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

RUSSELL SCOTT, MB CHB, PHD, FRACP[1]
RICHARD O'BRIEN, MB, PHD, FRACP[2]
GREG FULCHER, MB, MD, FRACP[3]
CHRIS PARDY[4]
MICHAEL D'EMDEN, MB BS, PHD, FRACP[5]
DANA TSE, PHD[4]
MARJA-RIITTA TASKINEN, MD[6]
CHRISTIAN EHNHOLM, MD, PHD[7]
ANTHONY KEECH, MB BS, FRACP, MSC(EPID)[4]
ON BEHALF OF THE FENOFIBRATE INTERVENTION AND EVENT LOWERING IN DIABETES (FIELD) STUDY INVESTIGATORS*

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 = 23) 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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Subjects with metabolic syndrome have a higher risk for future cardiovascular disease (CVD) events and are more likely to develop diabetes (1). The various components of metabolic syndrome (abdominal obesity, dyslipidemia, hypertension, and glucose deregulation) confer differential risk for CVD based on the extent to which they deviate from healthy normality. The guidelines most commonly used clinically to define metabolic syndrome are the National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines (2). The exact role of each individual metabolic syndrome component in modifying risk once diabetes is present has varied in previous studies (3,4).

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was designed to assess the long-term effect of fenofibrate on CVD events in subjects with type 2 diabetes (5–7). The cohort of 9,795 subjects followed for an average of 5 years was sufficient to explore whether CVD event rates were increased in subjects with or without various metabolic syndrome features. Because fenofibrate modifies lipid parameters by changing LDL particle morphology, increasing HDL cholesterol, and reducing triglycerides, CVD event rates may be reduced to a larger degree in those with metabolic syndrome features reflecting a more atherogenic lipid profile at baseline.

In this article, we explored the clinical relevance of metabolic syndrome and its

From the [1]Lipid and Diabetes Research Group, Christchurch Hospital, Christchurch, New Zealand; the [2]Department of Medicine, Austin Hospital, University of Melbourne, Melbourne, Australia; [3]Diabetes and Endocrinology, Royal North Shore Hospital, University of Sydney, Sydney, Australia; the [4]National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney, Australia; the [5]Endocrine Research Unit, Royal Brisbane Hospital, Brisbane, Australia; the [6]Department of Medicine, Helsinki University Central Hospital and Biomedicum, Helsinki, Finland; and the [7]Department of Molecular Medicine, National Public Health Institute, Biomedicum, Helsinki, Finland.
Corresponding author: Russell Scott, fieldtrial@ctc.usyd.edu.au.
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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 for each pair simultaneously against the null hypothesis. Confidence intervals for number needed to treat were found by transforming CIs for risk reductions, with Pearson's χ^2 tests used for P values. Results are unadjusted for multiple comparisons. All statistical analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC).

RESULTS

Prevalence of metabolic syndrome features and corresponding CVD event rates

Of the 4,900 subjects allocated to placebo, 4,103 had metabolic syndrome and 797 did not, and of the 4,895 subjects allocated to fenofibrate, 4,080 had metabolic syndrome and 815 did not. More than 80% (n = 8,183) of the participants met the ATP III criteria for metabolic syndrome, a finding that was largely driven by the high prevalence of increased blood pressure and increased waist circumference measurements, particularly among women. More than half of the FIELD population had low plasma HDL cholesterol or elevated triglyceride levels that met the criteria. All metabolic syndrome features were more prevalent in women than in men. Marked hypertriglyceridemia (≥2.3 mmol/l) occurred in approximately one-quarter of both men (n = 1,197) and women (n = 817) and in approximately one-fifth of men and women when combined with low HDL cholesterol (Table 1).

In those with metabolic syndrome, the 5-year placebo group CVD event rate was 14.5% compared with a rate of 11.3% for those not meeting the criteria (n = 1,612; P < 0.0001) (Table 1, Fig. 1). Among individuals with any particular feature of metabolic syndrome, the CVD event rates were similar to those seen in the overall population, varying from 13.3% for high waist circumference to 15.4% for elevated triglyceride levels (Table 1). However, each additional feature of metabolic syndrome to diabetes resulted in a cumulatively higher risk of CVD events (Fig. 1*A*). Low HDL cholesterol or elevated triglyceride levels as risk determinants for CVD appeared to be more strongly dependent on whether metabolic syndrome was present than hypertension or increased waist circumference (Fig. 1*B*). Furthermore, the presence of each ATP III feature for metabolic syndrome compared with its absence, apart from increased waist circumference, increased the absolute risk of CVD events over 5 years by 3% (Fig. 2). Those with marked dyslipidemia (triglycerides ≥2.3 mmol/l with low HDL cholesterol levels) had the highest risk of CVD (17.8% over 5 years).

