



Case report: a potential modulation of coronary atheroma by lowering triglyceride-rich lipoproteins with pemafibrate: insights from serial near-infrared spectroscopy imaging

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Background: Pemafibrate is a potent selective peroxisome proliferator-activated receptor α modulator. Whether this agent favorably modulates atherosclerosis *in vivo* remains unknown. This is the first case report to evaluate serial changes of coronary atherosclerosis under pemafibrate use in type 2 diabetic patients already taking a high-intensity statin.

Case Description: A 75-year-old gentleman was hospitalized due to peripheral artery disease, which was treated by endovascular treatment. One year later, non-ST-elevation myocardial infarction (NSTEMI) occurred and severe stenosis at his proximal segment of right coronary artery received primary percutaneous coronary intervention (PCI). Due to his suboptimal control of low-density lipoprotein cholesterol (LDL-C) level with moderate intensity statin, high-intensity one (20 mg atorvastatin) and 10 mg ezetimibe were commenced, which enabled to achieve very low LDL-C level (50 mg/dL). However, he required additional PCI due to progression of left circumflex artery one year after NSTEMI. Despite his optimally controlled LDL-C level (46 mg/dL), near-infrared spectroscopy and intravascular (NIRS/IVUS) imaging after PCI visualized the presence of lipid-rich plaque [maximum 4-mm lipid-core burden index (LCBI_{4mm}) = 482] at non-culprit segment in his right coronary artery. Given his continuing residual hypertriglyceridemia (triglyceride = 248 mg/dL), 0.2 mg pemafibrate was commenced, which lowered triglyceride to 106 mg/dL. One-year follow-up NIRS/IVUS imaging was conducted to evaluate coronary atheroma. A reduction of attenuated ultrasonic signals was observed, accompanied by plaque calcification. In addition, the amount of yellow signal was lowered, and its MaxLCBI_{4mm} was 358. Since then, this case does not experience any cardiovascular events. His LDL-C and triglyceride-rich lipoprotein levels are favourably controlled.

Conclusions: A delipidation of coronary atheroma, accompanied by greater plaque calcification was observed after the commencement of pemafibrate. This finding highlights potential anti-atherosclerotic benefit of pemafibrate use in patients receiving a statin.

Keywords: Triglyceride-rich lipoprotein; coronary atherosclerosis; pemafibrate; near-infrared spectroscopy imaging; case report

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Introduction

Despite a large body of evidence showing anti-atherosclerotic benefit of statin therapy, atherosclerotic cardiovascular disease (ASCVD) still occurs, which suggests the need to modulate additional atherogenic targets. Triglyceride-rich lipoproteins have been considered as residual risks associated with ASCVD (1). While observational and genetic studies have reported the association of triglyceride-rich lipoproteins with ASCVD (1), clinical benefit to modify these lipoproteins is not fully established yet. Pemafibrate is a potent selective peroxisome proliferator-activated receptor α modulator (2). This agent has been shown to decrease triglyceride level by 30–40%, accompanied by a favourable reduction of apolipoprotein CIII, remnant cholesterol and non-HDL-C. We present the current case which enabled to evaluate serial changes of coronary atherosclerosis under pemafibrate use in type 2 diabetic patients who already received a high-intensity statin. This is the first case report to monitor how coronary atherosclerosis changes under pemafibrate use. We present the following case in accordance with the CARE reporting checklist (available at <https://cdt.amegroups.com/article/view/10.21037/cdt-22-401/rc>).

