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Fenofibrate add-on to statin treatment is associated with low all-cause death and cardiovascular disease in the general population with high triglyceride levels☆

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ABSTRACT

Background: We investigated the effects of fenofibrate add-on to statin treatment on all-cause death and cardiovascular disease (CVD) in the general population who had high triglyceride (TG).
Methods: We performed a population-based cohort study using data from the Korea National Health Information Database for 2010 to 2017. Among participants who had already used statins and had TG ≥ 150 mg/dL, 277,836 fenofibrate users were identified and compared with 277,836 fenofibrate non-users with 1:1 age- and sex-adjusted matching.
Results: During a mean 4.13-year follow-up, the incidences per 1000 person years of all-cause death and CVD were lower in fenofibrate users than in fenofibrate non-users (4.812 vs. 5.354 for all-cause death, P < 0.0001; 6.283 vs. 6.420 for CVD, P < 0.0001). The hazard ratios (HR) for all-cause death and CVD among fenofibrate users were 0.826 (95 % CI 0.795–0.858) and 0.929 (95 % CI 0.898–0.962), respectively. In addition, 73.35 % of participants did not have diabetes and fenofibrate showed consistently beneficial effects on all-cause death or CVD in patients with and without diabetes. Use of fenofibrate for more than one year was associated with low risk for both all-cause death (HR 0.618) and CVD (HR 0.853), but use of fenofibrate for less than one year was not.
Conclusions: Fenofibrate as an add-on to statin treatment was associated with low risk of all-cause death and CVD in general population who had high TG. These beneficial effects were consistent regardless of the presence of diabetes, but at least one year of fenofibrate use was needed.

1. Introduction

Elevated low-density lipoprotein (LDL) cholesterol is a risk factor for cardiovascular disease (CVD) and reducing LDL cholesterol by taking statins lowers the risk of death and CVD [1–10]. Despite widespread statin use, remaining residual risk for CVD is an unresolved issue [11,12]. Among many factors associated with this residual risk, triglyceride (TG) is one of the most promising candidates to explain it. Hypertriglyceridemia has been associated with an elevated risk for CVD in many studies, but it is not clear that lowering TG is associated with risk reduction for CVD [13–17].

Fenofibrate is a peroxisome proliferator-activated receptor-α agonist and commonly prescribed drug for TG reduction in many countries [18]. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials investigated the effects of fenofibrate in patients with diabetes mellitus (DM) and found no reduction in the primary outcome of major cardiovascular events [16,17]. The failure for achieving primary outcome could have been due to relatively low baseline TG concentrations (median TG: 153 mg/dL in the FIELD trial, and 162 mg/dL in the ACCORD trial). Subgroup analyses have shown beneficial effects of fenofibrate on CVD only in patients with low high-density lipoprotein

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(HDL) cholesterol and high TG [19,20]. Furthermore, a recent study showed that the risk of major cardiovascular events was significantly lower when fenofibrate was used as an add-on to statin treatment in adult patients with metabolic syndrome than when patients received statin treatment alone [21]. In patients with type 2 DM, use of fenofibrate was associated with lower rates of total and cardiac mortality and cardiovascular events during a 3-year follow-up in large real-world population [22].

However, few studies have investigated whether fenofibrate has beneficial effects on death and/or CVD in the general population who had high TG. The aim of this study was to evaluate the effects of fenofibrate as an add-on to statin treatment on all-cause death and CVD in general population who had high TG using a large-scale population dataset from the National Health Information Database (NHID).

2. Methods

2.1. Data sources

We used the NHID produced by the National Health Insurance Service with linkage to the National Health Screening Program. The NHID was launched in 2000 by integrating 375 insurance associations and provides longitudinal data for 97 % of the Korean population. This database contains de-identified sociodemographic details and reimbursement claims with International Classification of Disease, 10th revision (ICD-10) coding. The National Health Screening Program includes a medical interview, anthropometric measurement, blood test (including lipid profile), urine test, and additional functions. Death information was obtained from the National Death Registry. Approval for the present study protocol (2021-11-026) was obtained from the Institutional Review Board of Kangbuk Samsung Hospital. The requirement for the informed consent was waived because we did not access personal identifying information.

2.2. Study design and participants

We selected 1,465,824 patients who had used fenofibrate from 2010 to 2017. Among them, we enrolled patients who had already used statins, were aged >20 years, and had TG $\geq$ 150 mg/dL. We excluded patients who had CVD (myocardial infarction [MI] or ischemic stroke) history and/or who had missing data. After additional exclusion of those who developed CVD within 1 year (1 year lag-period), 371,577 patients were candidates for analysis. To overcome potential bias and imbalance of baseline characteristics, we performed 1:1 age- and sex-adjusted matching (Supplementary Fig. 1 and Supplementary Table 1). Finally, 277,836 patients were included in the fenofibrate user group and the same number of patients was enrolled in the fenofibrate non-user group. They were followed until December 31, 2019.

