Original Article

Effects of Pitavastatin (LIVALO Tablet) on the Estimated Glomerular Filtration Rate (eGFR) in Hypercholesterolemic Patients with Chronic Kidney Disease

— Sub-analysis of the LIVALO Effectiveness and Safety (LIVES) Study

Kenjiro Kimura[1], Hitoshi Shimano[2], Koutaro Yokote[3], Mitsuyoshi Urashima[4], and Tamio Teramoto[5]

[1]Department of Nephrology and Hypertension, Internal Medicine, St. Marianna University School of Medicine, Kanagawa, Japan
[2]Department of Internal Medicine (Metabolism and Endocrinology), Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ibaraki, Japan
[3]Department of Clinical Cell Biology and Medicine, Chiba University Graduate School of Medicine, Chiba, Japan
[4]Division of Molecular Epidemiology, Jikei University School of Medicine, Tokyo, Japan
[5]Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan

***Aim*: In addition to the risk of progression to end-stage renal disease (ESRD), chronic kidney disease (CKD) is also known to be associated with an elevated risk of cardiovascular disease (CVD). Statins may improve renal function in CKD patients.**

***Methods*: The database of the LIVALO Effectiveness and Safety (LIVES) Study, a large-scale (n=20,279), long-term (104 weeks), prospective post-marketing surveillance study of hypercholesterolemic patients treated with pitavastatin, was used to evaluate the effects of pitavastatin on the estimated glomerular filtration rate (eGFR).**

***Results*: Of the 19,925 patients enrolled in the aforementioned study, data from 3,119 patients were analyzed to evaluate the effects of pitavastatin treatment for 104 weeks on the eGFR. In this sub-analysis, 958 patients with a baseline eGFR of less than 60 mL/min/1.73 m^2 (30.7%) were analyzed. A significant increase of the eGFR (+5.4 mL/min/1.73 m^2) was observed after 104 weeks of pitavastain treatment (p<0.001; one-sample t-test). In the analysis of the time-course of changes in the eGFR in response to pitavastatin treatment, the eGFR was elevated by 2.4 mL/min/1.73 m^2 after 12 weeks' treatment, and by 5.6 mL/min/1.73 m^2 after 104 weeks' treatment (p<0.001; repeated measures ANOVA). The results of multivariate analysis identified the presence/absence of proteinuria and the amount change of HDL-C as clinical factors associated with increased eGFR during pitavastatin treatment.**

***Conclusions*: Increased eGFR was noted after 104 weeks of treatment with pitavastatin, which suggests a possible effect of the statin on CKD.**

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Key words; Statin, HMG-CoA reductase inhibitor, Estimate of glomerular filtration rate, Urinary protein

Introduction

In addition to the risk of progression to end-stage renal disease (ESRD), chronic kidney disease (CKD) has also been reported to be associated with an elevated risk of cardiovascular disease (CVD)[1-3]. A recent study reported an increased risk of coronary heart disease (CHD) in patients with CKD[4]. In Japan, patients with an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 have been estimated to account for about 10% of the entire population[5, 6]. Early diagnosis and prompt treatment of

Address for correspondence: Tamio Teramoto, Department of Internal Medicine, Teikyo University School of Medicine, 2-11-1, Kaga, Itabashi, Tokyo, Japan
E-mail: ttera@med.teikyo-u.ac.jp
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CKD are important for the prevention of CVD and reduction of mortality and morbidity[1].

In a sub-analysis of the Treating to New Targets (TNT) study, treatment with 10 mg and 80 mg atorvastatin was found to increase the eGFR by 3.5 mL/min/1.73 m^2 and 5.2 mL/min/1.73 m^2, respectively[7]. In contrast, in the Prevention of Renal and Vascular ENd-stage Disease Intervention trial (PREVEND-IT), treatment with 40 mg pravastatin did not result in any change of the eGFR[8]. Thus, the beneficial effect of statins on the eGFR remained controversial.

The LIVALO Effectiveness and Safety (LIVES) Study was a large-scale, long-term, prospective post-marketing surveillance study of pitavastatin[9]. Since it included more than 20,000 hypercholesterolemic patients and was a prospective surveillance study, the database of the LIVES Study is considered to be useful for evaluation of the efficacy and safety of pitavastatin in routine clinical practice. Sub-analysis of the LIVES Study showed that pitavastatin significantly increased serum HDL-C[10]. In the present study, using the LIVES Study database, we analyzed the effect of pitavastatin on the eGFR in patients with a baseline eGFR of <60 mL/min/1.73 m^2.

