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ORIGINAL RESEARCH

Effects of Pemafibrate on Cardio-Ankle Vascular Index (CAVI) in Patients with Type 2 Diabetes or Ischemic Heart Disease: A 24-Week Observational Study

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Purpose: Pemafibrate is a novel selective peroxisome proliferator-activated receptor alpha modulator (SPPARMα) that improves lipid profile, but its effects on cardiovascular events remain unproven. This study examined changes in the cardio-ankle vascular index (CAVI), a marker of arterial stiffness, in high-risk patients with type 2 diabetes mellitus (T2DM) or ischemic heart disease (IHD) treated with pemafibrate.

Patients and Methods: In this single-center, prospective, observational study, 95 patients with T2DM and/or IHD, who had hypertriglyceridemia (≥150 mg/dL) and started pemafibrate (0.2 mg/day) were analyzed. CAVI was measured at baseline and after 24 weeks of treatment as an indicator of arterial stiffness, along with comprehensive assessment of lipid parameters including triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), non-HDL-C, and apolipoproteins.

Results: No significant change in CAVI was observed after 24 weeks of treatment (median [interquartile range (IQR)]; baseline vs 24 weeks: CAVI 9.4 [8.8–10.6] vs 9.6 [8.9–10.8], p=0.715). However, pemafibrate significantly reduced triglycerides (233 mg/dL [171–329] to 143 mg/dL [111–187], p<0.001), apolipoprotein C-II (8.1 mg/dL [6.1–10.2] to 6.3 mg/dL [5.3–8.3], p<0.001), apolipoprotein C-III (15.3 mg/dL [12.2–18.3] to 11.6 mg/dL [9.3–14.2], p<0.001) and liver enzymes; and increased HDL-C (45 mg/dL [39–52] to 50 mg/dL [40–60], p<0.001), LDL-C (92 mg/dL [70–111] to 103 mg/dL [79–128], p<0.001), apolipoprotein A-I and apolipoprotein A-II (both p<0.05). Calculated small dense low-density lipoprotein cholesterol also decreased significantly (40 mg/dL [31–49] to 36 mg/dL [28–45], p=0.002).

Conclusion: While pemafibrate improves lipid profile and liver enzymes, its short-term impact on vascular stiffness, as measured by CAVI, appears limited. Extended follow-up studies are needed to clarify its cardiovascular benefits in high-risk patients.

Keywords: pemafibrate, cardio-ankle vascular index, CAVI, type 2 diabetes mellitus, hypertriglyceridemia

Introduction

Atherosclerosis significantly contributes to the development of cardiovascular diseases, necessitating strict lipid-lowering therapies to mitigate associated risks. The cardio-ankle vascular index (CAVI) is a non-invasive measure of arterial stiffness, and its predictive value for cardiovascular events has been well established.[1–4] Additionally, hypertriglyceridemia has been linked to both cardiovascular diseases and increased CAVI,[5,6] highlighting the importance of triglyceride (TG) management in reducing arterial stiffness and cardiovascular risk. In patients with type 2 diabetes mellitus (T2DM), elevated TG levels represent a significant risk factor for cardiovascular complications.[7,8] Recent studies have shown that

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TG reduction can improve vascular function and potentially decrease cardiovascular events in high-risk populations.[9–11] Therefore, targeting TG with appropriate therapies may be an important strategy for reducing arterial stiffness and cardiovascular risk in patients with T2DM and/or IHD.

Bezafibrate, a traditional fibrate, has been shown to improve CAVI by reducing TG, remnant-like particle cholesterol (RLP-C), glycated hemoglobin (HbA1c), and derivatives of reactive oxygen metabolites (d-ROMs), while increasing high-density lipoprotein cholesterol (HDL-C) level.[10] The primary mechanism by which fibrates exert TG-lowering effects involves the activation of lipoprotein lipase (LPL).[12] LPL is an endothelial enzyme responsible for the hydrolysis of TG in lipoproteins, and its activity is influenced by insulin. Hence LPL activity reflects insulin sensitivity and endothelial function.[13] Fibrates typically enhance LPL activity, leading to reduced TG levels. However, comprehensive outcome studies for fibrates are limited, and the direct impact on cardiovascular events remains uncertain.

Pemafibrate is a novel selective peroxisome proliferator-activated receptor alpha modulator (SPPARMα) with approximately 2500-fold higher selectivity for PPARα than conventional fibrates. It was designed to maximize the beneficial effects of PPARα activation while minimizing off-target effects.[14,15] Pemafibrate effectively reduces triglycerides, non-HDL cholesterol, and apolipoprotein C-III while increasing HDL-C levels.[14] Unlike traditional fibrates, pemafibrate demonstrates a distinct hepatic gene expression profile and fewer adverse effects, allowing for safe use in patients with mild to moderate renal impairment. Transcriptomic analyses have shown that pemafibrate and fenofibrate regulate different sets of genes in the liver, suggesting that their metabolic actions are not identical.[16] In addition to traditional lipid parameters, recent studies have emphasized the role of small dense LDL-C (sdLDL-C) in the development of atherosclerosis due to its high atherogenic potential.[17] Pemafibrate has also been reported to reduce sdLDL-C levels, potentially contributing to cardiovascular risk reduction beyond conventional lipid targets.[18]

Despite the favorable effects of pemafibrate on lipid profile, its ability to reduce cardiovascular events remain unproven. For example, the PROMINENT trial reported no significant reduction in cardiovascular events among T2DM patients with hypertriglyceridemia, despite reductions in TG, very low-density lipoprotein (VLDL) cholesterol, remnant cholesterol, and apolipoprotein C-III levels.[19]

The primary aim of this study was to evaluate the effect of pemafibrate on CAVI, a key marker of arterial stiffness and a predictor of cardiovascular events, in high-risk patients with T2DM and/or ischemic heart disease (IHD). While previous studies with traditional fibrates have shown improvements in vascular parameters,[9,10] the effect of pemafibrate on arterial stiffness remains unclear. We hypothesized that pemafibrate may potentially improve CAVI through its lipid-lowering effects, particularly by reducing TG and sdLDL-C levels, though the observational nature of our study and limitations of prior research warrant cautious interpretation of our findings.

