Comparison of pleiotropic effects of statins vs fibrates on laboratory parameters in patients with dyslipidemia

A retrospective cohort study

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Abstract

Differences in the mechanism of action and potential pleiotropic effects between statins and fibrates would potentially drive a different effect on various laboratory parameters, but this remains controversial because of a paucity of reports comparing them. Therefore, the aim of this study was to compare the effects of statins and fibrates on laboratory parameters in Japanese patients in routine clinical practice.

This retrospective cohort study included patients with dyslipidemia who had been newly treated with statin or fibrate monotherapy between January 2005 and December 2017. Patients were randomly matched into two sets of pairs by sex, age, and baseline triglyceride (TG) or low-density lipoprotein (LDL) cholesterol level. The 830 patients in TG-matched pairs (415 fibrate users and 415 matched statin users) and 1172 patients in LDL cholesterol-matched pairs (586 fibrate users and 586 matched statin users) were included in this study. Generalized estimating equations were used to estimate the effects of the drugs on serum creatinine level, estimated glomerular filtration rate (eGFR), urea nitrogen, hemoglobin A_{1c}, aspartate aminotransferase, and alanine aminotransferase (ALT), in addition to LDL cholesterol and TG levels, and red blood cell (RBC) and platelet (PLT) counts, up to 12 months after the start of study drug administration.

In TG-matched pairs, the increases in creatinine and urea nitrogen levels ($P = .010$ and $P < .001$, respectively) and the decreases in eGFR, ALT level and RBC count ($P < .001$, $P = .003$, and $P = .014$, respectively) were greater in fibrate users than in statin users. The decrease in PLT count was greater in statin users than in fibrate users ($P < .001$). The mean changes in aspartate aminotransferase and hemoglobin A_{1c} levels were not significantly different between statin users and fibrate users. In LDL cholesterol-matched pairs, the differences in changes of all laboratory parameter levels between statin users and fibrate users were similar to those in TG-matched pairs.

We demonstrate here that fibrates have a greater effect of increasing creatinine and urea nitrogen levels and of reducing eGFR, ALT level, and RBC count than statins, and that the lowering effect on PLT count is greater with statins than with fibrates.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CDW = Clinical Data Warehouse, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, GEE = generalized estimating equation, HbA$_{1c}$ = hemoglobin A_{1c}, HDL = high-density lipoprotein, LDL = low-density lipoprotein, NUSM = Nihon University School of Medicine, PLT = platelet, PPARα = peroxisome proliferator-activated receptor α, RBC = red blood cell, TG = triglyceride.

Keywords: fibrate, laboratory parameter, propensity score, retrospective cohort study, statin

1. Introduction

Statins and fibrates are lipid-lowering drugs that improve different components of the lipid profile through different mechanisms of action. Statins, hydroxylmethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, suppress the synthesis of cholesterol and can primarily decrease low-density lipoprotein (LDL) cholesterol level, but have only a limited effect on hypertriglyceridemia and low high-density lipoprotein cholesterol level.[1] Statins effectively reduce cardiovascular events and mortality.[2–5] Current guidelines recommend statins for primary and secondary prevention of cardiovascular disease as assessed with a recommended risk score.[6,7] Besides their intrinsic cholesterol-lowering effect, statins also exhibit anti-inflammatory, antioxidant, and plaque-stabilizing capacities, resulting in the potential prevention of other disorders than cardiovascular disease.[8,9] The effect of statin treatment on proteinuria and decline of kidney function differs among individual statins, via potent anti-inflammatory effects in patients with chronic kidney disease (CKD), and is still being debated.[10–13] Although statins are generally considered to be safe and well tolerated,[14] there is concern about the relation between the use of statins and the development of diabetes mellitus.[15,16] On the other hand, fibrates are fibric acid derivatives that activate peroxisome proliferator-activated receptor α, which regulates gene transcription of enzymes involved in lipid synthesis and secretion, leading to reduction of plasma triglyceride (TG) and increase of high-density lipoprotein cholesterol level.[17,18] Peroxisome proliferator-activated receptor α activation decreases reactive oxygen species generation and inflammatory cytokine expression.[19] Fibrates improve atherogenic dyslipidemia, which is associated with the metabolic syndrome and type 2 diabetes mellitus.[20] Fibrates might also reduce cardiovascular events[21–23] and the risk of diabetic microvascular complications, such as amputation and laser treatment in patients with retinopathy.[24–26] However, careful administration is required for patients with renal dysfunction because of an increase in serum levels of creatinine, cystatin C and homocysteine during fibrate therapy, suggesting transient impairment of renal function.[19,27,28] Guidelines for the management of dyslipidemias recommend regular monitoring of some laboratory parameters including renal function, besides the lipid profile, in patients with lipid-lowering therapy.[29] What laboratory parameters are affected by differences in the mechanism of action and potential pleiotropic effects between statins and fibrates would be of interest. There is, however, a paucity of reports providing data from a comparison of the effects on laboratory parameters between statins and fibrates, especially in people with various comorbid conditions and concomitant drugs in clinical settings. In this study, therefore, we evaluated and compared the effects of statin and fibrate monotherapy on laboratory parameters including serum creatinine, estimated glomerular filtration rate (eGFR), urea nitrogen, hemoglobin A_{1c} (HbA$_{1c}$), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels and hematological parameters including red blood cell (RBC) count and platelet (PLT) count, which are typically used in clinical practice for checking side effects of drugs, in patients with various clinical backgrounds in a real-world setting.

2. Materials and methods

2.1. Data source

This was a retrospective cohort study using a clinical database. We obtained the study data from the Nihon University School of Medicine (NUSM) Clinical Data Warehouse (CDW). This CDW is a centralized anonymous data repository that integrates detailed clinical information, such as patient demographics, diagnosis, prescribing data, and laboratory data, from the electronic medical record system at 3 hospitals affiliated with NUSM; Nihon University Itabashi Hospital and Nerima Hikarigaoka Hospital, and Surugadai Nihon University Hospital, and is described elsewhere.[30] To protect patient privacy, patient identifiers are replaced with anonymous identifiers in all databases of this CDW. Several epidemiological studies examining the effects of drugs on glucose and lipid metabolism and renal function using NUSM's CDW have been published.[31–37] The study protocol was approved by the Ethical Committee of Nihon University School of Medicine, and it was conducted in compliance with the Helsinki Declaration and the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare, Japan. No informed consent was required because this was a retrospective observational study using anonymized archived data and did not compromise anonymity or confidentiality.

2.2. Study population

The cohorts identified for the study included Japanese patients with dyslipidemia aged over 20 and under 80 years who had been newly treated with statin or fibrate monotherapy for at least 2 months between January 1, 2005 and December 31, 2017 (defined as the entry period).

