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Non-lipid effects of rosuvastatin–fenofibrate combination therapy in high-risk Asian patients with mixed hyperlipidemia

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ABSTRACT

Objective: The aim of this study is to compare the non-lipid effects of rosuvastatin–fenofibrate combination therapy with rosuvastatin monotherapy in high-risk Asian patients with mixed hyperlipidemia.
Methods: A total of 236 patients were initially screened. After six weeks of diet and life style changes, 180 of these patients were randomly assigned to receive one of two regimens: rosuvastatin 10 mg plus fenofibrate 160 mg or rosuvastatin 10 mg. The primary outcome variables were the incidences of muscle or liver enzyme elevation. The patients were followed for 24 weeks during drug treatment and for an additional four weeks after drug discontinuation.
Results: The rates of the primary outcome variables were similar between the two groups (2.8% and 3.9% in the combination and the rosuvastatin groups, respectively, $p = 1.00$). The combination group had more, but not significantly, common treatment-related adverse events (AEs) (13.3% and 5.6%, respectively) and drug discontinuation due to AEs (10.0% and 3.3%, respectively) than the rosouvastatin group. Combination therapy was associated with higher elevations in homocysteine, blood urea nitrogen, and serum creatinine, whereas elevation in alanine aminotransferase was greater in the rosuvastatin group. Leukocyte count and hemoglobin level decreased to a greater extent in the combination group. The combination group showed greater reductions in TG and elevation in HDL-cholesterol.
Conclusion: In our study population, the rosuvastatin–fenofibrate combination resulted in comparable incidences of myo- or hepatotoxicity as rosuvastatin monotherapy. However, this combination may need to be used with caution in individuals with underlying pathologies such as renal dysfunction (NCT01414803).

1. Introduction

Fibrates can reduce risk of cardiovascular events in people with high cardiovascular risk and combined dyslipidemia [1,2]. Recently, treatment with fenofibrate has been shown to be associated with reduced diabetic retinopathy and nephropathy progression, reflecting microvascular benefits [3–5]. On the other hand, since a fibrate and statin combination could heighten the risk of adverse events (AEs) such as myopathy, caution is recommended with such

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a combination [6,7]. However, it is notable that the risk of this AE varies depending on the fibrate and statin used in the combination. Fenofibrate does not adversely influence the metabolism of commonly prescribed statins [8]. It has been reported that the coadministration of rosuvastatin and fenofibrate produces only minimal changes in the pharmacokinetics of either agent [9]. In simvastatin-based trials, the addition of fenofibrate did not increase the incidences of myopathy or thromboembolism [10,11]. Currently, fenofibrate is recommended as the fibrate of choice for combination therapy with a statin [12].

Rosuvastatin, one of the currently available statins, has the greatest LDL-lowering potency per milligram of drug of all statins, although there has been a dispute on the safety of rosuvastatin [13]. However, the US Food and Drug Administration claimed that its risks are no greater than those of other statins, although the agency ordered labeling that includes a warning for potential muscle or kidney damage, especially among Asians [14]. It has been reported that plasma exposure to rosuvastatin and its metabolite are higher in Asian subjects than in Western subjects [15]. Although ethnic difference in the tolerability of lipid-modifying drugs is a growing field of interest, data regarding statins and statin–fibrate combinations in Asian people is very limited. Only a few studies have demonstrated that the effect of statins in Asians may not be the same as in Western patients [16,17].

In the current study, we compared the effects of rosuvastatin–fenofibrate combination therapy with rosuvastatin monotherapy in high-risk Asian patients with mixed hyperlipidemia. Primary outcome variables were the incidences of elevation of muscle or liver enzyme elevation. Changes in homocysteine level, renal function, glucose control, blood cell count, and lipid profile were also compared between the two groups. Our study is the first randomized trial to evaluate a statin–fenofibrate combination in an Asian population.