2.3. Measurements and definitions

Venous blood samples were drawn after an overnight fast of at least eight hour duration to measure glucose, total cholesterol, TG, HDL cholesterol, and LDL cholesterol concentrations. Estimated glomerular filtration rate (eGFR) was calculated using the equation from the Modification of Diet in Renal Disease study: eGFR = 175 $\times$ serum creatinine$^{-1.154}$ $\times$ age$^{-0.203}$ $\times$ 0.742 (for women). Information about smoking status, alcohol consumption, and regular exercise was obtained using a standardized self-assessment questionnaire.

Heavy alcohol consumption was defined as drinking >30 g/day. Regular physical activity was defined as >30 min of moderate physical activity performed at least five times per week, or >20 min of strenuous physical activity performed at least three times per week. Low household income was defined as the lowest quintile for income along with being a medical aid beneficiary. Obesity was defined as having a body mass index (BMI) $\geq$ 25 kg/m^2. Hypertension was defined as blood pressure $\geq$ 140/90 mm Hg or having been prescribed anti-hypertensive drugs under ICD-10 codes I10–I15. Diabetes was defined as having fasting plasma glucose (FPG) concentrations $\geq$ 126 mg/dL or having been prescribed anti-diabetic drugs under ICD-10 codes E11–E14. Chronic kidney disease (CKD) was defined as eGFR <60 mL/min/1.73 m^2.

2.4. Study outcomes and follow-up

The end points of this study were death or incident CVD. Incident MI was defined as ICD-10 code I21 or I22 during hospitalization for more than three days with claims for percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Incident ischemic stroke was defined as ICD-10 codes I63 or I64 during hospitalization for more than three days with claims for brain magnetic resonance imaging (MRI) or computed tomography (CT). The study population was followed from baseline to the date of death or incident CVD, or until December 31, 2019 whichever came first. The mean follow-up duration was 4.13 years.

2.5. Statistical analyses

All data are presented as the mean $\pm$ standard deviation or median (interquartile range) values for continuous variables and number (%) values for categorical variables. The independent sample *t*-test and χ^2 test were used to compare the characteristics of the participants at baseline. Incidence rates are presented as the number of events occurring per 1000 person-years. Hazard ratios (HR) and 95 % confidence intervals (CI) for all-cause death or CVD were calculated using a Cox proportional hazards model. The multivariable models were adjusted for age, sex, smoking status, drinking history, regular physical activity, income, having DM and hypertension, BMI, HDL cholesterol, TG, eGFR, and LDL cholesterol. Kaplan-Meier survival curves were constructed to compare incidence rates of all-cause death or CVD according to fenofibrate use after adjustment for the aforementioned covariates and log-rank test was conducted. We performed subgroup analyses under the categories of age, sex, smoking status, drinking history, regular physical activity, income, obesity, having DM and hypertension, and duration of statin use. All data analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA). A P value < 0.05 was considered significant.

3. Results

The baseline characteristics of the participants are presented in Table 1. The mean age was 54.83 years and 61.34 % of participants were male. Especially, 73.35 % of participants did not have diabetes. Fenofibrate users were more likely to be current smokers and heavy drinkers, more likely to have low household income, and more likely to have obesity, DM, and hypertension than fenofibrate non-users. In addition, the BMI, waist circumference, blood pressure (systolic and diastolic), and FPG were elevated, while total cholesterol, HDL cholesterol, and LDL cholesterol were decreased in fenofibrate users. The mean TG concentration was 311.98 mg/dL in fenofibrate users and 226.78 mg/dL in fenofibrate non-users. There were no significant differences between fenofibrate users and non-users with respect to the percentages of patients who undertook regular physical activity, who had used statins for >2 years at baseline, and who had CKD.

The incidence rate of all-cause death was lower in fenofibrate users (4.812/1000 person-years) than in fenofibrate non-users (5.354/1000 person-years; Table 2). The unadjusted HR for all-cause death among fenofibrate users was 0.899 (95 % CI 0.867–0.932) when compared with fenofibrate non-users (Model 1). The multivariable-adjusted HR for all-cause death among fenofibrate users was 0.850 (95 % CI 0.819–0.881) when compared with fenofibrate non-users after adjusting for age, sex, smoking status, heavy alcohol consumption, regular physical activity, low income, having hypertension and DM, and BMI (Model 2).

Table 1
Baseline characteristics of the study population according to the use of fenofibrate.

