Effects of Fenofibrate Treatment on Cardiovascular Disease Risk in 9,795 Individuals With Type 2 Diabetes and Various Components of the Metabolic Syndrome

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study

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OBJECTIVE — We explored whether cardiovascular disease (CVD) risk and the effects of fenofibrate differed in subjects with and without metabolic syndrome and according to various features of metabolic syndrome defined by the Adult Treatment Panel III (ATP III) in subjects with type 2 diabetes in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study.

RESEARCH DESIGN AND METHODS — The prevalence of metabolic syndrome and its features was calculated. Cox proportional models adjusted for age, sex, CVD status, and baseline A1C levels were used to determine the independent contributions of metabolic syndrome features to total CVD event rates and the effects of fenofibrate.

RESULTS — More than 80% of FIELD participants met the ATP III criteria for metabolic syndrome. Each ATP III feature of metabolic syndrome, apart from increased waist circumference, increased the absolute risk of CVD events over 5 years by at least 3%. Those with marked dyslipidemia (elevated triglycerides ≥2.3 mmol/l and low HDL cholesterol) were at the highest risk of CVD (17.8% over 5 years). Fenofibrate significantly reduced CVD events in those with low HDL cholesterol or hypertension. The largest effect of fenofibrate to reduce CVD risk was observed in subjects with marked dyslipidemia in whom a 27% relative risk reduction (95% CI 9–42, P = 0.005; number needed to treat = 2.3) was observed. Subjects with no prior CVD had greater risk reductions than the entire group.

CONCLUSIONS — Metabolic syndrome components identify higher CVD risk in individuals with type 2 diabetes, so the absolute benefits of fenofibrate are likely to be greater when metabolic syndrome features are present. The highest risk and greatest benefits of fenofibrate are seen among those with marked hypertriglyceridemia.

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features when type 2 diabetes is established and whether reductions in CVD event rates with fenofibrate differ according to the presence of metabolic syndrome or its particular features. We also explored the value of a higher cut point for marked dyslipidemia, using an elevated triglyceride level (≥2.3 mmol/l) either alone or in combination with a low plasma HDL cholesterol level as defined in the Helsinki Heart Study (HHS) (8).

**RESEARCH DESIGN AND METHODS** — A detailed description of the FIELD study design was published previously (5,7). The prevalence of individual metabolic syndrome components according to the modified ATP III definition (1) was determined as follows: 1) increased blood pressure was defined as the patient stating a history of hypertension with documentation of hypertensive medication use or as mean blood pressure values (over three baseline visits) ≥130/85 mmHg; 2) a low HDL cholesterol level was defined as <1.03 mmol/l for men and <1.29 mmol/l for women; 3) an elevated triglyceride level was defined as ≥1.7 mmol/l; and 4) increased waist circumference was defined as >102 cm in men and >88 cm in women. Metabolic syndrome was present when at least three features (type 2 diabetes plus at least two other features) were found at baseline. Dyslipidemia was characterized by elevated triglyceride and low HDL cholesterol levels in combination. Marked hypertriglyceridemia and marked dyslipidemia were defined as triglyceride levels ≥2.3 mmol/l alone or with a low HDL cholesterol level, respectively.

CVD event rates were measured in subjects without prior CVD (n = 7,664, 78.2%) and in subjects with documented CVD (n = 2,131, 21.8%), according to features of metabolic syndrome, and in men (n = 6,138, 62.7%) and women (n = 3,657, 37.3%). The effect of fenofibrate according to baseline HDL cholesterol and triglyceride levels was also reported by prespecified cut points, corresponding to approximate tertiles.