2. Methods

2.1. Study patients

All patients in this study had cardiovascular risk factors plus mixed hyperlipidemia. Men and women who were between 20 and 70 years of age were eligible for the study if they had a history of coronary artery disease, cerebrovascular disease or transient ischemic attack, peripheral vascular disease, or diabetes mellitus. Patients who had at least two of the other cardiovascular risk factors (supplementary data) were also included. All patients instituted diet and life-style changes for six weeks. Patients who have been taking lipid drugs discontinued the drugs during this period. If the patient had a total cholesterol level higher than 220 mg/dl, TG level between 200 and 500 mg/dl, and LDL-C levels higher than 130 mg/dl after this period, they were enrolled in this trial. All patients provided written informed consent. Patients were excluded if they were pregnant or breast-feeding, had uncontrolled hypertension, uncontrolled diabetes mellitus, thyroid dysfunction, serum transaminase >2 times the upper limit of normal, a history of gall bladder disease, chronic alcoholism, serum creatinine >1.5 mg/dl, a history of myopathy, a history of acute myocardial infarction or acute stroke within 3 months before the study began, or other unstable vascular diseases such as unstable angina, an acute or chronic infection or inflammation, a history of cancer, or a history of adverse events associated with test drugs.

2.2. Study procedures

This was a 34-week (six-weeks of diet and life style changes and 24 weeks of drug treatment followed by a four-week safety follow-up), randomized, open-label, multi-center study conducted at 14 sites in Korea. The protocol was approved by the institutional review board at each center. At the screening visit, each patient was interviewed regarding medical history, underwent a complete physical examination, and had a laboratory assessment. Diet and life-style changes are described in the supplementary data. Patients who met the lipid criteria after this lead-in period were randomized at a 1:1 ratio into one of the two drug treatment groups: combination therapy with rosuvastatin 10 mg/day and fenofibrate 160 mg/day or monotherapy with rosuvastatin 10 mg/day. After randomization, patients were followed-up at the end of sixth, 12th, 24th, and 28th weeks. A total of 236 patients were initially screened and 180 were randomized to the two treatment groups after the diet and life-style change period.

Fasting blood samples were collected at the time of randomization and at the end of the study. Laboratory values, including muscle and liver enzymes and lipid parameters, were measured at these two time points. Tolerability assessments were based on reported adverse events, history taking and physical examinations at each visit, and laboratory evaluations. Investigators determined the association between test drugs and AEs.

2.3. Outcome variables

Tolerability was compared using primary and secondary outcome variables, and efficacy was compared based on tertiary outcome variables. The primary outcome variables were the incidences of creatine kinase (CK) elevation >5 times the upper limit of normal (ULN) or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation >3 times ULN. The secondary outcome variables were the incidence of AEs and the percent changes in the laboratory values of tolerability from baseline to week 24 of drug treatment. The incidence of AEs was sub-divided into categories as follows: number of patients with any AE, number of patients with treatment-related AEs, rhabdomyolysis, and discontinuation of test drugs due to AEs. Laboratory values included CK, AST, ALT, homocysteine, blood urea nitrogen, serum creatinine, hemoglobin A1c, leukocyte count, hemoglobin, and platelet count. The tertiary outcome variables were percent changes in lipid parameters including total cholesterol, TGs, HDL-C, LDL-C, and non-HDL-C.

2.4. Statistical analysis

A minimum of 82 patients per treatment group were needed to provide 80% power to detect a 9% difference [18] in the incidences of the primary outcome variables with a 2-sided alpha level of 0.05. The analysis of AEs was also performed in these patients through four weeks post-treatment. Changes in laboratory values were analyzed for all patients with baseline values and at least one post-baseline value through the 24 weeks of drug treatment. Efficacy analyses were conducted in the population that finished the study without any major protocol violation. Detailed statistical methods are shown in the supplementary data. Differences were considered significant if the p value was <0.05. All analyses were performed using SAS software (version 9.2, SAS Institute Inc., Cary, North Carolina).

3. Results

3.1. Study patients

A total of 236 patients were screened and 180 of these were randomized (Fig. 1). Fifty patients did not meet the lipid criteria after the lead-in period and 6 patients withdrew consent. Among the