	Fenofibrate non-user	Fenofibrate user	P
N	277,836	277,836	
Age, years	54.83 ± 10.58	54.83 ± 10.58	
20–39	18,954 (6.82)	18,954 (6.82)	
40–64	207,472 (74.67)	207,472 (74.67)	
≥65	51,410 (18.50)	51,410 (18.50)	
Male, %	170,421 (61.34)	170,421 (61.34)	
Height, cm	163.92 ± 9.35	163.87 ± 9.35	0.0383
Weight, kg	69.06 ± 12.30	69.85 ± 12.55	<0.0001
Body mass index, kg/m^2	25.58 ± 3.20	25.88 ± 3.21	<0.0001
Waist circumference, cm	85.80 ± 8.42	86.71 ± 8.33	<0.0001
Current smoker	77,408 (27.86)	84,136(30.28)	<0.0001
Heavy alcohol consumption	28,801 (10.37)	37,329 (13.44)	<0.0001
Regular physical activity	52,678 (18.96)	52,223 (18.80)	0.1188
Low income	43,410 (15.62)	47,131 (16.96)	<0.0001
Obesity	152,713 (54.97)	163,638 (58.90)	<0.0001
Hypertension	133,410 (48.02)	151,875 (54.66)	<0.0001
Diabetes	62,960 (22.66)	85,152 (30.65)	<0.0001
Chronic kidney disease	16,631 (5.99)	16,834 (6.06)	0.2523
Statin use (>2 years)	143,879 (51.79)	144,235 (51.91)	0.3392
Systolic blood pressure, mm Hg	127.83 ± 15.00	129.11 ± 15.24	<0.0001
Diastolic blood pressure, mm Hg	79.69 ± 10.20	80.52 ± 10.40	<0.0001
Fasting plasma glucose, mg/dL	110.98 ± 37.09	116.92 ± 42.28	<0.0001
Total cholesterol, mg/dL	223.43 ± 43.68	220.36 ± 45.87	<0.0001
Triglyceride, mg/dL	215.43 (215.19–215.67)	285.25 (284.82–285.68)	<0.0001
HDL cholesterol, mg/dL	49.84 ± 16.20	47.13 ± 14.56	<0.0001
LDL cholesterol, mg/dL	129.81 ± 42.50	116.60 ± 44.91	<0.0001
eGFR, ml/min/1.73 m^2	89.34 ± 47.31	89.33 ± 42.05	0.9669

Data are presented as mean ± standard deviation, median (interquartile range) or number (%).
HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate.

Furthermore, risk for all-cause death was lower by 17.4 % (95 % CI 0.795–0.858) in the fenofibrate users compared with non-users even after additional adjustment for HDL cholesterol, TG, eGFR, and LDL cholesterol (Model 5).

The incidence rate of CVD was lower in fenofibrate users (6.283/1000 person-years) than in fenofibrate non-users (6.420/1000 person-years; Table 2). The unadjusted HR for CVD was not different between fenofibrate users and non-users (Model 1), but the multivariable-adjusted HR for CVD among fenofibrate users was 0.933 (95 % CI 0.903–0.972) compared with fenofibrate non-users after adjusting for age, sex, smoking status, heavy alcohol consumption, regular physical activity, low income, having hypertension and DM, and BMI (Model 2). After additional adjustment for HDL cholesterol, TG, eGFR, and LDL cholesterol (Model 5), the risk of CVD among fenofibrate users was still lower than that of fenofibrate non-users (HR 0.929, 95 % CI 0.898–0.962).

The incidence rate of MI was lower in fenofibrate users (3.348/1000 person-years) than in fenofibrate non-users (3.466/1000 person-years; Table 2). The unadjusted HR for MI was not different between fenofibrate users and non-users (Model 1), but the multivariable-adjusted HR for MI among fenofibrate users was 0.930 (95 % CI 0.889–0.972) compared with fenofibrate non-users after adjusting for age, sex, smoking status, heavy alcohol consumption, regular physical activity, low income, having hypertension and DM, and BMI (Model 2). Furthermore, risk for MI was lower by 7.6 % (95 % CI 0.882–0.969) in the fenofibrate users compared to non-users even after additional adjustment for HDL cholesterol, TG, eGFR, and LDL cholesterol (Model 5). A similar pattern to that found for MI was evident for ischemic stroke. The incidence rate of ischemic stroke was lower in fenofibrate users (3.144/1000 person-year) than in fenofibrate non-users (3.176/1000 person-year). Although the unadjusted HR for ischemic stroke was not different between fenofibrate users and non-users (Model 1), the multivariable-adjusted HR for ischemic stroke among fenofibrate users was 0.934 (95 % CI 0.892–0.979) in Model 2, 0.923 (95 % CI 0.879–0.969) in Model 3, 0.923 (95 % CI 0.879–0.969) in Model 4, and 0.928 (95 % CI 0.884–0.975) in Model 5.

Kaplan-Meier survival curves showed that fenofibrate was associated with lower risk of all-cause death (Fig. 1A), CVD (Fig. 1B), MI (Fig. 1C) and ischemic stroke (Fig. 1D) after adjusting for age, sex, smoking status, heavy alcohol consumption, regular physical activity, low income, having hypertension and DM, BMI, HDL cholesterol, TG, eGFR, and LDL cholesterol (all-cause death, $P < 0.0001$; CVD, $P < 0.0001$; MI, $P < 0.0001$; ischemic stroke, $P = 0.0012$).

