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Long-Term Effects of Fenofibrate on Carotid Intima-Media Thickness and Augmentation Index in Subjects With Type 2 Diabetes Mellitus

Anne Hiukka, MD,* Jukka Westerbacka, MD, PhD,† Eeva S. Leinonen, MD, PhD,* Hiroshi Watanabe, MD, PhD,* Olov Wiklund, MD, PhD,‡ Lillemor Mattson Hultén, PhD,‡ Jukka T. Salonen, DMEDSC,§|| Tomi-Pekka Tuomainen, MD, PhD,§ Hannele Yki-Järvinen, MD, PhD,† Anthony C. Keech, MD, PhD,¶|| Marja-Riitta Taskinen, MD, PhD*
Helsinki and Kuopio, Finland; Göteborg, Sweden; and Sydney, Australia

- Objectives** The aim of this substudy was to ascertain whether long-term treatment with fenofibrate reduces surrogate measures of atherosclerosis, biomarkers of inflammation, and endothelial activation in patients with type 2 diabetes.
- Background** Some fibrates may decrease cardiovascular events, improve endothelial function, and reduce levels of acute-phase proteins. In the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study, fenofibrate failed to decrease the primary end point of coronary events in patients with type 2 diabetes.
- Methods** A total of 170 patients with type 2 diabetes of the FIELD Helsinki cohort were randomly assigned to micronized fenofibrate 200 mg/day or placebo in a double-blind design. Carotid intima-media thickness (IMT) and the augmentation index (a measure of large artery stiffness) were measured at baseline and at second- and fifth-year visits. Plasma levels of interleukin (IL)-6, C-reactive protein (CRP), serum amyloid A (SAA), secretory phospholipase A2 IIA (SPLA2), E-selectin, vascular cellular adhesion molecule (VCAM)-1, and intercellular adhesion molecule (ICAM)-1 were determined by commercial enzyme-linked immunosorbent assay kits at the same visits.
- Results** IMT and the augmentation index increased similarly in both treatment groups during the study. Plasma levels of CRP, IL-6, SPLA2, SAA, VCAM-1, ICAM-1, and E-selectin remained unchanged in both groups.
- Conclusions** Fenofibrate treatment was not associated with beneficial changes in IMT, augmentation index, or biomarkers of inflammation and endothelial function. (Fenofibrate Intervention and Event Lowering in Diabetes; [NCT00132886](#)) (J Am Coll Cardiol 2008;52:2190-7) © 2008 by the American College of Cardiology Foundation

Type 2 diabetes increases the risk of coronary heart disease at least 2- to 3-fold. Patients with type 2 diabetes without myocardial infarction (MI) have a risk for fatal MI similar to

nondiabetic subjects with histories of MI (1,2). Statins effectively reduce cardiovascular end points in type 2 diabetes (3). Regarding surrogate markers of atherosclerosis in type 2 diabetes, statins improve endothelial dysfunction (4,5) and reduce markers of endothelial activation and inflammation (6-8), progression of intima-media thickness (9), and augmentation index (10,11).

See page 2206

From the Departments of *Medicine and †Diabetes, University of Helsinki, Helsinki University Central Hospital and Biomedicum, Helsinki, Finland; ‡Wallenberg Laboratory for Cardiovascular Research, Sahlgrenska University Hospital, Göteborg, Sweden; §Research Institute of Public Health, University of Kuopio, Kuopio, Finland; ||Oy Jurilab Ltd., Kuopio, Finland; and the ¶NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia. This work was supported by grants from the Finnish Diabetes Association (to Drs. Leinonen and Taskinen), Jenny and Antti Wihuri Fund (to Dr. Leinonen), Helsinki University Central Hospital Research Foundation (to Drs. Hiukka, Leinonen, and Taskinen), Aarne Koskelo Foundation (to Dr. Hiukka), Aarne and Aili Turunen Foundation (to Dr. Hiukka), Alumni Association for Hiroshima University Graduate School of Biomedical Science (to Dr. Watanabe), and Sigrid Juselius Foundation (to Dr. Taskinen).