Subjects and Methods

Survey Participants

The design and results of the LIVES Study have been reported previously[9]. Patients with hypercholesterolemia, including familial hypercholesterolemia, were enrolled in this study using a central registration system, with each patient enrolled within 14 days of the start of treatment with pitavastatin. Patients were observed for 2 years after the start of treatment. Of the 20,279 patients recruited, 19,925 were included in the safety analysis and 18,031 in the efficacy analysis of pitavastatin.

The major objective of the LIVES Study was to investigate the occurrence of any unknown adverse reactions and to evaluate the incidence and pattern of adverse reactions of pitavastatin. In the 19,925 patients included in the safety analysis, the eGFR was calculated in patients for whom all data were available after 104 weeks' treatment with pitavastatin. Seven patients with serum creatinine levels above the normal range were excluded from the analysis as outliers.

eGFR Analysis

eGFR was assessed using the new Japanese revised equation[11], as follows:

$$\text{eGFR (mL/min/1.73 m}^2) = 194 \times \text{Cr}^{-1.094} \times \text{Age}^{-0.287} \ (\times 0.739, \text{ if female}).$$

According to the baseline eGFR, the patients were classified into CKD stages as defined in the K/DOQI guideline[12], as follows: stage 1 (≥ 90), stage 2 ($\geq 60 - < 90$), stage 3 ($\geq 30 - < 60$), stage 4 ($\geq 15 - < 30$), and stage 5 (< 15). Patients with baseline eGFR values < 60 mL/min/1.73 m^2 were enrolled for sub-analysis. Furthermore, the time-course of changes in the eGFR was evaluated at 0, 12, 28, 52 and 104 weeks in patients with a baseline eGFR of 60 mL/min/1.73 m^2 for whom all data were available after 104 weeks of pitavastatin treatment. The time-course of changes in the eGFR was analyzed using repeated measures ANOVA.

Lipid Profile Analysis

The percent changes of serum TC, LDL-C, TG (in the entire study population and in the high TG group (≥ 150 mg/dL) at baseline), HDL-C (in the entire study population and in the low HDL-C group (< 40 mg/dL) at baseline), non-HDL-C and LDL-C/HDL-C were calculated in patients with a baseline eGFR of < 60 mL/min/1.73 m^2. The serum concentration of LDL-C was estimated using the Friedewald formula (LDL-C = TC-HDL-C-TG $\times$ 0.2)[13] in patients with serum TG concentrations of less than 400 mg/dL. Correlations between the degree of change in the eGFR and that of the changes in the serum TC, LDL-C, TG, HDL-C, non-HDL-C and LDL-C/HDL-C were analyzed in patients with a baseline eGFR of less than 60 mL/min/1.73 m^2.

Analysis of the Clinical Factors Affecting Changes in the eGFR during Pitavastatin Treatment

The clinical factors affecting the changes in the eGFR during pitavastatin treatment were analyzed in patients with a baseline eGFR of < 60 mL/min/1.73 m^2. The patient baseline characteristics (gender, age, BMI and smoking history), presence/absence of underlying diseases (hypertension, diabetes and heart disease), presence/absence of proteinuria by the urinary dipstick test (+- or more), history/no previous history of lipid-lowering medication, the initial dose of pitavastatin, and the amount change of serum lipids (LDL-C, TG, and HDL-C) were entered into a multivariate regression model for this analysis.

Statistical Analysis

All data were expressed as the mean $\pm$ standard deviation. Statistical analysis was performed with a one-sample *t* test or paired *t* test, or a two-sample *t* test, as appropriate. One-way analysis of variance (ANOVA) and linear regression analysis were performed to analyze the time-course of changes in the

eGFR. In factorial analysis, changes in the eGFR were analyzed after adjustment for the baseline eGFR by ANOVA (*F*-test). Furthermore, multivariate analysis was applied by the stepwise method to identify factors that affected changes in the eGFR during treatment. JMP ver. 5.1.1 was used for all statistical analyses. The significance level was set at 0.05 (two-sided).