Among individuals with any particular feature of metabolic syndrome, as among those with metabolic syndrome and in the overall population, men had approximately twice the risk of women for CVD events. In both sexes, the highest event rates were seen in the setting of marked dyslipidemia (Table 1). As expected, those with prior CVD had a much higher risk for CVD events (2.5-fold) than those with no prior CVD across all features of metabolic syndrome (Table 1). Among subjects with metabolic syndrome, the CVD event rate for the 1,846 subjects with prior CVD was 25.5% and for those 6,337 subjects without prior CVD was 10.3%. Event rates were higher in both groups when marked dyslipidemia was present, at 29.8% and 11.0%, respectively (P < 0.01).

Effects of fenofibrate to reduce CVD risk

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 0–21%], P = 0.052; 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 [−19 to 35%], P = 0.375; 1.6%); these relative risk reductions were almost identical ($P_{interaction}$ value = 0.91) (Fig. 2).

The effects of fenofibrate were similar among individuals with and without any

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Table 1—*Prevalence rates and CVD event rates over 5 years according to ATP III features of metabolic syndrome, various baseline characteristics, and treatment assignment*

	Men	Women	No prior CVD	Prior CVD	Placebo	Fenofibrate	Total
n	6,138	3,657	7,664	2,131	4,900	4,895	9,795
Prevalence rates							
Increased waist circumference	3,613 (58.9)	3,034 (83.0)	5,220 (68.1)	1,427 (67.0)	3,320 (67.8)	3,327 (68.0)	6,647 (67.9)
Raised TGs (≥1.7 mmol/l)	3,073 (50.1)	2,020 (55.2)	3,926 (51.2)	1,167 (54.8)	2,525 (51.5)	2,568 (52.5)	5,093 (52.0)
Reduced HDL cholesterol level	3,365 (54.8)	2,455 (67.1)	4,477 (58.4)	1,343 (63.0)	2,896 (59.1)	2,924 (59.7)	5,820 (59.4)
Increased blood pressure	5,050 (82.3)	3,131 (85.6)	6,300 (82.2)	1,881 (88.3)	4,095 (83.6)	4,086 (83.5)	8,181 (83.5)
Metabolic syndrome criteria fulfilled	4,870 (79.3)	3,313 (90.6)	6,337 (82.7)	1,846 (86.6)	4,103 (83.7)	4,080 (83.4)	8,183 (83.5)
Raised TGs ≥1.7 mmol/l and reduced HDL cholesterol level	2,133 (34.8)	1,577 (43.1)	2,816 (36.7)	894 (42.0)	1,824 (37.2)	1,886 (38.5)	3,710 (37.9)
Raised TGs (≥2.3 mmol/l)	1,556 (25.4)	961 (26.3)	1,912 (24.9)	605 (28.4)	1,222 (24.9)	1,295 (26.5)	2,517 (25.7)
Raised TGs ≥2.3 mmol/l and low HDL cholesterol	1,197 (19.5)	817 (22.3)	1,521 (19.8)	493 (23.1)	970 (19.8)	1,044 (21.3)	2,014 (20.6)
CVD event rates							
Increased waist circumference	585 (16.2)	260 (8.6)	510 (9.8)	335 (23.5)	443 (13.3)	402 (12.1)	845 (12.7)
Raised TGs (≥1.7 mmol/l)	557 (18.1)	180 (8.9)	423 (10.8)	314 (26.9)	388 (15.4)	349 (13.6)	737 (14.5)
Reduced HDL cholesterol	588 (17.5)	228 (9.3)	468 (10.5)	348 (25.9)	437 (15.1)	379 (13.0)	816 (14.0)
Increased blood pressure	878 (17.4)	284 (9.1)	678 (10.8)	484 (25.7)	612 (14.9)	550 (13.5)	1,162 (14.2)
Metabolic syndrome criteria fulfilled	835 (17.1)	291 (8.8)	655 (10.3)	471 (25.5)	593 (14.5)	533 (13.1)	1,126 (13.8)
Raised TGs (≥1.7 mmol/l) and reduced HDL cholesterol	405 (19.0)	155 (9.8)	318 (11.3)	242 (27.1)	296 (16.2)	264 (14.0)	560 (15.1)
Raised TGs (≥2.3 mmol/l)	285 (18.3)	98 (10.2)	206 (10.8)	177 (29.3)	210 (17.2)	173 (13.4)	383 (15.2)
Raised TGs ≥2.3 mmol/l and low HDL cholesterol	226 (18.9)	88 (10.8)	167 (11.0)	147 (29.8)	173 (17.8)	141 (13.5)	314 (15.6)
Overall	980 (16.0)	315 (8.6)	756 (9.9)	539 (25.3)	683 (13.9)	612 (12.5)	1,295 (13.2)