Materials and Methods

Study Design

This clinical research was a single-center, prospective, observational study conducted at Toho University Sakura Medical Center. Because of the exploratory nature of the investigation of the effects of pemafibrate on arterial stiffness, we conducted this study without a control group to provide real-world evidence of its vascular effects.

Study Patients

This study enrolled patients with T2DM and/or a history of IHD, who had hypertriglyceridemia (TG ≥ 150 mg/dL) and started pemafibrate (0.2 mg/day) treatment between January 2022 and December 2022 and had undergone CAVI measurement within one month before or at the initiation of treatment. Exclusion criteria were an ankle-brachial index (ABI) below 0.9 (as peripheral arterial disease can interfere with the accuracy of CAVI measurements by altering pulse wave transmission characteristics), as well as severe liver or kidney dysfunction. A total of 102 patients were included.

Data Collection

Before treatment was started, data were collected on patient demographics, medical history, current medications, lifestyle factors, and baseline measurements. At baseline and after 24 weeks of pemafibrate treatment, the following were

measured: CAVI, body weight, BMI, blood pressure, fasting blood glucose, HbA1c, total cholesterol (TC), TG, HDL-C, low-density lipoprotein cholesterol (LDL-C), uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GTP), blood urea nitrogen, creatinine, estimated glomerular filtration rate (eGFR), lipoprotein fractions, LPL, urine albumin, high-sensitive C-reactive protein (CRP), and d-ROMs.

Measurement of Lipid Concentrations

Plasma levels of TC, TG, HDL-C and LDL-C (except for the LDL-C level used for calculating sdLDL-C) were measured by a colorimetric method using an automatic analyzer BioMajesty JCA-BM6070 from JEOL Ltd. (Tokyo, Japan) with an enzymatic kit from Sekisui Medical Co., Ltd. (Tokyo, Japan). Apolipoprotein (Apo) (A-I, A-II, B, C-II, C-III, E) concentrations were determined by a turbidimetric immunoassay using an automatic analyzer BioMajesty JCA-BM8060 from JEOL Ltd. with a kit from Nittobo Medical Co., Ltd. (Tokyo, Japan).

Calculation of SdLDL-C

LDL-C in this study was measured using a direct method as described above, but the LDL-C level used in computing sdLDL-C was calculated using TC, TG and HDL-C, as described below.

The Sampson equation was chosen due to its improved accuracy in estimating LDL-C and sdLDL-C, particularly in patients with elevated triglyceride levels. This method has been validated for use in individuals with dyslipidemia.[20]

The equations reported by Sampson et al[21,22] were used for calculating LDL-C and sdLDL-C, which are calculated based only on the standard lipid test panel values as follows:

1. First, LDL-C is calculated using the formula:
   LDL-C = TC/0.948 - HDL-C/0.971 - [TG/8.56 + (TG × Non-HDL-C)/2140 - TG^2/16100] - 9.44
2. Large buoyant LDL-C (lbLDL-C) is then calculated using the formula:
   lbLDL-C = 1.43 × LDL-C – [0.14 × (ln (TG) × LDL-C)] - 8.99,
   where ln (TG) is the natural logarithm of TG
3. Finally, sdLDL-C is calculated by subtracting lbLDL-C from LDL-C:
   sdLDL-C = LDL-C - lbLDL-C

Preheparin LPL Mass Assay

Preheparin serum LPL mass was measured by a sandwich enzyme-linked immunosorbent assay (ELISA) utilizing a specific monoclonal antibody against bovine milk LPL, following the methods described by Kobayashi et al.[23] A commercial kit from Sekisui Medical Co., Ltd. and a VERSAmax microplate reader (Molecular Devices Co., Ltd.) were used. The measurement range was 4–500 ng/mL, with a coefficient of variation less than 10% and measurement accuracy of 85–115% of the nominal value.

Measurement of CAVI

CAVI was determined using a VaSera CAVI instrument (Fukuda Denshi Co., Ltd, Tokyo). The procedure has been detailed in a prior report.[24] Cuffs were placed on both upper arms and ankles of a subject positioned supine with the head in a midline position. Measurements were taken after the subject had rested for 10 minutes. Brachial and ankle pulse waves were detected using low cuff pressures (30 to 50 mmHg) to minimize the impact of cuff pressure on hemodynamics. CAVI was calculated using the formula:

$CAVI = a\{(2\rho/\Delta P)\times Ln(Ps/Pd)\ PWV^2\} + b$, where Ps is systolic blood pressure, Pd is diastolic blood pressure, PWV is pulse wave velocity, ΔP is Ps - Pd, ρ is blood density, and a and b are constants.