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Considering the abundant data on slower progression of atherosclerosis with statins, studies on fibrates are surprisingly scarce. Fibrates reduced coronary heart disease events in subjects with type 2 diabetes or metabolic syndrome in subgroup analyses of the VA-HIT (Veterans Administration High-density lipoprotein Intervention Trial) and BIP

(Bezafibrate Infarction Prevention) studies (12,13). In DAIS (Diabetes Atherosclerosis Intervention Study), fenofibrate slowed progression of coronary atherosclerosis but did not significantly reduce cardiac end points (14). Studies with carotid intima-media thickness (IMT) as a surrogate end point have produced inconsistent results: one with slower progression of carotid atherosclerosis in patients on fenofibrate compared with placebo (15) and one with no effect of bezafibrate on IMT (16), whereas another study reported progression of atherosclerosis in patients on different fibrates compared with those on statins (17).

The augmentation index predicts both all-cause and cardiovascular mortality in patients with end-stage renal failure (18). In a recent small study of 16 obese men, a 3-month treatment with fenofibrate reduced the augmentation index significantly (19). In contrast, gemfibrozil did not change the augmentation index in a group of 27 patients with chronic kidney disease (20). There are no data on the long-term effects of fibrates on augmentation index in type 2 diabetes.

Studies on fenofibrate have shown promising results concerning low-grade inflammation. These have been mostly short-term studies, and only 1 included patients with type 2 diabetes (21). One large long-term study was performed with bezafibrate, but data for patients with type 2 diabetes were not reported separately (22). Fenofibrate has increased flow-mediated endothelium-dependent vasodilatation in a few small studies (23–25).

In this pre-specified FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) substudy, we examined the effect of 5-year fenofibrate treatment on surrogate measures of atherosclerosis, inflammation, and endothelial activation in statin-free patients with type 2 diabetes. We measured carotid IMT by ultrasound and augmentation index by radial applanation tonometry and pulse-wave analysis. We measured low-grade inflammation by analyzing plasma C-reactive protein (CRP), interleukin (IL)-6, phospholipase A2 IIA (PLA2), and serum amyloid A (SAA) and the endothelial activation markers vascular cellular adhesion molecule (VCAM)-1, intercellular adhesion molecule (ICAM)-1, and E-selectin.

Methods

Subjects. The main FIELD study design has been described (26). Briefly, men and women age 50 to 75 years with type 2 diabetes, with or without prior coronary heart disease, were eligible using the following lipid criteria: 115 to 210 mg/dl serum-cholesterol plus either 90 to 440 mg/dl serum-triglycerides or a serum-cholesterol/high-density lipoprotein (HDL) cholesterol ratio >4. Subjects with hepatic or renal dysfunction, gallstones, lipid-lowering medication, cyclosporine, alcohol overuse, or other severe mental or physical illness were excluded. Patients received dietary advice designed for patients with diabetes at the first main

study visit, and their physical activity was recorded at baseline and second- and fifth-year main study visits. The first substudy patient was screened in June 1998, and the last substudy patient visit was performed in March 2005. We recruited 270 subjects with type 2 diabetes to the FIELD study at the Helsinki Centre. Of these patients, 239 volunteered to participate in this substudy, and 228 were randomly assigned to receive, in a double-blind design, placebo or micronized fenofibrate (200 mg/day) for 5 years (113 vs. 115 patients, respectively). At the fifth-year substudy close, the respective numbers were 99 patients in the placebo group and 95 in the fenofibrate group. During the study, there were 2 deaths and 12 serious adverse events in the placebo group and 5 deaths and 15 serious adverse events in the fenofibrate group. We excluded patients who had statin added to their medications during the study (16 in the placebo group vs. 8 in the fenofibrate group). After this, 170 subjects were eligible for analysis (placebo group: n = 83, men/women 62/21; fenofibrate group: n = 87, men/women 63/24). In 151 patients (placebo group: n = 75, men/women 53/22; fenofibrate group: n = 76, men/women 55/21), pulse-wave analyses were performed. The characteristics of these patients did not differ from those of the entire substudy group. Patients with plasma CRP levels >10 mg/l were excluded from the cytokine analysis. All patients signed informed consent forms. The Ethics Committee of the Helsinki University Central Hospital approved the substudy protocol.

