Fenofibrate Use Is Associated With Lower Mortality and Fewer Cardiovascular Events in Patients With Diabetes: Results of 10,114 Patients From the Korean National Health Insurance Service Cohort

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OBJECTIVE

We investigated the long-term clinical efficacy of fenofibrate use with regard to mortality and cardiovascular outcomes in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

We performed a population-based cohort study using data of the South Korean National Health Insurance Service from 2003 to 2014. Of 63,727 participants with diabetes aged 40–79 years, 5,057 users of fenofibrate only were compared with 5,057 nonusers of fenofibrate and/or omega-3 fatty acid with 1:1 propensity matching. The primary end point was a composite of myocardial infarction, stroke, percutaneous coronary revascularization, and cardiac death for a median of 3 years.

RESULTS

The primary end point was significantly lower in fenofibrate users compared with those using neither fenofibrate nor omega-3 fatty acid (13.4 vs. 15.5 per 1,000 person-years; hazard ratio [HR] 0.76; 95% CI 0.62–0.94; $P = 0.010$). Cardiac death (1.8 vs. 3.1 per 1,000 person-years; HR 0.59; 95% CI 0.352–0.987; $P = 0.0446$), all-cause death (7.6 vs. 15.3 per 1,000 person-years; HR 0.437; 95% CI 0.340–0.562; $P < 0.0001$), and stroke (6.5 vs. 8.6 per 1,000 person-years; HR 0.621; 95% CI 0.463–0.833; $P = 0.0015$) were significantly lower in the fenofibrate group. When the duration of fenofibrate use was stratified by quartile, the risk decreased in quartile 4, with an HR of 0.347 (95% CI 0.226–0.532; $P < 0.0001$). In subgroup analysis, the favorable effect of fenofibrate was sustained consistently across all subsets of patients, including those classified by LDL cholesterol, HDL cholesterol, and triglyceride levels.

CONCLUSIONS

Use of fenofibrate was associated with a lower rate of total and cardiac mortality and cardiovascular events in patients with type 2 diabetes during a 3-year follow-up in real-world large populations.

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Patients with diabetes are at higher risk of cardiovascular disease (CVD) (1). Even with statin therapy to lower LDL cholesterol in the contemporary era, the residual risk of CVD remains substantial in these patients. Triglycerides (TG) are another target for the prevention and treatment of CVD, in addition to LDL cholesterol, for residual risk reduction. Major epidemiological (2,3) and genetic linkage studies using Mendelian randomization methods (4) have suggested that a high TG level is associated with CVD and even has a causal relationship with CVD (5).

Therefore, in an effort to reduce the remaining risk, the strategy of lowering TG levels has been investigated, but the results have been contradictory, although it has shown some potential in specific subset of patients. Large randomized clinical trials, such as the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) (6) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) (7) studies, which tested the efficacy of fenofibrate alone or as an add-on to statin in patients with diabetes, demonstrated overall negative outcomes, but some signs of improved clinical outcomes were detected in subgroup of patients with diabetes with low HDL cholesterol and high TG levels (6,7). Moreover, a recent study, the Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial (REDUCE-IT), aiming to reassess the efficacy of a specific formula of omega-3 fatty acid provided new insight into the lowering of TG levels and the novel concept of introducing a specific form of omega-3 fatty acid, an icosapent ethyl acid, for the secondary and primary prevention of CVD, especially in patients with diabetes (8,9).

Despite these promising data, there has been no large-scale long-term follow-up study to assess TG-lowering therapy with fenofibrate in patients with diabetes in real-world practice. We investigated the true efficacy of the TG-lowering drug fenofibrate on clinical outcomes in patients with diabetes in a real-world setting using the South Korean National Health Insurance Service (NHIS) database.

RESEARCH DESIGN AND METHODS

Study Data Source

We used the data from the South Korean NHIS cohort. A detailed description has been published and validated

Table 1—Baseline characteristics between fenofibrate only users vs. nonusers after PSM

Variable	Total	Users	Nonusers	ASD*
Total patients with type 2 diabetes	10,114	5,057	5,057	
Sex				0.0012
Male	5,911	2,957 (58.5)	2,954 (58.4)	
Female	4,203	2,100 (41.5)	2,103 (41.6)	
Age, y				0.017
Mean	61.95	62.01	62.04	
SD	8.46	8.7	8.76	
≥65	3,459	1,712 (33.9)	1,747 (34.5)	
<65	6,655	3,345 (66.1)	3,310 (65.5)	
Income (decile)				0.005
0–3	2,284	1,137 (22.5)	1,147 (22.7)	
4–10	7,830	3,920 (77.5)	3,910 (77.3)	
Disease history				
CAD	3,768	1,830 (36.2)	1,938 (38.3)	0.046
MI	527	252 (5.0)	275 (5.4)	0.022
Angina	2,934	1,421 (28.1)	1,513(29.9)	0.042
Other CAD	1,597	757 (15.0)	840 (16.6)	0.049
Stroke	1,681	804 (15.9)	877 (17.3)	0.042
Cancer	1,774	888 (17.6)	886 (17.5)	0.001
CKD	216	101 (2.0)	115 (2.3)	0.022
HTN	7,774	3,824 (75.6)	3,950 (78.1)	0.054
AF	417	206 (4.1)	211 (4.2)	0.005
HF	721	366 (7.2)	355 (7.0)	0.009
Statin intake history	6,635	3,224 (63.8)	3,411 (67.5)	0.077
Statin intensity				0.066
Low	138	53 (1.0)	85 (1.7)	
Moderate	5,864	2,854 (56.4)	3,010 (59.5)	
High	633	317 (6.3)	316 (6.2)	
PCI history	198	91 (1.8)	107 (2.1)	0.024
BMI, kg/m^2				0.039
Mean	25.19	25.22	25.16	
SD	2.94	2.9	2.99	
≥25	5,263	2,583 (53.0)	2,680 (53.0)	
<25	4,851	2,474 (47.0)	2,377 (47.0)	
TG and HDL cholesterol, mg/dL				
≥200 and <35	731	384 (7.6)	347 (6.9)	0.035
<200 or ≥35	9,383	4,673 (92.4)	4,710 (93.1)	
≥200 and <60	4,741	2,513 (49.7)	2,228 (44.1)	0.132
<200 or ≥60	5,373	2,544 (50.3)	2,829 (55.9)	
TG, mg/dL				0.069
Mean	238.64	242.75	234.52	
SD	144.59	139.83	149.1	
≥200	5,266	2,785 (55.1)	2,481 (49.1)	
<200	4,848	2,272 (44.9)	2,576 (50.9)	
HDL cholesterol, mg/dL				0.016
Mean	48.72	48.57	48.9	
SD	15.46	16.31	14.57	
≥60	1,680	812 (16.1)	868 (17.2)	
<60	8,434	4,245 (83.9)	4,189 (82.8)	
≥35	9,139	4,558 (90.1)	4,581 (90.6)	
<35	975	499 (9.9)	476 (9.4)	
LDL cholesterol, mg/dL				0.037
Mean	110.5	109.74	111.26	
SD	42.17	44.13	40.1	
≥130	3,084	1,485(29.4)	1,599 (31.6)	
<130	7,030	3,572 (70/6)	3,458 (68.4)	
≥100	5,946	2,915 (57.6)	3,031 (59.9)	
<100	4,168	2,142 (42.4)	2,026 (40.1)	
Non-HDL cholesterol				0.010
Mean	156.18	155.98	156.38	
SD	42.56	41.84	43.26	

