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Use of fenofibrate on cardiovascular outcomes in statin users with metabolic syndrome: propensity matched cohort study

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ABSTRACT

OBJECTIVE

To investigate whether fenofibrate as add-on to statin treatment reduce persistent cardiovascular risk in adults with metabolic syndrome in a real world setting.

DESIGN

Propensity matched cohort study.

SETTING

Population based cohort in Korea.

PARTICIPANTS

29 771 adults with metabolic syndrome (≥40 years) receiving statin treatment. 2156 participants receiving combined treatment (statin plus fenofibrate) were weighted based on propensity score in a 1:5 ratio with 8549 participants using statin only treatment.

MAIN OUTCOME MEASURE

Primary outcome was composite cardiovascular events including incident coronary heart disease, ischaemic stroke, and death from cardiovascular causes.

RESULTS

The incidence rate per 1000 person years of composite cardiovascular events was 17.7 (95% confidence interval 14.4 to 21.8) in the combined treatment group and 22.0 (20.1 to 24.1) in the statin group. The risk of composite cardiovascular events was significantly reduced in the combined treatment group compared with statin group (adjusted hazard ratio 0.74, 95% confidence interval 0.58 to 0.93; P=0.01). The significance was maintained in the on-treatment analysis (hazard ratio 0.63, 95% confidence interval 0.44 to 0.92; P=0.02). The risk of incident coronary heart disease, ischaemic stroke, and cardiovascular death was lower in the combined treatment group than statin group but was not significant. Participant characteristics did not appear to be associated with the low risk of composite cardiovascular events with combined treatment.

CONCLUSION

In this propensity weighted cohort study of adults with metabolic syndrome, the risk of major cardiovascular events was significantly lower with fenofibrate as add-on to statin treatment than with statin treatment alone.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Randomised clinical trials of fenofibrate treatment have failed to show a reduction in risk of major cardiovascular events in people with diabetes, but a statistically significant cardiovascular risk reduction was observed in subgroups with atherogenic dyslipidaemia

Meta-analyses of fibrates also indicated that people with atherogenic dyslipidaemia would benefit from fibrates on cardiovascular events reduction

Real world evidence was insufficient to prove the efficacy of fenofibrate in cardiovascular risk reduction especially in people of East Asian origin who are reported to be genetically susceptible to poor elimination of blood triglyceride

WHAT THIS STUDY ADDS

The risk of major cardiovascular events was reduced in adults with metabolic syndrome using fenofibrate as add-on to statin treatment

Introduction

Metabolic syndrome is a cluster of interrelated risk factors that leads to metabolic dysregulation and atherosclerotic cardiovascular diseases.[1] The increased risk of cardiovascular disease in people with metabolic syndrome has been well established by observational studies and meta-analyses,[2-4] and considered to be partly attributable to the accompanying atherogenic dyslipidaemia, which is characterised by increased triglyceride levels, small dense low density lipoprotein particles with low levels of high density lipoprotein (HDL) cholesterol.[5 6] Abundant evidence shows that lowering low density lipoprotein (LDL) cholesterol concentrations with statins is the primary treatment option for minimising cardiovascular disease in people at risk, including those with atherogenic dyslipidaemia.[7-9] In many clinical trials and observational studies, substantial cardiovascular risk persisted (residual cardiovascular risk) despite ongoing statin treatment.[10-12]

Fenofibrate, a peroxisome proliferator activated receptor-α agonist, has been suggested as an important treatment option in the management of dyslipidaemia owing to its effects on hypertriglyceridaemia and low HDL cholesterol concentrations.[13] Although large randomised clinical trials of fenofibrate, including the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial and the Action to Control Cardiovascular Risk in Diabetes (ACCORD)-Lipid trial failed to show a reduction in the primary outcome of major cardiovascular events in populations with diabetes but a statistically significant cardiovascular risk reduction was observed in subgroups with atherogenic dyslipidaemia.[14-16] Two meta-analyses of fibrates also indicated that the associated reduction of cardiovascular events would benefit people with atherogenic dyslipidaemia.[17 18]

The previous studies were mainly conducted in Western populations with high cardiovascular risk, which limits generalisability of the results to other ethnic populations or to people with a broader range of cardiovascular risk. Given that atherogenic dyslipidaemia is more prevalent in people of East Asian origin, in whom a genetic susceptibility to poor elimination of blood triglycerides has been reported,[19] study based evidence to evaluate fenofibrate efficacy in cardiovascular risk reduction in this population is necessary.