**Statistical analyses**

The main hypothesis was that individuals with metabolic syndrome would obtain greater benefits from fenofibrate than those without metabolic syndrome. All analyses concerning treatment were performed on an intention-to-treat basis. All statistical inferences were drawn using a two-sided P value of 0.05. Cox proportional hazards analyses were used to compute hazard ratios (HRs) and 95% CIs to assess the effects of fenofibrate on the time to first CVD event, with P values computed using Wald tests and trend tests where appropriate. Individual Cox models were fitted within prespecified subgroups of sex, prior CVD status, features of the modified ATP III metabolic syndrome definition, and approximate tertiles of baseline HDL cholesterol and triglyceride levels. A multivariable model was fitted simultaneously, with adjustment for the features of metabolic syndrome (using categorical variables) and baseline A1C, age, sex, prior CVD status, and treatment allocation. Significant interactions are presented as individual effects within subgroups, with Wald tests used for comparing HRs and 95% CIs to assess the effects of fenofibrate. In both sexes, the highest event rates were seen in the setting of metabolic syndrome, fenofibrate reduced CVD risk from 14.5 to 13.1%, representing a proportional reduction of 11% (adjusted HR 0.89 [95% CI 0.81–0.97], P = 0.01; absolute risk reduction 1.4%) (Table 2). In the smaller group without metabolic syndrome, fenofibrate reduced CVD risk from 11.3 to 9.7%, a 12% proportional reduction (0.88 [0.79–0.98], P = 0.03; absolute risk reduction 1.6%) (Table 2). Among individuals with metabolic syndrome, fenofibrate reduced the 5-year CVD risk from 14.5 to 13.1%, representing a proportional risk reduction of 11% (adjusted HR 0.89 [95% CI 0.81–0.97], P = 0.01; absolute risk reduction 1.4%) (Table 2). In the smaller group without metabolic syndrome, fenofibrate reduced CVD risk from 11.3 to 9.7%, a 12% proportional reduction (0.88 [0.79–0.98], P = 0.03; absolute risk reduction 1.6%); these relative risk reductions were almost identical (Pinteraction value = 0.91) (Fig. 2).

The effects of fenofibrate were similar among individuals with and without any
feature of metabolic syndrome: although the adjusted HRs were only independently significant in those with a low HDL cholesterol level and hypertension, there was no evidence of significant statistical interactions (Fig. 2). In contrast, the treatment effect appeared to be greater in women than in men and in primary rather than in secondary prevention of CVD. This was apparent in the overall population, among those with metabolic syndrome, and among those with any feature of metabolic syndrome. Among those with metabolic syndrome, fenofibrate reduced the proportional risk for CVD by 18% in women compared with 7% in men and by 17% in primary prevention and 1% in secondary prevention; however, the differences between the sexes and by history of CVD were not statistically significant.

Effects of fenofibrate in marked dyslipidemia
In all subgroups (women and men and primary and secondary prevention), the effects of fenofibrate were larger when marked hypertriglyceridemia or marked dyslipidemia was present. In those with marked dyslipidemia, fenofibrate reduced CVD rates by 30 and 24% in women and men, respectively, and by 40 and 12% in primary and secondary prevention, respectively, being separately statistically significant for men and primary prevention (Table 2). Indeed, the overall effect of fenofibrate in the presence of marked dyslipidemia was larger than that in all other groups, with borderline significance of treatment by group interaction: marked dyslipidemia group: 27% risk reduction (adjusted HR 0.73 [95% CI 0.68–0.81], P < 0.005); all others: 6% risk reduction (0.94 [0.83–1.06], P = 0.321; Pinteraction = 0.053). The absolute risk reduction in the presence of marked dyslipidemia was 4.3% (from 17.8 to 13.5%), compared with 0.8% (from 13.0 to 12.2%) in its absence (Fig. 2). This corresponds to a number needed to treat of 23 compared with 143, respectively. The effects of treatment according to the presence or absence of marked dyslipidemia were significantly different when only those subjects with metabolic syndrome were examined (P = 0.045) (data not shown).

Fenofibrate reduced total CVD events by 11% (95% CI 0.80–0.99, P = 0.035) (Fig. 2). In addition, the effect of fenofibrate among individuals with metabolic syndrome was close to being independently significant (P = 0.052) (Fig. 2), although not separately significant in its absence (P = 0.375). Nevertheless, there was no significant interaction between those with and without metabolic syndrome (P = 0.910).

Contribution of metabolic syndrome features to CVD risk
HDL cholesterol levels (P = 0.003), systolic blood pressure, and triglyceride levels (P = 0.0004) made independent significant contributions to CVD risk (after adjustment for age, sex, prior CVD status, baseline A1C, and LDL cholesterol), whereas waist circumference (P = 0.61) did not (Fig. 3). The effect of systolic blood pressure was significantly stronger in primary than in secondary prevention (Pinteraction = 0.019). Those with low HDL cholesterol levels had a 22% higher risk of CVD, and those with high triglyceride levels had a 24% higher risk. Elevated blood pressure almost doubled risk (93% increase) in primary prevention, whereas the 24% estimated risk increase in secondary prevention was not statistically signifi-
Increased waist circumference had no effect on CVD risk in this cohort. For comparison, a 1% higher A1C at baseline conferred a risk increase of 18% (95% CI 13–24%, \( P \leq 0.0001 \)) in primary prevention and 8% (2–15%; \( P \leq 0.0128 \)) in secondary prevention. Fenofibrate reduced risk by 12% after adjustment for all of the above factors (\( P = 0.026 \)) (Fig. 3). The estimated area under the curve for this risk model according to the \( c \) statistic was 70%.