Results

Effects on Renal Function

Of the 19,925 patients, 3,119 for whom the relevant data were available were included to evaluate changes in the eGFR after 104 weeks pitavastatin treatment. The patients were classified into CKD stages according to the baseline eGFR. The number of patients in each stage is shown in **Table 1**. Of the patients included in this analysis, the baseline eGFR was ≥60 mL/min/1.73 m^2 in 2,161 patients and <60 mL/min/1.73 m^2 in 958 patients. The demographic characteristics of these patients are shown in **Table 2**. The two groups were similar except for the mean age, hyperlipidemia phenotype, and prevalence of hypertension and renal disease. Patients with an eGFR of <60 mL/min/1.73 m^2 were included for the following analysis as cases of impaired renal function.

Table 1. Distribution of eGFR

eGFR (mL/min/1.73 m^2)	patients	%	mean eGFR (mL/min/1.73 m^2)
≧90	421	13.5	102.2
60≦<90	1,740	55.8	72.7
30≦<60	888	28.5	50.3
15≦<30	41	1.3	24.6
<15	29	0.9	5.2

The changes in the eGFR at 104 weeks are shown in **Fig. 1**. A significant increase in the eGFR from 47.8 ± 11.5 to 53.2 ± 18.6 mL/min/1.73 m^2 (+5.4 mL/min/1.73 m^2) was observed at 104 weeks ($p<0.001$). The average increase of the eGFR at 104 weeks was 6.3 mL/min/1.73 m^2 in treatment-naive patients ($n=731$, $p<0.001$) and 2.3 mL/min/1.73 m^2 in patients with a history of treatment with other cholesterol-lowering drugs ($n=227$, $p<0.01$) (data not shown). The increase in the eGFR at 104 weeks was 3.2 mL/min/1.73 m^2 in patients under treatment with an ACE inhibitor or ARB (baseline eGFR = 45.9 ± 12.6 mL/min/1.73 m^2, $n=470$, $p<0.001$), and 7.5 mL/min/1.73 m^2 in patients not under treatment with these classes of drugs (baseline eGFR = 49.7 ± 10.1 mL/min/

Table 2. Patient demographic characteristics

Item		Patients with eGFR ≧60 mL/min/1.73 m^2	Patients with eGFR <60 mL/min/1.73 m^2
No. of patients surveyed		2,161	958
Female		1,451 (67.1)	621 (64.8)
Age (years)		62.9 ± 10.8	68.8 ± 10.2
BMI (kg/m^2)		24.4 ± 3.7	24.4 ± 3.3
Hyperlipidemia phenotype	IIa	1,161 (53.7)	460 (48.0)
	IIb	907 (42.0)	436 (45.5)
Co-morbid conditions		1,810 (83.8)	836 (87.3)
Hypertension		1,134 (52.5)	583 (60.9)
Diabetes		759 (35.1)	308 (32.2)
Heart disease		329 (15.2)	207 (21.6)
Liver disease		211 (9.8)	73 (7.6)
Renal disease		43 (2.0)	124 (12.9)
Smoking history		261 (12.1)	105 (11.0)
Previous history of lipid-lowering medication		502 (23.2)	227 (23.7)
Initial daily dose	1 mg	845 (39.1)	374 (39.0)
	2 mg	1,305 (60.4)	577 (60.2)
	4 mg	11 (0.5)	6 (0.6)
Most frequent daily dosage	1 mg	855 (39.6)	380 (39.7)
	2 mg	1,267 (58.6)	557 (58.1)
	4 mg	32 (1.5)	8 (0.8)