Case presentation

All procedures performed in the study were in accordance

with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

A 75-year-old man with type 2 diabetes mellitus received endovascular treatment on September 18th, 2017. Following the completion of endovascular treatment, coronary angiography was concomitantly conducted and it showed multiple moderate stenotic lesions. Given the absence of significant myocardial ischemia on myocardial perfusion scintigraphy, coronary revascularization was not conducted. He has already received 10 mg atorvastatin since February 5th, 2016. On-treatment low-density lipoprotein cholesterol (LDL-C) and fasting triglyceride levels were 96 and 328 mg/dL, respectively (*Figure 1*). HbA1c was 6.9% under several glucose lowering agents. One year later (October 3rd, 2018), he presented non-ST-elevation myocardial infarction (NSTEMI) (troponin T level =0.016 ng/mL). Two severe stenosis in his right coronary artery were treated by two bioresorbable polymer sirolimus-eluting stents (Ultimaster[®], Terumo, Tokyo, Japan, 4.0 mm × 28 mm, 2.25 mm × 21 mm). Moderate stenosis in his left circumflex artery was medically treated with 2.5 mg bisoprolol, 2.5 mg enalapril, 100 mg aspirin and 3.75 mg prasugrel. Due to poorly controlled LDL-C level (104 mg/dL), dose escalation of atorvastatin to 20 mg with the commencement of 10 mg ezetimibe was conducted, which lowered LDL-C to 50 mg/dL at two months after PCI (December 8th, 2018), but hypertriglyceridemia (fasting triglyceride =278 mg/dL) still existed (*Figure 1*). One year later after primary PCI (August 20th, 2019), he was hospitalized again due to unstable angina pectoris. Due to typical anginal chest symptom, invasive coronary angiography was performed. There was a mild atherosclerotic disease in the distal segment of his right coronary artery (*Video 1*), whereas there was a progressed lesion in his left circumflex artery, which was considered as target lesion requiring PCI (*Figure 2*). One drug-eluting stent (Xience[®], 2.25 mm × 23 mm, Abbott Vascular, Santa Clara, USA) was successfully implanted with the use of near-infrared spectroscopy and intravascular imaging (NIRS/IVUS, DualPro[®], Nipro Tokyo, Japan) (*Figure 2*). NIRS/IVUS imaging after PCI showed very small yellow signal at untreated segment of his obtuse marginal branch [*Figure 2*, maximum 4-mm lipid-core burden index (MaxLCBI_{4mm}) =29]. NIRS/IVUS imaging of right coronary artery elucidated ultrasonic signal attenuation at the mild atherosclerotic

Highlight box

Key findings

- In a statin-treated diabetic patient with coronary artery disease (CAD), a reduction of NIRS-derived MaxLCBI_{4mm} at non-culprit segment was observed after the commencement of pemafibrate.

What is known and what is new?

- Hypertriglyceridemia has been considered as a residual risk associated with atherosclerotic cardiovascular disease in statin-treated patients.
- We observed that adding 0.2 mg pemafibrate to high-intensity statin therapy lowered levels of fasting triglyceride and triglyceride-rich lipoproteins, accompanied by a reduction of lipidic plaque materials in a diabetic patient with CAD.

What is the implication, and what should change now?

- This case suggests a potential benefit of lowering triglyceride with pemafibrate to modulate vulnerable form of disease in statin-treated patients. On-going study (PEMA-CORE) will elucidate how coronary atheroma responds to pemafibrate therapy under stain use.









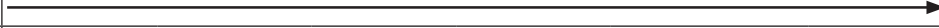

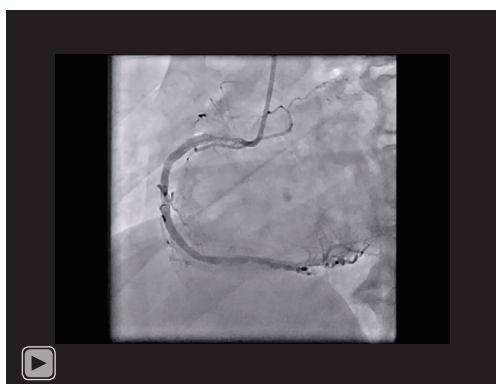
	2017.09.18	2018.10.03		2019.08.20	2021.02.15	2022.03.19
	EVT for PAD	NSTEMI (primary PCI)	Two months after PCI	uAP (PCI)	Follow-up coronary angiography	At the clinic
Risk factor control						
LDL-C	2.5 mmol/L	2.7 mmol/L	1.3 mmol/L	1.2 mmol/L	1.7 mmol/L	1.6 mmol/L
HDL-C	1.2 mmol/L	1.2 mmol/L	1.3 mmol/L	1.2 mmol/L	1.4 mmol/L	1.5 mmol/L
Triglyceride	3.2 mmol/L	3.1 mmol/L	3.1 mmol/L	2.8 mmol/L	1.2 mmol/L	1.6 mmol/L
Non-HDL-C	13.4 mmol/L	13.8 mmol/L	11.3 mmol/L	9.7 mmol/L	7.3 mmol/L	7.5 mmol/L
Apolipoprotein CIII	–	–	14.2 mg/dL	12.0 mg/dL	8.2 mg/dL	8.6 mg/dL
Remnant cholesterol	–	–	7.7	9.3	2.4	–
HbA1c	6.9%	7.1%	6.8%	6.5%	6.8%	6.7%
Medication use						
Anti-platelet therapy						
100 mg aspirin						
75 mg clopidogrel						
3.75 mg prasugrel						
Lipid-lowering therapy						
10 mg atorvastatin						
20 mg atorvastatin						
10 mg ezetimibe						
0.2 mg pemafibrate						
Glucose lowering therapy						
500 mg metformin						
5 mg linagliptin						
0.6 mg voglibose						

