

# Effects of Pemafibrate in Patients with Stroke and Hypertriglyceridemia: Baseline Cerebral Artery Diseases and 3-Month Laboratory Outcomes

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**Aims:** The role of hypertriglyceridemia in stroke is poorly understood. The Pemafibrate for Prevention of Atherosclerotic Diseases in Stroke (PPAR Stroke) study was designed to assess the effects of a novel selective peroxisome proliferator-activated receptor alpha modulator, pemafibrate, on vascular outcomes in stroke patients with hypertriglyceridemia.

**Methods:** This was a prospective single-arm study including 74 patients (mean age, 64.1 years; male 75.7%) with stroke and hypertriglyceridemia (defined as fasting serum triglycerides levels of  $\geq 150$  mg/dL) who were treated with pemafibrate at 0.2 mg or 0.1 mg/day. The present report assessed the association of hypertriglyceridemia with cerebral large and small vessel diseases at baseline and changes in laboratory parameters after a three-month pemafibrate therapy.

**Results:** Patients with triglycerides levels of  $\geq 227$  mg/dL (higher than the median) more often presented with intracranial artery atherosclerotic stenosis than those with triglycerides levels of 150–227 mg/dL (44.4% vs. 21.6%,  $p=0.037$ ). On the other hand, no differences were found in the prevalence of extracranial artery atherosclerosis and cerebral small vessel diseases. Mean triglycerides levels were significantly reduced from 285 mg/dL at baseline to 175 mg/dL at 3 months ( $p<0.001$ ). High-density lipoprotein cholesterol levels increased from 48 mg/dL to 53 mg/dL ( $p<0.001$ ). In addition, significant reductions in alanine aminotransferase,  $\gamma$ -glutamyl transpeptidase, and interleukin-6 levels were observed ( $p<0.001$ ,  $p=0.002$ , and  $p=0.044$ , respectively).

**Conclusions:** Higher triglycerides levels are associated with intracranial artery atherosclerosis. Pemafibrate showed pleiotropic effects not only in ameliorating atherogenic dyslipidemia but also in the reduction of the levels of inflammatory markers and hepatobiliary enzymes.

**Key words:** Anti-inflammatory, Cerebrovascular disease, Pemafibrate, Peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ), Triglycerides

## Introduction

The reduction of low-density lipoprotein cholesterol (LDL-C) is an established strategy for stroke prevention<sup>1</sup>. On the other hand, less attention has been paid to the effects of triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) on the risk of stroke. Epidemiological studies have demonstrated that both high TG and low HDL-C concentrations are associated with the risk of incident

stroke and other vascular events<sup>2</sup>). Moreover, atherogenic dyslipidemia, which designates high TG with low HDL-C levels, is predictive of recurrent vascular events in patients with stroke or transient ischemic attack (TIA)<sup>3, 4</sup>. However, there are not sufficient evidences that support cardiovascular benefits from treating atherogenic dyslipidemia thus far. Fibrates, peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ) agonists, have been the most effective agents for lowering TG and modestly increasing

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HDL-C levels. Several randomized trials of fibrates found conflicting results; some reported positive results, but others did not<sup>5</sup>). As such, current guidelines do not strongly recommend TG and HDL-C as therapeutic targets. Consequently, atherogenic dyslipidemia is often undertreated in clinical practice.

One of the limitations of fibrate therapy could be the relatively weak selectivity and activity of PPAR $\alpha$ . In addition, fibrates can cause side effects such as liver dysfunction and an increase in creatinine levels. To resolve these issues, a novel selective PPAR $\alpha$  modulator (SPPARM $\alpha$ ), pemafibrate, was developed, which differs from other currently available PPAR $\alpha$  agonists in terms of structure, the profile of activity, robust reduction in TG levels, and a favorable safety profile<sup>6, 7</sup>). SPPARM $\alpha$  is a new therapeutic class for the treatment of hypertriglyceridemia, possibly leading to the reduction of residual vascular risk.

The use of pemafibrate was launched in Japan in 2018, ahead of other countries. Clinical outcome data on pemafibrate are still scarce, especially in stroke patients. The Pemafibrate for Prevention of Atherosclerotic Diseases in Stroke (PPAR Stroke) study was designed to evaluate the vascular outcomes of stroke patients with hypertriglyceridemia who were treated with pemafibrate. The present report describes the association between hypertriglyceridemia and cerebral vessel disease and laboratory outcomes after a three-month pemafibrate therapy, which represents early experiences of pemafibrate use in stroke patients. In addition to the metabolic profiles, we evaluated the changes in inflammatory markers such as interleukin-6 (IL-6) and high-sensitivity C-reactive protein, given their pivotal role in the atherosclerotic process.