Laboratory analyses. The baseline examinations were performed during the placebo run-in period of the FIELD study before any fenofibrate intervention. Blood samples were obtained after overnight fasts. Serum and ethylenediaminetetraacetic acid plasma were separated by centrifugation and stored at -80°C until analyzed. Commercially available enzyme-linked immunosorbent assay kits were used to determine ICAM-1 (coefficient of variance [CV] 7.4%), VCAM-1 (CV 9.2%), E-selectin (CV 7.3%), and IL-6 (CV 15.1%) (R&D Systems, Minneapolis, Minnesota); ultra-sensitive CRP (CV 12.8%) (Medix Biochemica, Kauniainen, Finland); SAA (CV 21.9%) (Biosource International, Camarillo, California); and secretory phospholipase A2 IIA (SPLA2) (CV 22.1%) (Cayman Chemical Company, Ann Arbor, Michigan). Lipids, plasma glucose, and glycosylated hemoglobin were measured as described (27).

Measurement of carotid IMT. The method used in the present study has been described elsewhere (28). Briefly, ultrasound scans were performed with a Hewlett Packard

Abbreviations and Acronyms

CRP	= C-reactive protein
HDL	= high-density lipoprotein
ICAM	= intercellular adhesion molecule
IL	= interleukin
IMT	= intima-media thickness
MI	= myocardial infarction
SAA	= serum amyloid A
SPLA2	= secretory phospholipase A2 IIA
VCAM	= vascular cellular adhesion molecule

Image Point M2410A (Palo Alto, California) ultrasound system and a 10-MHz linear array transducer and videotaped with a Panasonic (Osaka, Japan) AG-MD830E PAL S-VHS VCR. All of the patients were scanned once at baseline, at the second year, and at the fifth year. Both carotid arteries were scanned from 3 projections for the distal 1 cm of the common carotid artery and entire carotid bulb. For the proximal 1 cm of the internal carotid artery, the best visualized view was selected by the sonographer. Both the far wall and near wall were measured. Computer analysis of the ultrasound images was performed using a PC with a video frame grabber interfaced to a PAL S-VHS VCR at the University of Kuopio, Kuopio, Finland. One hundred measurements per 1-cm edge length were measured with the Prosound software (Caltech, Pasadena, California).

The mean of the maximal IMT (IMT) was pre-specified as the primary outcome variable. Secondary outcome variables were: 1) the mean of mean IMT over all scanned carotid sites; 2) the mean of mean far-wall IMTs over all scanned carotid far-wall sites; 3) the mean of maximal IMTs over all scanned common carotid artery sites; 4) the mean of maximal IMTs over all scanned carotid bulb sites; 5) the mean of maximal IMTs for all scanned internal carotid artery sites; and 6) the plaque height difference between site-specific maximums and minimums averaged for all scanned carotid sites (plaque).

Dr. Leinonen performed the ultrasounds at baseline and the second year, and Dr. Hiukka at the fifth year. The intraobserver repeatability (R) for maximal IMT was 0.994 with a standard error of measurement errors (SE) of 0.0152 for Dr. Leinonen, and R was 0.971 with an SE of 0.029 for Dr. Hiukka. The interobserver R was 0.950 and SE was 0.035. The IMT scans of the patients were read by ultrasound technicians Arja Malkki (R = 0.996; SE = 0.0082) and Jarmo Tiikkainen (R = 0.986; SE = 0.032);

their inter-reader R was 0.977 and SE was 0.040. Both readers and sonographers were blinded to the treatment group but not to the time sequence.

Pulse-wave analyses. Pulse-wave analysis was used to determine central aortic pressures, central pressure augmentation, and the augmentation index (29). A single investigator (J.W.) used the applanation tonometry (SPC-301, Millar Instruments, Houston, Texas) to record the pressure waves from the radial artery. Data were processed with the SphygmoCor Blood Pressure Analysis System (BPAS-1, AtCor Medical, Sydney, Australia). An average radial artery waveform was calculated, and the corresponding ascending aortic pressure waveform was generated using a validated transfer factor. The augmentation index was calculated by dividing the central pressure augmentation by pulse pressure. The patients had fasted overnight and they did not take any medication in the morning of examination.