We identified treatment groups who fulfilled the following criteria:

1. Statin users: patients who had been newly treated with a statin during the entry period. We excluded patients who had received a fibrate or other lipid-lowering drugs (bile acid sequestrant, cholesterol absorption inhibitor (ezetimibe), nicotinic acid, PCSK9 inhibitor, or others, including omega-3 acid ethyl ester, icosapent ethyl, gamma-oryzanol, and pantethine) during the study period. The start of statin monotherapy was defined as the date of the first prescription of a statin.
2. Fibrate users: patients who had been newly treated with a fibrate during the entry period. We excluded patients who had received a statin or other lipid-lowering drugs during the study period. The start of fibrate monotherapy was defined as the date of the first prescription of a fibrate.

To minimize the influence of discontinuing a medication shortly after initiation and poor adherence, we excluded patients who received a study drug for less than 2 months or whose number of prescription days was less than 80% of the duration of exposure. (The duration of exposure was defined as the time from the first to the last prescription date.) We also excluded patients with a diagnosis of severe hepatic insufficiency, acute renal failure or end-stage kidney disease, receiving dialysis, or CKD category G5 during the study period. We subsequently excluded patients with missing values of serum TG, LDL cholesterol, or creatinine data during the 90 days before the start of statin or fibrate monotherapy. We identified 8354 new users of statin monotherapy and 703 new users of fibrate monotherapy who fulfilled the above criteria (Fig. 1). Because lipid profiles inevitably differed between statin and fibrate users in clinical settings, patients were randomly matched into 2 sets of pairs by TG level
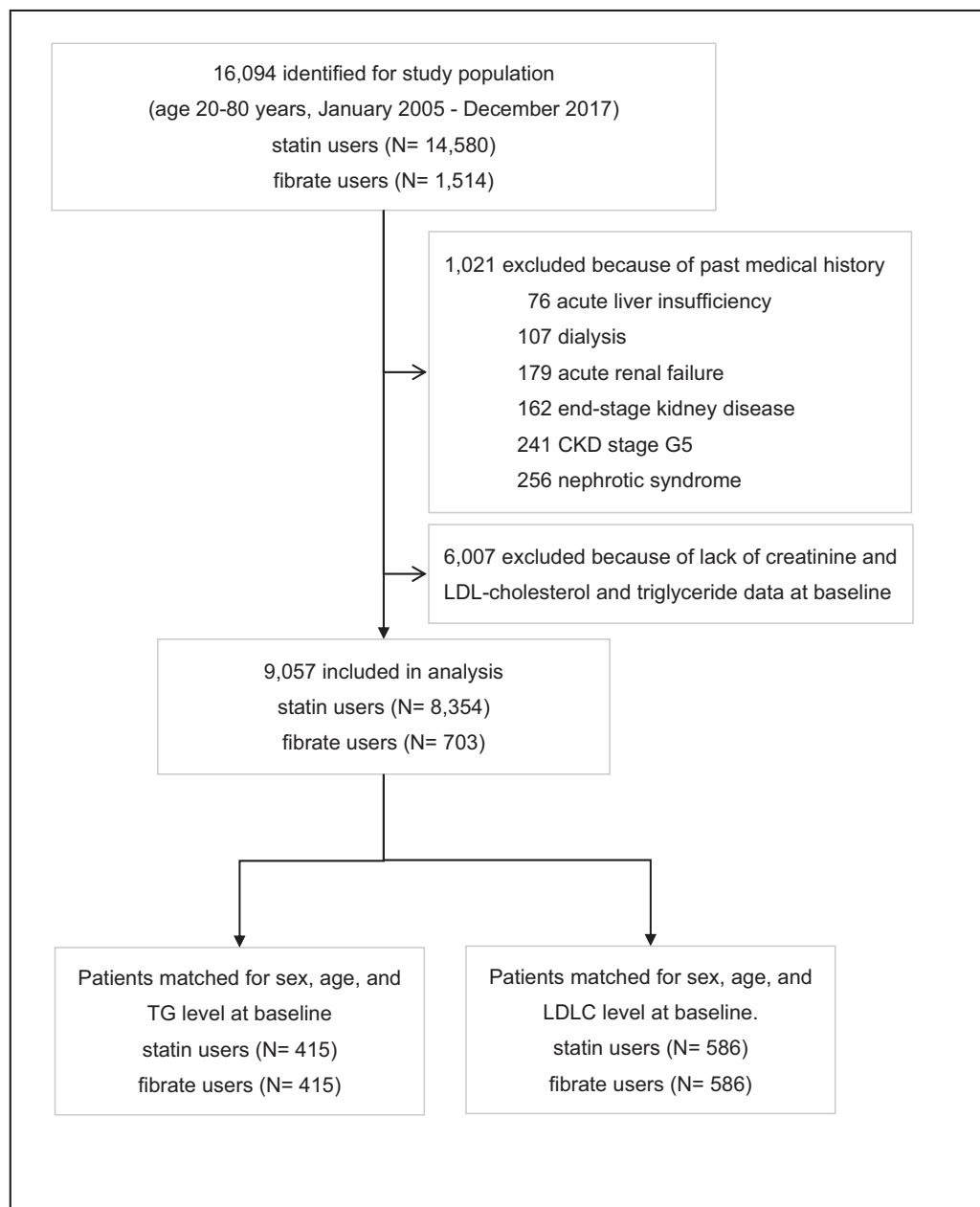
Figure 1. Identification of study population. The cohorts identified for the study included Japanese patients with dyslipidemia aged over 20 and under 80 years who had been newly treated with statin or fibrate monotherapy for at least 2 months between January 2005 and December 2017. Some patients were excluded for the reasons shown in the figure. Then, for each fibrate user, 1 statin user matched according to sex, age, and baseline TG level or baseline LDL cholesterol level, was randomly selected. Consequently, the study cohorts included TG-matched pairs (415 statin users and 415 matched fibrate users) and LDL cholesterol-matched pairs (586 statin users and 586 matched fibrate users). CKD = chronic kidney disease, LDLC = low-density lipoprotein cholesterol, TG = triglyceride.

or LDL cholesterol level to reduce bias in nonrandomized subjects. For each fibrate user, one statin user matched according to sex, age (±1 year), and serum TG level (±1 mg/dL) or serum LDL cholesterol level (±1 mg/dL) at baseline was randomly selected. Consequently, we identified 830 patients for TG-matched pairs (415 fibrate users and 415 matched statin users) and 1172 patients for LDL cholesterol-matched pairs (586 fibrate users and 586 matched statin users) and compared each pair set. The lipid-lowering drugs and their daily doses used in the statin and fibrate monotherapy groups are listed in Table 1. A data set

with both matched TG level and LDL cholesterol level was not analyzed in this study because of the small samples.