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previously (10,11). Briefly, the NHIS provides obligatory health care for all South Korean citizens, with an enrollment rate of 97% (11). The NHIS cohort had information on socioeconomic status, admission and discharge information, hospital visit data, drug prescription data, and hospital information. A health examination is performed by the NHIS annually or biannually for all people aged ≥20 years, which is composed of a survey on health status and behaviors, body weight, height, blood pressure, and laboratory tests for blood and urine.

The NHIS provides the aforementioned data as well as death records, including cause and date, which are merged from Statistics Korea for research purposes. We used the NHIS Health Examination Database 2.0 sample cohort combined with death data including people aged 40–79 years; this group comprised 10% (n = ~510,000) of the original NHIS full cohort of 5,150,000 people who underwent the national heath examination test in 2002–2003.

This study was approved by the Hallym University Sacred Heart Hospital Institutional Review Board (no. 2019-01-021-005). Informed consent was waived, because the database was made to be anonymous under the strict confidentiality guidelines of the NHIS (11).

Study Population

We used the NHIS Health Examination Database 2.0 sample cohort, which included ~510,000 people aged 40–79 years who underwent a health examination test in index years of 2002–2003. They were followed until 2015. Within this cohort, we enrolled 212,969 patients with type 2 diabetes first diagnosed between 2003 and 2014. Diagnosis of diabetes was made according to ICD-10 codes E11–E14. After excluding 149,242 people who had a combined type 1 diabetes code, history of fenofibrate or omega-3 fatty acid prescription before diagnosis of diabetes, and no data on laboratory tests, 63,727 patients were candidates for analysis (Supplementary Fig. 1).

To compare fenofibrate users versus nonusers, we divided these patients into two groups: patients receiving fenofibrate only and nonusers of fenofibrate and/or omega-3 fatty acid (controls). We excluded those receiving both omega-3 fatty acid and fenofibrate in the control group to investigate strictly the efficacy of fenofibrate. Patients who were prescribed fenofibrate at least once from January 2003 to December 2014 after diagnosis of diabetes were considered the study drug group, and those who were never prescribed either drug were considered the control group. Patients were matched 1:1 with propensity scoring, and 5,057 were included in each group (Supplementary Fig. 1).

Table 1—Continued

Variable	Total	Users	Nonusers	ASD*
TG/HDL cholesterol				0.068
Mean	5.46	5.58	5.35	
SD	4.17	4.06	4.28	
TC − HDL cholesterol − LDL cholesterol				0.037
Mean	45.68	46.25	45.12	
SD	32.59	33.97	31.14	
Current smoker				0.001
Yes	2,099	1,050 (20.8)	1,049 (20.7)	
No	8,015	4,007 (79.2)	4,008 (79.3)	
Current drinker				0.000
Yes	4,900	2,450 (48.4)	2,450 (48.4)	
No	5,214	2,607 (51.6)	2,607 (51.6)	

Data are presented as n or n (%) unless otherwise indicated. AF, atrial fibrillation; CKD, chronic kidney disease; HF, heart failure; HTN, hypertension; TC, total cholesterol. *Absolute standardized difference (ASD) ≥0.1 considered significant.

End Points

The primary end points were a composite of the first occurrence of myocardial infarction (MI), stroke, percutaneous coronary intervention (PCI), and cardiovascular death. Occurrence of any event among the four end points of MI, stroke, PCI, and cardiovascular death was considered to be a primary end point occurrence. Secondary end points were the first occurrence of each individual event (MI, stroke, PCI, or cardiac death) and all-cause death.

Each outcome was identified by ICD-10 code, in accordance with the American Heart Association statistics guidelines (12); death was categorized as all-cause death if a death record was present and as cardiac death if both a death record and ICD-10 code of I (ischemia code) were present.