After adjusting for age, sex, smoking status, heavy alcohol consumption, regular physical activity, low income, having hypertension and DM, BMI, HDL cholesterol, TG, eGFR, and LDL cholesterol, subgroup analyses were performed for strata by age, sex, smoking status, heavy alcohol consumption, regular physical activity, low income, obesity, DM, hypertension, and duration of statin use (Fig. 2). Across almost all subsets of patients, the use of fenofibrate was associated with reduced risk for all-cause death and CVD, except with respect to CVD in women or patients without obesity. In particular, in patients both with and without DM, fenofibrate use was associated with significantly reduced risk of all-cause death and CVD. Fenofibrate was consistently associated with reduced risk of MI and ischemic stroke in patients with and without DM, with the exception of the risk of ischemic stroke in patients with DM (Supplementary Fig. 2).

The risk of all-cause death or CVD was different between patients who had used fenofibrate for more or <1 year (Table 3). In patients with <1 year of fenofibrate use, the unadjusted HR for all-cause death was 1.175 times (95 % CI 1.127–1.226) higher than that of fenofibrate non-users. The risk for all-cause death in patients with <1 year of fenofibrate use was marginally elevated after multivariable adjustment (Model 3, Model 4, and Model 5). However, the risk for all-cause death was lower by 33 % (95 % CI 0.639–0.703) in patients with >1 year fenofibrate use than fenofibrate non-users (Model 1). Furthermore, risk for all-cause death was lower by 38.2 % (95 % CI 0.587–0.650) in patients with >1 year fenofibrate use compared with fenofibrate non-users after multivariable adjustment (Model 5).

A similar pattern with respect to all-cause death was also found for CVD (Table 3). In patients with <1 year of fenofibrate use, the unadjusted HR for CVD was 1.077 times (95 % CI 1.035–1.121) higher than that of fenofibrate non-users (Model 1), but it was not statistically significant after adjustment (Model 2, Model 3, Model 4, and Model 5). However, risk for CVD was lower by 10.4 % (95 % CI 0.861–0.932) in patients with >1 year fenofibrate use than fenofibrate non-users (Model 1). In addition, risk for CVD was lower by 14.7 % (95 % CI 0.817–0.890) in patients with >1 year fenofibrate use compared to fenofibrate non-user after multivariable adjustment (Model 5).

Incident MI or ischemic stroke did not differ among patients who used fenofibrate for <1 year compared with fenofibrate non-users (Table 3). Patients who used fenofibrate for >1 year were associated with 0.838 times (95 % CI 0.790–0.888) lower risk for MI and 0.866 times (95 % CI 0.816–0.920) lower risk for ischemic stroke than fenofibrate non-users in multivariable-adjusted modeling (Model 5).

4. Discussion

In this large-scale nationwide population-based study, we showed that the addition of fenofibrate to statin treatment in members of the general population who had TG concentrations ≥ 150 mg/dL was

Table 2
The risk of all-cause death and cardiovascular disease according to the use of fenofibrate.

	Number	Event	Incidence rate[a]	Hazard ratio (95 % confidence interval)				
				Model 1	Model 2	Model 3	Model 4	Model 5
All-cause death								
Fenofibrate non-user	277,836	6220	5.354	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Fenofibrate user	277,836	5602	4.812	0.899 (0.867, 0.932)	0.850 (0.819, 0.881)	0.825 (0.794, 0.857)	0.826 (0.795, 0.858)	0.826 (0.795, 0.858)
Cardiovascular disease								
Fenofibrate non-user	277,836	7352	6.420	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Fenofibrate user	277,836	7209	6.283	0.978 (0.947, 1.011)	0.933 (0.903, 0.964)	0.919 (0.887, 0.951)	0.919 (0.888, 0.952)	0.929 (0.898, 0.962)
Myocardial infarction								
Fenofibrate non-user	277,836	3998	3.466	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Fenofibrate user	277,836	3870	3.348	0.966 (0.924, 1.009)	0.930 (0.889, 0.972)	0.910 (0.868, 0.953)	0.911 (0.869, 0.954)	0.924 (0.882, 0.969)
Ischemic stroke								
Fenofibrate non-user	277,836	3662	3.176	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Fenofibrate user	277,836	3632	3.144	0.990 (0.945, 1.036)	0.934 (0.892, 0.979)	0.923 (0.879, 0.969)	0.923 (0.879, 0.969)	0.928 (0.884, 0.975)

Model 1 was unadjusted.
Model 2 was adjusted for age, sex, smoking status, heavy alcohol consumption, physical activity, low income, hypertension, diabetes, and body mass index.
Model 3 was adjusted for age, sex, smoking status, heavy alcohol consumption, physical activity, low income, hypertension, diabetes, body mass index, HDL cholesterol, and triglyceride.
Model 4 was adjusted for age, sex, smoking status, heavy alcohol consumption, physical activity, low income, hypertension, diabetes, body mass index, HDL cholesterol, triglyceride, and estimated glomerular filtration rate.
Model 5 was adjusted for age, sex, smoking status, heavy alcohol consumption, physical activity, low income, hypertension, diabetes, body mass index, HDL cholesterol, triglyceride, estimated glomerular filtration rate, and LDL cholesterol.
[a] Incidence per 1000 person-years.

associated with lower risk of all-cause death or CVD compared to statin treatment alone. Notably, 73.35 % of participants did not have diabetes and the beneficial effect of fenofibrate with respect to all-cause death and CVD was consistent regardless of the presence of diabetes. Interestingly, patients who had used fenofibrate for >1 year were associated with lower risk of all-cause death and CVD than fenofibrate non-users, although the use of fenofibrate for <1 year had no effects on those risks. This study was performed based on real-world data (RWD) obtained from a national database and included the largest number of people among the studies of fenofibrate conducted so far.