( ): %

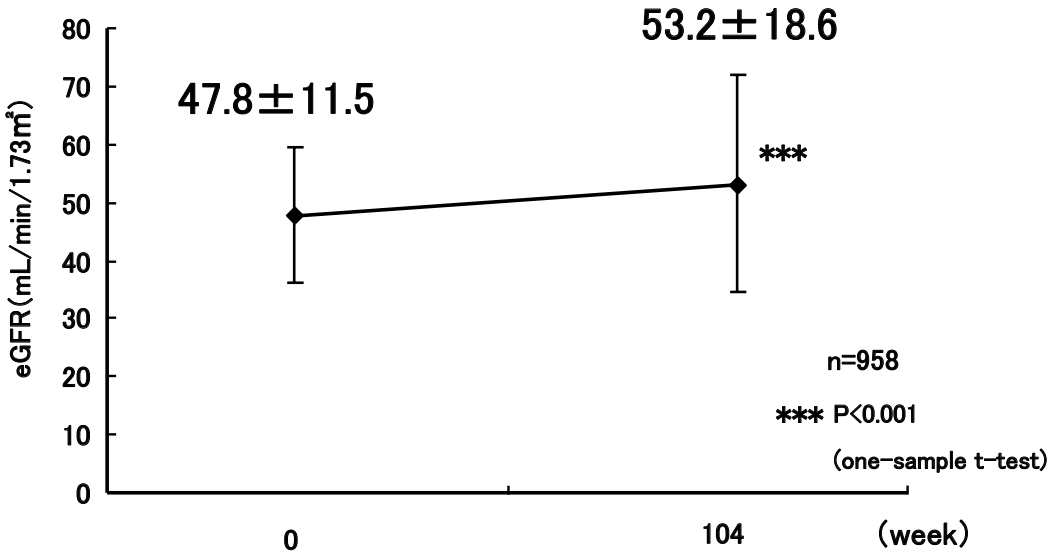
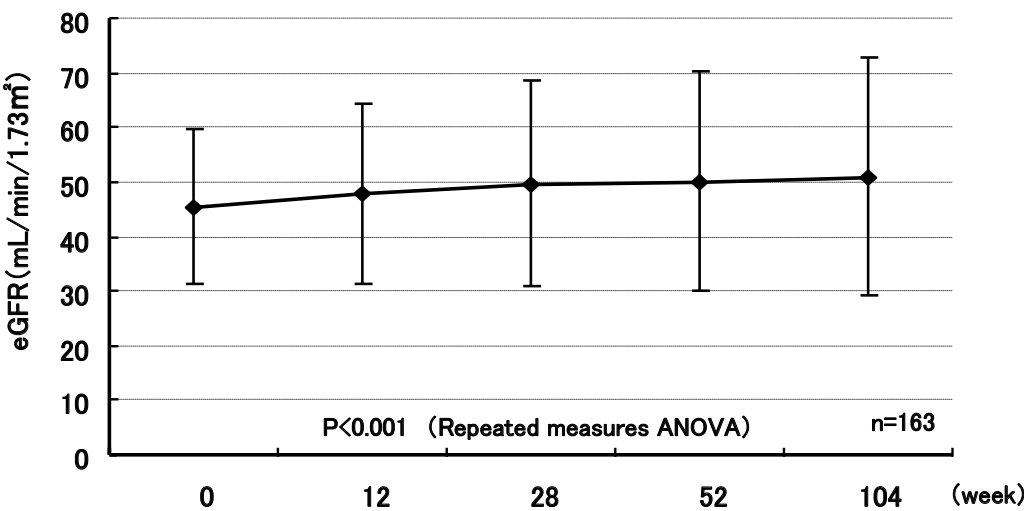


Fig. 1. Effect of pitavastatin on the eGFR. Baseline eGFR < 60 mL/min/1.73 m^2. Values are the mean ± SD



Degree of change of the eGFR (mL/min/1.73m²)	0	2.4±7.6	4.4±10.7	4.8±13.2	5.6±15.0
Percent change of the eGFR (%)	0	4.8±17.0	8.8±24.2	9.9±31.3	10.5±33.0

Fig. 2. Time-course of changes of the eGFR.Baseline eGFR < 60 mL/min/1.73 m^2. Values are the mean ± SD

1.73 m^2, n=488, p<0.001) (data not shown). Furthermore, in regard to the time-course of changes in the eGFR during pitavastatin treatment, the increase in the eGFR was 2.4 mL/min/1.73 m^2 at 12 weeks, and 5.6 mL/min/1.73 m^2 at 104 weeks (p<0.001; Repeated measures ANOVA) (**Fig. 2**).