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We evaluated the effects of fenofibrate treatment on major cardiovascular events in adults with metabolic syndrome using statins in a real world setting. We also assessed the degree of benefit from combined treatment with statin and fenofibrate in residual cardiovascular risk reduction. This study was conducted as part of the Effectiveness of Fenofibrate Therapy in Residual Cardiovascular Risk Reduction in the Real World Setting (ECLIPSE-REAL) study.

Methods

Data sources

We used the Korean National Health Insurance Service-Health Screening Cohort (NHIS-HEALS), which included 514 866 Koreans. This cohort represents 10% of a random selection of screened participants aged 40 to 79 in the index years 2002 or 2003 and followed-up to 2015. This database contains longitudinal information, including personal data, medical and pharmaceutical records, disease diagnoses (international classification of diseases, 10th revision), medical procedures, hospital admissions, prescribed drugs, health examination data (eg, anthropometric measures and laboratory data), and death records. The cohort protocol has been described previously.[20]

Patient selection and propensity score matching

We selected adults (≥40 years) from the original database who had used statins for at least three months from 1 January 2007 to 31 December 2014, as the national health examination programmes included lipid profiles from January 2007. Adults without documented lipid profiles before initiation of statin treatment were excluded. Potentially eligible participants were then selected who met the metabolic syndrome criteria, as defined by the Adult Treatment Panel III guidelines, before the index date.[21] Waist circumference cut-off points for metabolic syndrome were in accordance with the Asian standard set by the World Health Organization.[22] Thus, adults with metabolic syndrome were required to meet three or more of the following criteria: waist circumference ≥90 cm in men and ≥80 cm in women, serum triglyceride level ≥1.7 mmol/L, HDL cholesterol level <1.0 mmol/L in men and <1.3 mmol/L in women, fasting glucose level ≥5.6 mmol/L or antidiabetes treatment, and blood pressure ≥130/85 mm Hg or treatment for hypertension. Of 24 857 selected adults, 2457 had received fenofibrate for at least three months during the follow-up period.

Propensity score matching (maximum 1:5) was done for those who had used fenofibrate (combined treatment with statin and fenofibrate) and those who had not (statin treatment only). The propensity score analysis balances covariates between study groups of observational data using a propensity score, which is the conditional probability of assignment to a particular group given observed covariates only.[23] The use of a propensity score with time-to-event data by either weighting or matching techniques is well established.[24]

We derived the propensity score model from a multiple logistic regression that included age, sex, waist circumference; fasting glucose level; systolic blood pressure; serum creatinine level; smoking status (current, former, or never); alcohol consumption (≥3 times/week, ≤2 times/week, or never); physical activity (≥3 times/week, ≤2 times/week, or never); pre-existing cardiovascular disease, including coronary heart disease, ischaemic stroke, and heart failure; antithrombotic agents; antihypertensive agents; statin intensity based on the average expected LDL cholesterol response[8]; and duration of statin treatment before the index date. Baseline LDL cholesterol levels (<2.59, 2.59–3.36, 3.36–4.14 and ≥4.14 mmol/L), HDL cholesterol levels (<0.88, ≥0.88 mmol/L), and triglyceride levels (<2.3, ≥2.3 mmol/L) were also used as independent variables in the propensity score model. We used a greedy nearest neighbour matching on the logit of propensity score using calipers of width 0.2 of the standard deviation of the logit of the propensity score. The cut-off points for HDL cholesterol and triglyceride concentration were derived from the subgroups who benefited from fenofibrate treatment on cardiovascular outcomes in previous randomised controlled trials, including ACCORD-Lipid and FIELD.[15 25] Overall, we selected 2156 adults from the combined treatment group and 8549 from the statin only group. Supplementary figure 1 shows the distribution of propensity scores, indicating that the two groups were well matched.

Outcome measures

The cardiovascular outcomes of interest were incident coronary heart disease (ICD-10 codes I20-I25 plus a coronary artery angiography procedure), ischaemic stroke (ICD-10 codes I63-66 with an examination of brain imaging studies or procedures), and death from cardiovascular disease (ICD codes I00-I99). Composite cardiovascular disease events included any of the prespecified cardiovascular events.

Each participant was followed-up from the index date to the earliest occurrence of any study outcome, death, or end of the study period (31 December 2015). We defined the index date as three months after the initiation of treatment.