## Patients and Methods

The PPAR Stroke study is an ongoing, single-center, prospective, observational study that aimed to assess the effects of pemafibrate on the laboratory data, atherosclerosis progression in cervicocerebral arteries, and vascular event risk among patients with hypertriglyceridemia who had experienced an ischemic stroke or TIA. The study adhered to the ethical guidelines of the 1975 Declaration of Helsinki in line with the Ethical Guidelines for Epidemiological Research by the Japanese government and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The study protocol was approved by the ethics committee of Tokyo Women's Medical University Hospital (approval no. 5325). Written informed consent was obtained from all patients. The PPAR Stroke study was

registered at UMIN000040619 (<https://upload.umin.ac.jp>). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Eligible patients were individuals aged 20 years or older, who had experienced an ischemic stroke or TIA of non-cardioembolic origin more than one week prior to inclusion. All strokes and TIAs were diagnosed by board-certified stroke neurologists based on neurological and radiological findings. The study participants were required to have elevated TG levels of  $\geq 150$  mg in fasting conditions prior to the beginning of the pemafibrate treatment. If the patient had comorbid hyper LDL cholesterolemia, we prioritized the administration of statins and then reassessed the presence or absence of hypertriglyceridemia after at least two weeks of statin therapy. The exclusion criteria included (1) contraindications for pemafibrate (e.g., severe kidney dysfunction with estimated glomerular filtration rate  $< 40$  ml/min or serum creatinine  $> 2.5$  mg/dL, severe liver dysfunction); (2) a history or planning of carotid endarterectomy or stenting; and (3) stroke or TIA with high-risk cardioembolic sources according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria<sup>8</sup>).

Baseline data collected were demographics, medical history, physical examinations, laboratory and radiological findings, and treatment, using a structured case report form. Blood samples were collected under fasting conditions. Serum IL-6 levels were measured using the electrochemiluminescent immunoassay, reproducibility and sensitivity of which have been verified in a previous study<sup>9</sup>). All patients underwent carotid ultrasonography and brain magnetic resonance imaging (MRI) and angiography (MRA) at baseline.

## Treatment and Follow-Up

Patients were instructed to take a 0.1 mg tablet of pemafibrate twice a day. According to the manufacturer's recommendations, the dose was reduced to 0.1 mg once daily for those with a serum creatinine level of 1.5-2.5 mg/dL. Other lipid-lowering agents, such as statins, could be used together at the discretion of the attending physicians.

Follow-up visits were scheduled at three months and thereafter every year for four years after enrollment. The present study reports the baseline data and the three-month laboratory outcomes. At each follow-up visit, data on physical examinations, blood samples, compliance, concomitant treatments, any occurrence of clinical events, and a modified Rankin Scale score were collected. Carotid

ultrasonography, brain MRI, and MRA were scheduled at two-year and four-year follow-up visits.

### Evaluation of Large Artery Disease

Carotid ultrasound was performed on all patients according to standard procedures<sup>10</sup>, using a high-resolution B-mode ultrasound system (Nemio SSA-550A, Toshiba) with a 7.5-MHz transducer by trained ultrasonographers who were blinded to the purpose of this study. The intima-media thickness (IMT) of the far wall was electronically measured on both sides of the common carotid artery, carotid artery bulb, and internal carotid artery. Plaques were included in the IMT measurements. We used the mean of the right and left maximum IMTs at the three locations. We defined significant extracranial artery stenosis (ECAS) as the presence of atherosclerotic stenosis of  $\geq 50\%$  or occlusion according to the European Carotid Surgery Trial criteria<sup>11</sup>.

Intracranial arteries were examined using time-of-flight MRA using a 1.5 T MRI scanner (Ingenia 1.5 T, Philips; Magnetom Avanto fit 1.5 T, Siemens). The narrowest diameter of each stenosed vessel was measured and divided by the diameter of the normal vessel proximal to the lesion or distal to the lesion if the proximal artery was diseased. Significant intracranial artery stenosis (ICAS) was defined as  $\geq 50\%$  stenosis or occlusion. The location of ICAS was divided into anterior (i.e., internal carotid, middle cerebral, and anterior cerebral arteries) and posterior (i.e., vertebral, basilar, and posterior cerebral arteries) circulation.

