The Effects of Fenofibric Acid Alone and With Statins on the Prevalence of Metabolic Syndrome and Its Diagnostic Components in Patients With Mixed Dyslipidemia

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OBJECTIVE — To compare fenofibric acid (FA) + statin to respective monotherapies on the prevalence of metabolic syndrome and its diagnostic components in patients with mixed dyslipidemia.

RESEARCH DESIGN AND METHODS — Post hoc analysis of over 2,000 metabolic syndrome patients administered either FA + low- or moderate-dose statin; FA alone; or low-, moderate-, or high-dose statin alone.

RESULTS — FA + low- or moderate-dose statin combination therapy reduced the presence of metabolic syndrome (35.7 or 35.9%, respectively) more than low-, moderate-, or high-dose statin monotherapy (15.5, 16.6, or 13.8%, respectively), mostly due to improvements in triglycerides and HDL cholesterol levels. Mean glucose levels slightly decreased with FA monotherapy, slightly increased with statin monotherapy, and were essentially unchanged with FA + statin. FA with or without statin also reduced non-HDL cholesterol, apolipoprotein B, total cholesterol, VLDL cholesterol, and high-sensitivity C-reactive protein.

CONCLUSIONS — FA + statin in patients with mixed dyslipidemia reduces the prevalence of metabolic syndrome.

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Fenofibric acid (FA) is the active moiety of fenofibrate. Previous studies—including over 2,600 patients—support the safety and efficacy of a choline salt formulation of FA (ABT-335, Trilipix; Abbott, North Chicago, IL) as monotherapy or in combination with statins (1–4). This post hoc analysis of mixed dyslipidemic patients with metabolic syndrome compared the effects of FA combined with statins versus the individual monotherapies on the presence of metabolic syndrome, as well as on the individual diagnostic components of metabolic syndrome.

RESEARCH DESIGN AND METHODS

— Three similarly designed, phase III, randomized, double-blind, 12-week studies evaluated the efficacy and safety of FA in combination with either rosuvastatin (3), simvastatin (4), or atorvastatin (2). After a 6-week lipid-altering drug washout period, all studies enrolled patients with mixed dyslipidemia (HDL cholesterol <40 mg/dl [<1.04 mmol/l] for men, <50 mg/dl [<1.30 mmol/l] for women; triglycerides [TGs] ≥150 mg/dl [≥1.70 mmol/l]; and LDL cholesterol ≥130 mg/dl [≥3.37 mmol/l]). Patients were assigned in a 2:2:2:2:2:1 ratio to 1 of 6 treatment arms: FA 135 mg monotherapy; low-dose statin monotherapy; FA 135 mg + low-dose statin; moderate-dose statin monotherapy; FA 135 mg + moderate-dose statin; or high-dose statin monotherapy. Each study used a different statin, and the respective doses of low-, moderate-, or high-dose statin were rosuvastatin 10, 20, or 40 mg, or simvastatin or atorvastatin 20, 40, or 80 mg. Data were pooled across the 3 studies. For further details regarding patients and study design, see the article by Jones et al. (5).

Assessments included the number and percent of patients with metabolic syndrome (6) at the final visit for each treatment group, as well as the number and percent of patients having individual metabolic syndrome diagnostic criteria at the baseline visit and at the final visit. In order to be included in these analyses, patients were required to have a final visit value for each metabolic syndrome diagnostic criteria. Waist circumference was not measured at final visit; baseline values were carried forward.

Mean changes from baseline to final value in weight, blood pressure, and fasting glucose were analyzed using a one-way ANOVA, comparing combination therapy with corresponding-dose monotherapies. Percent changes in efficacy parameters were compared between combination therapy and corresponding-dose monotherapies as previously described (2–4).

RESULTS

Baseline characteristics

Baseline data for all five metabolic syndrome criteria were available for 2,654 treated patients, and 2,190 (82.5%) pa-

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Table 1—*Prevalence of each metabolic syndrome criterion at the baseline visit and at the final visit, and changes from baseline to the final visit in metabolic syndrome parameters*