Fibrosis-4 (FIB-4) Index and Nonalcoholic Fatty Liver Disease (NAFLD) Fibrosis Score

As markers of liver fibrosis, FIB-4 index and NAFLD fibrosis score (NFS) were evaluated in the patient cohort. These items were calculated using established formulas,[25,26] and their correlation with CAVI was analyzed to assess the potential association between liver fibrosis and arterial stiffness.

Statistical Analysis

Primary outcome was the change in CAVI from baseline to after 24 weeks of treatment. Secondary outcomes included changes in biochemical parameters and stratified analyses based on patient background factors. Comparisons of baseline data and changes in clinical parameters between the group with increase in CAVI ($\Delta CAVI \geq 0$) and the group without ($\Delta CAVI < 0$) were performed using Wilcoxon signed-rank test or Mann–Whitney *U*-test. Correlation between changes in TG level and other clinical parameters was analyzed using Spearman's rank correlation coefficient. A two-tailed p-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

This study included 102 patients, 95 of whom were analyzed after excluding three patients with an ABI below 0.9 and four patients with missing data. No patients discontinued medication due to adverse effects or serious adverse reactions. Patient background characteristics are summarized in Table 1. The 95 subjects analyzed had a median age of 70 years [interquartile range (IQR): 61–75], with a male to female ratio of 69.5% to 30.5%. The prevalence of hypertension and diabetes was 63.2% and 78.9%, respectively, while 41.1% had a history of ischemic heart disease (IHD). In addition, 65.3% of the patients were current or former smokers. Among the subjects, 47.4% were on ACE inhibitors or ARBs, 61.1% were on statins, 16.8% were taking ezetimibe, 38.9% were on metformin, 40.0% were using sodium–glucose co-transporter 2 (SGLT2) inhibitors, and 7.4% were on glucagon-like peptide-1 analogues.

Primary Endpoint (Change in CAVI After 24 weeks of Pemafibrate Treatment)

As shown in Figure 1, there was no significant change in CAVI after 24 weeks of pemafibrate treatment ($p = 0.715$). Subgroup analyses of patients with diabetes and those with IHD also showed no significant CAVI changes ($p = 0.447$ and $p = 0.136$, respectively).

Secondary Endpoints: Changes in Lipid Parameters and Liver Enzymes Over 24 weeks

Figure 2 shows the changes in various lipid parameters and Figure 3 shows the changes in liver enzymes from baseline to after 24 weeks of pemafibrate treatment. Pemafibrate treatment significantly reduced TG levels by approximately 39%

Table 1 Patient Background Characteristics

Characteristic	Median (IQR) or %
Median age (IQR) (yr)	70 (61–75)
Female (%)	30.5
Hypertension (%)	63.2
Diabetes (%)	78.9
Ischemic heart disease (%)	41.1
Current or past smoking history (%)	65.3
ACE inhibitor or ARB (%)	47.4
Statin (%)	61.1
Ezetimibe (%)	16.8
Metformin (%)	38.9
SGLT2 inhibitor (%)	40.0
GLP-1 analogue (%)	7.4

Notes: This table provides an overview of the baseline characteristics of the study population. Median age, sex distribution, and prevalence of common comorbidities are listed, along with the percentage of patients using various medications at the start of the study. Data are presented as median (IQR) or percentage.

Abbreviations: IQR, interquartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; SGLT2, sodium-glucose cotransporter 2; GLP-1, glucagon-like peptide-1.

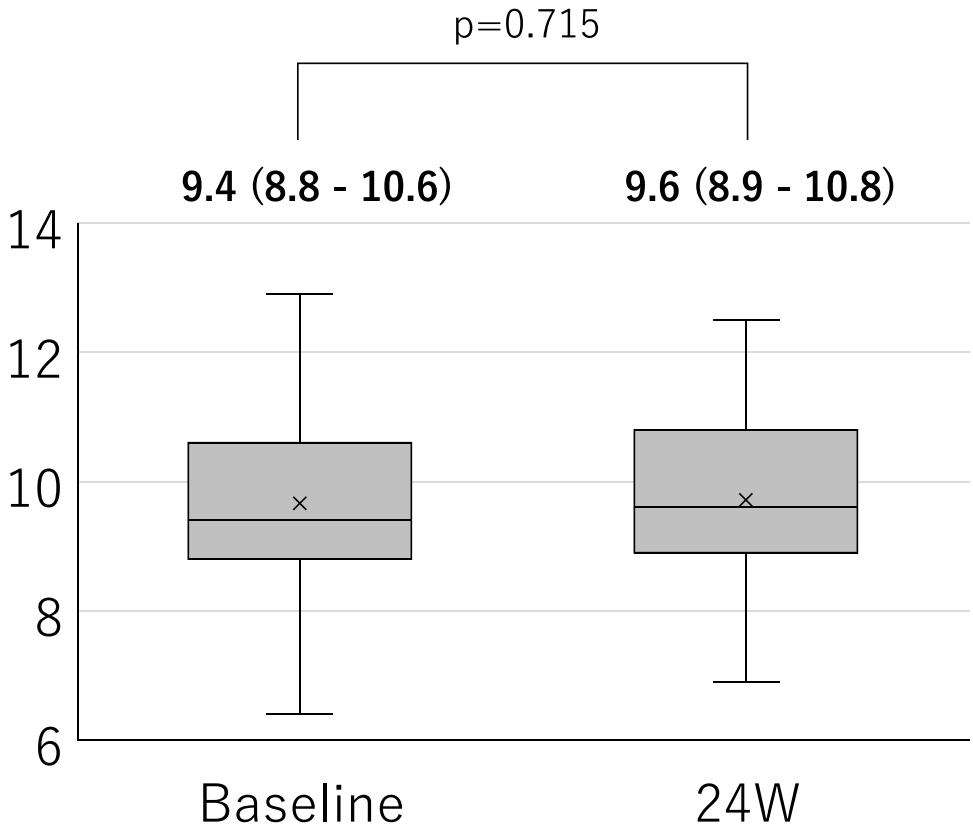

Figure 1 Change in CAVI after 24 weeks of pemafibrate treatment. This figure shows the primary endpoint, illustrating the change in cardio-ankle vascular index (CAVI) after pemafibrate treatment. The median CAVI showed no significant change after 24 weeks of treatment compared to baseline (p = 0.715, Wilcoxon signed-rank test).