Statistical analysis

Data are presented as means (standard deviations) for continuous variables and numbers (percentages) for categorical variables. A generalised estimating equation for matched data was used to compare personal and clinical characteristics between groups. We calculated incidence rates per 1000 person years with corresponding 95% confidence intervals for the individual outcomes. A stratified Cox proportional hazards regression model for matched data was used to evaluate the relation between the treatments and study outcomes. In the matched sample all absolute standardised differences in baseline covariates between the two groups were less than 0.1 except for β blocker use, diuretics use, and

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triglyceride category, which were further adjusted for the subsequent analyses. Characteristics for subgroup analysis included age (≥65, <65 years), sex (men, women), waist circumference (≥90, <90 cm), pre-existing cardiovascular disease, hypertension, type 2 diabetes, pretreatment HDL cholesterol concentration (<0.88, ≥0.88 mmol/L), triglyceride concentration (<2.3, ≥2.3 mmol/L), non-HDL cholesterol concentration calculated by total cholesterol minus HDL cholesterol concentration (<3.36, ≥3.36 mmol/L), and on-treatment LDL cholesterol concentration (<2.59, ≥2.59 mmol/L).

To reduce survival bias associated with time to fenofibrate initiation after statin treatment, we set the index date for propensity score matching to be the same as the date of initiation of fenofibrate treatment in participants and their matched controls.[26] The index date for participants in the statin group was the index date of matched participants in the combined treatment group.

Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC). We considered a two sided P value of <0.05 to be significant.

Patient and public involvement

Patients were not involved in research design or the outcome measures. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants.

Results

Figure 1 shows the flow of participants through the study. The mean age of participants was 62.5 years and mean body mass index was 25.8. Overall, 985 (9.2%) participants had pre-existing cardiovascular disease and 4046 (37.8%) had type 2 diabetes. The mean duration of statin treatment was 30.2 months. After propensity weighted matching, the baseline characteristics of the combined treatment group and statin group were well balanced (table 1), except for β blocker use, diuretic use, and triglyceride category—subsequent analyses were therefore adjusted for those variables. HDL cholesterol and triglyceride were matched by prespecified cut-offs (0.88 mmol/L and and 2.3 mmol/L, respectively) for lower and higher levels of each variable. According to the criteria, at baseline 891 (8.3%) had lower HDL cholesterol levels and 5604 (52.4%) had hypertriglyceridaemia. Mean duration of follow-up was 29.7 (SD 17.7) months.

Changes in serum lipid profiles with treatment

Supplementary table 1 shows changes in lipid profiles in each treatment group. At baseline, mean LDL and HDL cholesterol concentrations were well balanced between the groups, whereas the mean triglyceride concentrations were higher in the combined treatment group. On-treatment LDL and HDL cholesterol concentrations were also similar between the groups (mean LDL cholesterol 2.56 *v* 2.48 mmol/L, mean

