progressive increase in the proportion of patients who were prescribed additional lipid-lowering therapy, predominantly statins. By study end, 1657 patients allocated to placebo (34%) and 890 patients allocated to fenofibrate (18%) were on statins. This pattern corresponded with an average use of statins over the entire study significantly more important in patients on placebo (16%) than in those on fenofibrate (7.5%, $P < 0.0001$). Thus, we may think that the global results of FIELD have been somewhat 'polluted' by the larger use of statins in the placebo group than in the fenofibrate group. Indeed, after adjustment for statin therapy, fenofibrate reduced the risk of CHD events (primary endpoint) by 19% ($P = 0.01$) and of total cardiovascular events by 15% ($P = 0.004$). If the 'pollution' by statin therapy has undoubtedly weakened the results of FIELD, however, it does not totally explain why the

Table 1 Main characteristics of patients with diabetes in four major cardiovascular prevention trials (CARDS, HPS, PROactive and FIELD)

| | CARDS ($n = 2038$) [9] | HPS ($n = 5963$) [8] | PROactive ($n = 5238$) [10] | FIELD ($n = 9795$) [7*] |
|--------------------------------|--------------------------|------------------------|-------------------------------|---------------------------|
| Drug | Atorvastatin | Simvastatin | Pioglitazone | Fenofibrate |
| Age (years) | 61.6 | 62.1 | 61.7 | 62.2 |
| Duration of diabetes (years) | 7.8 | 9.3 | 8.0 | 5.0 |
| BMI (kg/m^2) | 28.8 | 28.6 | 30.8 | 29.8 |
| Hypertension (%) | 84% | 40% | 71.2% | 50% |
| Current smokers (%) | 23% | 13% | 14% | 9% |
| Prior coronary disease (%) | 0% | 33% | 65.5% | 22% |
| Retinopathy (%) | 30% | ND | 23% | 8% |
| HbA1c (%) | 7.8 | 7.02 | 7.8 | 6.9 |
| Treatment with insulin (%) | 20% | 25% | 33.5% | 14% |
| Antithrombotic treatment (%) | 15% | ND | 84% | 32% |
| ACE inhibitors/ARBs (%) | 44.5% | ND | 84% | 32% |
| LDL-cholesterol (mmol/l) | 3.02 | 3.20 | 2.90 | 3.07 |
| HDL-cholesterol (mmol/l) | 1.42 | 1.06 | 1.10 | 1.10 |
| Triglycerides (mmol/l) | 1.63 | 2.30 | 1.80 | 1.73 |

ND, no data.

Table 2 Results on lipids and coronary heart disease events of statins in patients with diabetes from five trials and of fenofibrate in FIELD

| | 4S (n = 202) [11] | CARDS (n = 2038) [9] | HPS (n = 5963) [8] | CARE (n = 586) [12] | TNT (n = 1500) [13] | FIELD (n = 9795) [7*] | |
|-----------------------|-----------------------------|------------------------------|-----------------------------|-----------------------------|---|---|--|
| Drug | Simvastatin 40 mg vs PCB | Atorvastatin 10 mg vs PCB | Simvastatin 40 mg vs PCB | Pravastatin 40 mg vs PCB | Atorvastatin 80 mg vs atorvastatin 10 mg | Fenofibrate 200 mg vs PCB | |
| Mean duration (years) | 5.4 | 3.9 | 5 | 5 | 4.9 | 5 | |
| | | | | | | <i>With adjustment for statin therapy</i> | <i>Without adjustment for statin therapy</i> |
| Change in LDL-C (%) | -36 | -40 | -31 | -27 | -20 | -15 | -6 |
| Change in HDL-C (%) | +7 | +1 | +3 | +4 | +2 | +2 | +1 |
| Change in TG (%) | -11 | -19 | -13 | -13 | -18 | -27 | -22 |
| Reduction in CHD (%) | -55 | -36 | -25 | -25 | -22 | -19 | -11 |
| | (P=0.002) | (P=0.001) | (P<0.001) | (P=0.05) | (P=0.026) | (P=0.01) | (P=0.16) |

LDL-C, LDL-cholesterol; HDL-C, HDL-cholesterol; TG, triglycerides; CHD, coronary heart disease.

reduction in CHD events was not as great as expected. Even after adjustment for statin therapy, reduction in CHD events remains less important than in patients with diabetes from other statin trials (Table 2) [7*,8,9,11–13].