Figure 1 Risk factor control and medication use. EVT, endovascular treatment; PAD, peripheral artery disease; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; uAP, unstable angina pectoris; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin.

disease in the distal segment of his right coronary artery (*Figure 3* and *Video 2*). Furthermore, an extensive lipidic yellow signal was visualized at the corresponding segment, reflected by MaxLCBI_{4mm} at 482 (*Figure 3*). Since he still continued to exhibit hypertriglyceridemia (fasting triglyceride =248 mg/dL) with very low LDL-C level (46 mg/dL), we added pemafibrate 0.2 mg.

Eighteen months later after his last PCI (February 15th, 2021), evaluation of his coronary arteries was conducted again due to chest pain at rest. Given that computed tomography is not capable to clearly evaluate stented segments due to its smaller size of stent diameter, invasive coronary angiography was undertaken. In-stent restenosis

and progression of coronary stenosis were not observed (*Figures 4,5*, and *Video 3*). Further evaluation of obtuse marginal branch and right coronary artery was conducted by NIRS/IVUS imaging. Newly formation of lipidic plaque was not observed in his obtuse marginal branch (*Figure 4*, MaxLCBI_{4mm} =20). With regard to his right coronary artery (*Video 4*), a reduction of attenuated ultrasonic signals was observed, accompanied by plaque calcification. In addition, the amount of yellow signal was lowered, and its MaxLCBI_{4mm} was 358 (*Figure 5*). Serial changes in percent atheroma volume and minimum lumen area at the non-culprit middle and distal segments of RCA (analyzed longitudinal length of matched segment =56 mm) were



Video 1 Coronary angiography of right coronary artery in 2020.

shown in [Table S1](#). This case does not experience any cardiovascular events since August 21st, 2019. His LDL-C and triglyceride-rich lipoprotein levels are favourably controlled (*Figure 1* and *Figure 6*).

Discussion

Several genetic studies have shown that triglyceride-rich lipoproteins and remnant cholesterol causally associate with ASCVD (1), which indicates these lipids as additional therapeutic targets to further reduce a risk of ASCVD under statin use. Pemafibrate is a potent