Many studies have shown that hypertriglyceridemia is associated with elevated risk of CVD [13–17]. Recently in Korea, two studies using RWD found that fenofibrate had beneficial effects on cardiovascular risk reduction in patients with metabolic syndrome and DM [21,22]. Kim et al. reported that the risk of major cardiovascular events was significantly lower when fenofibrate was prescribed as an add-on to statin treatment than when patients with metabolic syndrome received statin treatment alone; their mean TG concentrations were 254 mg/dL (statin + fenofibrate group) and 211 mg/dL (statin group) [21]. Jo et al. revealed that in patients with DM (mean TG 238 mg/dL) underwent statin treatment, the use of fenofibrate was associated with lower rates of total and cardiac mortality and cardiovascular events during the 3-year follow-up period [22]. Furthermore, in PESA (Progression of Early Subclinical Atherosclerosis) study, TG levels ≥150 mg/dl showed an association with subclinical noncoronary atherosclerosis (odds ratio 1.35; 95 % CI 1.08–1.68; P = 0.008) [23]. In general, there is consensus that ASCVD risk becomes clinically relevant at fasting TG levels >150 mg/dL [1,24]. In 2019 European Society of Cardiology/European Atherosclerosis Society guidelines for the management of dyslipidemias, n−3 polyunsaturated fatty acids (icosapent ethyl 4 g/day) should be considered in combination with a statin in only high-risk patients with TG levels between 135 and 499 mg/dL despite statin treatment [1]. However, fenofibrate may be considered in combination with statins both in primary prevention or high-risk patients who are at LDL-C goal with TG levels >200 mg/dL [1]. In our study, we enrolled patients from the general population who had serum TG concentrations ≥ 150 mg/dL: the median TG concentration was 285.25 mg/dL in fenofibrate users and 215.43 mg/dL in fenofibrate non-users. We showed that use of fenofibrate as add-on to statin treatment was associated with lower risk for all-cause death and CVD if baseline TG concentrations were sufficiently high to increase CVD risk even among member of the general population.

There have been many efforts to reduce residual risk in patients with statin treatment [25–30]. One strategy is further reduction of LDL cholesterol using ezetimibe and proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor [25–27]. However, reducing LDL alone might not be enough to reduce the residual risk of CVD, and other risk factors should be considered. Another strategy has focused on TG. The Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) investigated the effect of additional icosapent ethyl therapy in patients receiving statin therapy and showed a 25 % reduction in the risk of ischemic events [29]. The baseline median TG concentration was 216 mg/dL and an 18.3 % (−39 mg/dL) reduction occurred in the icosapent ethyl group. Unfortunately, since the completion of the FIELD and ACCORD trials, there have been no large-scale, randomized controlled trials (RCTs) of fenofibrate. Instead of RCTs, some studies using RWD revealed the beneficial effect of fenofibrate as an add-on to statin treatment [21,22]. Although our study was also a study using RWD, the strength of our study was that more than half a million people were enrolled, which made it much larger than in the aforementioned studies.

To date, the efficacy of fenofibrate with regard to reduction of cardiovascular risk has been evaluated in studies that included patients with major cardiovascular risk factors such as metabolic syndrome or DM [16,17,21,22]. Interestingly, even in patients without DM, fenofibrate significantly was associated with lower risk for all-cause death and CVD in this study. As far as we know, this is the first large-scale study to evaluate the beneficial effects of fenofibrate on all-cause death and CVD