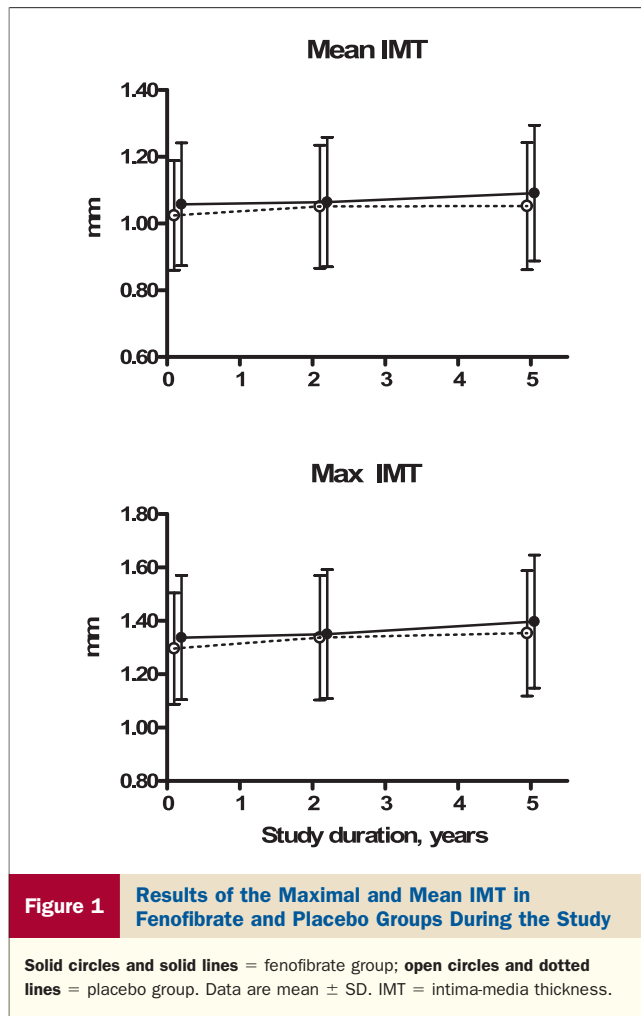
Statistical analysis. The statistical analysis was performed using SPSS 11.0 for Windows (SPSS Inc., Chicago, Illinois) and CIA 2.1.2 (University of Southampton School of Medicine, Hampshire, United Kingdom [30]). Results are shown as means ± standard errors of the mean or medians and interquartile ranges for non-normally distributed variables. We used repeated-measures analysis of variance or the Mann-Whitney *U* test to compare changes between the treatment groups and Wilcoxon signed-rank test for matched pairs to compare the changes within the groups. Treatment effect is shown with median difference of the percentage changes from baseline between the groups. Qualitative variables are presented as n (%), and their changes were compared by the 2 × 2 likelihood ratio test for transition probability matrixes (31) or Fisher exact test. We used linear regression analysis to calculate the individual slopes of IMT progression or regression. A *p* value of <0.05 was considered significant in all analyses.

Table 1 Characteristics of the Patients at Baseline and After 5 Years

	Placebo (n = 83)		Fenofibrate (n = 87)		p Value
	Baseline	Fifth Year	Baseline	Fifth Year	
BMI, kg/m ²	29.7 (26.9–33.0)	29.5 (26.7–32.9)	29.1 (26.3–32.5)	28.6 (26.3–33.4)	NS
Smoking					
Never	29 (35%)	29 (35%)	41 (47%)	41 (47%)	NS
Ex	41 (49%)	43 (52%)	35 (40%)	35 (40%)	
Current	13 (16%)	11 (13%)	11 (13%)	11 (13%)	
Glucose, mg/dl	139 (117–155)	128 (108–158)	142 (122–164)	130 (130–155)*	NS
HbA1c, %	7.0 (6.3–8.1)	7.0 (6.4–7.7)	7.2 (6.6–8.0)	7.3 (6.6–8.1)	NS
Systolic BP, mm Hg	140 (132–150)	138 (126–148)*	142 (134–152)	136 (126–142)†	NS
Diastolic BP, mm Hg	88 (80–92)	80 (74–88)†	88 (82–94)	80 (74–84)†	0.047
Serum cholesterol, mg/dl	190 (174–207)	197 (183–221)	190 (173–205)	167 (146–188)†	<0.001
LDL cholesterol, mg/dl	118 (105–130)	128 (110–145)	120 (103–133)	103 (85–120)†	<0.001
TG, mg/dl	147 (109–182)	134 (100–194)	136 (105–190)	97 (73–148)†	<0.001
HDL cholesterol, mg/dl	43 (37–50)	44 (38–53)	45 (40–55)	44 (39–53)	NS