	Fenofibric acid	Low-dose statin	Moderate-dose statin	High-dose statin	Fenofibric acid + low-dose statin	Fenofibric acid + moderate-dose statin
Prevalence of each metabolic syndrome criterion						
*n**	354	361	367	189	375	357
Low HDL cholesterol						
Met criterion at BL† (*n* [%])	321 (90.7)	319 (88.4)	325 (88.6)	168 (88.9)	331 (88.3)	315 (88.2)
Met criterion at final (*n* [%])	193 (54.5)	262 (72.6)	265 (72.2)	141 (74.6)	202 (53.9)	186 (52.1)
Elevated TG						
Met criterion at BL† (*n* [%])	332 (93.8)	342 (94.7)	338 (92.1)	171 (90.5)	356 (94.9)	340 (95.2)
Met criterion at final (*n* [%])	194 (54.8)	265 (73.4)	240 (65.4)	115 (60.8)	124 (34.8)	126 (35.3)
Elevated blood pressure						
Met criterion at BL (*n* [%])	269 (76.0)	266 (73.7)	289 (78.7)	140 (74.1)	294 (78.4)	266 (74.5)
Met criterion at final (*n* [%])	257 (72.6)	253 (70.1)	271 (73.8)	132 (69.8)	279 (74.4)	253 (70.9)
Elevated fasting glucose						
Met criterion at BL (*n* [%])	211 (59.6)	218 (60.4)	222 (60.5)	119 (63.0)	222 (59.2)	211 (59.1)
Met criterion at final (*n* [%])	197 (55.6)	219 (60.7)	236 (64.3)	126 (66.7)	212 (56.5)	207 (58.0)
Increased waist circumference						
Met criterion at BL (*n* [%])	300 (84.7)	285 (78.9)	290 (79.0)	158 (83.6)	289 (77.1)	277 (77.6)
Met criterion at final‡	N/A	N/A	N/A	N/A	N/A	N/A
Changes (**Δ**) in metabolic syndrome parameters						
HDL cholesterol						
n	346	358	352	186	356	343
BL mean, mg/dl (mmol/l)	38.3 (1.0)	37.7 (1.0)	38.1 (1.0)	37.8 (1.0)	38.1 (1.0)	37.9 (1.0)
Mean **Δ** ± SEM (%)	17.5 ± 1.06	7.6 ± 1.04	9.2 ± 1.05	8.0 ± 1.42	18.3 ± 1.04§	18.7 ± 1.06§
TG						
n	377	373	382	199	394	373
BL mean, mg/dl (mmol/l)	284.4 (3.2)	295.7 (3.3)	292.5 (3.3)	284.0 (3.2)	284.9 (3.2)	296.8 (3.4)
Mean **Δ** ± SEM (%)	−33.3 ± 1.43	−21.7 ± 1.43	−26.4 ± 1.42	−29.3 ± 1.94	−45.4 ± 1.40§¶	−45.8 ± 1.44§¶
Blood pressure						
n	387	379	391	201	403	383
Systolic						
BL mean (mmHg)	127.8	126.9	128.2	127.8	128.7	126.8
Mean **Δ** ± SD (mmHg)	−1.9 ± 14.14	−1.5 ± 13.25	−1.2 ± 13.47	−1.5 ± 14.34	−3.0 ± 13.23	−1.2 ± 13.47
Diastolic						
BL mean (mmHg)	78.6	78.6	79.9	79.0	79.3	78.7
Mean **Δ** ± SD (mmHg)	−1.5 ± 8.84	−0.9 ± 9.01	−1.3 ± 8.67	−1.1 ± 8.42	−2.7 ± 9.24§	−1.6 ± 9.42
Fasting blood glucose						
n	386	379	390	201	401	381
BL mean, mg/dl (mmol/l)	108.0 (6.0)	108.3 (6.0)	106.1 (5.9)	106.8 (5.9)	107.6 (6.0)	107.1 (5.9)
Mean **Δ** ± SD, mg/dl (mmol/l)	−1.9 ± 22.80# (−0.1 ± 1.27)	4.7 ± 20.68 (0.3 ± 1.43)	4.7 ± 17.38 (0.3 ± 0.96)	4.8 ± 20.68 (0.3 ± 1.15)	−0.0 ± 19.56§ (0.0 ± 1.09)	−0.2 ± 18.19§ (0.0 ± 1.01)
Waist circumference						
n	399	386	395	205	409	396
BL mean (cm)	105.4	105.4	105.3	105.6	104.5	104.5
Mean **Δ** ± SD‡	N/A	N/A	N/A	N/A	N/A	N/A

Metabolic syndrome was defined as 3 or more of the following 5 criteria: HDL-C, <40 mg/dl (<1.04 mmol/l) for men, <50 mg/dl (<1.30 mmol/l) for women; TG, ≥150 mg/dl (≥1.70 mmol/l); blood pressure, ≥130 mmHg systolic or ≥85 mmHg diastolic or receiving treatment for hypertension; fasting glucose, ≥100 mg/dl (5.55 mmol/l) or medical history of type 2 diabetes; waist circumference, ≥102 cm for men, ≥88 cm for women. Fasting blood glucose analyses included patients concomitantly using medication for type 2 diabetes. *For prevalence analyses, only patients with metabolic syndrome at baseline who had both baseline and final visit values for the criteria were included. †Although the HDL cholesterol and TG criteria were required entry criteria for participation in the studies, not all patients met these criteria at baseline because the lipid eligibility values were measured at the screening visit 1 week prior to randomization, while baseline lipid values occurred the day of randomization. ‡Waist circumference was measured at baseline, but not at the final visit. Therefore, baseline waist circumference values were carried forward to the final visit. §Statistically significant difference vs. corresponding-dose statin monotherapy ($P < 0.001$ for both HDL cholesterol and TG comparisons, $P < 0.01$ for all other comparisons noted). ¶Statistically significant difference vs. fenofibric acid monotherapy ($P < 0.001$). #Statistically significant difference vs. statin monotherapy ($P < 0.001$). BL, baseline.