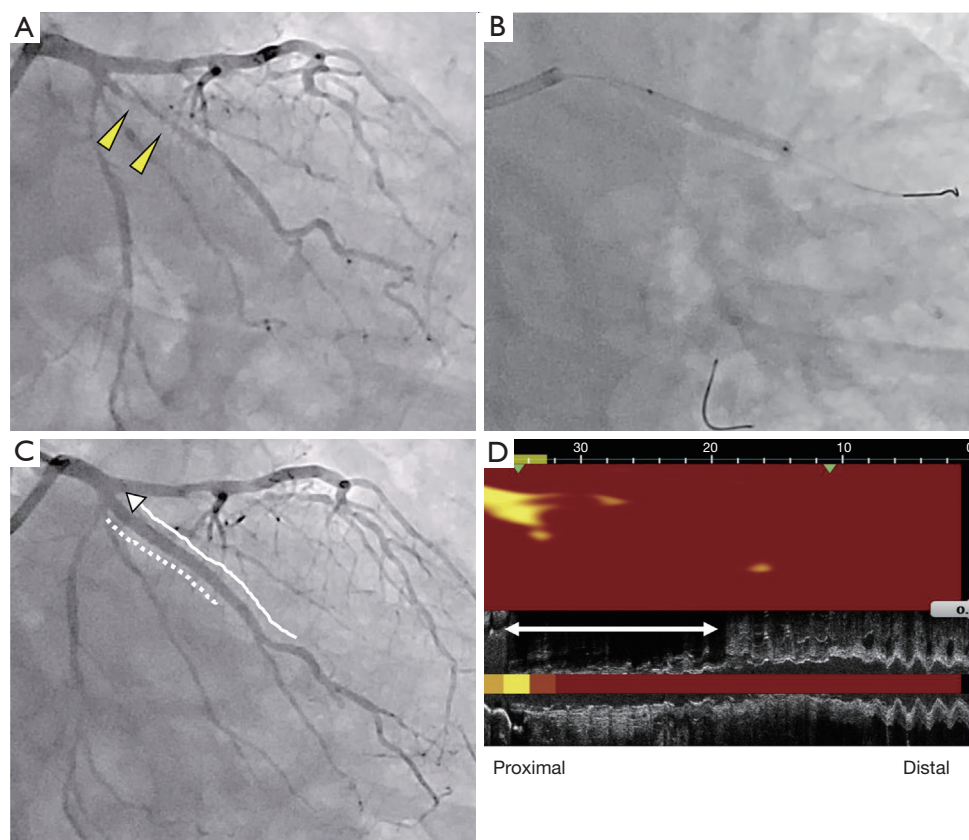


Figure 2 Elective PCI for progressed lesion at the obtuse marginal branch of left circumflex artery in 2020. (A) Coronary angiography revealed progression of coronary stenosis at the obtuse marginal branch of left circumflex artery (yellow arrow heads). (B,C) One everolimus-eluting stent (dotted white line) was implanted with the use of NIRS/IVUS. White arrow was the imaged segment by NIRS/IVUS. (D) Chemogram after stent implantation showed very small amount of yellow signal at this untreated segment (MaxLCBI_{4mm} = 29). Double heads white arrow indicates the segment receiving stent. PCI, percutaneous coronary intervention; NIRS/IVUS, near-infrared spectroscopy and intravascular; MaxLCBI_{4mm}, maximum 4-mm lipid-core burden index.

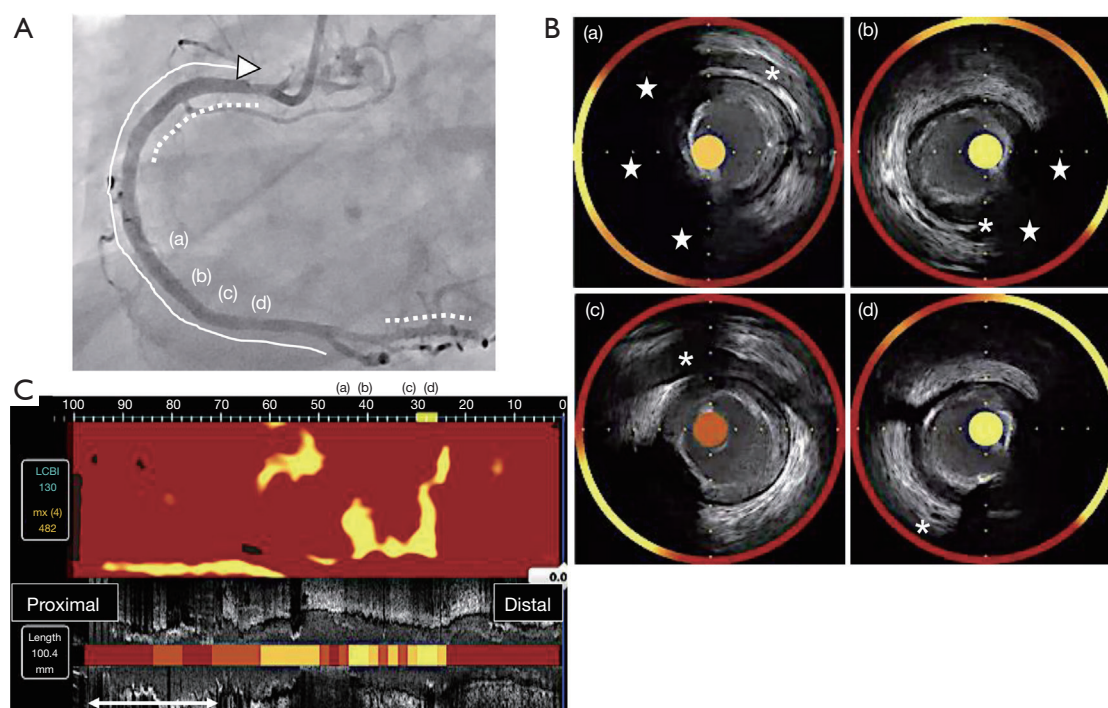
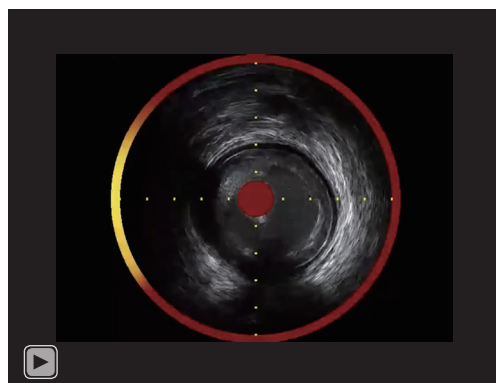