Data are median (interquartile range) and *p* values from repeated-measures analysis of variance. For "smoking," data are n (%) and *p* values are based on the Fisher exact test. *p* values between baseline and fifth year in each group are from the Wilcoxon signed-rank test for 2 related variables. **p* < 0.05; †*p* < 0.001.

BMI = body mass index; BP = blood pressure; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides.



Results

Characteristics of the patients. The mean age of subjects was 61.4 ± 6.7 years in the placebo and 62.5 ± 6.3 years in the fenofibrate group ($p = \text{NS}$). Median duration of diabetes was 5 years (range 2 to 10 years) in the placebo group and 6 years (range 3 to 11 years) in the fenofibrate group. There was a 29% history of cardiovascular disease with no difference between the groups (21 in the placebo group and 29 in the fenofibrate group). Because of intensified diabetes treatment, fasting serum glucose values decreased slightly in both groups, with no change in glycosylated hemoglobin (Table 1, Online Table). Antihypertensive treatment increased in both groups, and systolic blood pressure was decreased in both groups. Fenofibrate reduced total and low-density lipoprotein cholesterol and triglycerides, whereas HDL cholesterol remained comparable between the treatment groups (Table 1).

Effect of fenofibrate on IMT and the augmentation index. The primary measure of IMT in our study was maximal IMT (Fig. 1). Importantly, in both groups maximal IMT was thicker at closeout than at baseline. All of the IMT measures were comparable between treatment groups

during the study (Table 2). The augmentation index increased in both groups (fenofibrate $27.4 \pm 0.9\%$ vs. $30.4 \pm 1.0\%$ [baseline vs. 5 years], $p < 0.0001$; placebo $25.5 \pm 0.9\%$ vs. $29.3 \pm 1.0\%$, $p < 0.005$) with no significant effects of fenofibrate (Table 3). Heart rate and central pressure augmentation remained unchanged in both groups after 5 years. Similar to brachial blood pressures in the whole subgroup, aortic systolic and diastolic blood pressures decreased significantly in the fenofibrate group (Table 3). However, when treatment effect was analyzed using 2-way analysis of variance for repeated measures, there were no significant effects of fenofibrate on aortic blood pressures.

Effect of fenofibrate on markers of low-grade inflammation and endothelial activation. Fenofibrate treatment did not change plasma levels of CRP and IL-6 in the study group (Table 4). In the fenofibrate group, however, women ($n = 23$) had slightly but significantly higher plasma CRP and IL-6 levels compared with men ($n = 54$) during the study (data not shown). At the fifth year, plasma CRP values in the fenofibrate group were skewed toward higher values because of a nonsignificant median rise of 29.4% in women, whereas CRP levels in men did not change. Plasma CRP values did not differ between low- and high-risk patients, stratified by the cut-off value of plasma CRP = 2.0 mg/dl (data not shown).

The PLA2 values were comparable for fenofibrate and placebo, despite a decrease in levels after 5 years in the placebo group (Table 4). Decreases in SAA levels in the fenofibrate group were not significantly different compared with the decrease in the placebo group. Fenofibrate had no effect on plasma levels of VCAM-1, ICAM-1, and E-selectin compared with those in the placebo group after 5 years (Table 4). The plasma levels of VCAM-1, ICAM-1, or E-selectin did not differ between sexes.

Discussion

The present study showed that long-term fenofibrate treatment had no effect on carotid IMT or augmentation index in patients with type 2 diabetes. Consistently, the markers of low-grade inflammation and endothelial activation remained unchanged. To the best of our knowledge, this is the first long-term study to investigate the effects of fenofibrate on IMT and augmentation index in patients with type 2 diabetes.