and non-HDL-C levels ($p < 0.001$ and $p = 0.005$, respectively). Conversely, HDL-C and LDL-C levels significantly increased (both $p < 0.001$), while total cholesterol levels remained unchanged ($p = 0.307$).

Among apolipoprotein parameters, ApoC-II and ApoC-III decreased significantly (both $p < 0.001$), and the calculated sdLDL-C value showed a significant reduction ($p = 0.002$). ApoA-I and ApoA-II levels increased significantly ($p = 0.020$ and $p < 0.001$, respectively). No significant changes were observed in LPL and ApoB levels.

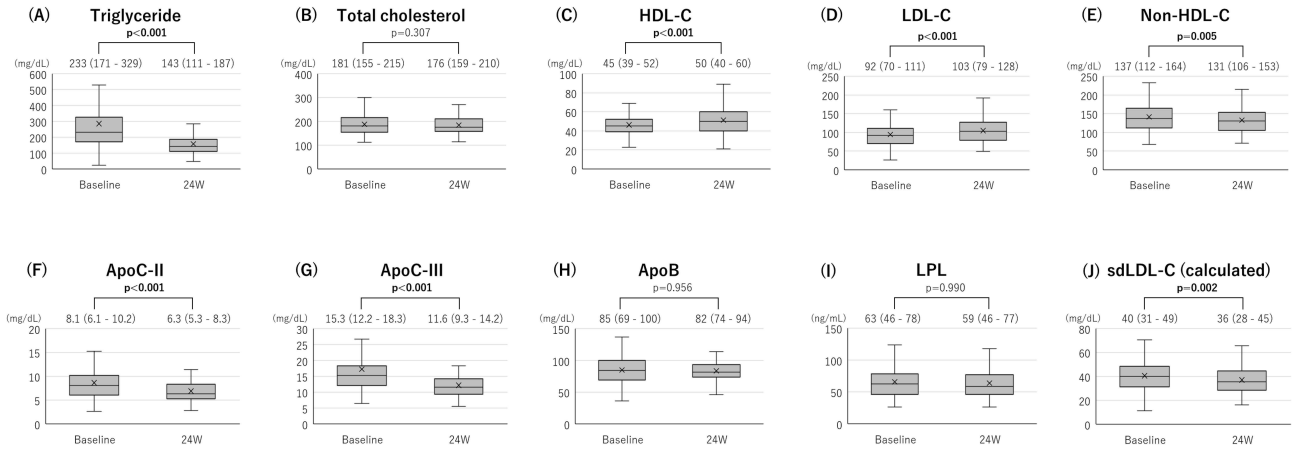

Figure 2 Changes in plasma lipid parameters from baseline to 24 weeks of pemafibrate treatment. This figure shows the changes in plasma lipid levels from baseline to after 24 weeks of treatment: (**A**) triglyceride (mg/dL), (**B**) total cholesterol (mg/dL), (**C**) HDL-C (mg/dL), (**D**) LDL-C (mg/dL), (**E**) non-HDL-C (mg/dL), (**F**) ApoC-II (mg/dL), (**G**) ApoC-III (mg/dL), (**H**) ApoB (mg/dL), (**I**) LPL (ng/mL), (**J**) sdLDL-C (calculated) (mg/dL). Data are presented as box plots with median (cross), interquartile range (lower and upper edges of box) and minimum and maximum values (whiskers). The p-values indicate the significance of changes over the 24-week period analyzed by Wilcoxon signed-rank test.

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; Apo, Apolipoprotein; LPL, lipoprotein lipase; sdLDL-C, small dense LDL-C.

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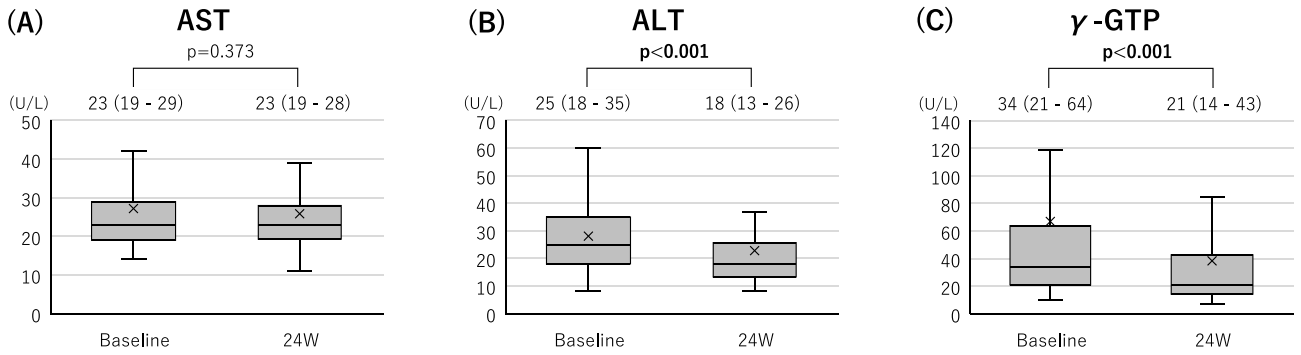