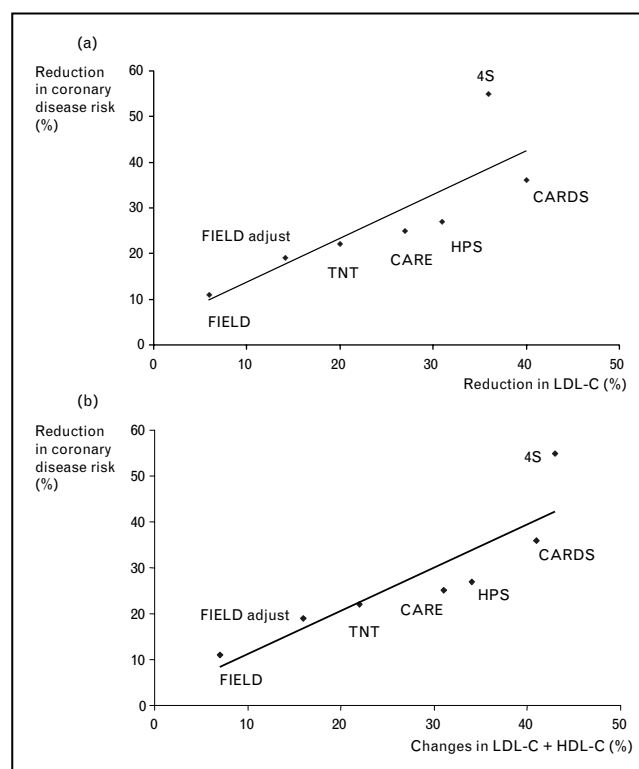
FIELD: relationship between the effects of fenofibrate on lipids and on coronary heart disease

In FIELD, allocation to fenofibrate resulted, at the end of the study, in reductions relative to placebo in LDL-cholesterol of 6%, in triglycerides of 22% and increases in levels of HDL-cholesterol of 1.2%. After adjustment for statin therapy, patients allocated to fenofibrate showed, at the end of the study, reductions in LDL-cholesterol of 15%, in triglycerides of 27% and increases in levels of HDL-cholesterol of 2% (Table 2). When we plot the reduction in relative coronary disease risk and the diminution in mean plasma LDL-cholesterol level in all groups of patients with diabetes from trials performed with statin (CARDS, CARE, HPS, TNT, 4S) and from FIELD, we obtain a linear curve (Fig. 1a) [8,9,11–13]. We have a similar linear curve when plotting the reduction in relative coronary disease risk and the changes in both plasma LDL-cholesterol and HDL-cholesterol levels (Fig. 1b). Given the minimal effects of fenofibrate on HDL-cholesterol in FIELD, it seems clear that the effects of fenofibrate on coronary disease are mainly related to the diminution of plasma LDL-cholesterol levels. Interestingly, a similar relationship between reduction in coronary disease events and diminution in mean plasma LDL-cholesterol is found in the whole FIELD population after adjustment for statin therapy, indicating that the main effect of fenofibrate on coronary disease, in FIELD, is driven by modification of plasma LDL-cholesterol levels. We may think that the poor effect of fenofibrate on CHD events, in FIELD, is related to the weak reduction in mean plasma LDL-cholesterol levels. Indeed, a metaanalysis of 14 randomized trials of statins has shown that statin therapy is associated with a 22–26% reduction in coronary events per 1 mmol/l difference in LDL-cholesterol [14].

Differences between FIELD and other fibrate clinical trials

Before FIELD, some important clinical outcome trials with fibrates have been performed: the primary prevention Helsinki Heart Study [15] and the secondary prevention study VAHIT (Veterans Affairs HDL

Figure 1 Relationships between LDL and HDL-cholesterol levels and reduction in relative coronary disease risk



(a) Relationship between the diminution in mean plasma LDL-cholesterol level and the reduction in relative coronary disease risk in patients with diabetes from five trials with statins (4S, CARDS, HPS, CARE, TNT) and in FIELD. (b) Relationship between the changes in mean plasma LDL-cholesterol and HDL-cholesterol levels (diminution in LDL-cholesterol + increase in HDL-cholesterol) and the reduction in relative coronary disease risk in patients with diabetes from five trials with statins (4S, CARDS, HPS, CARE, TNT) and in FIELD.