tients had metabolic syndrome at baseline. The percent of patients with metabolic syndrome at baseline was generally similar within each of the 6 treatment groups and ranged from 79.9% (low-dose statin) to 85.8% (high-dose statin). Across all treatment groups, 569 (26%) had a diagnosis of type 2 diabetes (supplemental appendix A, available in the online appendix at http://care.diabetesjournals.org/cgi/content/full/dc10-0357/DC1), and 461 (21.1%) received treatment with at least 1 antidiabetes drug.

Metabolic syndrome analyses

Of the 2,190 patients in the metabolic syndrome subgroup, 2,003 patients had a final visit value for all metabolic syndrome criteria (with the exception of waist circumference since baseline values were carried forward). Following 12 weeks of therapy in the 3 trials, FA + low- or moderate-dose statin reduced the number of patients meeting the diagnostic criteria for metabolic syndrome by 35.7 and 35.9%, respectively, compared with monotherapy with low-, moderate-, or high-dose statin (15.5, 16.6, and 13.8%, respectively). FA alone reduced metabolic syndrome diagnosis by 25.7%.

The percent of patients at baseline who met each individual metabolic syndrome criterion was comparable among all treatment groups (Table 1). At the final visit, FA + statin substantially reduced the prevalence of the metabolic syndrome diagnostic criteria regarding HDL cholesterol and TG compared with statin monotherapy. The prevalence of the blood pressure metabolic syndrome criteria decreased slightly at the final visit in each treatment group. At the final visit, the prevalence of the fasting blood glucose criterion was decreased slightly following treatment with FA monotherapy or FA + statin but increased slightly in the statin monotherapy groups.

Additional efficacy in the metabolic syndrome subgroup

Regarding metabolic syndrome-associated lipid parameters, FA + low- or moderate-dose statin significantly decreased TG compared with FA or corresponding-dose statin monotherapy ($P < 0.001$) and significantly increased HDL cholesterol ($P < 0.001$) compared with corresponding-dose statin (Table 1). FA + low- or moderate-dose statin also resulted in similar or greater reductions in non-HDL cholesterol, apolipoprotein B, total cholesterol, VLDL cholesterol, or high-sensitivity C-reactive protein compared with corresponding-dose statin (supplemental appendix B).

The mean changes in glucose were slightly increased in all statin monotherapy groups but were slightly decreased in the FA monotherapy group and essentially unchanged in the FA + statin groups. Mean increases in glucose with statin monotherapy ranged from 2.26 mg/dl (0.13 mmol/l) in the simvastatin 20 mg group to 7.46 mg/dl (0.41 mmol/l) in the atorvastatin 20 mg group. The mean change in fasting glucose was significantly different comparing FA + low- or moderate-dose statin with low- or moderate-dose statin monotherapy, respectively ($P \leq 0.002$). Overall, 54 (2.5%) of 2,190 patients in the metabolic syndrome subgroup initiated new antidiabetes medication during the study; percentages were similar among treatment groups. Mean changes in body weight ranged from −0.3 kg in the FA monotherapy group to +0.3 kg in the FA + moderate-dose statin group. Safety results in this metabolic syndrome subgroup were consistent with those observed in the overall population (7) (supplemental appendix C).

CONCLUSIONS — This analysis is the first to report the effects of fibrate and statin combinations versus their respective monotherapies on the individual diagnostic components of metabolic syndrome. According to this subgroup analysis, the greatest reduction in the presence of metabolic syndrome occurred with the FA + statin combination, primarily because of the improvements in the TG and HDL cholesterol diagnostic components. Although waist circumference was not measured at the end of the study, the lack of significant weight change in this study made it unlikely that changes in the waist circumference component altered the presence of metabolic syndrome.

Mean glucose levels rose with statins, but this effect was not statin-specific nor did it appear to be dose-related. The combination of FA with statins resulted in essentially no change in fasting blood glucose, similar to a recent report in type 2 diabetic patients (8), suggesting the possibility that FA may have mitigated the glucose-raising effect of statins. In summary, in this analysis of patients with mixed dyslipidemia and metabolic syndrome, FA combined with statins produced greater improvement in multiple metabolic parameters and in the percent of patients meeting diagnostic criteria for metabolic syndrome compared with either agent alone.

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