### Evaluation of Small Vessel Disease

All participants were scanned using a 1.5 T MRI scanner (Ingenia 1.5 T, Philips; Magnetom Avanto fit 1.5 T, Siemens). Images were assessed by two board-certified neurologists (T.H. and K.I.) for the presence of periventricular hyperintensity (PVH), deep white matter hyperintensity (DWMH), and cerebral microbleeds (CMBs), according to the published definition<sup>12</sup>. PVH and DWMH were rated using the Fazekas scale (0-3 for each hemisphere) on fluid-attenuated inversion recovery images. The CMBs were small (generally 2-5 mm in diameter, but occasionally up to 10 mm) areas devoid of signal, with associated blooming seen on T2\*-weighted MRI. The CMBs were assessed for the number of lesions and the location (i.e., lobar, basal ganglia, or both).

### Outcomes

The primary outcome of the PPAR Stroke study was the changes in carotid IMT and atherosclerotic plaque from baseline. Prespecified secondary outcomes

included changes in laboratory parameters, progression of ICAS and cerebral small vessel disease, and occurrence of major adverse cardiovascular events (nonfatal stroke, nonfatal acute coronary syndrome, and vascular death).

### Statistical Analysis

Quantitative variables were expressed as mean (standard deviation) in cases of normal distribution or median (interquartile range). Qualitative variables were expressed as frequencies (percentages). We dichotomized patients according to the median baseline TG levels (i.e., 227 mg/dL). Bivariate comparisons were made between patients with TG levels of 150-227 mg/dL and  $\geq 227$  mg/dL, using the *t*-test or Mann-Whitney *U*-test for quantitative variables and  $\chi^2$  test or Fisher's exact test for categorical variables as appropriate. Changes in laboratory data from baseline to 3 months were analyzed using a two-tailed paired *t*-test. For all analyses, statistical significance was set at  $p < 0.05$ .

## Results

Among 78 patients enrolled between October 2019 and January 2021, 74 patients were included in the present analysis; four patients were excluded: one due to discontinuation of the study drug as a result of a decline in renal function, one due to discontinuation of the study drug as a result of muscle pain without creatine kinase elevation, one due to consent withdrawal, and one who was lost to follow-up (**Supplementary Fig. 1**). Pemafigrate was used at 0.2 mg daily in 64 patients (86.5%) and at 0.1 mg daily in 10 patients (13.5%). **Table 1** shows the baseline characteristics of the patients. Patients with TG levels of  $\geq 227$  mg/dL were more likely to be current smokers than those with TG levels of 150-227 mg/dL. **Supplementary Table 1** shows medication use at enrollment. Statins were used simultaneously in 71.6% of the patients. There were no differences in the usage rates of lipid-lowering, antihypertensive, antidiabetic, and antithrombotic agents between the two groups.

### Cerebral Large and Small Vessel Diseases

**Table 2** shows the prevalence of cerebral artery disease at baseline. Higher TG levels were not associated with IMT or significant ECAS. In contrast, significant ICAS, especially in the anterior circulation, was more prevalent in patients with TG  $\geq 227$  mg/dL than in those with TG  $< 227$  mg/dL. The degree of cerebral small vessel disease was similar between the two groups.