Figure 3 Changes in plasma liver enzyme levels from baseline to 24 weeks of pemafibrate treatment. This figure shows the changes in serum liver enzyme levels from baseline to after 24 weeks of treatment: (**A**) AST (IU/L), (**B**) ALT (IU/L), (**C**) γ-GTP (IU/L). Data are presented as box plots with median (cross), interquartile range (lower and upper edges of box) and minimum and maximum values (whiskers). The p-values indicate the significance of changes over the 24-week period analyzed by Wilcoxon signed-rank test.

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma-glutamyl transpeptidase.

Regarding liver enzymes, ALT and γ-GTP levels decreased significantly (both $p < 0.001$), while AST levels remained stable ($p = 0.373$). The detailed values for all parameters are presented in Figures 2, 3 and Table 2.

Changes in Clinical Parameters According to CAVI Change

The changes in clinical parameters from baseline to 24 weeks were compared between two groups divided by CAVI status: a group with no change or increase in CAVI ($\Delta CAVI \geq 0$) and a group with decrease in CAVI ($\Delta CAVI < 0$). The results are shown in Table 3. The group with decrease in CAVI showed a significant reduction in LDL-C compared to the group with increase in CAVI ($p = 0.044$). Additionally, Apo B level decreased significantly in the group with decrease in CAVI compared to that with increase in CAVI ($p = 0.001$).

Table 2 Clinical Data Before and After Pemafibrate Administration

	0W	24W	p-value*
Body Weight (kg)	68.0 (60.0–76.1)	69.2 (60.0–76.0)	0.943
BMI (kg/m2)	25.8 (22.8–28.5)	25.6 (22.5–27.5)	0.891
SBP (mmHg)	133 (122–145)	135 (125–152)	0.110
DBP (mmHg)	81 (71–90)	81 (72–88)	0.895
eGFR (mL/min/1.73m2)	66 (51–77)	61 (50–75)	<0.001
Uric acid (mg/dL)	5.5 (4.8–6.3)	5.6 (4.7–6.5)	0.405
HbA1c (%)	6.9 (6.2–7.8)	6.9 (0.1–7.8)	0.433
Urinary albumin (mg/gCr)	14.8 (6.6–70.6)	20.2 (9.7–75.0)	0.248
hs-CRP (mg/dL)	0.081 (0.037–0.194)	0.081 (0.028–0.165)	0.474
d-ROM (U.CARR)	313 (276–356)	304 (267–357)	0.494
Apolipoprotein A-I level, measured (mg/dL)	137 (118–153)	140 (127–158)	0.020
Apolipoprotein A-II level, measured (mg/dL)	29.7 (26.9–33.3)	38.1 (32.7–43.7)	<0.001
Apolipoprotein E level, measured (mg/dL)	3.4 (2.3–4.7)	2.9 (2.2–3.7)	0.069
FIB-4 index	1.6 (1.1–2.2)	1.6 (1.1–2.3)	0.588
NAFLD Fibrosis Score (NFS)	−0.233 (−1.127–0.466)	−0.422 (−1.311–0.631)	0.116

Notes: This table presents a comparison of clinical parameters before and after 24 weeks of pemafibrate treatment. Data are presented as median (interquartile range). *p values were obtained by Wilcoxon signed-rank test, 0W vs 24W.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1; hs-CRP, high-sensitivity C-reactive protein; d-ROM, derivatives of reactive oxygen metabolites; FIB-4, Fibrosis-4; NAFLD, Nonalcoholic Fatty Liver Disease; W, week.

Table 3 Changes in Clinical Parameters According to the Status of Change in CAVI

	ΔCAVI≥0	ΔCAVI<0	p-value*
ΔTotal cholesterol (mg/dL)	5 (−7–21)	−8 (−35–9)	0.268
ΔTriglyceride (mg/dL)	−57 (−122–−37)	−86 (−126–−35)	0.849
ΔHDL-C (mg/dL)	5 (1–13)	2 (−1–8)	0.133
ΔLDL-C (mg/dL)	15 (2–29)	−2 (−13–14)	0.044
Δnon-HDL-C (mg/dL)	−2 (−9–12)	−14 (−28–10)	0.471
ΔSdLDL-C (mg/dL) (calculated)	0 (−5–3)	−6 (−11–2)	0.608
ΔLPL (ng/mL)	1 (−7–12)	−3 (−9–8)	0.285
ΔApolipoprotein A-I level, measured (mg/dL)	8 (−2–15)	1 (−4–7)	0.051
ΔApolipoprotein A-II level, measured (mg/dL)	8.9 (5.7–13.5)	6.9 (3.1–12.9)	0.067
ΔApolipoprotein B level, measured (mg/dL)	3 (−4–12)	−7 (−14–3)	0.001
ΔApolipoprotein C-II level, measured (mg/dL)	−1.1 (−2.6–−0.2)	−0.9 (−2.6–0.4)	0.579
ΔApolipoprotein C-III level, measured (mg/dL)	−3.0 (−5.0–−1.8)	−3.7 (−6.3–−1.2)	0.863
ΔApolipoprotein E level, measured (mg/dL)	0.1 (−0.4–0.5)	−0.6 (−1.2–0.5)	0.117
ΔFIB-4 index	0.0 (−0.1–0.3)	0.0 (−0.1–0.2)	0.652
ΔNAFLD fibrosis score (NFS)	−0.201 (−0.557–0.295)	0.017 (−0.542–0.217)	0.730

Notes: This table presents the changes in clinical parameters from baseline to 24 weeks between a group with increase in CAVI (ΔCAVI≥0) and a group with decrease in CAVI (ΔCAVI<0) during this period. Data are expressed as median (interquartile range). *p values were obtained by Mann–Whitney *U*-test, ΔCAVI≥0 vs ΔCAVI<0.