Intervention Trial) [16] with gemfibrozil and the secondary prevention study BIP (Bezafibrate Infarction Prevention) with bezafibrate [17]. Among the 4081 men included in the Helsinki Heart study, 135 had type 2 diabetes and gemfibrozil reduced cardiovascular risk by 68% in this subgroup, but the difference was not statistically significant because of the small number of diabetic patients included in the study [18]. VAHIT showed that gemfibrozil induced a significant 24% reduction in the incidence of acute cardiovascular events ($P < 0.001$). In the subgroup of 769 patients with diabetes, gemfibrozil induced a 32% reduction in the incidence of acute cardiovascular events ($P = 0.004$) and a 41% reduction in cardiovascular mortality risk ($P = 0.02$) [5]. In BIP, bezafibrate treatment was associated with a nonsignificant 9.6% reduction in the incidence of cardiovascular events, in the entire population [17]. In bezafibrate-treated patients, a significant reduction in fatal or nonfatal myocardial infarction was noted in the subgroup of patients with metabolic syndrome [19], but not in the subgroup of patients with diabetes [20]. The reduction in CHD events noted in FIELD is less than that observed in other randomized trials of fibrate therapy, particularly those with gemfibrozil, such as VAHIT. This may partly be due to different patients' characteristics and lipid profiles. In VAHIT, patients with diabetes were higher cardiovascular risk individuals and had lower LDL-cholesterol and HDL-cholesterol baseline values. The mean baseline HDL-cholesterol level was 0.80 mmol/l in VAHIT compared with 1.10 mmol/l in FIELD. These lower baseline HDL-cholesterol levels could partly explain the larger benefit of fibrate therapy in reducing CHD events in VAHIT. This is in accordance with the results of FIELD, in which fenofibrate showed a higher benefit in reducing total cardiovascular disease events in the subgroup of patients with low baseline HDL-cholesterol levels (−14%) than in the subgroup of patients with high baseline HDL-cholesterol levels (−4%). Moreover, the increase in HDL-cholesterol was much more important in patients with diabetes from VAHIT (+5%) than in patients from FIELD (+1%). Data from VAHIT have shown that concentrations of HDL-cholesterol achieved with gemfibrozil treatment during the trial predicted the reduction in CHD events [21]. The change in HDL-cholesterol, however, only partially explained the beneficial cardiovascular effect of gemfibrozil [21]. Indeed, changes in HDL-cholesterol do not totally explain the effects of fibrates on the reduction in CHD events. For instance, in BIP, a significant 18% increase in mean HDL-cholesterol was observed but the reduction in the incidence of cardiovascular events was limited and nonsignificant [17]. Many data indicate that the potential cardioprotective effect of fibrates could be related to additional actions such as the reduction in small, dense LDL particles [22], and vascular or anti-inflammatory effects mediated in part through the

activation peroxisome proliferator-activated receptors [23]. As the reduction in cardiovascular events is lower in FIELD than in patients with diabetes from the Helsinki Heart study or VAHIT, we cannot exclude potential differences between gemfibrozil and fenofibrate. Among potential differences between the two drugs, we may underline a higher increase in plasma homocysteine with fenofibrate than with gemfibrozil (see below).

FIELD: different effect of fenofibrate in primary and secondary prevention

In FIELD, fenofibrate induced a significant relative risk reduction in cardiovascular disease events of 19% in patients without previous cardiovascular disease but had no effect in patients with previous cardiovascular disease. This result is somewhat surprising because, in most trials, the greater cardiovascular risk reduction is observed in secondary prevention and in high-risk patients. It has been suggested that this result could partially be due to the large proportion of patients receiving statins in secondary prevention. The authors of FIELD, however, acknowledge that the differences between the primary and the secondary prevention groups do not seem to be explained by the differential use of statin therapy [7^{*}]. The reasons for the different effect of fenofibrate in primary and secondary prevention remain unclear. We could hypothesize that this may be related to the significant plasma homocysteine increase induced by fenofibrate (see below). As increased plasma homocysteine level is an established risk factor for thrombosis [24^{*}] and associated with atherothrombotic events [25], we can speculate that in patients with preexistent atherosclerotic plaques, such as in secondary prevention, the beneficial antiatherogenic effect of fenofibrate could have been abolished by a potential pro-thrombotic effect related to plasma homocysteine increase.

FIELD: modest effect of fenofibrate on HDL-cholesterol

In FIELD, allocation to fenofibrate resulted in an increase relative to placebo in plasma HDL-cholesterol of 5% after 4 months of treatment, but the difference decreased over time to 3.45% at 2 years and 1.2% at the end of the study. The fenofibrate-induced increase in HDL-cholesterol in FIELD is lower than in DAIS, in which the fenofibrate-treated patients showed a mean 7.5% increase in plasma HDL-cholesterol at the end of the 3-year study [22]. In FIELD, however, mean HDL-cholesterol at baseline was higher than in DAIS (1.10 compared with 1.01 mmol/l) and this could have somewhat attenuated the effect of fenofibrate on the increase in plasma HDL-cholesterol levels. In the primary prevention Helsinki Heart Study [15], an initial 14% increase in plasma HDL-cholesterol was noted with gemfibrozil but was followed by a small decline with time to 9% at the