**Table 1.** Baseline characteristics

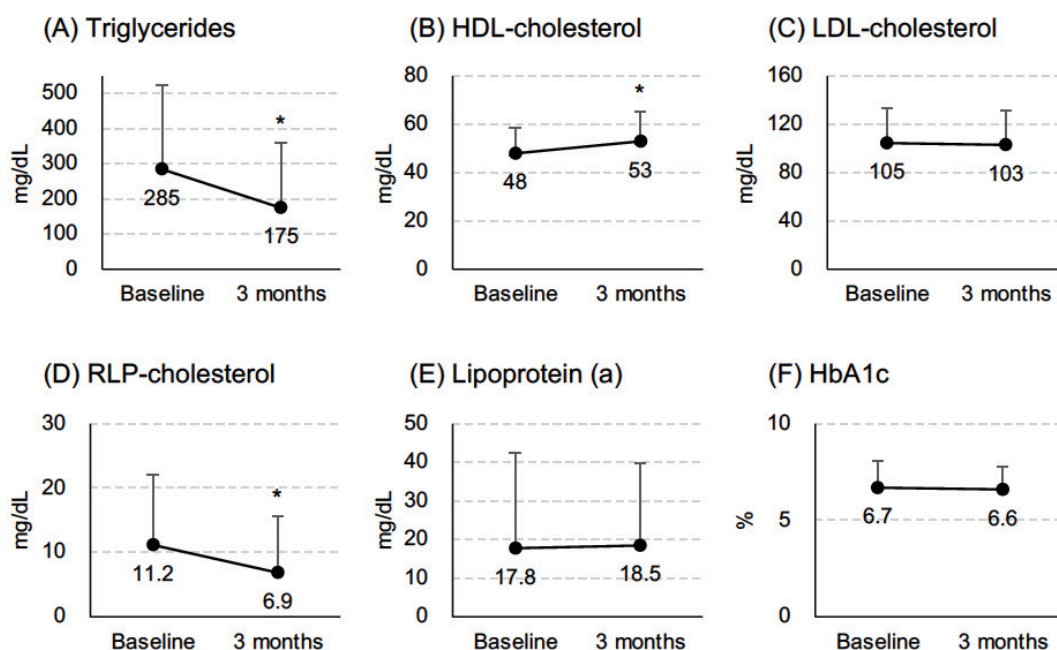
	All ( <i>n</i> = 74)	TG < 227 mg/dL ( <i>n</i> = 37)	TG ≥ 227 mg/dL ( <i>n</i> = 37)	<i>p</i> -value
Age, years	64.1 ± 13.4	66.5 ± 13.5	61.6 ± 12.9	0.12
Male	56 (75.7)	25 (67.6)	31 (83.8)	0.10
Body mass index, kg/m <sup>2</sup>	25.2 ± 4.1	24.9 ± 3.6	25.5 ± 4.6	0.53
Medical history				
Hypertension	57 (77.0)	31 (83.8)	26 (70.3)	0.16
Diabetes mellitus	27 (36.5)	12 (32.4)	15 (40.5)	0.47
Chronic kidney disease	35 (47.3)	19 (51.4)	16 (43.2)	0.48
Chronic heart failure	8 (10.8)	2 (5.4)	6 (16.2)	0.13
Coronary artery disease	8 (10.8)	3 (8.1)	5 (13.5)	0.45
Peripheral artery disease	4 (5.4)	3 (8.1)	1 (2.7)	0.29
Current smoking	7 (9.5)	1 (2.7)	6 (16.2)	0.037
Excessive alcohol	10 (13.5)	4 (10.8)	6 (16.2)	0.50
Index event				0.77
Ischemic stroke	59 (79.7)	30 (81.1)	29 (78.4)	
Transient ischemic attack	15 (20.3)	7 (18.9)	8 (21.6)	
Etiology of index event				0.63
Atherothrombosis	21 (28.4)	10 (27.0)	11 (29.7)	
Lacunar	28 (37.8)	13 (35.1)	15 (40.5)	
Other specific causes	1 (1.4)	1 (2.7)	0	
Undetermined	24 (32.4)	13 (35.1)	11 (29.7)	
Blood pressure, mm Hg				
Systolic	137 ± 16	137 ± 15	137 ± 16	0.97
Diastolic	79 ± 11	78 ± 12	79 ± 11	0.68

Figures are expressed as mean ± standard deviation or *n* (%).  
TG indicates triglycerides.

**Table 2.** Prevalence of cerebral large and small vessel diseases

	All ( <i>n</i> = 74)	TG < 227 mg/dL ( <i>n</i> = 37)	TG ≥ 227 mg/dL ( <i>n</i> = 37)	<i>p</i> -value
Large artery atherosclerosis				
Mean max IMT, mm				
Common carotid artery	1.13 ± 0.45	1.13 ± 0.41	1.15 ± 0.50	0.83
Bulb	1.70 ± 0.78	1.66 ± 0.78	1.74 ± 0.80	0.72
Internal carotid artery	1.55 ± 0.83	1.54 ± 0.83	1.56 ± 0.85	0.91
ECAS > 50%	7 (11.3)	4 (13.8)	3 (9.1)	0.56
ICAS > 50%	24 (32.9)	8 (21.6)	16 (44.4)	0.037
Anterior circulation	18 (24.3)	5 (13.5)	13 (35.1)	0.028
Posterior circulation	10 (13.5)	8 (16.2)	4 (10.8)	0.50
Small vessel disease				
PVH, Fazekas grade				
Right	1 (1-2)	1 (0-2)	1 (1-2)	0.64
Left	1 (1-2)	1 (0-2)	1 (1-2)	0.82
DWMH, Fazekas grade				
Right	1 (0.5-2)	1 (0-2)	1 (1-2)	0.51
Left	1 (1-2)	1 (0-2)	1 (1-2)	0.29
Cerebral microbleeds				
Deep	13 (17.8)	7 (18.9)	6 (16.7)	0.80
Lobar	10 (13.7)	5 (13.5)	5 (13.9)	0.96
Old lacunar infarcts	30 (41.1)	14 (37.8)	16 (44.4)	0.57

Figures are expressed as mean ± standard deviation, *n* (%), or median (interquartile range).  
DWMH indicates deep white matter hyperintensity; ECAS, extracranial artery stenosis; ICAS, intracranial artery stenosis; IMT, intima-media thickness; PVH, periventricular hyperintensity; and TG, triglycerides.