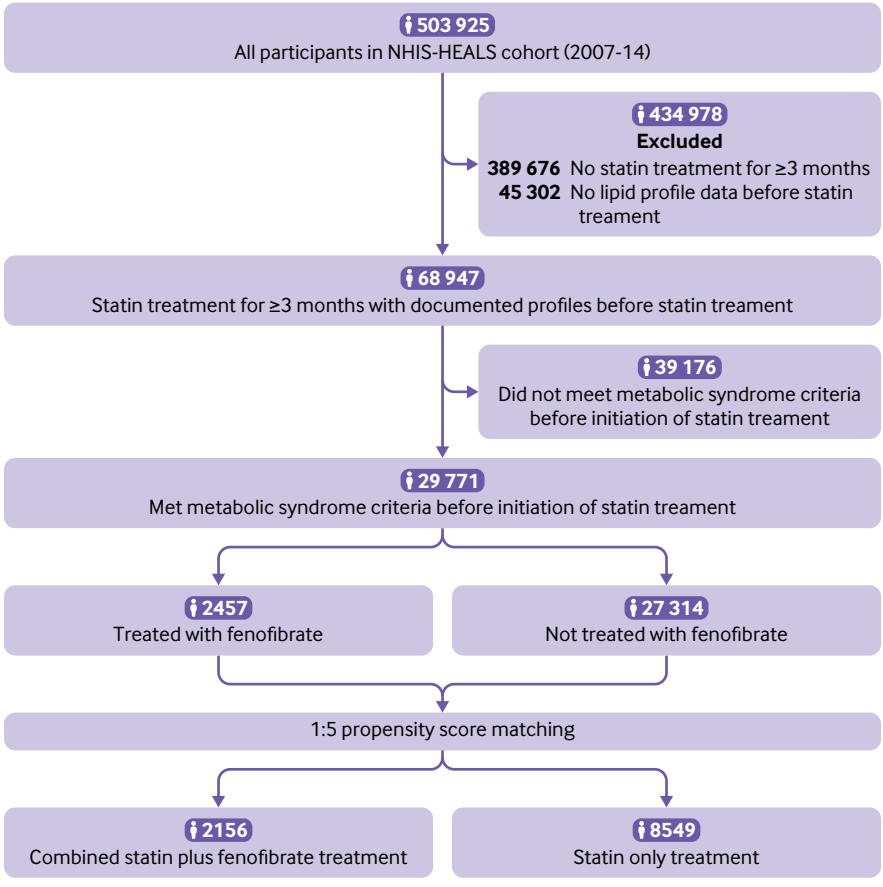

Fig 1 | Flow diagram of participant selection

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Table 1 | Baseline characteristics of participants. Values are percentages (numbers) unless stated otherwise

Characteristics	Combined statin and fenofibrate (n=2156)	Statin only (n=8549)	Absolute standardised difference	
			Before matching	After matching
Mean (SD) age (years)	62.3 (7.9)	62.6 (8.0)	0.39	0.03
Men	54.2 (1169)	52.7 (4505)	0.26	0.03
Mean (SD) body mass index	25.8 (2.8)	25.8 (2.9)	0.09	0.01
Mean (SD) waist circumference (cm)	87.2 (7.7)	87.2 (7.9)	0.13	0.01
Mean (SD) fasting glucose (mmol/L)	6.5 (1.9)	6.5 (2.0)	0.12	0.01
Mean (SD) systolic blood pressure (mm Hg)	130.9 (14.8)	131.4 (15.1)	0.02	0.03
Mean (SD) creatinine (μmol/L)	88.9 (131.8)	88.0 (89.7)	0.04	0.01
Current smoker	18.5 (399)	17.3 (1480)	0.20	0.03
Alcohol consumption	48.9 (1054)	45.1 (3856)	0.15	0.08
Regular exercise	53.3 (1149)	52.8 (4510)	<0.01	0.01
Comorbidities:				
Coronary heart disease	3.5 (75)	4.2 (360)	0.15	0.04
Ischaemic stroke	3.9 (85)	4.4 (377)	0.08	0.02
Heart failure	1.4 (31)	1.4 (122)	0.07	<0.01
Concurrent drug treatment:				
Antithrombotic agents	46.1 (994)	44.6 (3811)	0.18	0.03
RAS inhibitor	70.2 (1513)	67.5 (5772)	0.24	0.06
Calcium channel blocker	55.9 (1205)	51.1 (4365)	0.31	0.09
β blocker	31.3 (674)	26.7 (2286)	0.37	0.10*
α blocker	15.6 (337)	12.8 (1098)	0.24	0.08
Vasodilator	0.7 (14)	0.6 (48)	0.03	0.01
Diuretics	46.4 (1000)	40.8 (3490)	0.38	0.11*
Statin intensity†:			0.06	0.03
High	2.4 (51)	2.3 (193)		
Moderate	92.4 (1991)	93.0 (7949)		
Low	5.3 (114)	4.8 (407)		
Duration of statin treatment before index date (months)	10.1 (11.9)	9.9 (11.0)	0.248	0.016
LDL cholesterol (mmol/L):			0.18	0.04
<2.59	40.7 (877)	39.3 (3356)		
2.59-3.36	25.5 (549)	24.9 (2125)		
3.36-4.14	20.0 (432)	21.2 (1813)		
≥4.14	13.8 (298)	14.7 (1255)		
HDL cholesterol (mmol/L):			0.13	0.01
<0.88	8.6 (186)	8.2 (705)		
≥0.88	91.4 (1970)	91.8 (7844)		
Triglyceride (mmol/L):			0.71	0.11*
<2.3	43.5 (937)	48.7 (4164)		
≥2.3	56.5 (1219)	51.3 (4385)		

RAS=renin-angiotensin-aldosterone system; LDL=low density lipoprotein; HDL=high density lipoprotein.
*Absolute standardised difference ≥0.1 after matching.
†Defined based on average expected LDL cholesterol response.[8]

HDL cholesterol 1.33 *v* 1.28 mmol/L). The combined treatment group showed a greater reduction in triglyceride concentration than the statin group and the achieved mean triglyceride concentration was lower in the combined treatment group (1.64 *v* 1.85 mmol/L). Mean non-HDL cholesterol concentration was similar between the groups (3.28 *v* 3.32 mmol/L).