Data are *n* (%). TGs, triglyceride levels.

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 0.58–0.91], $P = 0.005$); all others: 6% risk reduction (0.94 [0.83–1.06], $P = 0.321$; $P_{interaction} = 0.053$) (Fig. 2). 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 ($P_{interaction} = 0.019$). 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-

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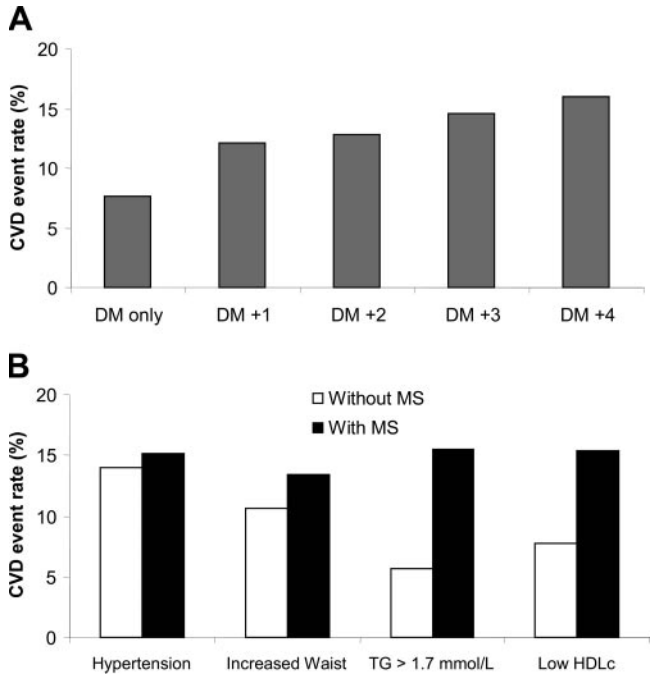

Figure 1—A*: CVD event rates (percentage) in subjects receiving placebo who had diabetes (DM) alone or diabetes with any of one to four additional features of metabolic syndrome.* B*: CVD event rates (percentage) for subjects with hypertension, increased waist circumference, triglyceride levels (TG) >1.7 mmol/l, and low HDL cholesterol (HDLc) levels with or without metabolic syndrome (MS).*

cant. 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%, $P < 0.0001$) in primary prevention and 8% (2–15%; $P = 0.0128$) 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 (≥2.3 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 (≥1.7 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 (≥1.7 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 (≥2.3 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 (≥2.3 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 ($P < 0.05$).