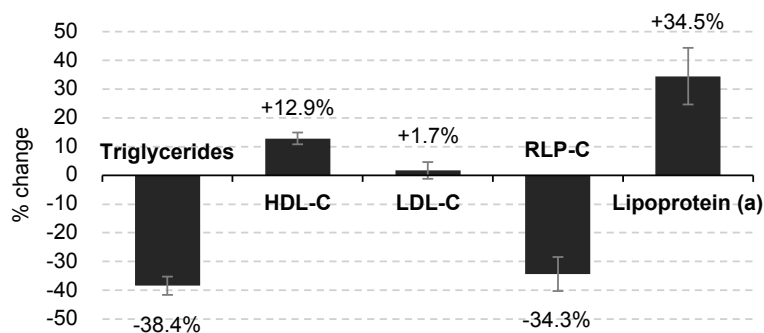
**Fig. 1.** Changes in lipid and glucose profiles

Changes from baseline at 3 months in (A) triglycerides, (B) HDL-cholesterol, (C) LDL-cholesterol, (D) RLP-cholesterol, (E) lipoprotein (a), and (F) HbA1c are shown.

Data are presented as mean and standard deviation.

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and RLP, remnant-like lipoprotein.

\* $p < 0.001$



**Fig. 2.** Percent changes in lipid profiles

Percent changes from baseline at 3 months are shown.

Data are presented as mean and standard error.

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and RLP, remnant-like lipoprotein cholesterol.

### Laboratory Outcomes

**Fig. 1** shows changes from baseline in lipid and HbA1c levels after the three-month pemafibrate treatment. Mean serum TG levels significantly decreased from 285 mg/dL to 175 mg/dL ( $p < 0.001$ ), and HDL-C levels increased from 48 mg/dL to 53 mg/dL ( $p < 0.001$ ). Remnant-like particle cholesterol (RLP-C) levels also decreased from 11.2 mg/dL to 6.9 mg/dL, whereas LDL-C, lipoprotein (a), and HbA1c

levels remained unchanged. The percent changes in TG, HDL, and RLP-C levels were 38.4%, 12.9%, and 34.3%, respectively (**Fig. 2**). The significant reduction in TG level and elevation in HDL-C level were consistent when patients were stratified by age, sex, presence or absence of diabetes, baseline TG levels, and HDL-C levels (**Table 3**).

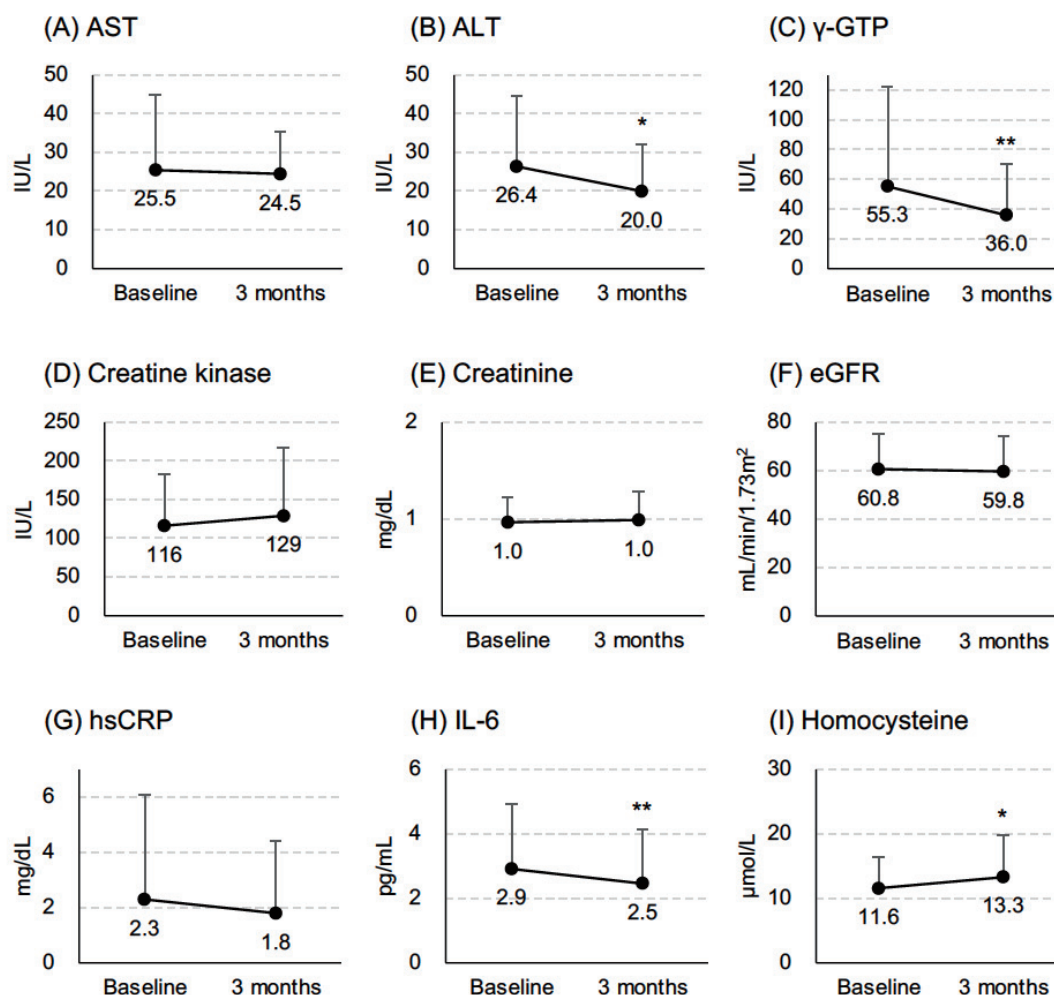
**Fig. 3** shows changes in other key laboratory parameters. Significant reductions in alanine