2.3. Exposure and measurements

The baseline period was defined as within 3 months before the start of statin or fibrate monotherapy. The exposure period (treatment duration) was defined as the number of days since the start of treatment as follows: 0 to 3 M (>0, ≤3 months), 3 to 6 M (>3, ≤6 months), 6 to 9 M (>6, ≤9 months), and 9 to 12 M (>6,

Class	Generic name	TG-matched pairs		LDLC-matched pairs	
		N	**Dose**	**N**	**Dose**
Statins	All	**415**		**586**	
	Atorvastatin	125	7.7 (7.2, 8.2)	145	8.7 (7.8, 9.6)
	Fluvastatin	8	31 (19, 43)	26	24 (20, 28)
	Pitavastatin	98	1.4 (1.3, 1.6)	145	1.4 (1.3, 1.6)
	Pravastatin	59	8.6 (7.8, 9.5)	77	8.8 (8.0, 9.5)
	Rosuvastatin	88	3.3 (3.0, 3.6)	138	3.6 (3.3, 3.8)
	Simvastatin	9	6.7 (4.7, 8.6)	10	7.5 (5.6, 9.4)
	Switch[*]	28	–	45	–
Fibrates	**All**	**415**		**586**	
	Bezafibrate	331	305 (293, 317)	454	309 (299, 319)
	Fenofibrate	78	123 (112, 134)	116	126 (117, 134)
	Switch[*]	6	–	16	–

The daily dose in each individual is given as the average daily amount of drug prescribed. Doses are shown as mean (95% confidence interval) in mg/d.
LDLC = low-density lipoprotein cholesterol, TG = triglyceride.
[*] Drugs were switched within the same medication class.

≤12 months), to evaluate the long-term effects of the study drugs. Blood test data, including serum TG, LDL cholesterol, HbA_{1c}, creatinine, urea nitrogen, ALT, and AST levels, and hematological parameters including RBC count and PLT count were collected for each individual at the date nearest the start of the study drug administration in the baseline period, and at dates nearest 3, 6, 9, and 12 months after the start of treatment during the exposure period. eGFR was calculated according to the formula for Japanese specified by the Japanese Society of Nephrology: eGFR (mL/min/1.73 m^2) = 194*SCr$^{-1.094*}$ Age$^{-0.287}$ (*0.739 if female).[38] GFR category was assigned as follows: G1 (eGFR ≥90 mL/min/1.73 m^2), G2 (eGFR 60–89 mL/min/1.73 m^2), G3a (eGFR 45–59 mL/min/1.73 m^2), G3b (eGFR 30–44 mL/min/1.73 m^2), G4 (eGFR 15–29 mL/min/1.73 m^2), G5 (eGFR < 15 mL/min/1.73 m^2).

2.4. Data elements

For each individual, information on patient demographics (age and sex), medical history, current medication, and laboratory results were collected. Medical history included information on cerebrovascular disease (ICD-10 codes, I60-I69), ischemic heart disease (I20-I25), other heart disease (I30-I52), rheumatoid disease (M5, M6), liver disease (K70-K77), kidney disease (N00-N19), diabetes mellitus (E10-E14), and hypertension (I10) during the 365 days preceding the start of statin or fibrate monotherapy. We recorded current users of medication including anti-diabetic drugs (insulin, oral anti-hyperglycemic agents, and other anti-diabetic drugs), antihypertensive agents (angiotensin type II receptor blockers, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, calcium channel blockers, antihypertensive diuretics and other antihypertensive drugs), antithrombotic drugs, liver disease therapeutics, kidney disease therapeutics, steroids, nonsteroidal anti-inflammatory drugs, diuretics, and antiarrhythmic drugs, defined as patients who had received these agents in the 90 days preceding the start of statin or fibrate monotherapy.

2.5. Statistical analysis

To compare differences in baseline characteristics, we used t-test for continuous variables and chi-squared test for categorical data.

Also, we used t-test to compare the mean values of all laboratory parameters at baseline between statin users and fibrate users, and TG and LDL cholesterol levels during the overall exposure period. All reported P-values are 2 sided. To estimate the effects on outcome parameters, we used generalized estimating equations (GEE; GENMOD procedure in SAS software) with a compound symmetry correlation structure to account for repeated measures. GEE was used to estimate the differences in changes of values of laboratory parameters from the baseline value to the exposure value between statin users and fibrate users. Also, GEE was used to calculate adjusted least-squares means of changes from baseline of values of laboratory parameters in each exposure period in each user group. We used covariate adjustment using the propensity score to reduce bias in nonrandomized studies[39,40]; this method is described elsewhere.[41] The propensity score for each subject was calculated using all baseline covariates including GFR category, medical history, and current medication (except for age, sex, and laboratory parameters), as shown in Table 2. Consequently, the model for TG-matched pairs was adjusted for the propensity score, treatment duration, and baseline values of each outcome parameter and LDL cholesterol. The model for LDL cholesterol-matched pairs was adjusted for the propensity score, treatment duration, and baseline values of each outcome parameter and TG. The propensity score for each subject was recalculated in each analysis for all laboratory parameters because the number of patients varied for some laboratory test data, which included several missing values. All reported P values of less than .05 were considered to indicate statistical significance. All analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Study subjects

Based on our initial inclusion and exclusion criteria, we identified a total of 9057 patients for this study; 8354 new users of statin monotherapy and 703 new users of fibrate monotherapy. After the 1:1 matching procedure, the study included 415 fibrate users and 415 statin users who were matched for sex, age, and baseline

Table 2

Baseline characteristics.