**CONCLUSIONS**— The clustering of risk factors described as constituting metabolic syndrome is most important in predicting the incidence of diabetes, although it also identifies individuals who have an increased risk of CVD events (9,10). The high prevalence of metabolic syndrome seen in the FIELD population is similar to that observed in the U.S. National Health and Nutrition Examination Survey III survey and also in individuals with newly diagnosed diabetes (11,12). The CVD event rates in the FIELD population with metabolic syndrome and with individual features of metabolic syndrome (elevated blood pressure, low HDL cholesterol level, and elevated triglyceride level) were significantly higher than in those without metabolic syndrome, indicating that, even in the presence of established type 2 diabetes, metabolic syndrome still confers important additional prognostic information. Waist circumference (adjusted for sex) did not add further prognostic information for CVD risk.

Marked hypertriglyceridemia (\( \geq 2.3 \text{ mmol/l} \)) with or without a low HDL cholesterol level was associated with a higher CVD risk than meeting the criteria for metabolic syndrome, supporting a continuous positive relationship between triglyceride levels and CVD (13). This level of hypertriglyceridemia was associated with increased CVD events in earlier stud-

**Table 2—Effect of fenofibrate on CVD risk over 5 years according to ATP III features of metabolic syndrome**

|                                | Men          | Women        | No prior CVD | Prior CVD | Unadjusted | Adjusted* |
|--------------------------------|--------------|--------------|--------------|-----------|------------|-----------|
| Increased waist circumference  | 0.95 (0.80–1.11) | 0.80 (0.63–1.02) | 0.86 (0.73–1.03) | 0.96 (0.77–1.18) | 0.90 (0.79–1.03) | 0.90 (0.78–1.03) |
| Raised TGs (\( \geq 1.7 \text{ mmol/l} \)) | 0.92 (0.78–1.09) | 0.76 (0.57–1.02) | 0.83 (0.69–1.01) | 0.92 (0.74–1.15) | 0.88 (0.76–1.01) | 0.87 (0.75–1.00) |
| Reduced HDL cholesterol        | 0.88 (0.75–1.03) | 0.80 (0.61–1.03) | 0.75 (0.62–0.90)  | 1.01 (0.82–1.25) | 0.85 (0.74–0.97) | 0.86 (0.75–0.99) |
| Triglycerides (\( \geq 1.7 \text{ mmol/l} \)) and reduced HDL cholesterol | 0.90 (0.74–1.09) | 0.76 (0.55–1.04) | 0.77 (0.62–0.97) | 0.96 (0.75–1.24) | 0.86 (0.73–1.01) | 0.84 (0.71–1.00) |
| Increased blood pressure       | 0.92 (0.80–1.05) | 0.82 (0.65–1.04) | 0.80 (0.69–0.93) | 1.04 (0.87–1.25) | 0.89 (0.80–1.00) | 0.88 (0.79–0.99) |
| Metabolic syndrome criteria fulfilled | 0.93 (0.81–1.06) | 0.82 (0.65–1.03) | 0.83 (0.71–0.97) | 0.99 (0.83–1.19) | 0.90 (0.80–1.01) | 0.89 (0.79–1.00) |
| Raised TGs (\( \geq 2.3 \text{ mmol/l} \)) | 0.75 (0.60–0.95) | 0.79 (0.53–1.18) | 0.65 (0.49–0.86) | 0.89 (0.67–1.20) | 0.76 (0.62–0.93) | 0.77 (0.63–0.94) |
| Raised TGs (\( \geq 2.3 \text{ mmol/l} \)) and reduced HDL cholesterol | 0.76 (0.58–0.98) | 0.70 (0.46–1.07) | 0.60 (0.44–0.82) | 0.88 (0.64–1.21) | 0.74 (0.59–0.92) | 0.73 (0.58–0.91) |

Whole FIELD cohort | 0.92 (0.81–1.04) | 0.80 (0.64–0.99) | 0.81 (0.70–0.93) | 1.02 (0.86–1.20) | 0.89 (0.80–0.99) | 0.89 (0.80–0.99) |

Data are HRs (95% CI). TGs, triglyceride levels. *Adjusted for sex, age at visit 1, prior CVD, and baseline A1C. Treatment effect within the specified subgroup: \( P < 0.05 \), \( \#P < 0.01 \). \( P_{interaction} \) values compare subjects in the specified group with those who are not (\( P < 0.05 \)).