Recently, regression in carotid IMT was observed with a combination therapy of statin and ezetimibe in patients with type 2 diabetes achieving aggressive low-density lipoprotein cholesterol lowering (32). IMT studies with fenofibrate are lacking in type 2 diabetic patients, but the DAIS study (14) demonstrated a significant reduction of focal angiographic coronary artery lesions after 3 years of fenofibrate treatment in 418 men with type 2 diabetes. The reduction in the progression of mean segment diameter in coronary arteries was not significant. Moreover, the correlation between coronary angiography and carotid IMT is only moderate

Table 2 Results of Carotid IMT Analysis at Baseline and After 5 Years

IMT	Baseline	Second Year	Fifth Year	Rate of Change (mm/yr) (95% Confidence Interval)	p Value
Mean, mm					
Placebo	1.01 (0.89-1.15)	1.03† (0.92-1.16)	1.03† (0.91-1.17)	0.069 (-0.0059 to 0.0149)	0.987
Fenofibrate	1.03 (0.95-1.14)	1.03 (0.95-1.17)	1.05† (0.96-1.19)	0.054 (-0.0028 to 0.0177)	
Max, mm					
Placebo	1.29 (1.12-1.43)	1.30* (1.18-1.46)	1.33* (1.17-1.47)	0.140 (-0.0029 to 0.0245)	0.722
Fenofibrate	1.30 (1.20-1.48)	1.31 (1.20-1.50)	1.35* (1.24-1.53)	0.098 (0.000 to 0.0267)	
Far wall, mm					
Placebo	1.01 (0.87-1.11)	1.04† (0.91-1.16)	1.01‡ (0.88-1.14)	0.0033 (-0.0093 to 0.0148)	0.763
Fenofibrate	1.02 (0.90-1.17)	1.03 (0.90-1.22)	1.04 (0.91-1.22)	0.0035 (-0.0099 to 0.0170)	
Plaque, mm					
Placebo	0.54 (0.47-0.63)	0.56‡ (0.48-0.63)	0.58* (0.51-0.67)	0.0111 (-0.0031 to 0.0283)	0.633
Fenofibrate	0.55 (0.49-0.65)	0.57‡ (0.49-0.67)	0.61* (0.52-0.71)	0.0091 (-0.0032 to 0.0281)	
CCA, mm					
Placebo	1.14 (0.99-1.30)	1.17 (0.99-0.30)	1.19‡ (1.03-1.29)	0.0069 (-0.0087 to 0.0185)	0.858
Fenofibrate	1.21 (1.09-1.31)	1.19 (1.06-1.29)	1.22‡ (1.13-1.32)	0.0050 (-0.0051 to 0.0177)	
CB, mm					
Placebo	1.45 (1.20-1.67)	1.51† (1.30-1.74)	1.51* (1.28-1.73)	0.0162 (-0.0064 to 0.0419)	0.870
Fenofibrate	1.45 (1.27-1.68)	1.51‡ (1.26-1.73)	1.51* (1.37-1.74)	0.0141 (-0.0039 to 0.0378)	
ICA, mm					
Placebo	1.12 (0.96-1.31)	1.13 (1.01-1.35)	1.18† (1.05-1.48)	0.0197 (-0.0171 to 0.0587)	0.966
Fenofibrate	1.12 (1.01-1.32)	1.15† (1.01-1.41)	1.22† (1.02-1.45)	0.0167 (-0.0154 to 0.0601)	

Data are median (interquartile range) for annual change median (95% confidence intervals). p values are from the Mann-Whitney U test, comparing the annual change between the groups. p values between baseline and second year or fifth year in each group are from the Wilcoxon signed-rank test for 2 related variables. *p < 0.001; †p < 0.01; ‡p < 0.05. CB = carotid bulb; CCA = common carotid artery; ICA = internal carotid artery; IMT = intima-media thickness.

(33). In a Japanese study of 594 hypertensive nondiabetic patients, fenofibrate slowed the progression of IMT/arterial diameter ratio, although the mean IMT did not change (15). A nonrandomized observational study demonstrated a lipid-independent effect toward greater IMT and steeper IMT progression in patients on different fibrates (n = 82) compared with those on statins (n = 291) (17). In the present study, we observed no difference between placebo and fenofibrate treatment on carotid IMT during the 5-year study. It is also noteworthy that a similar progression of IMT parameters over time was observed in both groups.