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; sdLDL-C, small dense low-density lipoprotein cholesterol; LPL, lipoprotein lipase; FIB-4, Fibrosis-4; NAFLD, Nonalcoholic Fatty Liver Disease.

Correlation Between Change in TG Levels and Change in LPL or Apolipoprotein C-III

Figure 4 illustrates the correlation analysis between changes in TG levels and changes in LPL or ApoC-III. No significant correlation was found between changes in TG and LPL, whereas a significant positive correlation was observed between changes in TG and ApoC-III ($Rs = 0.541$, $p < 0.001$).

Other Clinical Parameters

As shown in Table 2, most clinical parameters including body weight, BMI, blood pressure, HbA1c, urinary albumin, hs-CRP, FIB-4 index, NFS, and d-ROM levels remained unchanged. However, estimated GFR decreased significantly ($p < 0.001$), while ApoA-I and ApoA-II levels significantly increased ($p = 0.020$ and $p < 0.001$, respectively). ApoE showed a trend toward decrease but did not reach statistical significance. Supplementary Figure 1 demonstrates a positive correlation between CAVI and both the FIB-4 index and NAFLD fibrosis score.

Discussion

This observational study demonstrated that 24-week treatment with pemafibrate in patients with T2DM and/or a history of IHD significantly improved lipid profile, including reduction in TG. Elevated TG levels are known to adversely affect vascular function through multiple mechanisms. Several studies have established that hypertriglyceridemia is independently associated with increased arterial stiffness in various populations.[27–29] The pathophysiological mechanisms linking TGs to arterial stiffness include promotion of endothelial dysfunction, increased oxidative stress, and stimulation of inflammatory processes in the arterial wall. Additionally, TG-rich lipoproteins can penetrate the arterial wall and contribute to atherosclerotic plaque formation, further increasing arterial stiffness. Despite significant TG reduction with pemafibrate in our study, the lack of CAVI improvement suggests that other factors, such as the concurrent increase in LDL-C or the relatively short treatment duration, may have overshadowed the potential vascular benefits of TG reduction in our specific patient population.

However, no significant change was observed in CAVI, suggesting that the effect of pemafibrate on arterial stiffness may be limited in short-term treatment. CAVI is a well established marker for arterial stiffness and a predictor of