end of the study. In the secondary prevention VAHIT study, gemfibrozil induced a 5% increase in HDL-cholesterol at the end of the study in the group of patients with diabetes (5%). Although the different results of fibrates on HDL-cholesterol levels in those trials may be due to different patients' characteristics and lipid profiles, we can also hypothesize that the declining effect of fibrates, and more particularly fenofibrate, on HDL-cholesterol effect over time could also be due to the increase in plasma homocysteine. Indeed, it has recently been reported [26^{*}] that elevated plasma homocysteine reduces apoA-I expression in mice and humans, and a negative correlation between plasma homocysteine and HDL-cholesterol has been found. It has been shown, in several studies, that fenofibrate and bezafibrate lead to a 20–40% elevation in plasma level of homocysteine [27], which is confirmed in FIELD, in which a 39% homocysteine increase is observed in fenofibrate-treated patients. As homocysteine reduces apoA-I expression, we may think that the rise in plasma homocysteine induced by fenofibrate could explain the reduction in plasma HDL-cholesterol increase over time. Gemfibrozil has been shown to increase less plasma homocysteine than fenofibrate [28]. This could partially explain the better effect in reducing cardiovascular risk of gemfibrozil in VAHIT and the Helsinki Heart Study than fenofibrate in FIELD.

FIELD: effects on microvascular disease

In FIELD, fenofibrate therapy was associated with a significant improvement in diabetic microvascular disease with a 2.6% reduction in grade of albuminuria ($P=0.002$) and a 1.6% reduction in laser treatment for retinopathy ($P=0.0003$). These results confirm the beneficial effect of fenofibrate on the progression of albuminuria as reported in DAIS [29]. The mechanisms of these effects are unknown and cannot be explained by changes in HbA1c or by the minor reduction in blood pressure noted in the fenofibrate group. We cannot totally exclude that the effects of fenofibrate on microvascular disease may be partially explained by modifications of lipid profiles. Indeed, LDL-cholesterol level, small, dense LDL particles and plasma triglycerides have been shown to be factors for diabetic nephropathy [30–33] and retinopathy [33,34]. Moreover, reduction in plasma LDL-cholesterol with statins has been shown to retard the progression of both nephropathy [35] and retinopathy [36]. The beneficial effects of fenofibrate on microvascular disease could also be related to its vascular or anti-inflammatory effects mediated through the activation of peroxisome proliferator-activated receptors [23].

FIELD: tolerability and side effects

A nonsignificant increase in cardiovascular mortality was observed in FIELD. Such a nonsignificant increase in sudden cardiac death among patients treated with fibrates

has also been noted in the Helsinki Heart Study [15] and in BIP [17]. This increase in sudden death, although nonsignificant, is still a matter of debate and it is not clear whether it should be a concern.

A slight, but significant, increase in pancreatitis (0.5 compared with 0.8%, $P=0.031$) was observed in FIELD. This excess pancreatitis has been noted in many fibrate trials and may reflect the lithogenic potential of fibrates [37]. An important point is both the significant increase in homocysteine plasma levels and the incidence of venous thrombotic events. As increased plasma homocysteine level is a risk factor for thrombosis [24^{*}], we may think that the significant plasma homocysteine increase induced by fenofibrate could account for the augmented number of venous thrombotic events.

An interesting result from FIELD is the good tolerance of fenofibrate when associated with statin without any increased risk for muscle pains or rhabdomyolysis.

Conclusion

FIELD was needed to provide valuable information and robust data on the ability of fibrates to reduce cardiovascular risk in patients with type 2 diabetes. We must acknowledge, however, that results from FIELD are somewhat disappointing. The significant 24% reduction in nonfatal myocardial infarction is shadowed by the 19% increase in CHD mortality leading to a nonsignificant reduction in the primary endpoint (CHD death, nonfatal myocardial infarction). Another intriguing result is the absence of effect of fenofibrate in secondary prevention when a significant reduction in cardiovascular disease events of 19% is observed in primary prevention. The relatively low cardiovascular risk population from FIELD and the 'pollution' by statin therapy may not totally explain the weak results of fenofibrate on the reduction in CHD events. The significant increase in plasma homocysteine levels observed in fenofibrate-treated patients from FIELD could partly explain not only the higher number of venous thrombotic events and pulmonary emboli, but also the poor effect of fenofibrate in reducing clinical outcomes, more particularly in patients with previous cardiovascular disease. Thus, FIELD has not been able to show a robust effect of fenofibrate in reducing cardiovascular risk in type 2 diabetes. If the question is 'Can fenofibrate replace statin therapy for reducing cardiovascular risk in patients with type 2 diabetes?', the clear answer from FIELD is 'no' because the effects of fenofibrate on cardiovascular outcomes are not as important and conclusive as the ones observed with statins in patients with diabetes from other large trials. The remaining question is to know whether there is a potential benefit to add fenofibrate to statin therapy, in patients with diabetes, more particularly when having low HDL-cholesterol and increased

triglycerides. We will have to wait for the results of the on-going Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [38], studying the effects of the combination therapy (fenofibrate + simvastatin) on CHD events.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 667).

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