Risk of major cardiovascular events

Table 2 shows incidence rates per 1000 person years and risk of cardiovascular outcomes between the groups. The risk of coronary heart disease (hazard ratio 0.82, 95% confidence interval 0.62 to 1.09; P=0.2), ischaemic stroke (0.74, 0.49 to 1.12; P=0.2), and cardiovascular death (0.48, 0.18 to 1.23; P=0.1) was non-significantly lower in the combined treatment compared with statin group. During six years of follow-up, however, the risk of composite endpoints was significantly reduced in the combined treatment group compared with statin group (0.74, 0.58 to 0.93; P=0.01) (table 2, fig 2). Significance was maintained in the on-treatment analysis (0.63, 0.44 to 0.92; P=0.02).

Subgroup analysis for risk of composite cardiovascular events

In most subgroups, combined treatment was associated with a lower risk of composite cardiovascular events compared with statin treatment (fig 3). The hazard ratios of composite cardiovascular events were lower in those with high triglyceride or low HDL cholesterol levels compared with those with low triglyceride and high HDL cholesterol levels (fig 2), although the results were non-significant (P for interaction=0.2).

Sensitivity analyses

We performed a sensitivity analysis with propensity score matching based on non-HDL cholesterol category (<3.36, 3.36–4.14, 4.14–4.92, ≥4.92 mmol/L). The direction and statistical significance of this sensitivity analysis was comparable to those of the primary

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Table 2 | Cardiovascular outcomes by treatment group

Outcomes	Combined statin and fenofibrate (n=2156)	Statin only (n=8549)	P value
Coronary heart disease:			
No of events	64	302	
Incidence rate per 1000 person years	12.5 (9.8 to 16.0)	14.0 (12.5 to 15.7)	
Hazard ratio (95% CI)	0.82 (0.62 to 1.09)	1.00	0.2
Ischaemic stroke:			
No of events	28	150	
Incidence rate per 1000 person years	5.4 (3.7 to 7.8)	6.8 (5.8 to 8.0)	
Hazard ratio (95% CI)	0.74 (0.49 to 1.12)	1.00	0.2
Cardiovascular deaths:			
No of events	5	45	
Incidence rate per 1000 person years	1.0 (0.1 to 2.3)	2.0 (1.5 to 2.7)	
Hazard ratio (95% CI)	0.48 (0.18 to 1.23)	1.00	0.1
Composite cardiovascular events:			
No of events	90	471	
Incidence rate per 1000 person years	17.7 (14.4 to 21.8)	22.0 (20.1 to 24.1)	
Hazard ratio (95% CI)	0.74 (0.58 to 0.93)	1.00	0.01
Composite cardiovascular events (on-treatment):			
No of events	34	244	
Incidence rate per 1000 person years	20.3 (14.5 to 28.4)	29.4 (26.0 to 33.4)	
Hazard ratio (95% CI)	0.63 (0.44 to 0.92)	1.00	0.02

analysis (supplementary table 2). The risk of composite cardiovascular events was significantly lower in the combined treatment group compared with statin group (0.77, 0.62 to 0.96; P=0.02) and in the on-treatment analysis (0.67, 0.46 to 0.96; P=0.03).

Safety

Between the groups similar proportions of participants had liver enzyme (aspartate aminotransferase and alanine aminotransferase) levels more than twice the upper limit of the normal range (supplementary table 3). Within six months after treatment mean serum creatinine level had increased from 88.9 to 91.0 µmol/L in the combined treatment group but had decreased from 88.0 to 85.3 µmol/L in the statin group (supplementary table 4). Change over time was not, however, significantly different between the groups (P=0.4). In addition, the proportion of participants with serum creatinine levels more than double the baseline value was slightly, but not significantly, higher in the combined treatment group compared with statin group (1.4% and 0.8%) within six months.

Discussion

In this propensity weighted cohort study, the addition of fenofibrate to statin treatment in adults with metabolic syndrome was associated with a significantly lower risk of major cardiovascular events compared with statin treatment alone.