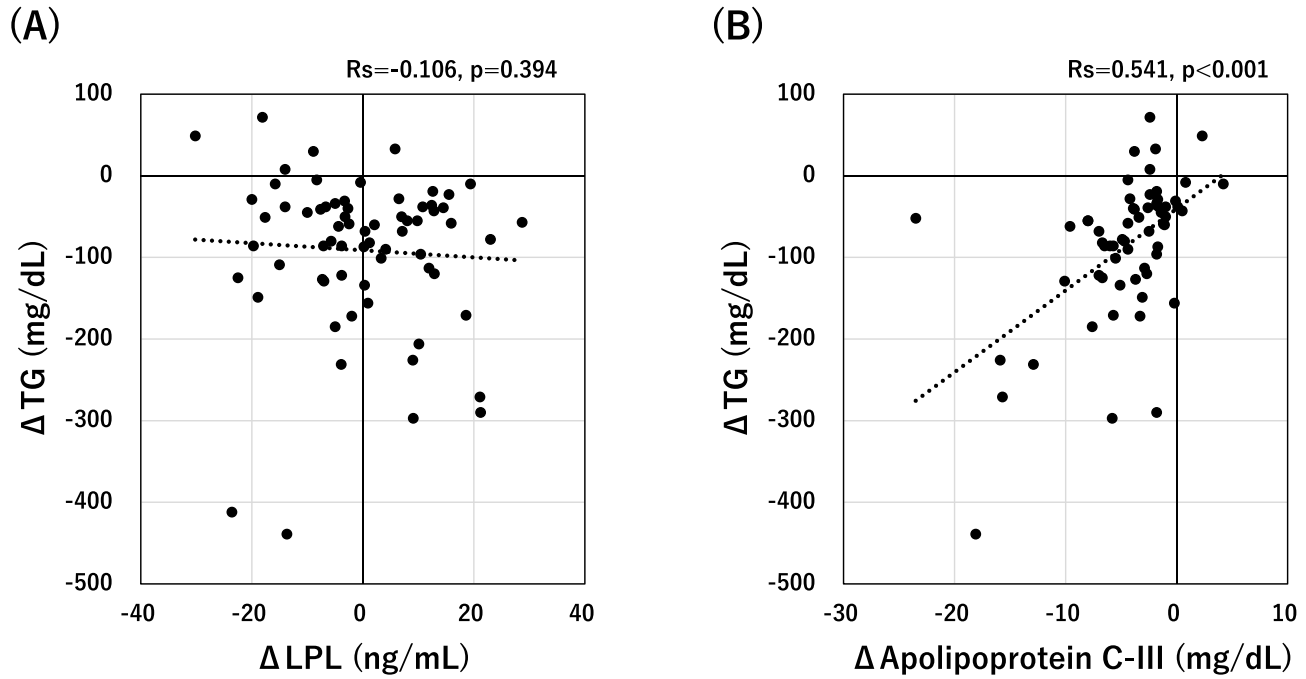

Figure 4 Correlation between change in triglyceride level and change in LPL and apolipoprotein C-III. This figure displays scatter plots illustrating the correlation between (**A**) change in TG level and change in LPL, and (**B**) change in TG level and change in apolipoprotein C-III. (**A**) No significant correlation between changes in TG and LPL is detected. (**B**) A positive correlation between changes in TG and apolipoprotein C-III is observed.
Abbreviations: TG, triglycerides; LPL, lipoprotein lipase.

cardiovascular events. In a previous study, bezafibrate treatment reduced CAVI, indicating improvement in arterial stiffness.[10] However, pemafibrate did not show similar result in the present study.

The lack of significant change in CAVI despite improvements in lipid profile may be attributed to several factors. One possible explanation for this discrepancy is the study duration. While a period of 24 weeks is sufficient to observe changes in lipid profile, it may not be long enough to detect changes in vascular structure and function. Additionally, due to the advanced age (median 70 years) and high prevalence of comorbidities, our study population may have had more established arterial changes that were less responsive to short-term interventions. Another consideration is that, although there was a significant reduction in TG levels, it may not have been sufficient to influence arterial stiffness as measured by CAVI.[5]

The lack of significant change in CAVI despite improvements in lipid profile contrasts with previous studies on traditional fibrates. For example, Yamaguchi et al demonstrated that bezafibrate treatment improved arterial stiffness measured by CAVI in patients with hypertriglyceridemia and T2DM.[10] Similar vascular benefits have been reported with other fibrates in various studies.[10,30–32] These studies suggested that bezafibrate and other fibrates may improve vascular function through multiple mechanisms including enhanced nitric oxide production, reduced oxidative stress, and improved insulin sensitivity. The disparity between our findings with pemafibrate and these prior studies with traditional fibrates may be attributed to differences in the mechanism of action, particularly regarding effects on LPL activity, study populations, or duration of treatment.

Another important factor to consider is that lipid-lowering agents that do not increase LPL level may not be as effective in reducing CAVI than those that elevate LPL. High serum LPL may contribute to improve arterial stiffness.[13] Among statins, pitavastatin has been reported to increase LPL and decrease CAVI.[33,34] Among fibrate drugs, bezafibrate has also been reported to elevate LPL and reduce CAVI,[10,12] suggesting that LPL may play a role in the reduction of CAVI by bezafibrate. In our study, although pemafibrate showed significant efficacy in improving several lipid parameters including TG, HDL-C, and non-HDL-C, it did not significantly alter LPL levels. While the significant reduction in ApoC-III supports the mechanism of action of pemafibrate in lowering TG levels,[35] the lack of increase in LPL may explain why a reduction in CAVI was not observed, despite favorable changes in the lipid profile.

Another notable finding was a significant increase in LDL-C after pemafibrate treatment. This increase in LDL-C might be crucial in explaining our results, as patients who demonstrated decreased CAVI showed greater reduction in LDL-C

compared to those without CAVI improvement. This observation suggests that the overall effect of pemafibrate on CAVI might be influenced by its varying effects on LDL-C levels among patients. The mechanism behind this LDL-C elevation is not fully understood, but it might be related to increased conversion of VLDL to LDL particles through enhanced lipolysis, as LDL is produced as an ultimate product of the lipolytic conversion of VLDL. This finding is consistent with the PROMINENT trial, where pemafibrate treatment was also associated with an increase in LDL-C levels, potentially offsetting some of its beneficial effects on cardiovascular outcomes.[19] Komiya et al also reported that pemafibrate decreases triglycerides and small, dense LDL, but increases LDL-C depending on baseline triglycerides and LDL-C levels in type 2 diabetes patients with hypertriglyceridemia.[18] Their study suggested that this increase in LDL-C may reflect actual improvement in lipoprotein metabolism, particularly in patients with higher baseline TGs and lower baseline LDL-C, rather than a harmful effect. While fibrates typically reduce triglycerides and increase HDL-C, their effects on LDL-C can vary significantly between individuals. The observed increase in LDL-C in our study might have counteracted the potential benefits of TG reduction on arterial stiffness, as elevated LDL-C is a well-established risk factor for endothelial dysfunction and arterial stiffening. This highlights the complex interplay between different lipid parameters in determining vascular health and underscores the importance of comprehensive lipid management in high-risk patients.

In this context, previous research has established correlations between sdLDL-C, carotid artery IMT, and CAVI.[36–38] Our study observed a reduction in calculated sdLDL-C level despite the increase in total LDL-C, but this did not translate to a change in CAVI. This finding could suggest that progressed arterial stiffening caused by long-term lipid exposure and cumulative atherosclerotic burden may not be improved readily by short-term changes in lipid profile, particularly when accompanied by an increase in total LDL-C. This observation is consistent with the findings from the PROMINENT trial, where Hirano et al[39] suggested that insufficient sdLDL-C reduction and concurrent LDL-C elevation may contribute to the lack of cardiovascular benefits.