Characteristics	TG-matched pairs			LDLC-matched pairs		
	Statin users (n=415)	Fibrate users (n=415)	*P* value	Statin users (n=586)	Fibrate users (n=586)	*P* value
Exposure period (d, mean±sd)	290±89	264±106	.0002	276±96	269±102	.1986
Age (years, mean±sd)	60.3±11.5	60.2±11.4	.9492	59.1±11.8	59.0±11.8	.8543
Women	137 (33.0)	137 (33.0)	1	178 (30.4)	178 (30.4)	1
GFR category						
G1	64 (15.4)	68 (16.4)	.0485	94 (16.0)	96 (16.4)	.3882
G2	246 (59.3)	235 (56.6)		353 (60.2)	346 (59.0)	
G3a	73 (17.6)	73 (17.6)		87 (14.9)	101 (17.2)	
G3b	18 (4.3)	34 (8.2)		34 (5.8)	34 (5.8)	
G4	14 (3.4)	5 (1.2)		18 (3.1)	9 (1.5)	
G5	0 (—)	0 (—)		0 (—)	0 (—)	
Medical history						
Cerebrovascular disease	70 (16.9)	50 (12.0)	.0484	99 (16.9)	68 (11.6)	.0096
Ischemic heart disease	163 (39.3)	61 (14.7)	<.0001	269 (45.9)	91 (15.5)	<.0001
Other heart disease	164 (39.5)	99 (23.9)	<.0001	281 (48.0)	147 (25.1)	<.0001
Rheumatoid arthritis	10 (2.4)	9 (2.2)	.8165	16 (2.7)	15 (2.6)	.8556
Liver disease	84 (20.2)	159 (38.3)	<.0001	95 (16.2)	216 (36.9)	<.0001
Kidney disease	53 (12.8)	35 (8.4)	.0424	83 (14.2)	56 (9.6)	.0147
Diabetes mellitus	222 (53.5)	223 (53.7)	.9445	336 (57.3)	310 (52.9)	.1268
Hypertension	273 (65.8)	218 (52.5)	.0001	453 (77.3)	314 (53.6)	<.0001
Medication						
Antihypertensive drugs	253 (61.0)	207 (49.9)	.0013	425 (72.5)	294 (50.2)	<.0001
ARB	121 (29.2)	128 (30.8)	.596	230 (39.2)	189 (32.3)	.0125
ACE inhibitor	53 (12.8)	16 (3.9)	<.0001	96 (16.4)	23 (3.9)	<.0001
Beta blocker	47 (11.3)	34 (8.2)	.1284	76 (13.0)	50 (8.5)	.0142
CCB	161 (38.8)	140 (33.7)	.1295	257 (43.9)	197 (33.6)	.0003
Antihypertensive diuretic	17 (4.1)	10 (2.4)	.1708	18 (3.1)	17 (2.9)	.8637
Other antihypertensive drugs	66 (15.9)	54 (13.0)	.2363	144 (24.6)	74 (12.6)	<.0001
Antidiabetic drugs	100 (24.1)	112 (27.0)	.3395	189 (32.3)	160 (27.3)	.064
Insulin	21 (5.1)	32 (7.7)	.1184	45 (7.7)	41 (7.0)	.6541
Oral antidiabetic drug	80 (19.3)	91 (21.9)	.3451	151 (25.8)	132 (22.5)	.1947
Other antidiabetic drugs	12 (2.9)	4 (1.0)	.0434	15 (2.6)	7 (1.2)	.0851
Antithrombotic drugs	187 (45.1)	96 (23.1)	<.0001	314 (53.6)	124 (21.2)	<.0001
Liver disease therapeutics	6 (1.4)	36 (8.7)	<.0001	11 (1.9)	37 (6.3)	.0001
Kidney disease therapeutics	3 (0.7)	2 (0.5)	.6537	4 (0.7)	2 (0.3)	.413
Steroids	31 (7.5)	29 (7.0)	.7886	35 (6.0)	45 (7.7)	.2468
NSAID	106 (25.5)	90 (21.7)	.191	186 (31.7)	107 (18.3)	<.0001
Diuretics	61 (14.7)	29 (7.0)	.0004	92 (15.7)	41 (7.0)	<.0001
Antiarrhythmic drugs	62 (14.9)	40 (9.6)	.02	116 (19.8)	65 (11.1)	<.0001
Baseline laboratory parameters						
Triglyceride (mg/dL, mean±sd)	207.9±108.2	208±108.2	.9921	163.8±104.7	289.3±158.8	<.0001
LDLC (mg/dL, mean±sd)	149.2±36.6	116.2±35.3	<.0001	117.9±33.2	117.8±33.3	.9839

Note: Data are number of individuals (%) unless otherwise stated.

Comparisons of differences in patient characteristics between groups were performed using *t*-test for continuous variables and chi-squared test for categorical data.

ACE inhibitor = angiotensin-converting enzyme inhibitor, ARB = angiotensin type II receptor blocker, CCB = calcium channel blocker, GFR = glomerular filtration rate, LDLC = low-density lipoprotein cholesterol, NSAID = non-steroidal anti-inflammatory drug, TG = triglyceride.

TG level (TG-matched pairs), and 586 fibrate users and 586 statin users who were matched for sex, age, and baseline LDL cholesterol level (LDL cholesterol-matched pairs) (Fig. 1). Baseline characteristics are described in Table 2. The mean length of exposure was longer in statin users (290 days) than in fibrate users (261 days) in TG-matched pairs. Also, the length was likely to be longer in statin users (276 days) than in fibrate users (269 days) in LDL cholesterol-matched pairs, but the difference was not significant. There were no significant differences in age and male/female ratio between statin and fibrate users, in both TG-matched and LDL cholesterol-matched pairs. More than half of each cohort had hypertension or diabetes mellitus, suggesting the possible existence of patients with metabolic syndrome. Statin users were more likely to have cerebrovascular disease, ischemic heart disease, other heart disease, kidney disease, and hypertension, and were less likely to have liver disease than fibrate users in both TG-matched and LDL cholesterol-matched pairs. Regarding current medications, statin users were more likely to use antihypertensive drugs, antithrombotic drugs, diuretics, and antiarrhythmic drugs than fibrate users in both TG-matched and LDL cholesterol-matched pairs. Also, statin users were more likely to use non-steroidal anti-inflammatory drugs in LDL cholesterol-matched pairs. On the other hand, fibrate users were more likely to use liver disease therapeutics in both TG-matched and LDL cholesterol-matched pairs. Table 3 shows the mean values of laboratory parameters at baseline. In TG-matched pairs, mean serum AST and ALT levels were lower (*P* = .007 and *P* < .001, respectively), and mean RBC count was higher

Table 3

Baseline laboratory parameters of study subjects.

Laboratory parameters	TG-matched pairs					LDLC-matched pairs				
	Statin users		Fibrate users			Statin users		Fibrate users		
	N	Mean (95% CI)	N	Mean (95% CI)	P value	N	Mean (95% CI)	N	Mean (95% CI)	P value
Creatinine (mg/dL)	415	0.86 (0.82, 0.89)	415	0.85 (0.82, 0.88)	.7927	586	0.87 (0.84, 0.90)	586	0.84 (0.82, 0.87)	.2519
eGFR (ml/min/1.73m^2)	415	72.1 (70.2, 74.0)	415	71.1 (69.3, 73.0)	.4780	586	72.6 (70.9, 74.2)	586	72.4 (70.8, 73.9)	.8759
Urea nitrogen (mg/dL)	412	16.0 (15.5, 16.6)	412	15.5 (15.0, 16.0)	.1854	584	15.4 (15.0, 15.9)	584	15.2 (14.8, 15.6)	.4572
HbA$_{1c}$ (%)	345	6.46 (6.34, 6.59)	322	6.51 (6.36, 6.67)	.5957	521	6.58 (6.46, 6.69)	457	6.56 (6.43, 6.69)	.8330
AST (U/L)	407	30.6 (27.3, 33.9)	406	36.7 (33.7, 39.7)	.0074	576	33.5 (30.3, 36.8)	577	35.1 (32.8, 37.5)	.4317
ALT (U/L)	412	29.8 (27.2, 32.4)	411	37.7 (34.0, 41.4)	.0006	583	30.8 (28.5, 33.1)	582	37.5 (34.6, 40.4)	.0003
RBC (10^6/μL)	413	4.52 (4.47, 4.57)	411	4.38 (4.32, 4.43)	.0003	581	4.43 (4.38, 4.48)	581	4.48 (4.43, 4.52)	.1646
PLT (10^3/μL)	414	236 (230, 242)	409	233 (226, 240)	.5364	580	228 (222, 233)	579	236 (230, 242)	.0413

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, eGFR = estimated glomerular filtration rate, HbA$_{1c}$ = hemoglobin A$_{1c}$, LDLC = low-density lipoprotein cholesterol, PLT = platelet, RBC = red blood cell, TG = triglyceride.