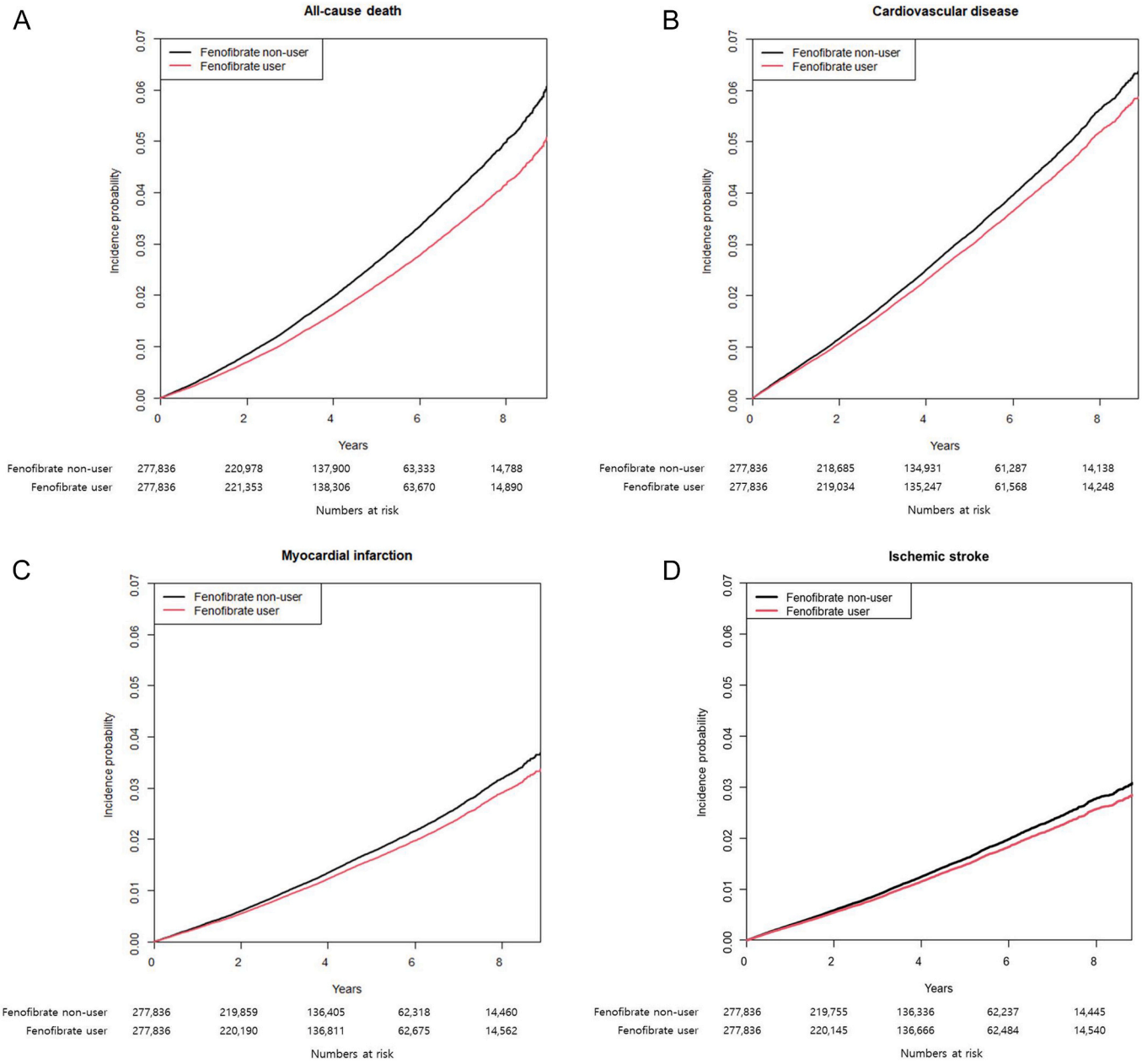

Fig. 1. Kaplan-Meier survival curves for all-cause death (A), cardiovascular disease (B), myocardial infarction (C), and ischemic stroke (D) among fenofibrate users and non-users after adjusting for age, sex, smoking status, heavy alcohol consumption, regular physical activity, low income, having hypertension and diabetes mellitus, body mass index, HDL cholesterol, and triglyceride. A. all-cause death: fenofibrate users vs. non-users ($P < 0.0001$); B. cardiovascular disease: fenofibrate users vs. non-users ($P < 0.0001$); C. myocardial infarction: fenofibrate users vs. non-users ($P < 0.0001$); D. ischemic stroke: fenofibrate user vs. non-user ($P = 0.0012$).

in patients without DM. The results of this study may be even more meaningful because fenofibrate users had unfavorable metabolic profiles, including being more likely to be heavy drinkers and current smokers, to have DM, hypertension, higher BMIs and waist circumferences than fenofibrate non-users. Furthermore, the beneficial effect of fenofibrate remained after adjusting for HDL cholesterol, TG, eGFR and LDL cholesterol. These results may indicate how important it is to not only to treat hypertriglyceridemia but also to use fenofibrate itself. Considering that another TG lowering agent, pemafibrate, in the PROMINENT trial came to a sudden halt after failing to reduce CVD outcomes, it can be seen that lowering TG alone is not sufficient to lower CVD risk. We could not determine an exact mechanism for the beneficial effect of fenofibrate, but many studies have reported that fenofibrate has favorable effects on lipoprotein metabolism, inflammation, vascular dysfunction, and CVD [31–33]. The advantage of fenofibrate is that it is relatively inexpensive and generally well tolerated [1,34]. In addition, because fenofibrate does not share the glucuronidation pathway with statins, there is very little increased risk for myopathy when combined with statins [34].