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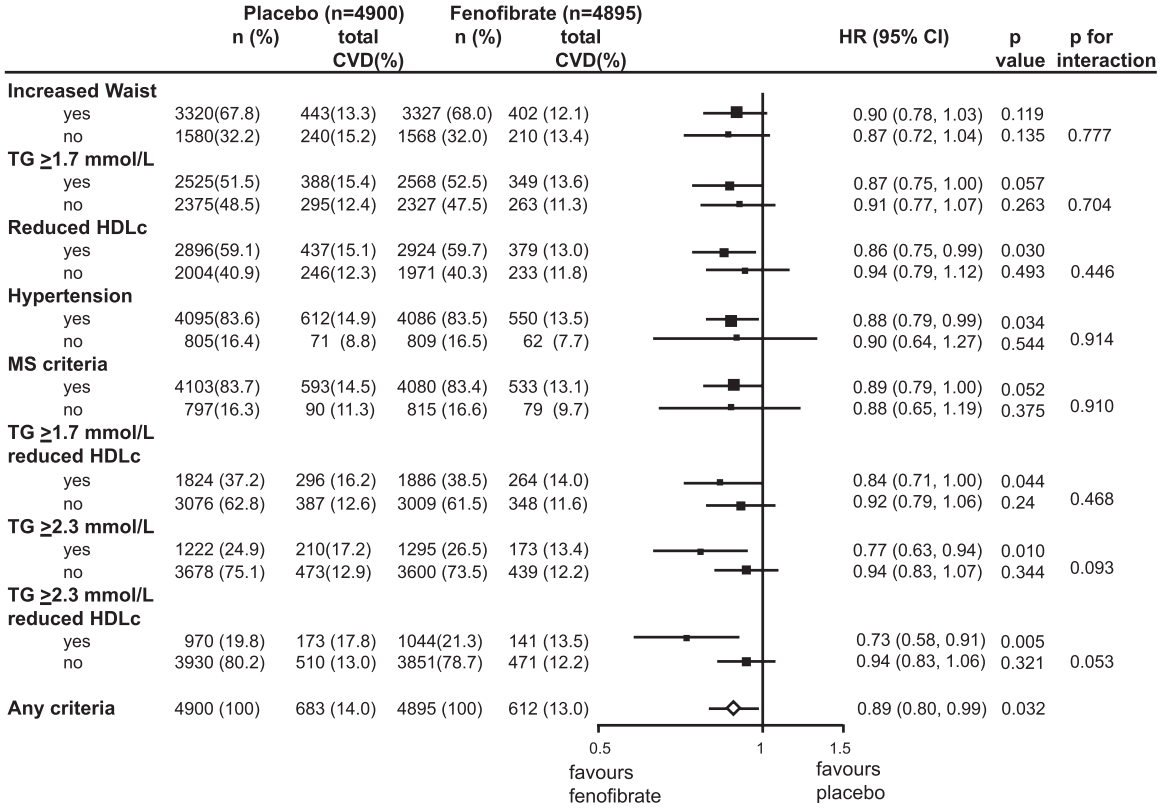

Figure 2—*Forest plot of effects of fenofibrate on cardiovascular events adjusted for sex, prior CVD, age at visit 1, and baseline A1C (HR and 95% CI): ATP III waist circumference criteria (men >102 cm and women >88 cm), raised triglyceride levels (TG) (≥1.7 mmol/l or ≥2.3 mmol/l), reduced HDL cholesterol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

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 nonsignificant 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 >25%, it is not surprising that individuals with elevated triglyceride levels appear to obtain

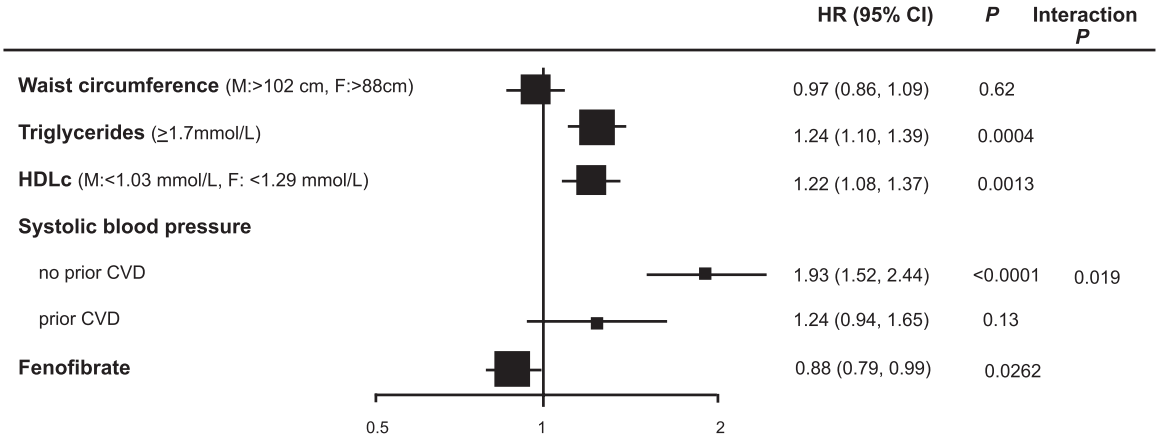

Figure 3—*Cox regression model for effect of metabolic syndrome features on total CVD events, adjusted for age, sex, prior CVD status, A1C, and LDL cholesterol levels at baseline. F, female; HDLc, HDL cholesterol; M, male.*

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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 has appeared 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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