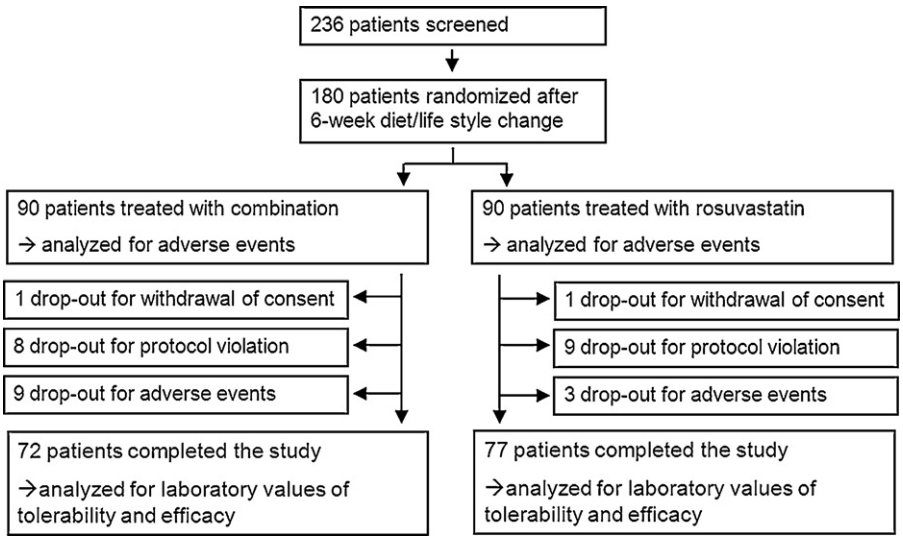

Fig. 1. Study profile showing the numbers of subjects who participated or dropped out at each step.

180 patients, 72 in the combination group and 77 in the rosuvastatin group completed the study. Thirty-one patients were dropped from the study and excluded from the analysis of laboratory values, two due to withdrawal of consent, 17 due to protocol violations and 12 due to AEs (Fig. 1). Baseline characteristics, lipid levels, and other laboratory values were similar between the two groups (Tables 1–3).

3.2. Primary and secondary outcome variables

The rates of the primary outcome variables were similar between the two groups (2.8% and 3.9% in the combination and rosuvastatin groups, respectively, $p = 1.00$) (Table 2). CK elevations > 5× ULN did not occur in the combination group but it occur in two patients (2.6%) in the rosuvastatin group. AST or ALT elevations > 3× ULN occurred in two patients (2.8%) in the combination group and one (1.3%) in the rosuvastatin group.

Data on secondary outcome variables is shown in Table 2 and Fig. 2. The proportions of patients who experienced any AEs or serious AEs were not different between the two groups. Although not significant, the combination group had higher rates of treatment-related AEs (supplementary Table 1) and drug discontinuation due to AEs. No patient in either group experienced rhabdomyolysis during the study. Rosuvastatin monotherapy resulted in significantly greater percent elevations in ALT, whereas the percent increases in homocysteine, blood urea nitrogen, and serum creatinine were significantly higher in the combination therapy group. Percent changes in CK, AST, and hemoglobin A1c levels were not different between the two treatments. The percent decrease in leukocyte count was marginally greater in the combination group, while the percent decrease in hemoglobin level was significantly greater in the combination group.

3.3. Tertiary outcome variables

As shown in Table 3 and Fig. 2, treatment with the rosuvastatin–fenofibrate combination resulted in a significantly greater reduction in TG compared with that of rosuvastatin monotherapy. In addition, the combination therapy resulted in higher elevations of HDL-C. Both regimens were similar with regard to percent changes in total cholesterol, LDL-C, and non-HDL-C.

Table 1
Baseline characteristics of the patients.

	All patients	Combination	Rosuvastatin	*p*
	(*n* = 180)	(*n* = 90)	(*n* = 90)	
Age, years	55.8 ± 10.0	55.2 ± 9.9	56.4 ± 10.1	0.43
Female gender	86 (47.8)	40 (44.4)	46 (51.1)	0.23
Duration of hyperlipidemia, months	17.2 ± 31.3	16.5 ± 30.9	17.8 ± 31.8	0.77
Weight, kg	69.6 ± 12.9	70.8 ± 14.0	68.4 ± 11.7	0.21
Body mass index, kg/m^2	26.0 ± 3.4	26.2 ± 3.7	25.7 ± 3.1	0.28
Statin use	9 (6.5)	5 (7.4)	4 (5.7)	0.74
Risk factors in inclusion criteria				
CAD	35 (19.4)	20 (22.2)	15 (16.7)	0.35
Cerebrovascular disease/TIA	4 (2.2)	0 (0)	4 (4.4)	0.12
Peripheral vascular disease	0 (0)	0 (0)	0 (0)	–
Diabetes Mellitus	15 (8.3)	6 (6.7)	9 (10.0)	0.42
Age ≥45 years or ≥55 years	139 (77.2)	70 (77.8)	69 (76.7)	0.86
Hypertension	83 (46.1)	39 (43.3)	44 (48.9)	0.45
Low HDL-cholesterol	39 (23.4)	22 (26.5)	17 (20.2)	0.34
Family history of CAD in young age	0 (0)	0 (0)	0 (0)	–
Fasting glucose ≥110 mg/dL	58 (35.4)	26 (31.7)	32 (39.0)	0.33
Left ventricular hypertrophy	1 (0.6)	1 (1.1)	0 (0)	1.00