Interpretation and implications

With the adoption of statin treatment to manage dyslipidaemia and cardiovascular risk, strategies for residual cardiovascular risk after statin treatment have remained important.[10 11] In recent large randomised clinical trials, certain old and novel drugs, such as ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors, have shown some promising results in residual cardiovascular risk reduction; however, those trials only included participants with high cardiovascular risk or established coronary diseases.[27-29] Evidence favouring lipid modifying agents over statins for residual cardiovascular risk reduction in in people with a broad range of cardiovascular risk, such as people with metabolic syndrome, is limited.

Fenofibrate, a peroxisome proliferator activated receptor-α (PPAR-α) agonist, has been proposed as a potent agent in the treatment of dyslipidaemia, especially in the context of hypertriglyceridaemia and low HDL cholesterol levels. Numerous preclinical and clinical studies have shown its benefits on atherogenesis, which include favourable effects on lipoprotein metabolism, inflammation, and vascular dysfunction.[13 30 31] Randomised clinical trials have not provided evidence for beneficial effects on hard cardiovascular outcomes compared with statins however. In the ACCORD-Lipid trial, the rate of major cardiovascular outcomes was not reduced by the addition of fenofibrate to simvastatin compared with simvastatin alone. Only several subpopulations, such as men and people with high triglyceride and low HDL cholesterol concentrations at baseline seemed to benefit from fenofibrate add-on treatment.[15]

In contrast, our study in a real world setting showed that fenofibrate might play a role in residual cardiovascular risk reduction. It is unclear why the cardiovascular benefits of fenofibrate plus statin that we observed in our cohort study was not shown in earlier randomised controlled trials. Although a fundamental difference and an inferiority in the evidence level exist between our cohort study and the randomised clinical trials, we studied a group of people with metabolic syndrome and a wide range of cardiovascular risk, including 9% with pre-existing cardiovascular disease and 38% with type 2 diabetes. Thus the rate of primary outcome was lower in our study (5.5% during six years in the statin group) than in the ACCORD-Lipid trial (annual rate 2.4% in placebo group). These differences in populations and cardiovascular disease risk might have mitigated the effects of statins in our study so that the benefits of fenofibrate on reduction of cardiovascular events became more apparent. Furthermore, in the FIELD and ACCORD-Lipid trials and a meta-analysis comprising other fibrates, participants with metabolic syndrome or its components, such as hypertension, were identified and categorised into a responder group for fenofibrate treatment,[17 25 32] indicating that we recruited a more appropriate target population for fenofibrate treatment in our study. Notably, median triglyceride concentrations at baseline were substantially higher in our study (2.35 mmol/L) than those in the FIELD and ACCORD-Lipid (1.73 mmol/L and 1.83 mmol/L, respectively) trials.

As only a few clinical trials of fenofibrate or other PPAR-α agonists have been done in Asian populations, we did not have enough data to compare the effects of fenofibrate in different ethnic groups. Nevertheless, people of Asian origin are metabolically more

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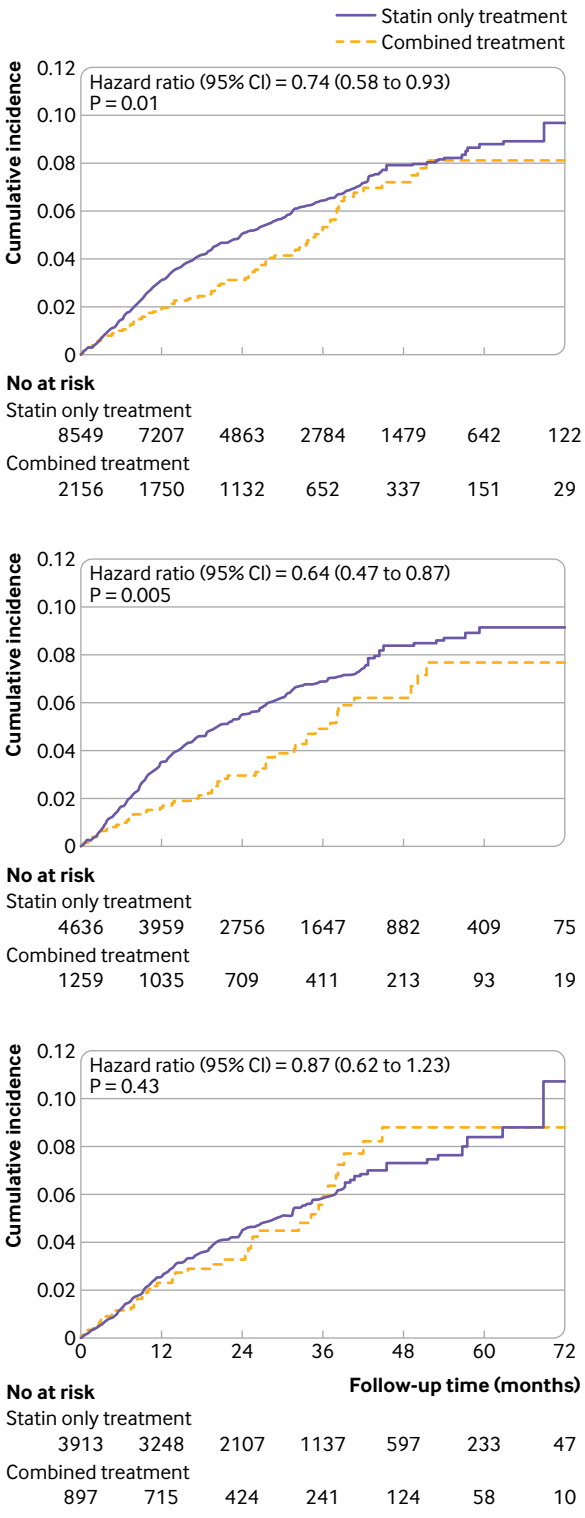

