Contents available at ScienceDirect

Diabetes Research and Clinical Practice

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

Fenofibrate effects on carotid artery intima-media thickness in adults with type 2 diabetes mellitus: A FIELD substudy

Jason A. Harmer[a,b,c,*], *Anthony C. Keech*[a,d,e], *Anne-Sophie Veillard*[e], *Michael R. Skilton*[a,d], *Gerald F. Watts*[f,g], *David S. Celermajer*[a,d], *for the FIELD Vascular Study Investigators*

[a] *Sydney Medical School, University of Sydney, Sydney, NSW, Australia*
[b] *Department of Cardiology, Royal North Shore Hospital, Sydney, NSW, Australia*
[c] *Faculty of Medicine, Western Sydney University, Sydney, NSW, Australia*
[d] *Department of Cardiology, Royal Prince Alfred Hospital, Sydney, NSW, Australia*
[e] *NHMRC Clinical Trials Center, University of Sydney, Sydney, NSW, Australia*
[f] *Lipid Disorders Clinic, Department of Cardiology, Royal Perth Hospital, Perth, WA, Australia*
[g] *School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia*

ARTICLE INFO

Article history:
Received 19 February 2018
Received in revised form
16 April 2018
Accepted 8 May 2018

Keywords:
Diabetes mellitus
Carotid intima-media thickness
Atherosclerosis
Fenofibrate
Randomised controlled trial
Cardiovascular disease

ABSTRACT

Aim: Dyslipidemia in type 2 diabetes contributes to an increased risk of cardiovascular disease. Fenofibrate, a lipid-regulating peroxisome proliferator-activated receptor-α (PPARα) agonist, has been shown to reduce vascular complications in adults with type 2 diabetes. The mechanisms for such benefit, however, are not yet well understood. We examined the effects of fenofibrate on carotid intima-media thickness (IMT), a marker of subclinical atherosclerosis, in adults with type 2 diabetes.

Methods: In a prospectively designed substudy of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, we assessed carotid IMT in a subset of 422 representative adults. Traditional risk factors and IMT were assessed at 2 and 4 years after randomisation to fenofibrate (200 mg daily) or placebo. The prespecified primary study endpoint was the difference in IMT between treatment groups at 4 years. *Post-hoc* analyses were performed according to dyslipidemia and metabolic syndrome status.

Results: There was no difference in carotid IMT comparing those assigned to fenofibrate or placebo at 2 or 4 years, despite statistically significant improvement in lipid and lipoprotein parameters at 2 and 4 years, including TC, LDL-C and TG, and HDL-C at 4 months and 2 years. Similarly, there was no difference in carotid IMT on fenofibrate compared with placebo in those with dyslipidemia or metabolic syndrome.

Conclusions: Fenofibrate was not associated with improved carotid IMT in adults with type 2 diabetes when compared with placebo, despite a statistically significant improvement in TC, LDL-C and TG at 2 and 4 years, and HDL-C at 4 months and 2 years.

* Corresponding author at: Department of Cardiology, Royal North Shore Hospital, Reserve Road, St Leonards, NSW 2065, Australia.
E-mail address: jhar2154@uni.sydney.edu.au (J.A. Harmer).

https://doi.org/10.1016/j.diabres.2018.05.006
0168-8227/

1. Introduction

CVD is the leading cause of mortality and morbidity in patients with type 2 diabetes. Dyslipidemia is highly prevalent in type 2 diabetes and is characterised by an abnormal lipoprotein pattern: low HDL-C, high TG and the presence of smaller, dense LDL-C particles. Despite improvement in CVD mortality from the use of statins there remains considerable residual risk of CVD events in patients with type 2 diabetes with lipid and lipoprotein abnormalities.

Fibrates, a class of lipid-modifying peroxisome proliferator-activated receptor-α (PPAR-α) agonists, can improve lipid and lipoprotein abnormalities, in particular those defined by dyslipidemia. Fibrates (*e.g.* fenofibrate, gemfibrozil and bezafibrate) also have non-lipid-modifying effects, which may regulate other pathways implicated in the pathogenesis of atherosclerosis. Until recently, however, there has been limited evidence in support of the use of fibrates for improving clinical cardiovascular endpoints such as CVD mortality or events.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a multi-center trial designed to investigate the potential effects of fenofibrate on cardiovascular mortality and events in patients with type 2 diabetes. This study showed a significant reduction in total CVD mortality on fenofibrate mostly due to a reduction in non-fatal events and coronary revascularisations. In addition, various substudies of the FIELD study exploring microvascular clinical endpoints – such as diabetic retinopathy [1], nephropathy [2–4], and amputations [5] – reported important fenofibrate-related benefits.