**Table 3.** Changes in TG and HDL-C levels by patient background

Patient background	TG, mg/dL		p-value	HDL-C, mg/dL		p-value
	Baseline	3 months		Baseline	3 months	
Age < 70 years (n = 45)	322 (299)	203 (228)	< 0.001	47 (11)	52 (13)	< 0.001
Age ≥ 70 years (n = 29)	227 (67)	128 (65)	< 0.001	49 (10)	55 (11)	< 0.001
Male (n = 56)	306 (271)	189 (210)	< 0.001	46 (11)	52 (12)	< 0.001
Female (n = 18)	218 (56)	129 (67)	< 0.001	53 (9)	59 (11)	0.004
Diabetes mellitus (n = 27)	332 (376)	213 (293)	< 0.001	44 (8)	50 (12)	< 0.001
TG < 227 mg/dL (n = 37)	186 (28)	129 (65)	< 0.001	49 (10)	55 (12)	0.001
TG ≥ 227 mg/dL (n = 37)	383 (310)	219 (248)	< 0.001	46 (11)	52 (13)	< 0.001
Low HDL-C (n = 27)	353 (373)	212 (287)	0.001	39 (7)	46 (8)	0.016

Figures are expressed as mean (standard deviation).  
HDL-C indicates high-density lipoprotein cholesterol; TG, triglycerides.



**Fig. 3.** Changes in key laboratory parameters

Changes from baseline at 3 months in (A) AST, (B) ALT, (C)  $\gamma$ -GTP; (D) creatine kinase, (E) creatinine, (F) eGFR, (G) hsCRP, (H) IL-6, and (I) homocysteine are shown.

Data are presented as mean and standard deviation.

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate;  $\gamma$ -GTP, gamma-glutamyl transpeptidase; hsCRP, high-sensitivity C-reactive protein; and IL-6, interleukin-6.

\* $p < 0.001$

\*\* $p < 0.05$

aminotransferase (ALT) and gamma-glutamyl transpeptidase ( $\gamma$ -GTP) levels were found ( $p < 0.001$  and  $p = 0.002$ , respectively). There were no significant changes in creatine kinase and renal function parameters. Regarding inflammatory markers, while high-sensitivity C-reactive protein levels did not significantly change ( $p = 0.24$ ), IL-6 levels decreased from 2.9 mg/dL to 2.5 mg/dL ( $p = 0.044$ ). A significant elevation in homocysteine levels ( $p < 0.001$ ) was observed.

## Discussion

We found that higher TG levels were associated with the presence of ICAS, but not with ECAS and cerebral small vessel disease. After months of pemafibrate therapy, serum TG and RLP-C concentrations significantly decreased and HDL-C levels increased, whereas LDL-C levels did not change. In addition, significant reductions in ALT,  $\gamma$ -GTP, and IL-6 levels were observed. Concomitant treatment with statins seemed to be well-tolerated, without creatine kinase elevation or deterioration of kidney function. Our data suggest the potential of pemafibrate in improving atherogenic dyslipidemia, as well as in treating some hepatobiliary diseases such as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), although further studies are warranted.