($P < .001$) in statin users than in fibrate users. In LDL cholesterol-matched pairs, mean serum ALT level and PLT count were lower in statin users than in fibrate users ($P < .001$ and $P = .041$, respectively). None of the other parameters showed any significant difference in mean values at baseline between statin and fibrate users in both TG-matched and LDL cholesterol-matched pairs.

3.2. Lipid levels

In TG-matched pairs, the difference in mean TG level at baseline between statin and fibrate users was not significant, and mean LDL cholesterol level at baseline was higher by 33.0 mg/dl in statin users than in fibrate users ($P < .001$) (Table 2). There was no significant difference in the overall mean TG level during the exposure period between statin and fibrate users (Fig. 2A). The overall mean LDL cholesterol level during the exposure period was lower by 12.1 mg/dl in statin users than in fibrate users ($P < .001$). On the other hand, in LDL cholesterol-matched pairs, mean TG level at baseline was lower by 122.2 mg/dl in statin users than in fibrate users ($P < .001$), and the difference in mean LDL cholesterol level at baseline between statin and fibrate users was not significant. The overall mean TG level during the exposure period was lower by 34.1 mg/dl, and the overall mean LDL cholesterol level was lower by 27.3 mg/dl in statin users than in fibrate users ($P < .001$ for both comparisons) (Fig. 2B).

3.3. Effects on outcomes

Because differences in baseline covariates, including GFR category, comorbid diseases, and current medication, between statin users and fibrate users, may create potential bias, we used covariate adjustment using the propensity score and baseline levels of laboratory parameters to control for potential confounding covariates in our observational study. In TG-matched pairs, the increases in creatinine and urea nitrogen levels ($P = .010$ and $P < .001$, respectively) and the decreases in eGFR, ALT level, and RBC count ($P < .001$, $P = .003$, and $P = .014$, respectively) were greater in fibrate users than in statin users (Fig. 3 and Table 4). Also, the difference in change of PLT count, which showed an increase in fibrate users and a reduction in statin users, was significant ($P < .001$). The mean changes in AST and HbA$_{1c}$ levels were not significantly different between statin users and fibrate users. In LDL cholesterol-matched pairs, the

differences in changes of all laboratory parameter levels between statin users and fibrate users were similar to those in TG-matched pairs (Fig. 4 and Table 4).

4. Discussion

In this study, we evaluated and compared the effects of statin monotherapy and fibrate monotherapy on laboratory parameters in routine clinical settings in a long-term administration period up to 12 months. We found greater increases in serum creatinine and urea nitrogen levels in fibrate users than in statin users, and greater reductions of eGFR, ALT level, and RBC count in fibrate users than in statin users. Also, there was a greater reduction of PLT count in statin users than in fibrate users. These findings suggest that the adverse effects on renal function and erythrocytes, and the favorable effect on liver enzymes are greater with fibrates than with statins. Furthermore, our results suggest that the lowering effect on PLT count is greater with statins than with fibrates. Our findings contain useful information for predicting in advance what laboratory parameters and by how much their values will change with the administration of statins or fibrates. This information will be extremely informative to physicians when considering the initiation of statin or fibrate therapy and drug selection in clinical practice, especially in patients with comorbid conditions causing abnormal values of laboratory parameters.

The effects of statins on proteinuria and decline of kidney function differ among individual statins[10] and remain controversial. Atthobari et al reported that pravastatin did not change urinary albumin excretion or GFR, irrespective of whether or not an angiotensin-converting enzyme inhibitor was used.[11] The GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) study showed probable favourable changes in eGFR and SUA levels induced by statin (mainly atorvastatin) treatment.[42] Some randomized controlled trials did not demonstrate a favorable effect of atorvastatin on eGFR in patients with CKD.[12,13] A recent epidemiological study showed that statins effectively delayed CKD progression in CKD stage 3B-5 patients, suggesting a protective effect of statins on CKD progression, particularly in advanced stage.[43] On the contrary, clinical trials have consistently shown that fibrates increase serum levels of creatinine, cystatin C and homocysteine, suggesting transient impairment of renal function.[19,27,28] As expected, we demonstrated greater increases in creatinine and urea nitrogen
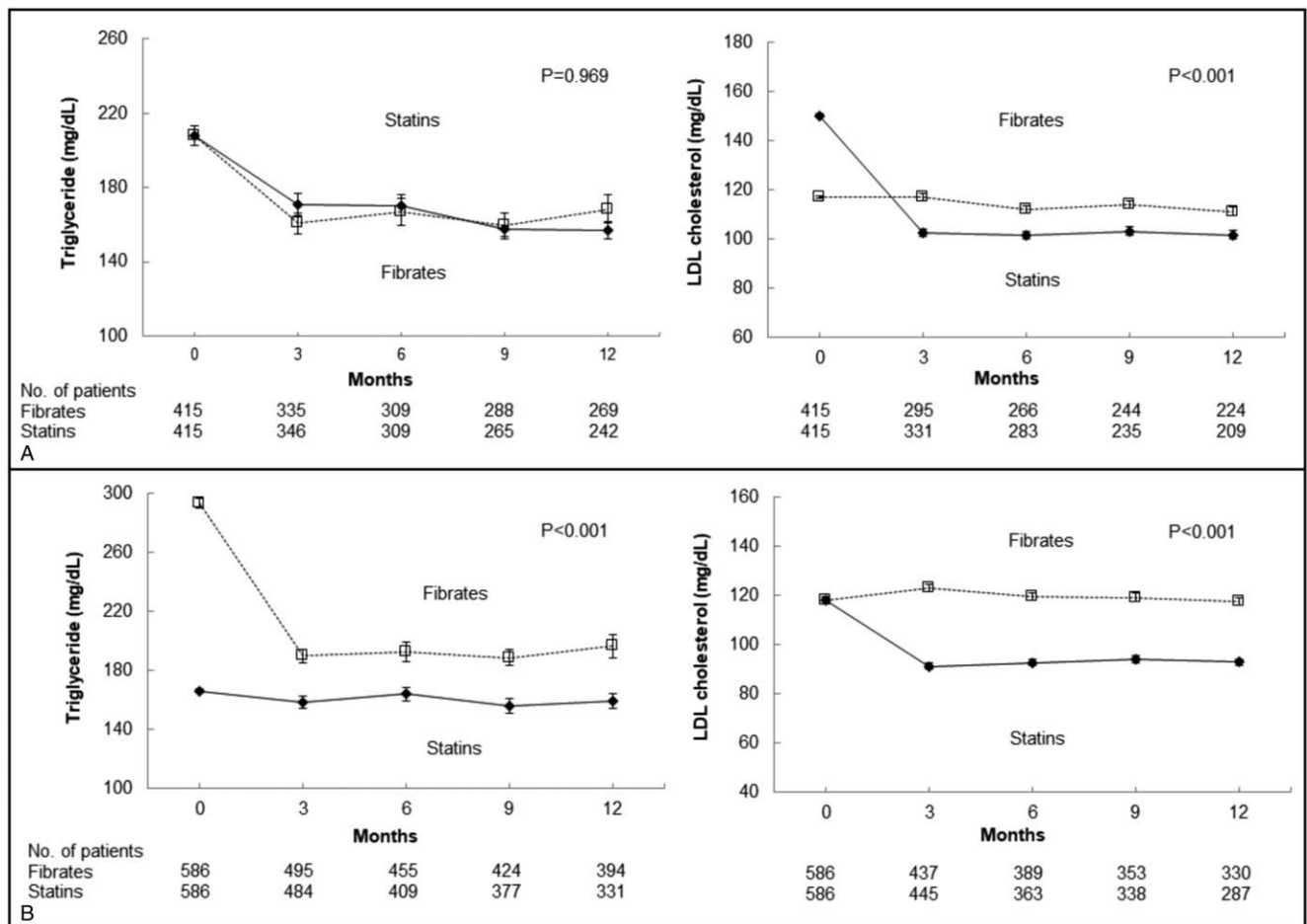
Figure 2. Levels of serum triglyceride and LDL cholesterol. A and B show triglyceride-matched pairs and LDL cholesterol-matched pairs, respectively. Data points are least-squares mean of laboratory parameters at each time-point. I bars indicate standard errors. Open squares indicate fibrate users and solid circles indicate statin users. *P* values are for comparisons between fibrate users and statin users for the overall mean lipid levels during the exposure period. LDL = low-density lipoprotein, TG = triglyceride.