We also examined the covariates of age; sex; BMI; comorbidities; history of statin intake; history of PCI; laboratory data such as TG, HDL cholesterol, and LDL cholesterol; history of smoking; history of alcohol intake; and household income. MI was confirmed if the ICD-10 code was I21–I23, and stroke was confirmed if the ICD-10 code was I60–I64. Diagnosis of comorbidities such as angina (I20), other coronary artery disease (CAD) (I24–I25), chronic kidney disease (N18), cancer (C**), hypertension (I10), atrial fibrillation (I48), and heart failure (I50) was confirmed if ICD-10 code for each disease was present. The ICD-10 codes for use of the study drugs (fenofibrate, omega-3 fatty acid, and statins) and receipt of PCI are listed in Supplementary Table 1. The median follow-up period was 3.06 years (interquartile range [IQR] 1.94–4.45): 2.86 years (IQR 1.90–4.19) in the fenofibrate group, and 3.30 years (IQR 2.01–4.66) in the nonuser group.

We performed a subgroup analysis under the categories of BMI, with a cutoff value of 25 kg/m^2; TG, 200 mg/dL; HDL cholesterol, 35 mg/dL; and LDL cholesterol, 130 or 100 mg/dL, as well as HDL cholesterol <35 mg/dL, TG ≥200 mg/dL, sex, age, income, and some medical and social histories.

Propensity Score Matching Analysis

We tried to overcome bias and the imbalance of baseline characteristics and control for confounders by performing a 1:1 propensity score matching (PSM) analysis with greedy nearest-neighbor matching between the fenofibrate and control groups. We entered age, sex, BMI, household income stratified by high and low levels (low level included 0–3, and high level 4–10 in decile classification of original

data), LDL cholesterol, TG, HDL cholesterol, alcohol habits, smoking habits, statin intake, and aforementioned comorbidities including history of MI, angina, other CAD, stroke, cancer, chronic kidney disease, hypertension, atrial fibrillation, heart failure, and PCI.

Statistical Analysis

Categorical variables were presented as numbers and percentages and compared using the χ^2 test or Fisher exact test. Continuous variables are presented as mean ± standard deviation and were compared using the independent sample Student *t* test.

After PSM, we used the paired Student *t* test for continuous variables in comparing the two groups and the Cochran-Mantel-Haenszel test for categorical variables. We categorized age with a cutoff value of 65 years; BMI, 25 kg/m^2; TG, 200 mg/dL; HDL cholesterol, 35 mg/dL; and LDL cholesterol, 100 or 130 mg/dL for analysis. We also calculated the absolute standardized difference to examine the differences in comorbidities between the fenofibrate and control groups, regarding it as negligible if the value was <0.1.

The main outcomes were identified after PSM analysis, and we performed logistic regression analysis. We present the absolute event rate and the event rate per 1,000 person-years for primary end points, individual events, and all-cause mortality.

In addition, a stratified Cox proportional hazards regression analysis was used for risk analysis. The hazard ratio (HR) and 95% CI are presented. The incidence of the end points is shown with Kaplan-Meier curves, and differences were assessed using the stratified log-rank test.

A subgroup analysis was conducted to compare the incidence of the primary outcomes across different clinical conditions that can influence prognosis, and an interaction analysis was conducted to examine heterogeneity. A *P* value of <0.05 (two sided) or absolute standardized difference of ≥ 0.1 was regarded as statistically significant. Statistical analyses were performed with SAS Enterprise Guide 7.1. (SAS Institute).

RESULTS

Fenofibrate Only Versus Neither Fenofibrate nor Omega-3 Fatty Acid

The fenofibrate or omega-3 fatty acid group included 8,383 patients, and the nonuser group included 55,344. After excluding 3,244 patients using omega-3 fatty acid, 5,139 were fenofibrate only users (Supplementary Fig. 1). After 1:1 PSM, 10,114 patients were allocated, 5,057 to the fenofibrate only group and 5,057 to the nonuser group. Baseline characteristics of patients are presented in Table 1. The overall characteristics were well balanced after PSM, except for TG $\geq$200 mg/dL and HDL cholesterol $<$60 mg/dL (Table 1). The median follow-up was 3.1 years.

The primary composite outcome was significantly lower in the fenofibrate group compared with the control group (13.4 vs. 15.5 per 1,000 person-years; HR 0.76; 95% CI 0.62–0.94; $P = 0.010$) (Table 2 and Fig. 1*A*).

Incidence of the individual outcome of stroke was lower in the fenofibrate group compared with the control group (6.5 vs. 8.6 per 1,000 person-years, respectively; HR 0.621; 95% CI 0.463–0.833; $P = 0.0015$) (Table 2 and Fig. 1*C*). Rates of cardiac death and all-cause death were also significantly lower in the fenofibrate group, at 1.8 vs. 3.1 per 1,000 person-years (HR 0.59; 95% CI 0.352–0.987; $P = 0.0446$) and 7.6 vs. 15.3 per 1,000 person-years (HR 0.437; 95% CI 0.340–0.562; $P < 0.0001$), respectively (Table 2 and Fig. 1*E* and *F*).

However, MI and PCI were not different between the fenofibrate and control groups, at 1.6 vs. 1.6 per 1,000 person-years (HR 1.158; 95% CI 0.627–2.139; $P = 0.640$) and 5.7 vs. 4.7 per 1,000 person-years (HR 1.159; 95% CI 0.827–1.623; $P = 0.392$), respectively (Table 2 and Fig. 1*B* and *D*).