**Figure 1**—A: CVD event rates (percentage) in subjects receiving placebo who had diabetes (DM) alone or diabetes with any of one to four additional features of metabolic syndrome. B: CVD event rates (percentage) for subjects with hypertension, increased waist circumference, triglyceride levels (TG) \( \geq 1.7 \text{ mmol/l} \), and low HDL cholesterol (HDLc) levels with or without metabolic syndrome (MS).
ies (8,14), presumably reflecting a tendency for high nonfasting triglyceride levels and higher numbers of remnant particles and may be associated with more extreme abnormalities in other biological processes (such as oxidative stress, inflammation, and hypercoagulability), leading to more aggressive atherosclerosis (12,14,15).

Accordingly, with higher baseline risk, the absolute benefits of fenofibrate are likely to be greater when metabolic syndrome features are present. Whereas the effect of fenofibrate on CVD events was statistically significant overall, it was of only borderline significance in the group with metabolic syndrome and non-significant in those without, although with similar proportional reductions.

Although LDL cholesterol levels are effectively lowered by statins (16), elevated baseline (17) and on-treatment (18) triglyceride levels remain risk markers for CVD in individuals with and without diabetes who are already taking statins and are a potential target for fibrate therapy. Given that the largest effect of fibrates is to lower triglyceride levels by $\frac{1}{2}$ to $\frac{2}{3}$, it is not surprising that individuals with elevated triglyceride levels appear to obtain

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**Figure 2**—Forest plot of effects of fenofibrate on cardiovascular events adjusted for sex, prior CVD, age at visit 1, and baseline A1C (HR and 95% CI): ATP III waist circumference criteria (men $>102$ cm and women $>88$ cm), raised triglyceride levels (TG) ($\geq 1.7$ mmol/l or $\geq 2.3$ mmol/l), reduced HDL cholesterol (HDLc) levels (men $<1.03$ mmol/l and women $<1.29$ mmol/l), and ATP III metabolic syndrome (MS) criteria (diabetes and two others).

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**Figure 3**—Cox regression model for effect of metabolic syndrome features on total CVD events, adjusted for age, sex, prior CVD status, A1C, and LDL cholesterol levels at baseline. F, female; HDLc, HDL cholesterol; M, male.
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the largest benefits from fibrates. This result is supported by findings from the Bezafibrate Infarct Prevention (BIP) study (19) showing that fibrate therapy was more effective in treatment of individuals with than without metabolic syndrome; further, the BIP study and the HHS (8) showed particular benefit among subjects with markedly elevated triglyceride levels, and the Veterans Administration High-Density Lipoprotein Intervention Trial Intervention Trial (20) showed a relation of benefits to low HDL cholesterol levels. In the FIELD study, fenofibrate had the greatest absolute benefit in those with markedly high triglyceride levels together with low HDL cholesterol levels, now confirming similar findings in a population with type 2 diabetes and metabolic syndrome. Nevertheless, because these results are presented with P values unadjusted for multiple comparisons, these findings should be regarded as exploratory.

In a short-term study, fenofibrate was effective in lowering postprandial triglyceride levels, particularly when metabolic syndrome and elevated triglyceride levels were present. In the setting of metabolic syndrome and hypertriglyceridemia, fenofibrate was shown to be more effective in reducing fasting triglyceride and increasing HDL cholesterol levels and in reducing postprandial triglyceride levels and oxidized fatty acid levels, which corresponded with a decrease in VLDL particle size and an increase in LDL particle size (21).

Multivariate modeling confirmed the independent contributions of HDL cholesterol, triglyceride levels, and blood pressure to CVD risk, whereas the contribution from waist circumference was substantially explained by other factors. Hypertriglyceridemia is an important marker of CVD risk in type 2 diabetes and an important marker of benefit from fenofibrate, even though the risk conferred appears to be mediated through other conventional factors in other settings (22). These findings should interest physicians considering lipid-lowering therapy for patients with diabetes.

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