Fig 2 | Kaplan-Meier survival curves for composite cardiovascular outcomes between treatment groups in all participants (top), participants with high triglyceride or low high density lipoprotein cholesterol concentrations (middle), and participants with low triglyceride and high high density lipoprotein cholesterol concentrations (bottom)

susceptible to hypertriglyceridaemia and metabolic syndrome than other ethnicities. For example, more than 30% of adults in Korea, in whom body mass index is considerably lower, had metabolic syndrome of a similar degree to adults in the USA.[33] In addition, a specific *APOA5* gene polymorphism predisposing to high fasting and postprandial triglyceride levels was reported to be more prevalent in Koreans, even in healthy, non-obese people,[19] which is consistent with the high prevalence of hypertriglyceridaemia in this population.[34] Furthermore, triglyceride concentration as an independent risk factor of cardiovascular disease, especially coronary heart disease, is well established in Asian populations.[35 36] Considering that the antiatherosclerotic action of fibrates primarily reduces the secretion of triglyceride-rich very low density lipoprotein particles by enhancing fatty acid oxidation and reducing hepatic lipogenesis,[37] we suggest that our participants were good candidates for showing the cardiovascular benefits of fenofibrate treatment.

In subgroup analyses, the hazard ratios for the composite outcome of incident coronary heart disease, ischaemic stroke, and death from cardiovascular causes were lower in participants in the combined treatment group with low HDL cholesterol or high triglyceride concentrations than in those without these characteristics, even though the P value for interaction was non-significant between paired groups in individual subgroup analyses. The treatment effects of fenofibrate were noticeable on signs of metabolic syndrome such as hypertension, indicating that individual symptoms might provide information related to the beneficial treatment effects of fenofibrate, which has already been supported by other previous studies.[16-18]

A few safety concerns have been raised about using fenofibrate combined with statins.[14 38] These include an increase of serum creatinine levels as well as an increased risk of myopathy or myalgia. In our study, mean serum creatinine level was increased within six months after combined treatment and gradually decreased. The mean change in serum creatinine level from baseline in the combined treatment group was only 2.4%, however, and no statistically significant difference was found in changes over time compared with the statin group. We were not able to determine the effects on myopathy or myalgia owing to a lack of information in the database. Instead, we identified changes in transaminase levels and found that mean levels were similar between the groups during follow-up, as was the proportion of participants with transaminase levels more than twice the upper limit of the normal range.

Strengths and weaknesses of this study

Immortal and time lag biases have been problematic in pharmacoepidemiological studies.[39 40] To exclude such biases, we set the index date for propensity score matching to be the same as the date for starting fenofibrate treatment in participants and their matched controls. In addition, we also analysed the outcomes only during the fenofibrate treatment period in participants and matched controls and found that the statistically significant reduction in cardiovascular events with combined treatment was maintained. The