Effects of Pitavastatin Treatment on Plasma Lipid Levels

The percent changes in serum lipid levels at 104 weeks are listed in **Table 3**. A significant reduction of the serum TC (−22.5%) and LDL-C (−31.3%) was observed at 104 weeks. Serum non-HDL-C and LDL-C/HDL-C were also reduced significantly (p<0.0001)

Table 3. Changes in lipid levels (eGFR < 60 mL/min/1.73 m^2)

	No. of patients	Period	Lipid value (mg/dL) (Mean ± SD)	% change from baseline (Mean ± SD)	p value*
TC	914	Baseline 104 weeks	254.0 ± 41.6 193.4 ± 34.3	− 22.5 ± 15.5	< 0.0001
LDL-C#	341	Baseline 104 weeks	165.7 ± 37.4 109.0 ± 28.5	− 31.3 ± 24.1	< 0.0001
TG	903	Baseline 104 weeks	186.8 ± 126.7 152.1 ± 88.2	− 6.4 ± 50.6	< 0.001
TG (Baseline value ≧ 150 mg/dL)	494	Baseline 104 weeks	253.3 ± 137.7 182.5 ± 98.3	− 21.8 ± 38.1	< 0.0001
HDL-C	739	Baseline 104 weeks	56.8 ± 16.7 59.2 ± 16.0	6.6 ± 20.5	< 0.0001
HDL-C (Baseline value < 40 mg/dL)	91	Baseline 104 weeks	34.7 ± 4.0 41.9 ± 7.7	21.5 ± 22.3	< 0.0001
non-HDL-C	714	Baseline 104 weeks	197.6 ± 42.7 133.8 ± 32.9	− 30.2 ± 19.5	< 0.0001
LDL-C#/HDL-C	341	Baseline 104 weeks	3.1 ± 1.2 1.9 ± 0.8	− 33.1 ± 26.5	< 0.0001

#LDL-C was estimated by the Friedewald formula. *one-sample t-test

at 104 weeks. The percent reduction of serum TG was 6.4% in the entire population, but 21.8%, much higher, in the high TG group (≥150 mg/dL). The percent increase of serum HDL-C was 6.6% ($p < 0.0001$) in the entire population, but 21.5%, much higher ($p < 0.0001$), in the low HDL-C group (<40 mg/dL).

There were no significant correlations between the changes of the eGFR and those of serum TC, LDL-C, TG, non-HDL-C or LDL-C/HDL-C (**Table 4**). A weak correlation was observed between the change in the eGFR and that of serum HDL-C following pitavastatin treatment ($r = 0.092$; $p = 0.013$).

Table 4. Correlation between eGFR and lipid level changes (eGFR < 60 mL/min/1.73 m^2)

Variable	No. of patients	Coefficient (r)	p value*
TC	914	− 0.049	0.136
LDL-C#	341	− 0.049	0.365
TG	903	− 0.047	0.160
HDL-C	739	0.092	0.013
non-HDL-C	714	− 0.068	0.071
LDL-C#/HDL-C	341	− 0.057	0.297

#LDL-C was estimated by the Friedewald formula. *t-test

Analysis of the Clinical Factors Affecting Changes in the eGFR During Pitavastatin Treatment

The clinical factors affecting changes in the eGFR during pitavastatin treatment are shown in **Table 5**. According to the results of ANOVA (F-test), gender, age, presence/absence of hypertension, diabetes, heart disease, proteinuria, and history/no previous history of lipid-lowering medication were identified as significant factors affecting changes in the eGFR during pitavastatin treatment.

Multivariate analysis by the stepwise method was used to identify the factors influencing changes in the eGFR during pitavastatin treatment. The results identified the presence/absence of proteinuria and the amount change of HDL-C as significant factors influencing changes in the eGFR during pitavastatin treatment (**Table 6**). Changes in the eGFR in the presence/absence of hypertension, diabetes, and proteinuria are shown in **Fig. 3**. The increase in the eGFR in patients with diabetes/hypertension was less than that in patients without diabetes/hypertension. Similar results were obtained in patients with/without proteinuria.

Safety

Of the 19,925 patients included in the safety evaluation in the LIVES study, 2,069 patients (10.4%) developed adverse drug reactions[9]. Of the 3,119 patients included in the present analysis, 173 (5.5%) developed adverse drug reactions. Myopathy-associated adverse reactions were seen in 74 patients (2.4%), and hepatic adverse reactions in 68 patients (2.2%).