Our study showed consistently beneficial effects of fenofibrate on all-cause death or CVD across almost all subsets of patients in the subgroup analyses. The use of fenofibrate for <1 year have seemed to increase the risk of all-cause death and CVD in unadjusted model, but the effects on the risk of all-cause death and CVD were disappeared after multivariable adjustments. On the contrary, the use of fenofibrate for >1 year was associated with reduced risk of all-cause death and CVD. These findings might reflect the time required for metabolic changes to occur, such that reductions in the risk of cardiovascular events may require more than a

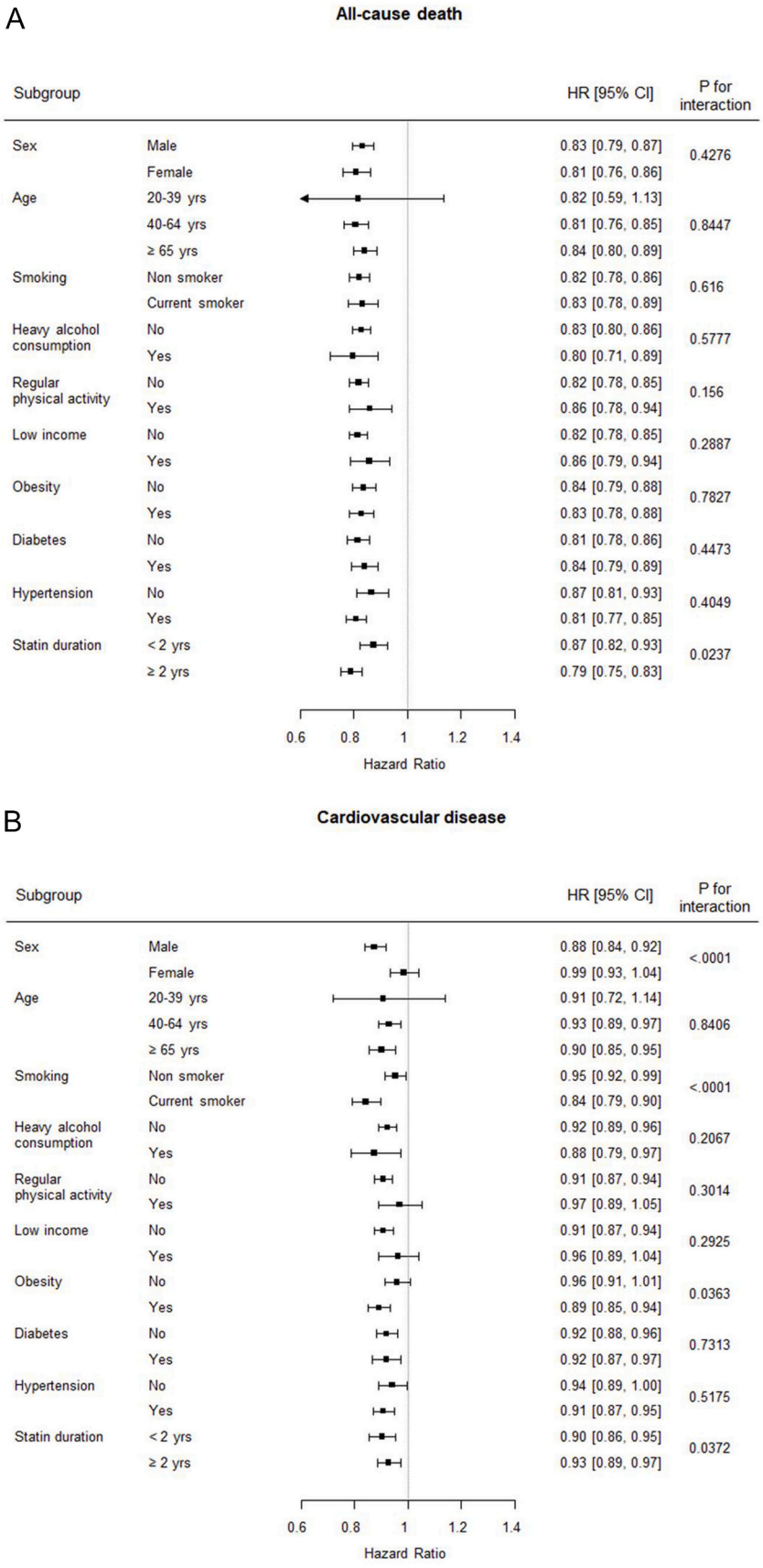

Fig. 2. Hazard ratios (HR) for all-cause death (A) and cardiovascular disease (B) when comparing fenofibrate users and non-users after subgroup analyses and adjusting for age, sex, smoking status, heavy alcohol consumption, regular physical activity, low income, having hypertension and diabetes mellitus, body mass index, HDL cholesterol, and triglyceride. CI, confidence interval.

Table 3
The risk of all-cause death and cardiovascular disease according to the use of fenofibrate and duration of treatment.