The higher prevalence of ICAS, but not ECAS, among hypertriglyceridemia patients is in line with previous studies that found significant associations between atherogenic dyslipidemia<sup>3)</sup> or metabolic syndrome<sup>13)</sup> and ICAS. It is unclear how the effect of hypertriglyceridemia on atherosclerotic progression differs by vascular domain. Potential explanations could be due to distinct vessel wall structure and metabolism of the intracranial arteries. Compared with extracranial arteries, thinner media, less abundant adventitia, and only a few elastic fibers have been reported for intracranial vessels<sup>14)</sup>. Such histological features can be linked to the permeability of molecules. Among stroke etiologies, ICAS carries an especially high residual risk<sup>15)</sup>, and hypertriglyceridemia may be an important therapeutic target for this subgroup of patients.

A significant reduction in TG by 38% and elevation of HDL-C by 13% are similar to results from previous phase 2 and 3 trials of pemafibrate<sup>16)</sup>. In parallel, RLP-C, which is closely related to TG metabolism, significantly decreased by 34%. It would be informative to show the changes in non-HDL-C levels, although this study did not afford it because of a lack of data on serum total cholesterol levels. The

cholesterol content of TG-rich lipoproteins (remnant cholesterol) is more likely to be the cause of atherosclerosis than the raised TG per se<sup>17)</sup>. This is because remnant lipoproteins contain 5 to 20 times more cholesterol per particle than LDL and can cross the endothelial barrier<sup>18)</sup>. Once in the intima, the remnants cause low-grade inflammation<sup>19)</sup> and foam cell formation<sup>20)</sup>, leading to the development of atherosclerotic plaques, and consequently atherothrombosis. Previous epidemiological studies indicated that serum RLP-C levels were associated with an increased risk of cerebro- and cardiovascular events<sup>21, 22)</sup>, suggesting TG-rich lipoproteins as novel therapeutic targets to reduce the residual vascular risk. To date, however, strong evidences are still lacking from randomized intervention trials targeting individuals with hypertriglyceridemia. Two randomized trials of omega-3 fatty acid therapy showed contradictory results: one reported favorable outcomes<sup>23)</sup> but the other showed no cardiovascular benefits<sup>24)</sup>. Pemafibrate may represent a new treatment class to address the residual risk, given its stronger TG-lowering and HDL-c elevation actions compared to existing agents. Cardiovascular outcomes will be assessed in an ongoing Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Diabetic Patients (PROMINENT) trial<sup>25)</sup>. In addition, our patients will be followed for up to four years to evaluate the progress of cerebral atherosclerotic diseases, as well as the risk of vascular events.

It is worth noting that IL-6 concentrations were significantly reduced by pemafibrate. IL-6 is an upstream inflammatory cytokine that plays a central role in propagating the downstream inflammatory response responsible for atherosclerosis and has been established as a predictor of cardiovascular diseases in many clinical studies<sup>26, 27)</sup>. PPAR $\alpha$  is known to bind to cytokine-activated transcription factors, such as nuclear factor-kappa B and activator protein-1, and inhibit inflammatory responses<sup>28)</sup>. Experimental data have been accumulated on the potent anti-inflammatory effects of pemafibrate<sup>29-31)</sup>. In a mouse model, pemafibrate increased macrophage cholesterol efflux to HDL-C, reduced markers of inflammation and macrophages in the aorta, and attenuated atherosclerotic lesion development<sup>29)</sup>. To our knowledge, our study is the first report of the reduction in the levels of serum inflammatory markers by pemafibrate in a clinical setting.

Another important finding was the significant reduction in ALT and  $\gamma$ -GTP levels, which is consistent with the findings of previous studies<sup>16, 32, 33)</sup>. NAFLD, a hepatic manifestation of metabolic

syndrome, has recently emerged as a major health concern due to its increasing prevalence worldwide. In addition to the risk of advanced liver disease, NAFLD confers an increased risk of cardiovascular events<sup>34</sup>. Hepatic TG accumulation contributes to the development of NAFLD and NASH<sup>35</sup>, and epidemiological data revealed a linear relationship between TG levels and NAFLD prevalence<sup>36</sup>. Moreover, patients with NASH showed a reduced expression of PPAR $\alpha$ <sup>37</sup>, suggesting PPAR $\alpha$  as a therapeutic target. In small sample studies, pemafibrate therapy exhibited preferable effects on hepatic marker enzymes in NAFLD patients<sup>32, 33</sup>. Although further evaluations are necessary, pemafibrate may be expected to be a new treatment option for NAFLD and NASH.