Augmentation index is associated with cardiovascular morbidity and mortality in patients with type 2 diabetes (34). The present study is the first to examine the long-term effect of a fibrate on augmentation index in a study powered

by a sufficient number of patients. A few smaller short-term studies have been published. The effect of either gemfibrozil or atorvastatin was compared with placebo in a 6-week double-blind randomized study in patients with chronic kidney disease (n = 101) (20). Approximately 20% of the patients had diabetes. No significant changes were seen in either endothelial function or large artery stiffness, consistent with our present study. In another small study of 16 nondiabetic obese men, 3-month treatment with fenofibrate significantly reduced the augmentation index, although no changes in blood pressure were detected (19). Interestingly, a significant decrease in plasma ICAM- and VCAM-1 levels were also demonstrated, which may reflect the detected changes. In the present study, neither a reduction in endothelial markers nor a decrease in augmentation index

Table 3 Results of Pulse-Wave Analysis at Baseline and After 5 Years

Variable	Placebo (n = 75)		Fenofibrate (n = 76)	
	Baseline	Fifth Year	Baseline	Fifth Year
Aortic systolic BP, mm Hg	136 ± 18	132 ± 16	136 ± 17	129 ± 14*
Aortic diastolic BP, mm Hg	81 ± 11	81 ± 9	81 ± 9	78 ± 9†
Aortic mean arterial BP, mm Hg	105 ± 13	102 ± 10	105 ± 11	99 ± 10*
Aortic pulse pressure, mm Hg	55 ± 14	51 ± 14	55 ± 16	51 ± 14†
Heart rate, beats/min	67 ± 9	67 ± 9	68 ± 11	65 ± 12†
Augmentation, mm Hg	15 ± 7	16 ± 7	16 ± 8	16 ± 7
Augmentation index, %	26 ± 8	29 ± 8†	27 ± 8	30 ± 9*

There were no significant treatment effects when 2-way analysis of variance for repeated measures was used. Data are means ± SD. *p < 0.001 for fifth year versus baseline; †p < 0.01 for fifth year versus baseline. BP = blood pressure.

Table 4 Biomarkers of Inflammation and Endothelial Function at Baseline and at 5 Years

	Baseline	Fifth Year	Median Difference of Change (95% Confidence Interval)	p Value
VCAM-1, ng/ml				
Placebo	561 (434–668)	627* (534–786)	+5.6% (–4.5 to +16.2)	0.271
Fenofibrate	558 (432–641)	697* (568–874)		
ICAM-1, ng/ml				
Placebo	264 (222–308)	256‡ (216–290)	–1.1% (–7.1 to +5.5)	0.761
Fenofibrate	256 (224–306)	244‡ (208–299)		
E-selectin, ng/ml				
Placebo	56 (42–75)	49* (35–59)	–4.4% (–12.8 to +4.5)	0.325
Fenofibrate	54 (43–72)	43* (33–53)		
CRP, mg/l				
Placebo	1.7 (1.0–3.6)	1.6 (0.8–3.5)	+20.1% (–3.4 to +45.0)	0.101
Fenofibrate	1.8 (1.0–4.0)	2.5 (0.8–4.8)		
SPLA, ng/ml				
Placebo	3.1 (2.1–5.3)	2.4* (1.7–4.0)	+13.6% (–0.8 to +28.0)	0.064
Fenofibrate	2.7 (1.8–4.5)	2.9 (1.8–3.9)		
IL-6, pg/ml				
Placebo	2.6 (1.7–3.8)	2.5 (1.6–3.9)	+0.8% (–19.2 to +22.5)	0.946
Fenofibrate	2.3 (1.7–3.6)	2.7 (1.9–4.1)		
SAA, µg/ml				
Placebo	21 (13–45)	20‡ (14–28)	–12.0% (–27.9 to +3.6)	0.123
Fenofibrate	25 (15–38)	17* (13–23)		

Data are median (interquartile range) and treatment effect as median difference of change between the groups (95% confidence intervals). p values are from the Mann-Whitney U test, comparing the relative changes from baseline to fifth year between the groups. p values between baseline and fifth year in each group are from the Wilcoxon signed-rank test for 2 related variables. n = 73 for placebo and n = 77 for fenofibrate. *p < 0.001; †p < 0.01; ‡p < 0.05.