Table 5. Analysis of the clinical factors affecting the eGFR Adjusted eGFR baseline

Variable	Number of patients		Difference or Level	Difference in the degree of change of the eGFR	*p* value*
Gender	Female/male	621/337	Female	2.39	0.0076
Age	≧65/＜65	672/286	≧65	−1.92	0.0401
BMI	≧25 kg/m^2/＜25 kg/m^2	265/412	≧25 kg/m^2	−0.68	0.5263
Hypertension	Yes/No	583/375	Yes	−3.68	＜0.0001
Diabetes	Yes/No	308/650	Yes	−4.31	＜0.0001
Heart disease	Yes/No	207/751	Yes	−3.22	0.0021
Smoking history	Yes/No	105/851	Yes	−0.79	0.5635
Proteinuria	Yes/No	156/407	Yes	−6.83	＜0.0001
Previous history of lipid-lowering medication	Yes/No	227/731	Yes	−3.73	0.0002
Initial daily dose	2 mg/day/1 mg/day	577/374	2 mg/day	0.88	0.3166

*ANOVA (*F* test)

Table 6. Analysis to identify the clinical factors affecting the eGFR (multivariable analysis) Adjusted eGFR baseline

Variable		Difference or Level	Difference in the degree of change of the eGFR	*p* value*
Previous history of lipid-lowering medication	Yes/No	Yes	−1.98	0.2013
Diabetes	Yes/No	Yes	−2.74	0.0512
Proteinuria	Yes/No	Yes	−4.65	0.0029
HDL-C		1 mg/dL	0.17	0.0032

*ANOVA (*F* test)

Discussion

In this study, a significant increase of the eGFR was seen after pitavastatin treatment for 104 weeks in hypercholesterolemic patients with a baseline eGFR of ＜60 mL/min/1.73 m^2. In view of the decrease of the eGFR by 0.36 mL/min/1.73 m^2 per year in healthy Japanese subjects[14], the increase in eGFR by 5.4 mL/min/1.73 m^2 induced by pitavastatin treatment after 104 weeks in patients with a baseline eGFR of ＜60 mL/min/1.73 m^2 is noteworthy. The increase in the eGFR observed after pitavastatin treatment in the present study is similar to that reported for other statins, i.e. 3.5 and 5.2 mL/min/1.73 m^2 for 10 mg and 80 mg atorvastatin[7] and 4.8 mL/min/1.73 m^2 for rosvastatin[15]. Thus, it was confirmed in this study that the increase in eGFR is a class effects of statins. Athyros *et al.* reported that the increase in the eGFR induced by statins was also related to a reduction in the hazard ratio for CHD[16]. In sub-analysis of the TNT trial[4, 7], 80 mg atorvastatin produced greater elevation of the eGFR and reduction of the CVD risk than 10 mg atorvastatin in patients with CKD.

The possible mechanisms underlying the increase in the eGFR induced by statins have been reported in several papers and include improvement of the endothelial function[17]. Statins have also been suggested to increase renal blood flow and suppress monocyte recruitment, mesangial cell proliferation, and inflammation[18]. Nakamura *et al.* reported that pitavastatin reduced urinary albumin and liver-type fatty acid-binding protein (L-FABP) in patients with early diabetic nephropathy, which might be attributable to the antioxidant effects of pitavastatin[19]. In spontaneously hypercholesterolaemic Imai rats, pitavastatin showed a renal protective effect via reduction of the urinary protein and antioxidant actions, independent of the lipid-lowering effects[20]. Thus, we assume that the increased eGFR observed in the present study could be attributed to the pleiotropic effects of pitavastatin. Meanwhile, changes in the eGFR were significantly related with those of serum HDL-C in this analysis, although the correlation coefficient was small. Also, the amount change of HDL-C was identified as a significant factor