Table 2—Cardiovascular event rate between fenofibrate only users vs. nonusers

	Users (*n* = 5,057)	Nonusers (*n* = 5,057)
Composite events (MI, stroke, PCI, and cardiac death)		
No. of events	207	258
Incidence rate per 1,000 person-years	13.4	15.5
HR (95% CI)	0.76 (0.617–0.936)	1.00
P	0.010	
MI		
No. of events	26	27
Incidence rate per 1,000 person-years	1.6	1.6
HR (95% CI)	1.158 (0.627–2.139)	1.00
P	0.6397	
Stroke		
No. of events	101	145
Incidence rate per 1,000 person-years	6.5	8.6
HR (95% CI)	0.621 (0.463–0.833)	1.00
P	0.0015	
PCI		
No. of events	90	80
Incidence rate per 1,000 person-years	5.7	4.7
HR (95% CI)	1.159 (0.827–1.623)	1.00
P	0.3916	
Cardiac death		
No. of events	29	53
Incidence rate per 1,000 person-years	1.8	3.1
HR (95% CI)	0.59 (0.352–0.987)	1.00
P	0.0446	
Death		
No. of events	121	262
Incidence rate per 1,000 person-years	7.6	15.3
HR (95% CI)	0.437 (0.34–0.562)	1.00
P	<0.0001	

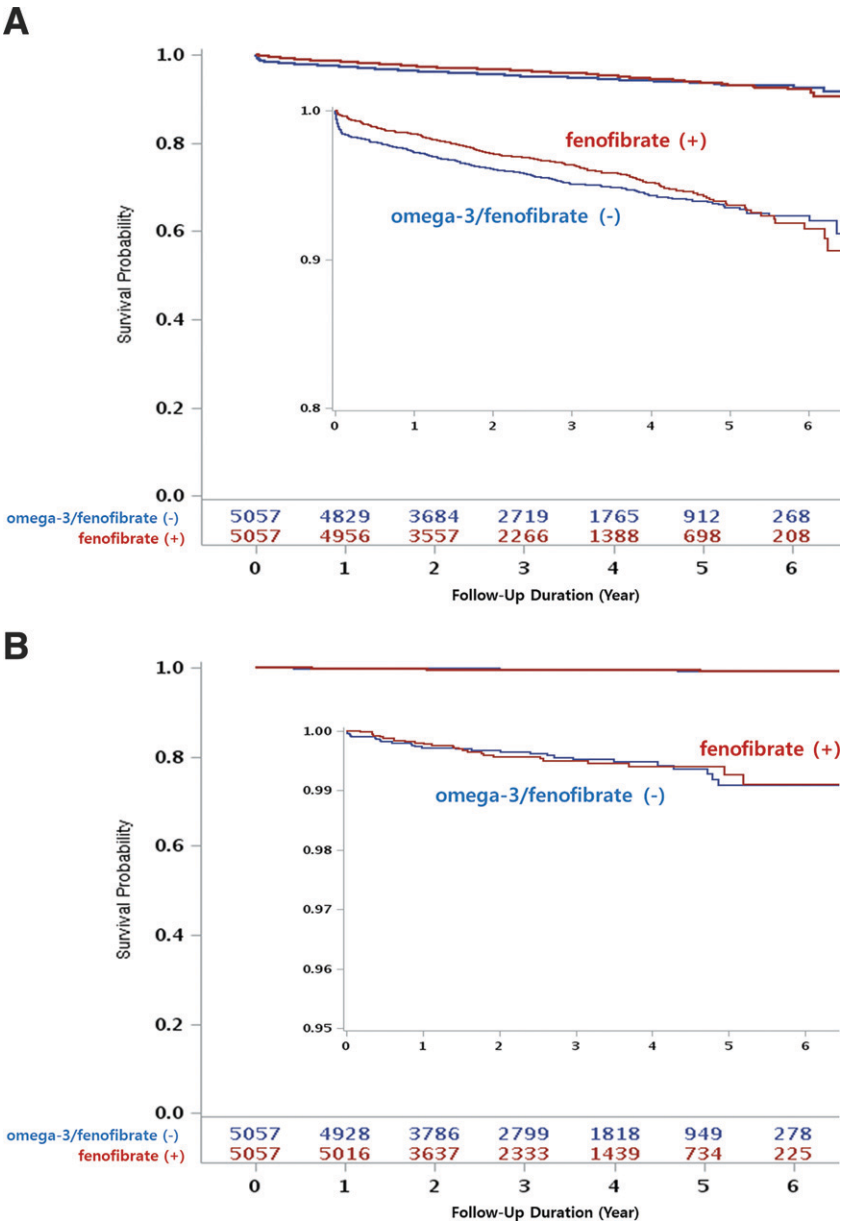

Figure 1—Survival of composite and individual outcomes according to fenofibrate use vs. fenofibrate and omega-3 fatty acid nonuse. *A*: Survival for primary composite outcome of MI, stroke, PCI, and cardiac death according to fenofibrate use vs. nonuse (log-rank $P = 0.0097$). *B*: Survival for MI according to fenofibrate use vs. nonuse (log-rank $P = 0.6394$). *C*: Survival for stroke according to fenofibrate use vs. nonuse (log-rank $P = 0.0013$). *D*: Survival for PCI according to fenofibrate use vs. nonuse (log-rank $P = 0.3912$). *E*: Survival for cardiac death according to fenofibrate use vs. nonuse (log-rank $P = 0.0422$). *F*: Survival for all-cause death according to fenofibrate use vs. nonuse (log-rank $P < 0.0001$).

Kaplan-Meier analysis showed statistically significantly favorable efficacy with fenofibrate only use versus nonuse in the primary outcome, stroke, cardiac death, and all-cause death (Fig. 1).

Stratification by Duration of Fenofibrate Use

When we stratified the duration of fenofibrate use by quartile (Q), with Q1 as 1–59 days, Q2 as 60–193 days, Q3 as 194–485 days, and Q4 as ≥486 days, in increasing order, the adjusted HR of the composite outcome in the Q1 group increased to 1.52 (model 8; 95% CI 1.169–1.977; $P = 0.0018$) (Supplementary Table 2), with no change in the Q2 or Q3 group compared with the control group. However, the risk decreased in Q4, with an HR of 0.347 (95% CI 0.226–0.532; $P < 0.0001$) (adjustment model 8). (Supplementary Table 2 and Supplementary Fig. 2).

Subgroup Analysis in Fenofibrate Users

In the subgroup analysis, the favorable effect of fenofibrate was sustained consistently across all subsets of patients (Fig. 2). Notably, the efficacy of fenofibrate persisted regardless of LDL cholesterol, HDL cholesterol, TG level, or the combination of both high TG and low HDL cholesterol levels. The efficacy was more pronounced in men, patients with a history of stroke, and patients with LDL cholesterol of <100 mg/dL, with significant *P* values for interaction.