Values are mean ± SD or *n* (%); CAD: coronary artery disease; TIA: transient ischemic attack; HDL: high-density lipoprotein.

Table 2
Primary and secondary outcome variables: incidence of muscle or liver enzyme elevation, adverse events (AEs) and changes in laboratory values.

Primary outcome variables	Combination ($n=72$)	Rosuvastatin ($n=77$)	p^a
Elevation of any primary outcome variables> predefined levels	2 (2.8)	3 (3.9)	1.00
Elevation of CK > 5× ULN	0 (0)	2 (2.6)	0.50
Elevation of AST or ALT > 3× ULN	2 (2.8)	1 (1.3)	0.61
Secondary outcome variables: patients with AEs	($n=90$)	($n=90$)	
Patients with any AEs	26 (28.9)	20 (22.2)	0.31
Patients with treatment-related AEs*	12 (13.3)	5 (5.6)	0.07
Patients with serious AEs	2 (2.2)	2 (1.1)	1.00
Rhabdomyolysis	0 (0)	0 (0)	–
Discontinuation of test drugs due to AEs	9 (10.0)	3 (3.3)	0.13
Secondary outcome variables: changes in laboratory values	($n=72$)	($n=77$)	
CK, IU/L			
Before	91 (75–125)	91 (67–118)	0.42
After	107 (73–165)	98 (65–146)	0.38
p^b	0.02	0.01	
AST, IU/L			
Before	24 (20–30)	23(13–57)	0.97
After	25 (22–32)	26 (14–86)	0.65
p^b	0.004	<0.001	
ALT, IU/L			
Before	25 (18–38)	26 (20–37)	0.57
After	24 (19–33)	31 (24–42)	0.005
p^b	0.63	0.02	
Homocysteine, μmol/L			
Before	12.2 (9.4–17.5)	12.5 (9.4–15.6)	0.85
After	16.6 (12.2–20.0)	11.9 (9.8–14.8)	0.007
p^b	<0.001	0.40	
Blood urea nitrogen, mg/dL			
Before	15.0 ± 4.8	15.0 ± 3.8	0.99
After	17.7 ± 5.2	15.1 ± 4.3	<0.001
p^b	<0.001	0.88	
Serum creatinine, mg/dL			
Before	0.86 ± 0.25	0.82 ± 0.19	0.23
After	0.97 ± 0.25	0.84 ± 0.19	<0.001
p^b	<0.001	0.98	
Hemoglobin A1c, %			
Before	6.12 ± 0.78	6.06 ± 0.62	0.65
After	6.32 ± 1.28	6.19 ± 0.58	0.50
p^b	0.10	0.22	
Leukocyte, $\times 10^6/\mu L$			
Before	7.1 (5.8–8.3)	6.9 (5.9–8.4)	0.76
After	6.6 (5.5–8.0)	6.7 (5.9–8.2)	0.38
p^b	0.002	0.49	
Hemoglobin, %			
Before	14.2 ± 1.3	14.3 ± 1.3	0.44
After	13.6 ± 1.3	14.1 ± 1.5	0.03
p^b	<0.001	0.01	
Platelet, $\times 10^6/\mu L$			
Before	271 ± 69	267 ± 60	0.75
After	266 ± 69	251 ± 55	0.13
p^b	0.32	<0.001	

Values are n (%) or mean ± SD or median (interquartile range); CK: creatine kinase; ULN: upper limit of normal; AST: aspartate aminotransferase; ALT: alanine aminotransferase; p^a: comparison between groups, p^b: comparison in a group before and after treatment.