	Number	Event	Incidence rate[a]	Hazard ratio (95 % confidence interval)				
				Model 1	Model 2	Model 3	Model 4	Model 5
All-cause death								
Fenofibrate non-user	277,836	6220	5.354	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Fenofibrate user, ≤1 year	134,558	3314	6.207	1.175 (1.127, 1.226)	1.078 (1.034, 1.125)	1.044 (1.000, 1.091)	1.045 (1.001, 1.092)	1.045 (1.000, 1.091)
Fenofibrate user, >1 year	143,278	2288	3.631	0.670 (0.639, 0.703)	0.646 (0.616, 0.678)	0.618 (0.588, 0.650)	0.619 (0.589, 0.651)	0.618 (0.587, 0.650)
Cardiovascular disease								
Fenofibrate non-user	277,836	7352	6.420	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Fenofibrate user, ≤1 year	134,558	3613	6.872	1.077 (1.035, 1.121)	1.022 (0.982, 1.063)	1.006 (0.965, 1.048)	1.006 (0.966, 1.048)	1.010 (0.969, 1.052)
Fenofibrate user, >1 year	143,278	3596	5.784	0.896 (0.861, 0.932)	0.857 (0.823, 0.892)	0.838 (0.803, 0.874)	0.839 (0.804, 0.875)	0.853 (0.817, 0.890)
Myocardial infarction								
Fenofibrate non-user	277,836	3998	3.466	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Fenofibrate user, ≤1 year	134,558	1954	3.688	1.073 (1.016, 1.133)	1.031 (0.977, 1.089)	1.009 (0.955, 1.067)	1.010 (0.955, 1.068)	1.016 (0.961, 7.074)
Fenofibrate user, >1 year	143,278	1916	3.060	0.876 (0.830, 0.925)	0.842 (0.797, 0.890)	0.818 (0.772, 0.867)	0.819 (0.773, 0.868)	0.838 (0.790, 0.888)
Ischemic stroke								
Fenofibrate non-user	277,836	3662	3.176	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Fenofibrate user, ≤1 year	134,558	1803	3.405	1.078 (1.019, 1.140)	1.003 (0.948, 1.062)	0.991 (0.935, 1.050)	0.991 (0.935, 1.050)	0.993 (0.937, 1.052)
Fenofibrate user, >1 year	143,278	1829	2.924	0.916 (0.866, 0.969)	0.874 (0.826, 0.925)	0.859 (0.809, 0.911)	0.859 (0.810, 0.912)	0.866 (0.816, 0.920)

Model 1 was unadjusted.
Model 2 was adjusted for age, sex, smoking status, heavy alcohol consumption, physical activity, low income, hypertension, diabetes, and body mass index.
Model 3 was adjusted for age, sex, smoking status, heavy alcohol consumption, physical activity, low income, hypertension, diabetes, body mass index, HDL cholesterol, and triglyceride.
Model 4 was adjusted for age, sex, smoking status, heavy alcohol consumption, physical activity, low income, hypertension, diabetes, body mass index, HDL cholesterol, triglyceride, and estimated glomerular filtration rate.
Model 5 was adjusted for age, sex, smoking status, heavy alcohol consumption, physical activity, low income, hypertension, diabetes, body mass index, HDL cholesterol, triglyceride, estimated glomerular filtration rate, and LDL cholesterol.
[a] Incidence per 1000 person-years.

year of medication. In a meta-analysis including 18 trials, the use of fenofibrate for >5 years was associated with 15 % reduction in the relative risk for coronary events, but no risk reduction was noted among patients using fenofibrate for <5 years [35]. We would like to emphasize that continuous fenofibrate treatment is needed to reduce the risk of all-cause death and CVD in patients with hypertriglyceridemia even if they undergo statin treatment.

Some limitations should be considered when interpreting the results of this study. First, we could not evaluate TG concentrations after fenofibrate treatment because of limited information in the database. And follow-up data on critical biomarkers including plasma lipid and glucose levels, and blood pressure were not available as same reason. Second, we could not know the information on statin type or intensity. Third, the use of fenofibrate was dependent on each clinician's decision. Fourth, the results of this study might not be generalizable to other ethnicities because this study was conducted using the Korean NHID. Finally, a study using RWD has inevitable biases. To overcome biases, we performed 1:1 age- and sex-adjusted matching. This study was nonetheless valuable because it assessed members of the general population who were undergoing statin treatment and included the largest number of people among the studies of fenofibrate.

In conclusion, fenofibrate as add-on to statin treatment was associated with lower risk of all-cause death and CVD in general population who were TG ≥ 150 mg/dL. Especially, the beneficial effect of fenofibrate for all-cause death and CVD was consistent regardless the presence of DM. Because only patients who had used fenofibrate for >1 year were associated with lower risk of all-cause death and CVD than fenofibrate non-users, consistent use of fenofibrate is required to reduce the risk of all-cause death and CVD in patients with hypertriglyceridemia even if they are also undergoing statin treatment. We simply summarized the results as graphical abstract in Supplementary Fig. 3.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2022.155327.

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CRediT authorship contribution statement

Conceptualization, K.S.K., C.Y.P.; data curation or formal analysis, K.S.K., S.H., K.H., C.Y.P.; funding acquisition, C.Y.P.; investigation, K.S.K., S.H., K.H., C.Y.P.; supervision, C.Y.P.; visualization, K.S.K., C.Y.P.; writing original draft preparation, K.S.K.; writing – review and editing, K.S.K., S.H., K.H., C.Y.P.. All authors have read and agreed to the final version of the manuscript.

Declaration of competing interest

We declare no competing interests.

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