CONCLUSIONS

We demonstrated that fenofibrate use is associated with a better long-term clinical outcome of the composite of MI, stroke, PCI, and cardiac death, as well as some individual outcomes, including stroke, cardiac death, and all-cause death, in patients with type 2 diabetes. The benefit was consistent across all subgroups and was pronounced in longer-duration users of fenofibrate.

Our study has value in its large scale, its reflection of a real-world practice setting, and its definite and consistent results after thorough multiple adjustments of covariables and subgroup analyses.

Patients with diabetes are prone to a more atherogenic environment, with small dense LDL cholesterol, high TG-rich lipoprotein (TRL) cholesterol, and low HDL cholesterol (13–15). An elevated TG level, aside from the number of particles carrying TG, has been reported to be associated with CVD, despite of some controversies, even when LDL cholesterol is under control with statin treatment (16–18). Furthermore, some genetic studies using Mendelian randomization methods have raised the possibility that TG or TRL cholesterol could cause CVD (4,19). Therefore, we can assume that lowering of TG levels can be a therapeutic target, and fenofibrate can be an alternative to statins to reduce residual risk, especially for patients with diabetes (15,20). Koreans and other Asian people are

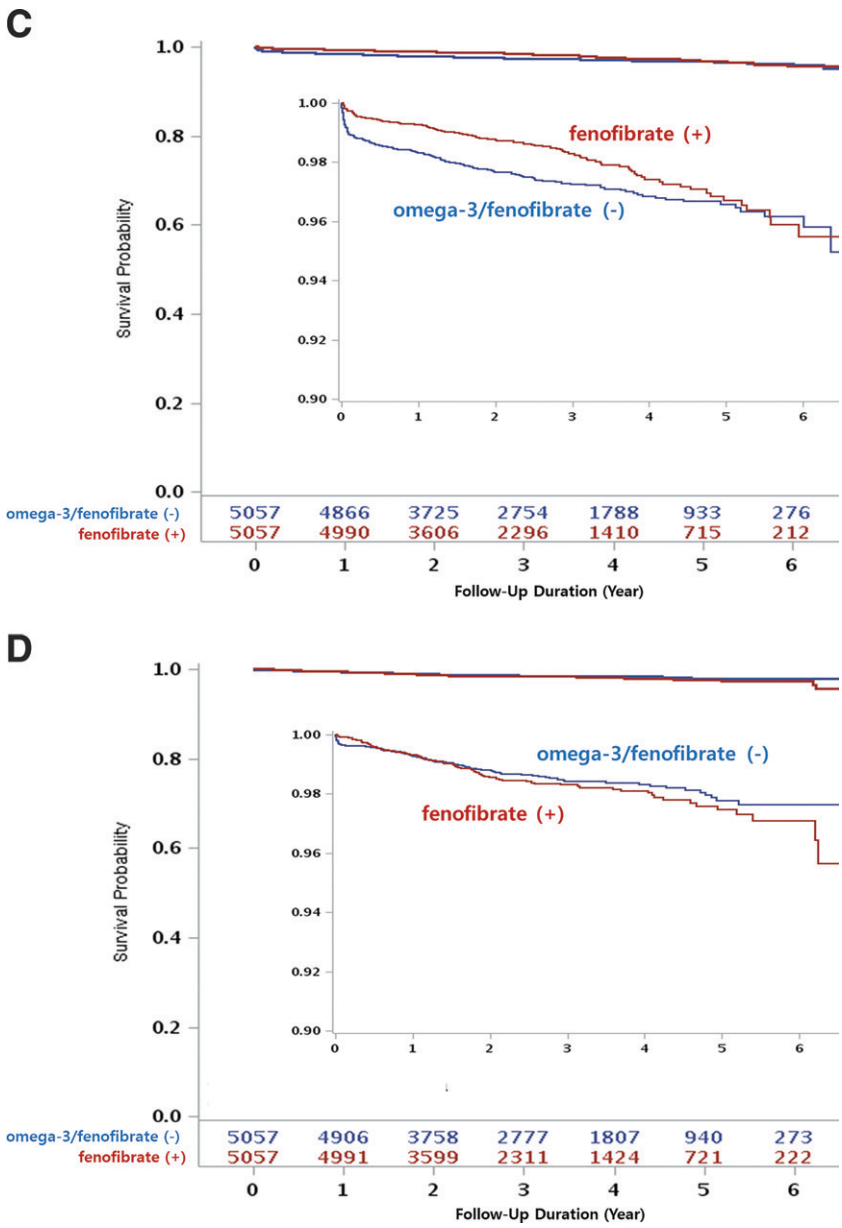

Figure 1—Continued

appropriate candidates for TG lowering, because they tend to have a lipid profile including high TG and low HDL cholesterol, mainly as a result of a sedentary lifestyle and high-carbohydrate diet (21). Thus, Korean patients with diabetes may be fit for fenofibrate treatment, and our study results support this. Moreover, a recent South Korean study corresponds well with our study in that the authors also showed positive results with fenofibrate in a population of patients with metabolic syndrome, a group at lower risk than our patients with diabetes (22). Considering that the cardiovascular risk of patients in our study was higher (e.g., 10-fold CAD history) as well as the fact that our entire study population had diabetes and the population was larger (2.34-fold), our study results firmly support the role of fenofibrate in Koreans.