CRP = C-reactive protein; ICAM = intercellular adhesion molecule; IL = interleukin; SAA = serum amyloid A; SPLA = secretory phospholipase A2 IIA; VCAM = vascular cellular adhesion molecule.

was detected in older patients with type 2 diabetes. Rather, a similar progression of augmentation index was shown in both the fenofibrate and placebo groups.

Previously fibrates have been shown to reduce inflammatory markers in short-term studies, but data from studies of longer duration are scarce. The biomarkers of endothelial dysfunction, namely ICAM-1, VCAM-1, and E-selectin, decrease with fenofibrate intervention (23,35); however, in a recent 6-week study by Hogue *et al.* (36), fenofibrate decreased only plasma E-selectin levels but not ICAM-1, VCAM-1, or CRP levels. In other short-term studies, fenofibrate treatment was reported to reduce plasma CRP levels, along with its upstream regulator IL-6 (7,15,21, 24,25). Fenofibrate reduced CRP levels in patients with mixed hyperlipidemia in a 60-week trial, although data from patients with type 2 diabetes were not reported separately (21). Notably, the response to fibrates may differ between subjects with and without diabetes, which is the case for plasma HDL cholesterol (12). Contrary to these short-term findings, here we reported that fibrate treatment did not significantly alter circulating cytokine levels. This is consistent with the 6-year BIP study, which showed that long-term bezafibrate treatment did not reduce plasma CRP levels (22).

Study limitations. The present study was limited by the relatively small size of the study cohort. However, 2 distinct surrogate markers of atherosclerosis (*i.e.*, IMT and the

augmentation index) showed similar progression in both groups with no significant effect of fenofibrate. Relatively high baseline IMT (37) and a study population with no prior lipid medication should have facilitated the appearance of significant treatment effect. Systolic blood pressure was slightly lower in the fenofibrate treatment group, which was also observed in the main FIELD study. Use of beta-blockers was more common, and the use of nitrates increased more in the fenofibrate treatment group. Also, the reduction in fasting glucose was significant only in the fenofibrate group. In a small study sample, the effect of separate medications to the results cannot be speculated.

Conclusions

Our findings indicate that long-term fenofibrate treatment has no effect on low-grade inflammation, endothelial activation, augmentation index, or progression of carotid IMT in patients with type 2 diabetes. The natural progression of atherosclerosis was validated by our IMT and augmentation index results. The outcomes of fibrate trials have been mixed. The FIELD study, the largest fibrate study so far, yielded a nonsignificant 11% reduction in coronary heart disease events (38). This was less than expected compared with other fibrate studies such as VA-HIT and BIP (12,13). Thus, in patients with type 2 diabetes and prior cardiovascular disease, fenofibrate should only be used to treat severe

hypertriglyceridemia. Whether the combination therapy of fenofibrate and statin beneficially influences cardiovascular disease end points will be answered by the ongoing ACCORD (Action to Control Cardiovascular Risk in Diabetes) study.

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Reprint requests and correspondence: Dr. Marja-Riitta Taskinen, Department of Medicine, Division of Cardiology, Helsinki University Hospital and Biomedicum, Haartmaninkatu 8, 00029 Helsinki, Finland. E-mail: marja-riitta.taskinen@helsinki.fi.

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Key Words: type 2 diabetes ■ fenofibrate ■ intima-media thickness ■ augmentation index ■ inflammation.

 **APPENDIX**

For a supplementary table on the medication at baseline and at 5 years, please see the online version of this article.

Long-Term Effects of Fenofibrate on Carotid Intima-Media Thickness and Augmentation Index in Subjects With Type 2 Diabetes Mellitus

Anne Hiukka, Jukka Westerbacka, Eeva S. Leinonen, Hiroshi Watanabe, Olov Wiklund, Lillemor Mattson Hulten, Jukka T. Salonen, Tomi-Pekka Tuomainen, Hannele Yki-Järvinen, Anthony C. Keech, and Marja-Riitta Taskinen
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