levels and a greater decrease in eGFR in fibrate users than in statin users. Supporting previous reports, our findings are reasonable.

Regarding liver enzymes, elevation of transaminases is one of the most commonly known hepatic adverse events reported with statins. However, most cases are asymptomatic and usually temporary, and clinically significant liver injury is very rare in statin users.[44] In recent years, clinical evidence that statins have a potential beneficial impact on chronic liver disease, including cirrhosis, portal hypertension, and its complications,[45,46] has accumulated. In this study, we found a decrease in AST level and a minimal alteration of ALT level from the baseline period to the exposure period in statin users with various comorbid conditions. Our findings suggest that statins do not worsen liver function in clinical settings, and support the evidence from clinical studies that the use of statins needs not be avoided in patients with preexisting liver dysfunction. On the other hand, there is a paucity of reports providing clinical data from assessments of the effects of fibrates on chronic liver diseases. A recent trial showed that combination therapy with ursodeoxycholic acid and bezafibrate significantly improved liver function in patients with primary biliary cholangitis who had an inadequate response to therapy with ursodeoxycholic acid alone.[47] Supporting this, our

study showed a decrease of ALT level from the baseline period to the exposure period in fibrate users, and a greater reduction of ALT level in fibrate users than in statin users. Our findings, combined with a previous report, suggest that fibrates may have a favorable effect on liver function, and that future research may be needed to assess potential therapeutic roles of fibrates for liver diseases. In our study, however, the prevalence of liver disease and the mean serum ALT level at baseline were higher in fibrate users than in statin users. The possibility that these discrepancies between statin and fibrate users might impact the results of ALT should be considered. Therefore, we used covariate adjustment using a propensity score and baseline values of each laboratory parameter to minimize these concerns, and to improve the reliability of the findings of our study.

There is much evidence from experimental and clinical studies that statins influence antithrombotic effects via variable inhibitory actions on hemostasis, including activation of PLTs and the coagulation cascade.[48,49] An interesting new finding of the present study is that there was a greater reduction of PLT count in statin users than in fibrate users. Also, the decrease of PLT count from the baseline period to the exposure period in statin users was significant (data not shown). The precise link responsible for
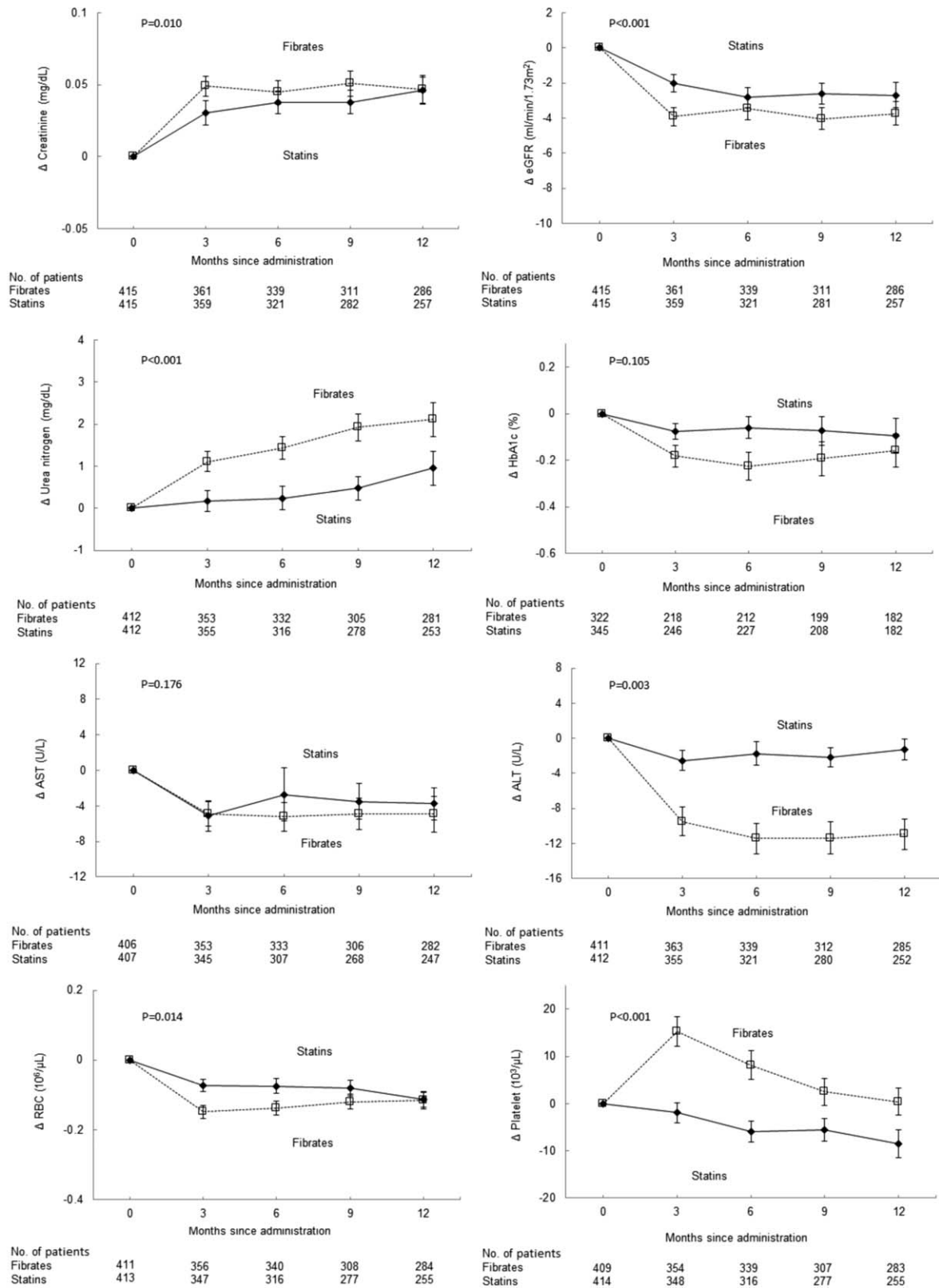
Figure 3. Change from baseline of laboratory parameters in TG-matched pairs. Data points are least-squares mean changes from baseline of laboratory parameters during exposure period. I bars indicate standard errors. Δ indicates change from baseline of laboratory parameters during exposure period. Open squares indicate fibrate users and solid circles indicate statin users. To compare the effects on laboratory parameter levels between statin monotherapy and fibrate monotherapy, generalized estimating equations were used, with fibrate monotherapy as the reference group. Analyses were adjusted for the propensity score, treatment duration, and baseline values of each laboratory parameter and LDL cholesterol. ALT = alanine aminotransferase, AST = aspartate aminotransferase, eGFR = estimated glomerular filtration rate, HbA$_{1c}$ = hemoglobin A$_{1c}$, RBC = red blood cell, TG = triglyceride.