* Total AE–AE considered by investigators to be definitely or probably not related to study drugs.

4. Discussion

In the present study, the incidences of the primary outcome variables were not different between the two groups. Although the incidences of any AEs were similar between the two arms, the combination group had more, but not significantly, frequent treatment-related AEs and drug discontinuation due to AEs. Combination therapy was associated with higher elevations of homocysteine, blood urea nitrogen, and serum creatinine, rosuvastatin monotherapy resulted in greater ALT elevations. In addition, the percent reductions in leukocyte count and hemoglobin were greater in the combination group, although these differences were modest. The combination group showed greater TG reduction and HDL-C elevation. Our study is the first randomized trial to compare these two regimens in Asian patients, for whom drug tolerability is of growing interest. In addition, the comprehensive evaluation of multiple parameters in the study may provide useful information for clinical practice in this population.

As in other studies that examined statin and fenofibrate combinations in mostly non-Asian subjects, muscle or liver enzyme elevations were uncommon in our study. The combination of older statins and fenofibrate has been a focus of several prior studies. In the ACCORD study, the combination of simvastatin and fenofibrate induced CK elevations >5× ULN in 1.9% of patients and ALT elevations >3× ULN in 1.9% of patients, and these incidences were not different from those in the control group receiving simvastatin monotherapy [11]. A comparison of the atorvastatin–fenofibrate combination therapy and monotherapy with each agent did not