Previous trials have been frustrating, mainly because sample sizes have been relatively inadequate to determine statistical significance or because patients with diabetes have already been using statins, as was the case in the ACCORD trial (7). However, in the FIELD study, the benefit of fenofibrate was seen more prominently than in the ACCORD trial in that incidence of nonfatal MI and total CVD was lower in the fenofibrate group, despite the overall failure to show a significant risk reduction (6). We believe this was mainly due to the nonuse of statins at baseline and the larger sample size compared with the ACCORD trial. In both trials, a specific subset of patients with high TG and low HDL cholesterol benefited from fenofibrate, even with the use of statins, because these patients were at a risk high enough to realize the effect of fenofibrate. Our study population was much larger at ~10,000 (ACCORD n = ~5,500; FIELDS n = ~6,000), the baseline risk was higher, with a CAD history of 37% among our participants (ACCORD 36%; FIELDS 22%), and the rate of statin use was 65% compared with ACCORD (statin use 100% in the active drug group of simvastatin plus fenofibrate) and FILED (no statin use). These factors may have contributed to the definite positive results seen in the fenofibrate group in our study.

Notably, when we consider the moderate to high levels of baseline non-HDL and indirect TRL cholesterol (total cholesterol − HDL cholesterol − LDL cholesterol) along with the moderate LDL cholesterol (110 mg/dL) and TG levels (240 mg/dL), it is possible for fenofibrate to have had a beneficial effect in our study (18) (Table 1). In view of the importance of remnant lipoprotein particles in the setting of elevated TG in diabetes, the indirect calculation of TRL cholesterol has value and may help interpret the positive results of our study.

The ACCORD lipid extension study, which extended the follow-up period of the original ACCORD study by 5 years (total of 10 years), still demonstrated an overall neutral effect. However, it also showed a potential benefit of fenofibrate in a specific subset of patients with high TG and low HDL cholesterol (23). Another extended posttrial follow-up study (total of 10 years) of the ACCORD trial also demonstrated a legacy effect of fenofibrate, with reduced CVD death and all-cause death. These results complement our results (24).

Our study showed consistently favorable results with fenofibrate in all subsets of patients across all TG, HDL cholesterol, and LDL cholesterol levels, as well as in the group with a combination of high TG and low HDL cholesterol, irrespective of statin use. Moreover, the effect was more pronounced in longer-duration users (Q4) of fenofibrate, whereas users in Q1 experienced a high event rate in composite outcomes. This might have occurred by

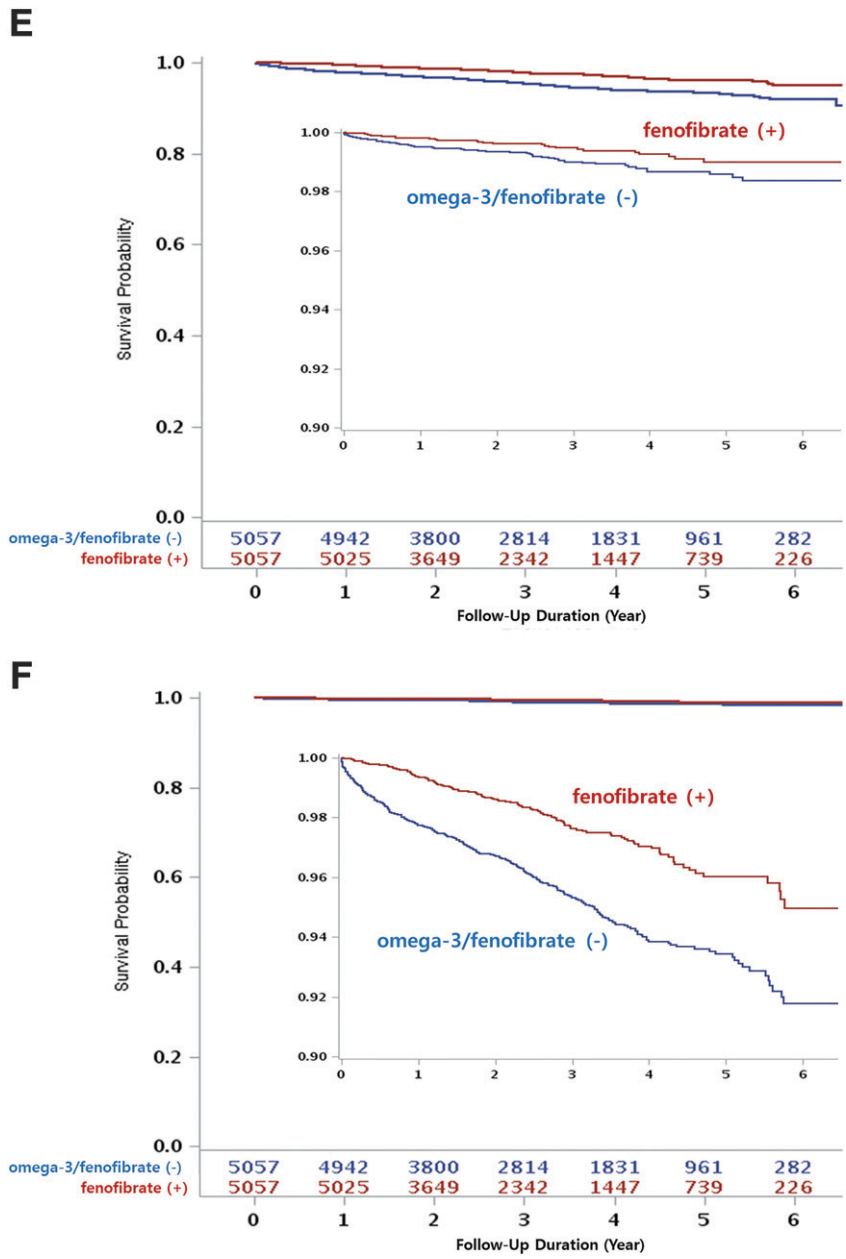

Figure 1—Continued

chance, but it might also be explained by the high probability of experiencing a clinical event among patients at risk of CVD in the initial stage of study drug use, when duration of use was not yet long enough for the drug to have efficacy. Consistent subgroup analysis and examination of the effect of duration on response are major strengths of our study.