Table 4

Model comparing effect of treatment on laboratory parameters between statin and fibrate users.

Laboratory parameters	TG-matched pairs*				LDLC-matched pairs†			
	N	Estimate	95% CI	P value	N	Estimate	95% CI	P value
ΔCreatinine (mg/dL)								
Statin users	415	−0.031	(−0.055, −0.007)	.0104	586	−0.023	(−0.046, −0.001)	.0373
Fibrate users	415	0	0	Reference	586	0	0	Reference
ΔeGFR (ml/min/1.73 m^2)								
Statin users	415	1.91	(0.87, 2.96)	.0003	586	1.62	(0.63, 2.61)	.0013
Fibrate users	415	0	0	Reference	586	0	0	Reference
ΔUrea nitrogen (mg/dL)								
Statin users	412	−1.12	(−1.62, −0.61)	<.0001	584	−0.87	(−1.32, −0.42)	.0001
Fibrate users	412	0	0	Reference	584	0	0	Reference
ΔHb$_{A1c}$ (%)								
Statin users	345	0.08	(−0.02, 0.17)	.1053	521	−0.02	(−0.11, 0.06)	.5707
Fibrate users	322	0	0	Reference	457	0	0	Reference
ΔAST (U/L)								
Statin users	407	−1.56	(−3.82, 0.70)	.1756	576	−0.32	(−2.40, 1.75)	.7599
Fibrate users	406	0	0	Reference	577	0	0	Reference
ΔALT (U/L)								
Statin users	412	2.81	(0.93, 4.69)	.0034	583	5.14	(3.07, 7.21)	<.0001
Fibrate users	411	0	0	Reference	582	0	0	Reference
ΔRBC (10^6/μL)								
Statin users	413	0.05	(0.01, 0.09)	.0136	581	0.08	(0.04, 0.12)	<.0001
Fibrate users	411	0	0	Reference	581	0	0	Reference
ΔPLT (10^3/μL)								
Statin users	414	−13.99	(−18.88, −9.10)	<.0001	580	−12.88	(−17.44, −8.31)	<.0001
Fibrate users	409	0	0	Reference	579	0	0	Reference

Generalized estimating equation was used to estimate the effects of statin monotherapy on changes in laboratory parameter levels compared with fibrate monotherapy (reference).

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, eGFR = estimated glomerular filtration rate, HbA$_{1c}$ = hemoglobin A$_{1c}$, LDLC = low-density lipoprotein cholesterol, PLT = platelet, RBC = red blood cell, TG = triglyceride.

Δ indicates change in laboratory parameter level during the exposure period from baseline.

* Analyses were adjusted for the propensity score, treatment duration, and baseline values of each laboratory parameter and LDL cholesterol.

† Analyses were adjusted for the propensity score, treatment duration, and baseline values of each laboratory parameter and triglyceride.

the decreased PLT count with statin therapy is not clear. These results suggest that the lowering effect of statins on PLT count may enhance their antithrombotic properties previously reported, which may contribute to early reduction in thrombosis-related events in some clinical settings and potential negative properties including the association between statin therapy and cerebral hemorrhage.[50] Therefore, clinical assessment of bleeding tendency including PLT count should be carefully performed before starting statin therapy, especially in patients receiving antithrombotic therapy.

Generally, statins are used in patients with higher levels of LDL cholesterol, and fibrates are used in patients with hypertriglyceridemia. In clinical practice, however, we encounter patients with mixed dyslipidemia, characterized by high serum concentrations of both TGs and LDL cholesterol. Our findings are expected to help physicians make decisions on drug selection, because the adverse effects of statin and fibrate therapy on renal function, liver function, and erythrocytes and PLTs would be of clinical concern, especially in patients with mixed dyslipidemia. In this study, we analyzed 2 datasets of subjects who were matched for baseline TG level or baseline LDL cholesterol level between statin and fibrate users. Our study showed that the differences in changes of all laboratory parameter levels between statin and fibrate users were similar between the two datasets of pairs, although baseline LDL cholesterol level in TG-matched pairs and baseline TG level in LDL cholesterol-matched pairs differed between them. These results suggest that the effects of statin

monotherapy and fibrate monotherapy on laboratory parameters, including serum creatinine, eGFR, BUN, HbA$_{1c}$, AST, ALT levels, RBC, and PLT counts, may manifest even in patients with an unbalanced level of TG or LDL cholesterol at baseline. However, there is a possibility that the difference in LDL cholesterol level during the exposure period between statin and fibrate users might impact our findings, because the overall mean LDL cholesterol level during the exposure period was lower in statin users than in fibrate users in both TG-matched and LDL cholesterol-matched pairs.