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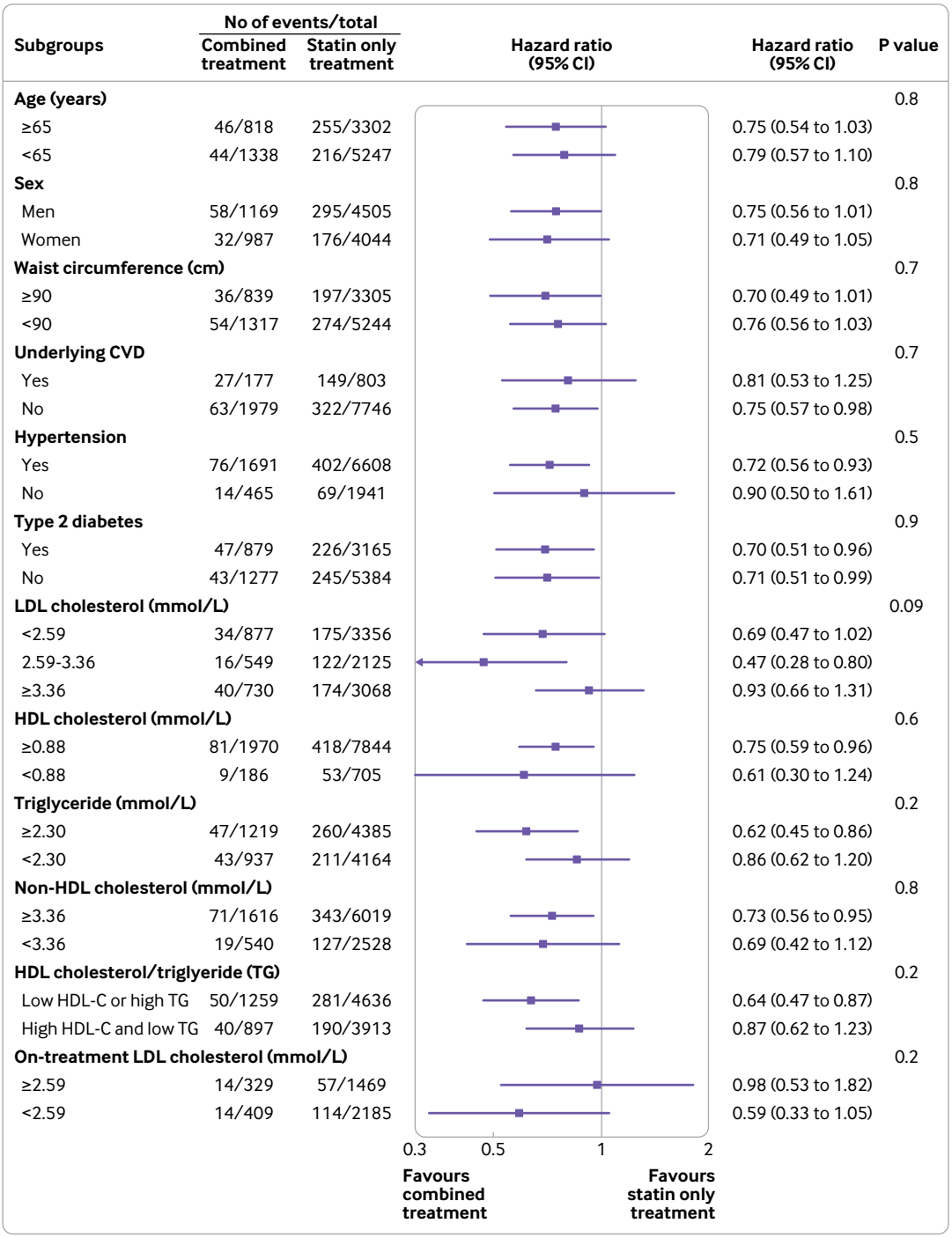

Fig 3 | Hazard ratio of composite cardiovascular events by subgroups. CVD=cardiovascular disease; LDL=low density lipoprotein; HDL=high density lipoprotein

other possible bias is that some variables (β blocker use, diuretic use, and triglyceride concentrations) were not balanced at baseline even after matching. We therefore adjusted for those variables in further analyses.

Conclusion

We found a beneficial role of add-on fenofibrate to statin treatment in cardiovascular risk reduction in adults with metabolic syndrome.

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Contributors: SGK and KHH conceived and designed the study. JC analysed the data. JL supervised the data analysis. NHK wrote the manuscript. SGK supervised the study and is the guarantor. All authors contributed to the review and revision of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from Abbott Laboratories Korea; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the institutional review board of Korea University Anam Hospital (IRB No ED17181). Data from the NHIS cohort do not involve any personally identifiable data. Thus the NHIS approved the cohort study without informed consent from participants.

Data sharing: Additional data are available through approval and oversight by the Korean National Health Insurance Service.

The lead authors (NHK, SGK) affirm that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supplementary material: additional figure and tables 1-4

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