Interestingly, while the PROMINENT trial showed no significant reduction in ApoB,[19] our study found a significant decrease in ApoB in the group with reduced CAVI. This suggests that improvement in arterial stiffness is associated with reduction in ApoB. Thus, pemafibrate not only improves lipid profile but may also contribute to cardiovascular risk reduction in a subgroup of patients with decreased ApoB.

Another important aspect of this study is the significant reduction in liver enzyme levels, including ALT and γ-GTP, indicating a hepatoprotective effect of pemafibrate. This is particularly beneficial, since hepatic adverse effects are often associated with other lipid-lowering therapies. Although pemafibrate is not considered to affect eGFR,[40] eGFR decreased after pemafibrate treatment in the present study. The exact mechanism for the decrease in eGFR is not fully understood, but reduction in eGFR appears to be a known reversible effect of fibrates.[41,42] Additionally, patients with high CAVI are susceptible to rapid eGFR decline,[43] suggesting the observed renal function decline may be related to the progression of atherosclerosis rather than a direct effect of pemafibrate.

In our study, no significant changes in body weight, BMI, systolic blood pressure, diastolic blood pressure, HbA1c, urinary albumin, hs-CRP, FIB-4 index, NFS, and d-ROM levels were observed after pemafibrate treatment. The stability of these parameters may partially explain the lack of CAVI improvement, as previous studies have shown that changes in glycemic control, blood pressure, and inflammatory markers can influence arterial stiffness in patients with T2DM and/or IHD. For instance, improved glycemic control has been associated with reduced arterial stiffness in patients with diabetes[44] while elevated inflammatory markers such as hs-CRP have been linked to increased arterial stiffness.[45] Similarly, urinary albumin excretion, a marker of endothelial dysfunction and microvascular damage, has been shown to correlate with arterial stiffness in patients with diabetes.[46]

In this study, a significant correlation was observed between CAVI and both the FIB-4 index and NAFLD fibrosis score, suggesting a close relationship between arterial stiffness and liver fibrosis. Previous studies have also shown that liver stiffness measured by elastography is associated with CAVI,[47] further strengthening the connection between liver fibrosis and vascular stiffness. These findings imply that underlying inflammation and oxidative stress, which are common in patients with dyslipidemia, diabetes, and cardiovascular diseases, may contribute to both liver dysfunction and arterial stiffness.

This study has several limitations. First, this was a single-center, single-arm observational study with a relatively small sample size, which limits our ability to establish causality and definitively attribute the observed changes to

pemafibrate treatment. The lack of a control group means that changes in vascular parameters might have been influenced by various confounding factors or the natural course of the disease. Second, as the study was conducted at a single institution, the results may not be generalizable to other populations or clinical settings. Third, the 24-week study period may have been insufficient to fully observe significant changes in vascular stiffness, and longer follow-up would be needed to evaluate the long-term effects of pemafibrate. In addition, the potential effects of concomitant medications such as statins, SGLT2 inhibitors, or GLP-1 analogues, as well as unrecorded lifestyle factors (eg, diet, physical activity), may have acted as confounding variables and should be considered in future controlled trials.

Conclusion

Pemafibrate treatment for 24 weeks significantly improved lipid profile and liver enzymes in patients with high TG and T2DM and/or IHD, but did not alter CAVI. This suggests that pemafibrate's favorable effects on dyslipidemia may not translate to immediate improvements in vascular function. Longer-term studies with larger populations are needed to determine pemafibrate's cardiovascular benefits.

Abbreviations

ABI, Ankle-brachial index; ACE, Angiotensin-converting enzyme; ALT, Alanine aminotransferase; Apo, Apolipoprotein; ARB, Angiotensin receptor blocker; AST, Aspartate aminotransferase; BMI, Body mass index; CAVI, Cardio-Ankle Vascular Index; CRP, C-reactive protein; d-ROMs, Derivatives of reactive oxygen metabolites; eGFR, Estimated glomerular filtration rate; ELISA, Enzyme-linked immunosorbent assay; FIB-4, Fibrosis-4; γ-GTP, Gamma-glutamyl transpeptidase; HbA1c, Glycated hemoglobin; HDL-C, High-density lipoprotein cholesterol; IHD, Ischemic heart disease; IMT, Intima-media thickness; LDL-C, Low-density lipoprotein cholesterol; LPL, Lipoprotein lipase; NAFLD, Nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; RLP-C, Remnant-like particle cholesterol; sdLDL-C, Small dense low-density lipoprotein cholesterol; SGLT2, Sodium-glucose co-transporter 2; SPPARMα, Selective peroxisome proliferator-activated receptor alpha modulator; T2DM, Type 2 diabetes mellitus; TC, Total cholesterol; TG, Triglyceride; VLDL, Very low-density lipoprotein.

Data Sharing Statement

The datasets generated and analyzed during the current study are not publicly available due to the sensitive nature of the patients' personal information and the ethical restrictions imposed by the Ethics Committee of Toho University Sakura Medical Center. However, de-identified data may be available from the corresponding author on reasonable request and with permission from the Ethics Committee of Toho University Sakura Medical Center. Any data sharing will be subject to ethical approval and will be in accordance with the guidelines of the institution.

Ethics Approval and Informed Consent

This study was performed in compliance with the principles of the Declaration of Helsinki, and written informed consent was obtained from all participants. The study protocol was reviewed and approved by the Ethics Committee of Toho University Sakura Medical Center (approval number: S21038) and registered in the UMIN Clinical Trials Registry (UMIN000046474).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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