4.1. Limitations

Our study has several limitations. It was a retrospective observational study with nonrandomized data, which has some issues with respect to the potential for selection bias. We used rigorous statistical methods to balance potential confounding variables between statin and fibrate users, including covariate adjustment using a propensity score. However, their ability to control for differences was limited to variables that were available or measurable. Second, the cohorts identified for the study included only Japanese patients. Therefore, it cannot be concluded whether the present findings can be extended to people of other races such as Caucasians. Third, we did not fix the daily dosage in both statin and fibrate users, because the achievement of lipid goals requires various doses of an agent among different individuals or even in the same individual in
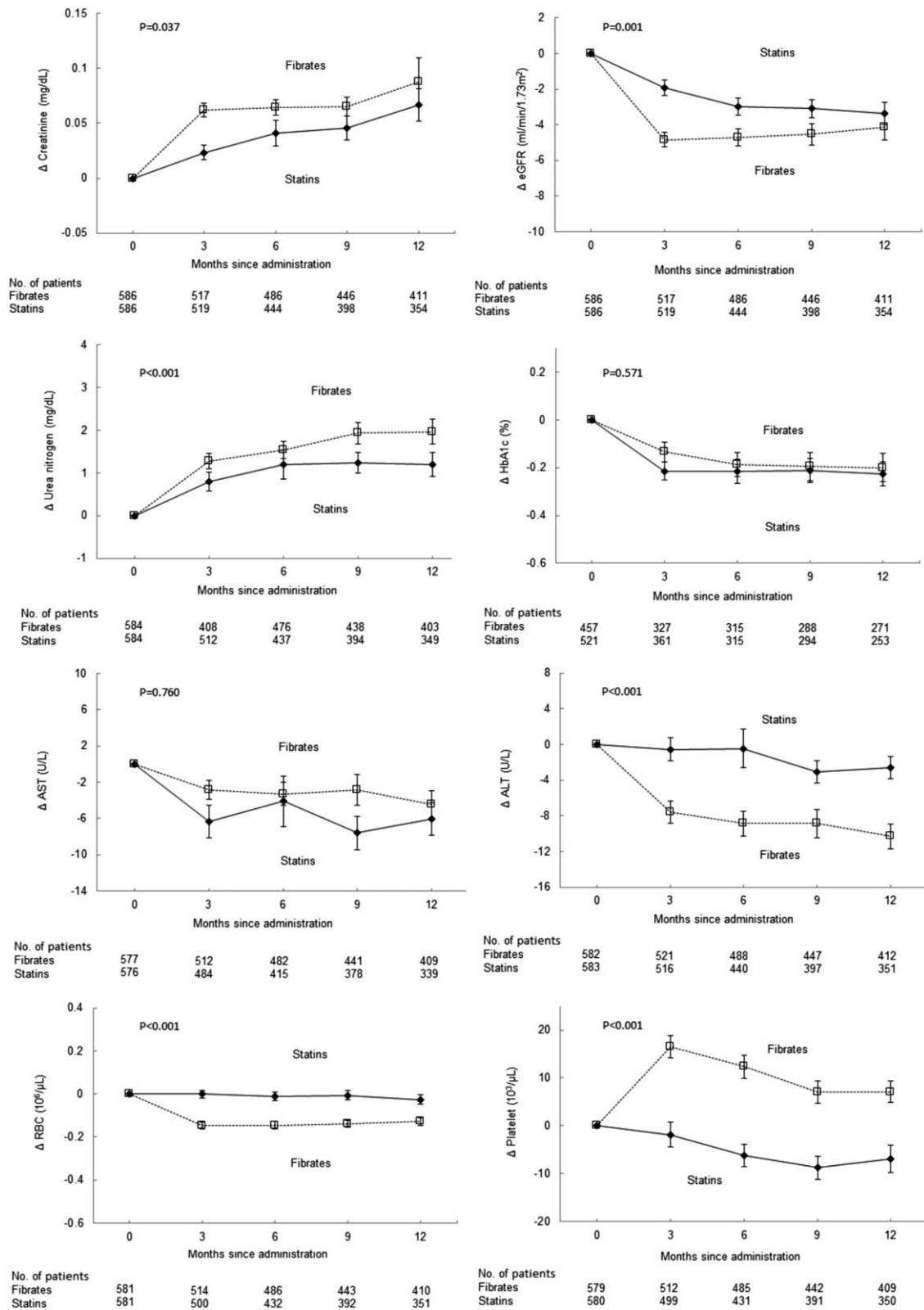
Figure 4. Change from baseline of laboratory parameters in LDL cholesterol-matched pairs. Data points are least-squares mean changes from baseline of laboratory parameters during exposure period. I bars indicate standard errors. Δ indicates change from baseline of laboratory parameters during exposure period. Open squares indicate fibrate users and solid circles indicate statin users. To compare the effects on laboratory parameter levels between statin monotherapy and fibrate monotherapy, generalized estimating equations were used, with fibrate monotherapy as the reference group. Analyses were adjusted for the propensity score, treatment duration, and baseline values of each laboratory parameter and triglyceride. ALT = alanine aminotransferase, AST = aspartate aminotransferase, eGFR = estimated glomerular filtration rate, HbA$_{1c}$ = hemoglobin A$_{1c}$, LDL = low-density lipoprotein, RBC = red blood cell.

clinical practice. This study was not designed to assess the effects of statins and fibrates at each dosage, because it is difficult to determine whether or not pharmacodynamics are dose-dependent in clinical settings. Fourth, we compared the effects of statins and fibrates in this study. However, the effect of statins on proteinuria and renal function differs among individual statins.[10] The comparative effects of treatment with various statins, such as high potency vs low potency, lipophilic vs hydrophilic, or among individual statins, are of interest, and further studies are needed to compare the effects of individual drugs on laboratory parameters, including parameters of renal function, hepatic function, and glucose metabolism. Fifth, the sample size markedly differed between statin and fibrate users, and the number of statin users was much larger before the matching procedure in this study. Physicians prefer to lower LDL cholesterol level rather than TG level, and statins are frequently used as the first-line drug for dyslipidemia. Therefore, this unbalanced sample size between statin and fibrate users might reflect their market shares in Japan. Sixth, to increase statistical precision and efficiency, we used individual matching to identify a statin user for each fibrate user according to sex, age, and TG level or LDL cholesterol level at baseline. We succeeded in selecting one statin user for each fibrate user in this study, but excluded a large number of statin users who did not meet all the matching criteria. This may be explained in part by differences in components of the lipid profile, which inherently differ between statin and fibrate users through different mechanisms of action and different treatment targets. Thus, more than 90% of statin users were excluded from the analysis in this study, limiting the ability to generalize the results.

4.2. Future directions

The concern that the differences of lipid profiles between statin and fibrate users may impact the outcomes comparing the effects of statins and fibrates on laboratory parameters is not completely resolved. In the future, further studies using a dataset with both matched TG level and LDL cholesterol level are needed, when sufficient data are accumulated. Also, the findings of our study, based on a nonrandomized design, call for further studies, such as similar analyses of larger international databases and randomized clinical trials, for confirmation.

5. Conclusions

We demonstrated that fibrates have a greater effect of increasing creatinine and urea nitrogen levels and of reducing eGFR, ALT level, and RBC count than statins, and that the lowering effect on PLT count is greater with statins than with fibrates.

Acknowledgments

Author contributions

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