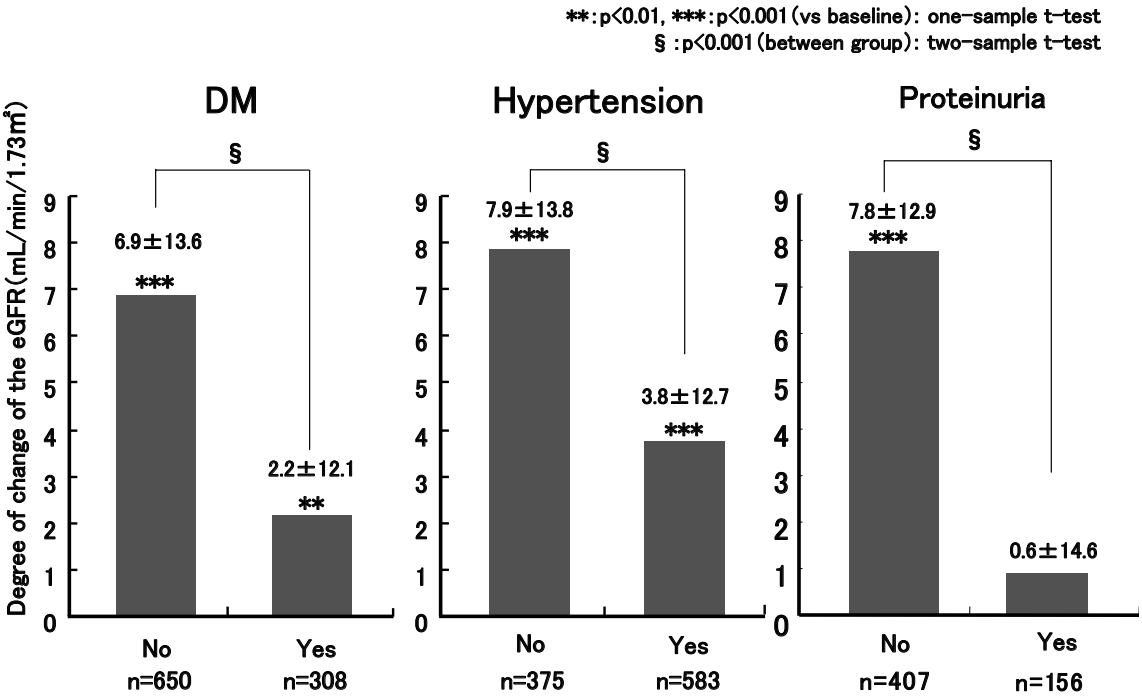


Fig. 3. Change of the eGFR in patients with each factor. Baseline eGFR < 60 mL/min/1.73 m^2. Values are the mean ± SD

influencing changes in the eGFR during pitavastatin treatment; therefore, the increase of HDL-C might be attributed to the increase of the eGFR. In fact, the results of sub-analysis of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study suggested a relation between increased serum HDL-C and increased eGFR following atorvastatin treatment[21]. The antioxidant effects of HDL-C were considered to possibly underlie this correlation[22]; however, further analysis is needed to clarify the mechanism underlying the increase of the eGFR induced by pitavastatin.

At the baseline, the percentage of patients with an eGFR < 60 mL/min/1.73 m^2 was 30.7% in this sub-analysis, higher than that estimated in the Japanese general population, which is about 10%[5, 6]. Therefore, it may be assumed that CKD is more prevalent in hypercholesterolemic patients than in the general population. Indeed, in a sub-analysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study[23] conducted in mild hypercholesterolemic patients, the percentage of patients with an eGFR between 30 and 60 mL/min per 1.73 m^2 was higher than in the general population.

In factorial analysis of the current sub-analysis, proteinuria was identified as a significant factor attenuating the elevation of the eGFR observed during pitavastatin treatment. Proteinuria is known as a major factor related to the decline of eGFR and the progression of renal disease[14, 24]; therefore, it is understandable why patients with proteinuria showed a less pronounced effect of pitavastatin in increasing the eGFR in this study. Diabetes was identified as a factor attenuating the elevation of eGFR during pitavastatin treatment with borderline significance (p=0.0512). Diabetes is well known to be associated with the progressive impairment of renal function. The rate of renal function deterioration in CKD patients is higher in those with than without diabetes[25]. The increase of the eGFR in patients taking an ACE inhibitor or ARB was lower than in patients not under treatment with these classes of drugs. The baseline eGFR in patients with an ACE inhibitor or ARB was significantly lower than in patients without an ACE inhibitor or ARB; therefore, patients taking an ACE inhibitor or ARB might show less increase of eGFR because of severe renal dysfunction; however, it is also possible that ACE-I/ARB treatment affects the potency of pitavastatin for the eGFR directly.

In this study, we analyzed the effects of pitavastatin on the eGFR under actual use conditions using the database of the LIVES Study. Since the LIVES Study is post-marketing surveillance study, there is no

control group; thus, a further randomized controlled trial is needed to confirm the effects of pitavastatin on the eGFR.

In conclusion, pitavastain showed a significant increase of the eGFR after treatment for 104 weeks, suggesting that pitavastatin might maintain the glomerular filtration rate and also contribute to reduce the risk of CVD in patients with CKD. Further prospective long-term clinical trials are needed for more precise evaluation of the effects of pitavastatin on renal function.

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