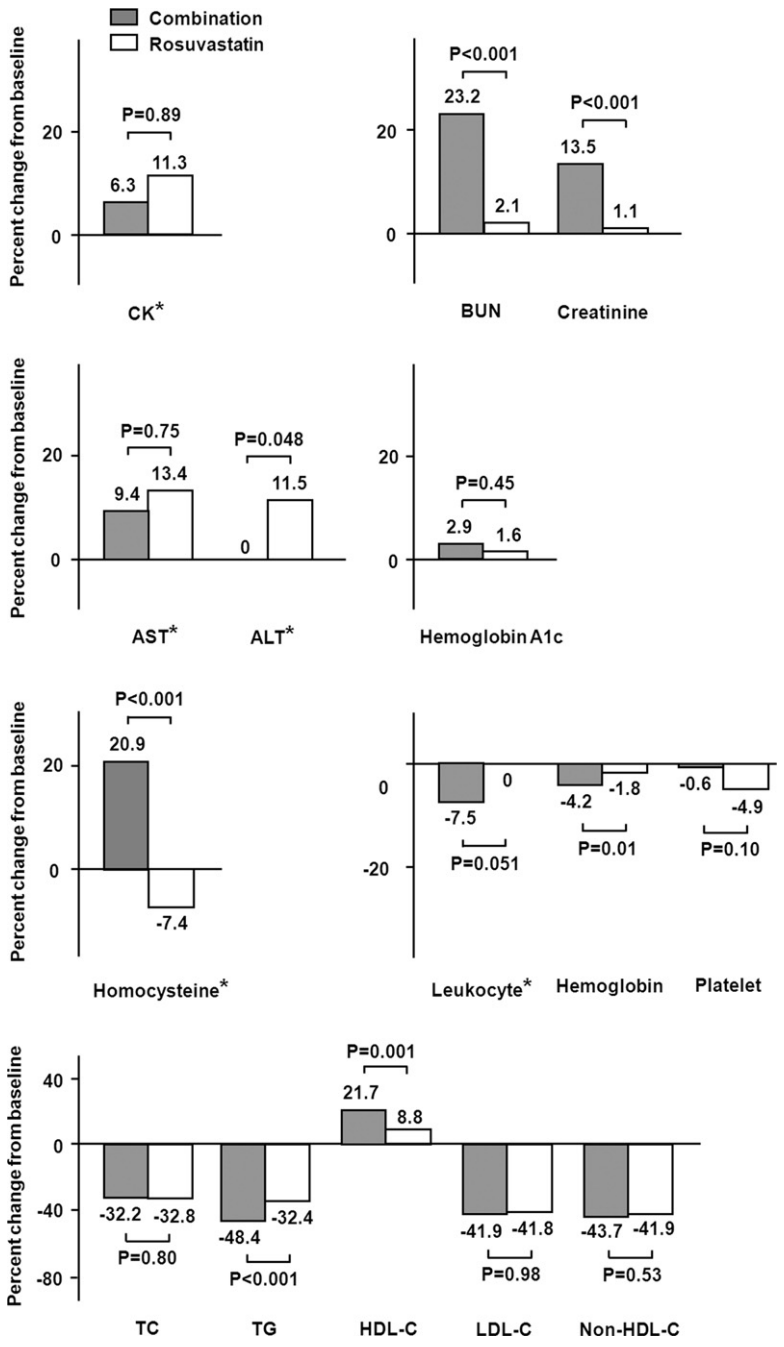

Fig. 2. Bar graph showing the percent changes in CK (first row left panel), liver enzymes (second row left panel), homocysteine (third row left panel), renal parameters (first row right panel), hemoglobin A1c (second row right panel), hematologic parameters (third row right panel), and lipid profile (fourth row) after drug treatment. CK: creatine kinase; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

show any differences in regard to muscle or liver enzyme elevations [19]. Recently, a few studies that evaluated rosuvastatin and fenofibric acid combination therapy have demonstrated acceptable tolerability of this combination for up to two years [20–22]. Jones et al. showed elevations of CK > 5× ULN in 0.4% of the patients in the combination arm and 2.3% of patients in the rosuvastatin arm [20]. The rates of ALT and/or AST elevation >3× ULN were 0% and 1.1% in each arm, respectively. To date, the only study that compared rosuvastatin and fenofibrate combination therapy to rosuvastatin alone included diabetic patients and reported the occurrence of CK > 3× ULN to be 3.5% and ALT > 3× ULN to be 5.2% in the combination group [18]. Although these values were slightly higher than ours, they nevertheless are regarded as low and tolerable. Compared to that previous study, our study had a simpler dosing regimen and administration frequency and enrolled a greater number of patients in each arm.

In the present study, the number of patients who experienced any AEs was similar in the two groups. In some studies that tested statin–fenofibric acid combination therapy, drug discontinuation rates were higher with the combination regimen than with statin monotherapy [20,22]. On the other hand, most studies have reported that the incidences of AEs or serious AEs in the statins–fenofibrate or fenofibric acid combinations were similar to those in the statin only-treated patients [11,19,21]. In our study, the combination group showed more frequent treatment-related AEs and drug discontinuation due to AEs than the rosuvastatin group. Although this difference was not significant, it is worth noting that the power of our study was based on the incidences of the primary

Table 3
Tertiary outcome variables: changes in lipid parameters.

	Combination	Rosuvastatin	
	(n = 72)	(n = 77)	p^a
Total cholesterol, mg/dL			
Before	251 ± 33	248 ± 31	1.00
After	168 ± 38	165 ± 32	0.57
p^b	<0.001	<0.001	
Triglycerides, mg/dL			
Before	285 ± 82	282 ± 131	0.85
After	143 ± 81	180 ± 87	0.01
p^b	<0.001	<0.001	
HDL-cholesterol, mg/dL			
Before	44.3 ± 6.6	45.7 ± 8.3	0.26
After	53.7 ± 12.8	49.1 ± 9.6	0.02
p^b	<0.001	<0.001	
LDL-cholesterol, mg/dL			
Before	160 ± 26	156 ± 25	0.35
After	91 ± 34	89 ± 28	0.68
p^b	<0.001	<0.001	
Non-HDL-cholesterol, mg/dL			
Before	207 ± 32	203 ± 31	0.46
After	115 ± 40	116 ± 30	0.83
p^b	<0.001	<0.001	

Values are mean ± SD; HDL: high-density lipoprotein; LDL: low-density lipoprotein; p^a: comparison between groups, p^b: comparison in a group before and after treatment.

outcome variables, and the number of subjects might not be sufficiently large to detect a possible difference in AEs between the two arms.