To induce benefits in addition to lowering TG levels, we believe peroxisome proliferator–activated receptor α (PPAR-α) agonists, which have anti-inflammatory and antioxidative effects and improve endothelial function, could contribute to the beneficial effect of fenofibrate (25–27). More specifically, PPAR-α agonists modulate the expression of cytokines and adhesion molecules and have antiatherosclerotic effects (28). They reduce activation of nuclear factor-κB and prevent nuclear factor-κB translocation to the nucleus, terminating activation of the inflammatory pathway (28). In vascular smooth muscle cells, activation of PPAR-α inhibits interleukin-1–induced production of interleukin-6 and prostaglandins as well as the expression of cyclooxygenase II (28).

Clinical Implications

Our study demonstrated the definite and consistent beneficial effect of fenofibrate in a Korean population of patients with diabetes. For Koreans and presumably other Asian people with diabetes who have a sedentary lifestyle and carbohydrate-oriented food culture, lowering of TG with fenofibrate, with or without statins, could potentially improve cardiovascular outcomes, including reduction of cardiac death and all-cause death rates, regardless of TG and/or HDL cholesterol level.

Limitations

Our study has some limitations. First, this was a population-based cohort study, which has inevitable biases, even though we tried to avoid expected confounders by PSM analysis. However, hidden biases may have remained. Therefore, our real-world results should be interpreted with caution, in contrast to the results of a randomized clinical trial. We recognize there may be limitations in drawing the conclusion of fenofibrate benefit in patients with type 2 diabetes based on our study results. However, we consider our results to be in accordance with previous registry data, and fenofibrate might be a treatment option for high-risk patients with diabetes, at least in the Korean population (22).

Second, the diagnosis codes for baseline comorbidities could have been missed or inaccurate as a result of, for example, government insurance reimbursement issues. Third, the criteria for inclusion in each group were dependent on prescription of the study drug at least once. The true drug intake and adherence are uncertain. To overcome this limitation, we analyzed the group according to drug use duration by Q and found efficacy of the study drug with longer-duration use. Fourth, because of a lack of data, we do not present information on drug name or dose or patient adherence, which could have made some difference in the study results. Data on blood and urine examinations were also sparse. Fifth, our study results were derived from a population-based cohort based on data from the South Korean NHIS. We acknowledge that the results indicating a fenofibrate benefit cannot necessarily be applied to other ethnicities or populations. Finally, we could not provide information on the level of LDL cholesterol achieved or other lipid data,

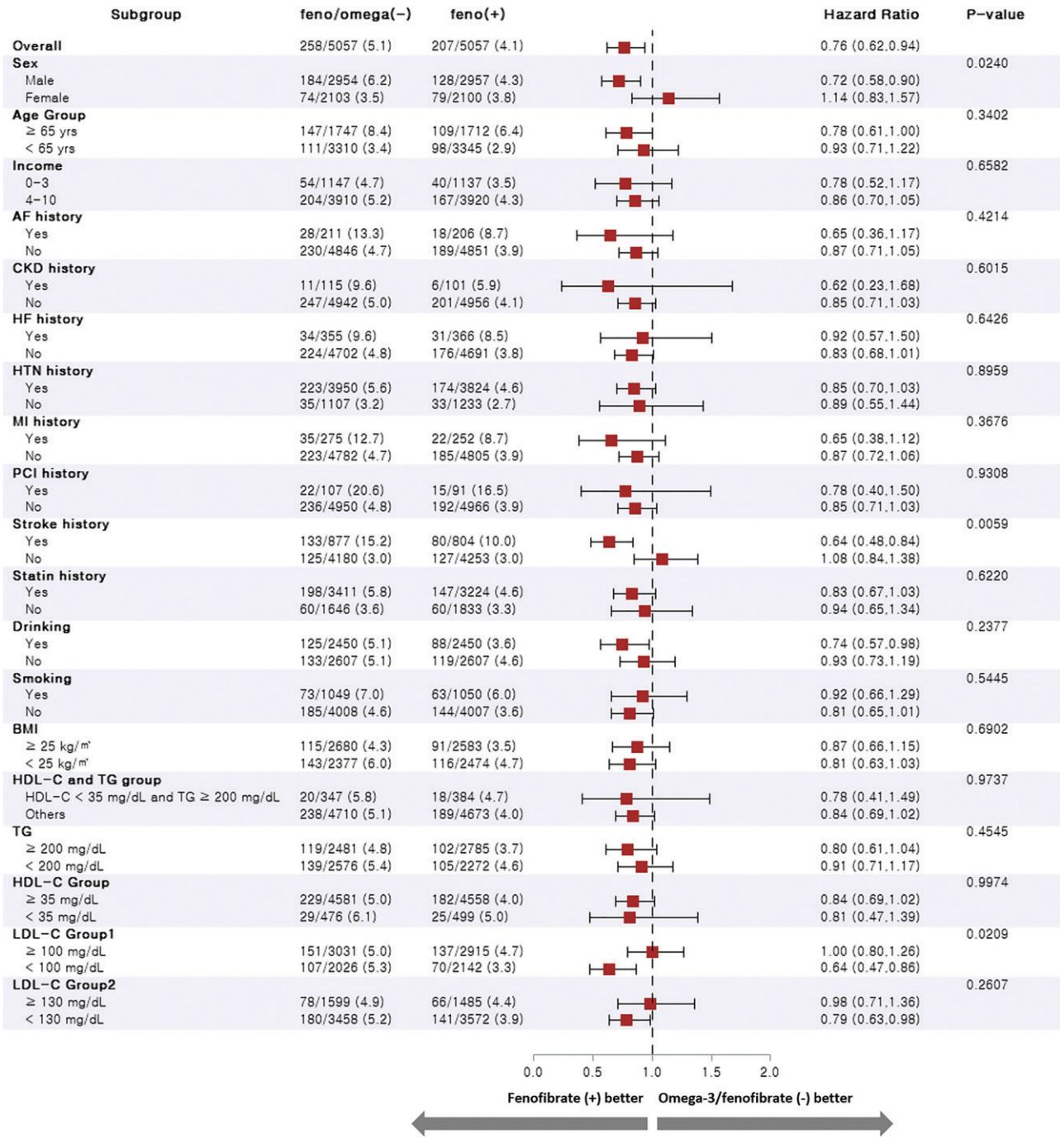

Figure 2—Subgroup analysis for fenofibrate use vs. nonuse. AF, atrial fibrillation; CKD, chronic kidney disease; HF, heart failure; HTN, hypertension.

which could have affected the outcomes of fenofibrate users, because we had so few consecutive data on these factors.