### Limitations

This study had several limitations. First, this was a single-center study with a relatively small sample without a control group. Second, ICAS was measured using time-of-flight MRA, which is more prone to overdiagnosis than computed tomography angiography or digital subtraction angiography. In addition, MRA is not sufficient to exclude the stenosis due to non-atherosclerotic origins such as dissection, vasculitis, or other vasculopathies. Third, the concomitant use of statins and other lipid-lowering agents, antihypertensive agents, antidiabetic agents, or antithrombotic agents could bias our results. Finally, the follow-up period was only three months, and we plan to analyze the long-term outcomes, including vascular event risk and progression of atherosclerotic disease.

### Conclusions

In this study conducted on Japanese subjects with stroke and hypertriglyceridemia, a three-month treatment with pemafibrate showed not only amelioration of atherogenic lipid profiles but also reduction in the levels of inflammatory markers and hepatobiliary enzymes.

### Acknowledgements

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### Conflict of Interest

Dr. Kitagawa reports personal fees from Kyowa Kirin, grants and personal fees from Daiichi Sankyo, grants from Bayer, and grants from Dainihon Sumitomo outside the submitted work. Other authors have nothing to disclose.

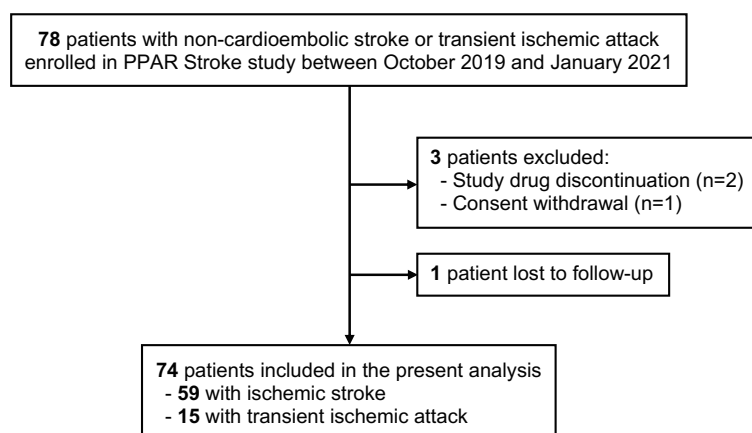
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Supplementary Fig. 1. Study flow chart

Supplementary Table 1. Medication use at baseline

	All (n = 74)	TG < 227 mg/dL (n = 37)	TG ≥ 227 mg/dL (n = 37)	p-value
Lipidloweringagent				
Statin	53 (71.6)	26 (70.3)	27 (73.0)	0.80
Ezetimibe	5 (6.8)	1 (2.7)	4 (10.8)	0.15
Eicosapentaenoicacid	3 (4.1)	1 (2.7)	2 (5.4)	0.55
Antihypertensiveagent				
Calciumchannelblocker	39 (52.7)	20 (54.1)	19 (51.4)	0.82
ARB	35 (47.3)	17 (46.0)	18 (48.7)	0.82
Diuretics	6 (8.1)	3 (8.1)	3 (8.1)	1.00
Antidiabeticagent				
Insulin	7 (9.5)	4 (10.8)	3 (8.1)	0.69
Sulfonylurea	8 (10.8)	3 (8.1)	5 (13.5)	0.45
Biguanide	11 (14.9)	3 (8.1)	8 (21.6)	0.10
α-glucosidaseinhibitor	2 (2.7)	1 (2.7)	1 (2.7)	1.00
DPP-4inhibitor	12 (16.2)	6 (16.2)	6 (16.2)	1.00
SGLT2inhibitor	6 (8.1)	4 (10.8)	2 (5.4)	0.39
GLP-1receptoragonist	3 (4.1)	1 (2.7)	2 (5.4)	0.55
Antiplateletagent				
Clopidogrel	41 (55.4)	20 (54.1)	21 (56.8)	0.82
Aspirin	16 (21.6)	9 (24.3)	7 (18.9)	0.57
Cilostazol	3 (4.1)	1 (2.7)	2 (5.4)	0.55
Anticoagulantagent				
Warfarin	4 (5.4)	1 (2.7)	3 (8.1)	0.29
Directoral anticoagulants	3 (4.1)	1 (2.7)	2 (5.4)	0.55

Figures are expressed as *n* (%).

ARB indicates angiotensin II receptor blocker; DPP, dipeptidyl peptidase; GLP, glucagon-like peptide; SGLT, sodium glucose transporter; and TG, triglycerides.