It has been previously documented that plasma homocysteine level is increased by fenofibrate [10]. Likewise, in our results, post-treatment median homocysteine level was 4.7 mol/L higher in the combination group, and the percent change of the level was also significantly greater. The clinical relevance of homocysteine elevation after fenofibrate administration is still unclear [23], although some reports have demonstrated the relative innocence of the elevation [24]. The risk of renal dysfunction after statin–fibrate therapy has been controversial [25]. In our study, the median percent elevation of serum creatinine in the combination group was 13.5%, which was higher than in the rosuvastatin monotherapy group. This degree of elevation is similar to the 8–18% that was reported by other studies analyzing the effects of fenofibrate [11,26]. We did not observe serious changes in renal function in either the combination group or the rosuvastatin monotherapy group. However, because we excluded patients with serum creatinine >1.5 mg/dl, it cannot be entirely ruled out that such AEs can occur in individuals with renal dysfunction at baseline. In the current study, changes in hemoglobin A1c were not different between the two arms. To date, clinical studies evaluating the effects of fenofibrate or fenofibric acid on glucose control have revealed contradictory results. Some of these studies demonstrated no effects on insulin sensitivity or glucose control [27,28], whereas others showed significant improvements in these parameters after fenofibrate therapy [29,30]. Of note, in these latter studies, the authors indicated that the beneficial effects of fenofibrate were more obvious in subjects with pre-diabetic conditions. With this result in mind, the lack of distinct effect of fenofibrate on glucose control in our study may be partly related to the low prevalence of impaired fasting glucose in our study population. Interestingly, we observed that leukocyte count and hemoblogin level decreased more in the combination treatment group than in the rosuvastatin monotherapy group. To date, data regarding the influence of fenofibrate, either alone or in combination with statins, on hematologic parameters is extremely limited. In one study that analyzed collected data from the US and Europe, mild leukopenia and eosinophilia were reported to be associated with fenofibrate [31]. Although we found no difference in platelet count changes between the two groups in our study, this parameter was significantly lowered only in the rosuvastatin monotherapy group. To date, only a few case reports have been published regarding statin-related thrombocytopenia [32,33]. To our knowledge, our data is the first to systemically compare the effects of a statin and fenofibrate combination with a statin alone on hematological variables.

TG lowering and HDL raising efficacy were stronger in the combination therapy group than in the rosuvastatin monotherapy group. Our efficacy data is comparable to the results of a recent trial that used rosuvastatin and fenofibric acid in patients with similar baseline lipid profiles to our subjects [20]. Although it is not the major focus of the current study, efficacy is the major factor that guides the choice of drugs. Therefore, it is important to recall that the neutral effects of fenofibrate on clinical outcomes [10,11] when one consider using this agent. In addition, the benefits of HDL-raising by pharmacologic agents after LDL lowering are still unclear [34].

A few limitations can be pointed out in our study. First, although we enrolled patients with high cardiovascular risk, individuals with elevated serum creatinine or liver enzymes were excluded. Therefore, our safety data cannot be generalized to patients with these conditions. Second, we monitored the tolerability of test drugs for 28 weeks. Longer-term data might be needed in order to more completely clarify the tolerability of this combination. In addition, we used rosuvastatin 10 mg plus fenofibrate 160 mg in this study. The segment of patients who did not reach the lipid target with this combination may need either higher doses of these drugs or a different combination of drugs. Further study may be required to fully examine the effects of these regimens. Third, the patients completed the study was short of pre-specified number for statistical power. Provisions in the recruitment could have made the study more complete. Finally, because the main focus of this study was the tolerability of the test drugs, a larger number of subjects would have made our study more conclusive. However, when this study was designed, power was calculated using best available data.

In summary, the incidences of the primary outcome variables and AEs were not significantly different between the two groups. The combination group was associated with higher elevations in homocysteine, blood urea nitrogen, and serum creatinine and greater reductions in leukocyte and hemoglobin levels. It is not appropriate to show the clinical relevance of these changes in our relatively short-term study. Further study is required to explore whether combination therapy-induced changes in homocysteine, creatinine, and other parameters might cause harmful effect after longer-term follow-up. In conclusion, the incidences of myo- or hepatotoxicity in rosuvastatin–fenofibrate combination therapy were comparable to those in rosuvastatin monotherapy in high-risk Asian patients with mixed hyperlipidemia. However, this combination may need to be used with caution in individuals with underlying pathologies such as renal dysfunction.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.atherosclerosis.2011.12.042.

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