Vascular substudies were prospectively planned in the FIELD study design to investigate possible mechanisms explaining the potential arterial benefits of fenofibrate in this population. The aim of this substudy was to investigate the effect of fenofibrate (versus matched placebo) on the progression of carotid IMT as a measure of subclinical large vessel atherosclerosis which has been linked to CV event rates. The primary study endpoint was the difference in carotid IMT between treatment groups at 4 years expressed as a change from baseline.

2. Materials and Methods

2.1. *Subjects*

A detailed description of subjects in the FIELD study has been published [6–8]. The FIELD study was a multinational, double-blind, placebo-controlled randomised trial involving 9795 patients in 63 sites in Australia, New Zealand and Finland, investigating the effects of comicronised fenofibrate (200 mg) versus placebo on fatal and non-fatal coronary events in patients with type 2 diabetes, aged 50–75 years. Inclusion and exclusion criteria have been well described elsewhere [6–8].

Of the 9795 subjects in the FIELD study, 6051 were randomised in 39 sites within Australia. Seven sites were chosen to participate in the FIELD IMT vascular substudy on the basis of demonstrated expertise in conducting carotid artery ultrasound scans for the assessment of IMT. At these sites, subjects were randomised to receive either fenofibrate or matching placebo and subsequently invited to participate in the vascular substudy. Entry into the substudy required a baseline ultrasound scan of suitable quality to accurately assess carotid IMT. At baseline, 422 subjects had carotid artery ultrasound scans performed and 387 (91%) were considered of acceptable quality for inclusion. At 2 years, 333 subjects (86%) returned for carotid artery ultrasound scans and were included in the IMT analyses. At 4 years, 338 subjects (87%) were studied and included in the IMT analyses. Subjects who were lost to follow-up or had declined participation at 2 years were contacted again, if possible, and invited to participate in the vascular substudy at 4 years. There were no statistically significant differences when comparing baseline characteristics of subjects who underwent IMT testing at baseline, 2 or 4 years.

There were no significant differences between the 422 subjects in the vascular substudy and the 9795 subjects in the entire FIELD cohort in the proportions of males and females, age at visit 1, duration of diabetes, body mass index, waist: hip ratio, prior history of CVD, hypertension, cigarette smoking status, fasting blood levels of insulin, triglycerides, homocysteine, or urinary albumin. There were minor statistically significant differences in systolic blood pressure (139 mmHg in the vascular substudy versus 141 mmHg for the entire FIELD cohort, $P < 0.01$), diastolic blood pressure (81 mmHg versus 82 mmHg, $P < 0.01$), prior history of angina (8.5% versus 12.3%, $P = 0.02$), fasting levels of total cholesterol (4.87 mmol/L versus 5.04 mmol/L, $P < 0.001$), low-density lipoprotein (LDL)-cholesterol (2.91 mmol/L versus 3.07 mmol/L, $P < 0.001$), HDL-cholesterol (1.06 mmol/L versus 1.10 mmol/L, $P < 0.01$), glucose (8.28 mmol/L versus 8.45 mmol/L, $P = 0.02$), haemoglobin A1c (6.8% versus 6.9%, $P = 0.04$), plasma creatinine (75.5 μmol/L versus 77.7 μmol/L, $P < 0.01$), and reported regular use of angiotensin II receptor antagonists (10.9% versus 5.1%, $P < 0.001$) and β-blockers (10.9% versus 14.7%, $P = 0.03$).

A detailed clinical history was obtained in all subjects. A prior history of CVD included any one of the following: myocardial infarction, angina (stable or unstable), stroke, claudication or peripheral vascular disease, or arterial revascularisations (including coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, or peripheral revascularisations). A family history of CVD was defined as CVD in a first degree relative before the age of 55 years. Smoking history was recorded as present (current smoker), past (ex-smoker) or never smoker based on self-report. History of hypertension, age at diagnosis of diabetes and the presence of diabetes complications were also obtained by self-report. The method of diabetes control was documented as any one of the following: diet only, oral hypoglycaemic agents only (distinguishing those using metformin, a sulfonylurea, both metformin and a sulfonylurea, or another class of oral agent alone or in combination with other agents), diet