Conclusion

Fenofibrate use was associated with a reduced risk of cardiovascular events, cardiac death, and all-cause death during 3-year follow-up in patients with type 2 diabetes in a real-world setting.

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References

1. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. Ann Intern Med 2004;141:413–420

2. Madsen CM, Varbo A, Nordestgaard BG. Unmet need for primary prevention in individuals with

hypertriglyceridaemia not eligible for statin therapy according to European Society of Cardiology/European Atherosclerosis Society guidelines: a contemporary population-based study. Eur Heart J 2018;39:610–619
3. Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation 2007;115:450–458
4. Ference BA, Kastelein JJP, Ray KK, et al. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. JAMA 2019;321:364–373
5. Watts GF, Ooi EM, Chan DC. Demystifying the management of hypertriglyceridaemia. Nat Rev Cardiol 2013;10:648–661
6. Keech A, Simes RJ, Barter P, et al.; FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849–1861
7. Ginsberg HN, Elam MB, Lovato LC, et al.; ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563–1574
8. Bhatt DL, Steg PG, Miller M, et al.; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11–22
9. Jo SH, Han SH, Kim SH, Eckel RH, Koh KK. Cardiovascular effects of omega-3 fatty acids: hope or hype? Atherosclerosis 2021;322:15–23
10. Son JS, Choi S, Kim K, et al. Association of blood pressure classification in Korean young adults according to the 2017 American College of Cardiology/American Heart Association guidelines with subsequent cardiovascular disease events. JAMA 2018;320:1783–1792
11. Cheol Seong S, Kim YY, Khang YH, et al. Data resource profile: the National Health Information Database of the National Health Insurance Service in South Korea. Int J Epidemiol 2017;46:799–800
12. Benjamin EJ, Muntner P, Alonso A, et al.; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2019 update: a report from the American Heart Association [published correction appears in Circulation. 2020;141:e33]. Circulation 2019;139:e56–e528
13. Chapman MJ, Ginsberg HN, Amarenco P, et al.; European Atherosclerosis Society Consensus Panel. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. Eur Heart J 2011;32:1345–1361
14. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet 2014;384:626–635
15. Saeed A, Feofanova EV, Yu B, et al. Remnant-like particle cholesterol, low-density lipoprotein triglycerides, and incident cardiovascular disease. J Am Coll Cardiol 2018;72:156–169
16. Duran EK, Aday AW, Cook NR, Buring JE, Ridker PM, Pradhan AD. Triglyceride-rich lipoprotein cholesterol, small dense LDL cholesterol, and incident cardiovascular disease. J Am Coll Cardiol 2020;75:2122–2135
17. Schwartz GG, Abt M, Bao W, et al. Fasting triglycerides predict recurrent ischemic events in patients with acute coronary syndrome treated with statins. J Am Coll Cardiol 2015;65:2267–2275
18. Vallejo-Vaz AJ, Fayyad R, Boekholdt SM, et al. Triglyceride-rich lipoprotein cholesterol and risk of cardiovascular events among patients receiving statin therapy in the TNT trial. Circulation 2018;138:770–781
19. Do R, Willer CJ, Schmidt EM, et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. Nat Genet 2013;45:1345–1352
20. Lawler PR, Akinkuolie AO, Chu AY, et al. Atherogenic lipoprotein determinants of cardiovascular disease and residual risk among individuals with low low-density lipoprotein cholesterol. J Am Heart Assoc 2017;6:e005549
21. Lee YJ, Song S, Song Y. High-carbohydrate diets and food patterns and their associations with metabolic disease in the Korean population. Yonsei Med J 2018;59:834–842
22. Kim NH, Han KH, Choi J, Lee J, Kim SG. Use of fenofibrate on cardiovascular outcomes in statin users with metabolic syndrome: propensity matched cohort study. BMJ 2019;366:l5125
23. Abdelhamid AS, Brown TJ, Brainard JS, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev 2020;3:CD003177
24. Zhu L, Hayen A, Bell KJL. Legacy effect of fibrate add-on therapy in diabetic patients with dyslipidemia: a secondary analysis of the ACCORDION study. Cardiovasc Diabetol 2020;19:28
25. Li CB, Li XX, Chen YG, et al. Effects and mechanisms of PPARalpha activator fenofibrate on myocardial remodelling in hypertension. J Cell Mol Med 2009;13:4444–4452
26. Rosenson RS, Wolff DA, Huskin AL, Helenowski IB, Rademaker AW. Fenofibrate therapy ameliorates fasting and postprandial lipoproteinemia, oxidative stress, and the inflammatory response in subjects with hypertriglyceridemia and the metabolic syndrome. Diabetes Care 2007;30:1945–1951
27. Koh KK, Han SH, Quon MJ, Yeal Ahn J, Shin EK. Beneficial effects of fenofibrate to improve endothelial dysfunction and raise adiponectin levels in patients with primary hypertriglyceridemia. Diabetes Care 2005;28:1419–1424
28. Israelian-Konaraki Z, Reaven PD. Peroxisome proliferator-activated receptor-alpha and atherosclerosis: from basic mechanisms to clinical implications. Cardiology 2005;13:240–246