Figure 3 Evaluation of right coronary artery with NIRS/IVUS imaging in 2020. (A) There was no in-stent restenosis and disease progression in the right coronary artery. (a-d) corresponds to cross-sectional images in (B) and chemogram in (C). White dotted-lines indicate the implanted drug-eluting stents. While arrow was the imaged segment by NIRS/IVUS. (B) Atherosclerotic plaques of right coronary artery showed extensive ultrasonic attenuation with yellow signals [white stars: (a) and (b)]. Asterisk showed cardiac veins which were landmarks for matching IVUS images in 2020 and 2021. (C) MaxLCBI_{4mm} was 482 at this segment. Double heads white arrow indicates the segment receiving stent. NIRS/IVUS, near-infrared spectroscopy and intravascular; MaxLCBI_{4mm}, maximum 4-mm lipid-core burden index.



Video 2 NIRS/IVUS images of right coronary artery in 2020. NIRS/IVUS, near-infrared spectroscopy and intravascular.

selective peroxisome proliferator-activated receptor α modulator, which lowers triglyceride level by 30–40% with a reduction of apolipoprotein CIII, remnant cholesterol and non-HDL-C (2). In the current case, serial NIRS/IVUS imaging elucidated a reduction of MaxLCBI_{4mm}, accompanied by lowering triglyceride-rich lipoproteins with pemafibrate use. Mechanistically, apolipoprotein CIII promotes atherosclerosis via stimulating the production of adhesion molecules and inflammatory cytokines (3). Remnant cholesterol contains a large amount of cholesterol per particle and more avidly crosses the endothelial barrier (3), which potentially causes lipid-rich plaque formation. Modulating these triglyceride-rich lipoproteins

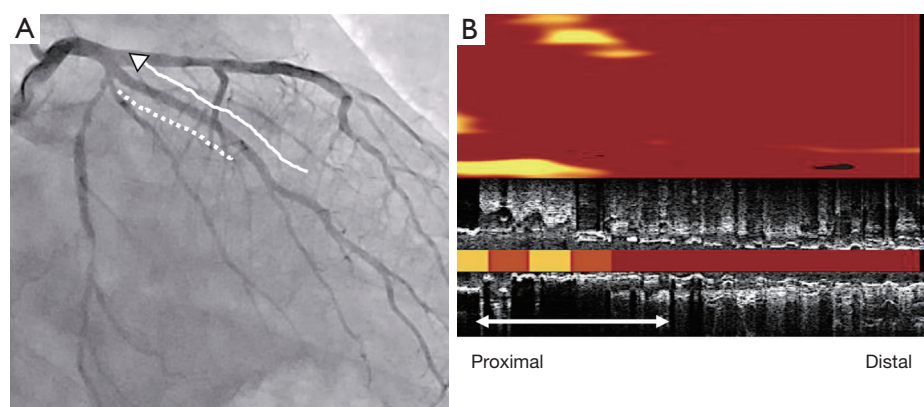


Figure 4 Coronary angiography of left coronary artery in 2021. (A) After pemafrbrate use for 18 months, in-stent restenosis and disease progression were not observed in left circumflex artery. White dotted line indicates the stented segment. White arrow indicates the segment imaged by NIRS/IVUS imaging. (B) On NIRS-derived chemogram, detected yellow signal was very small at this untreated segment ($\text{MaxLCBI}_{4\text{mm}} = 20$). Double heads white arrow indicates the segment receiving stent. NIRS/IVUS, near-infrared spectroscopy and intravascular; $\text{MaxLCBI}_{4\text{mm}}$, maximum 4-mm lipid-core burden index.

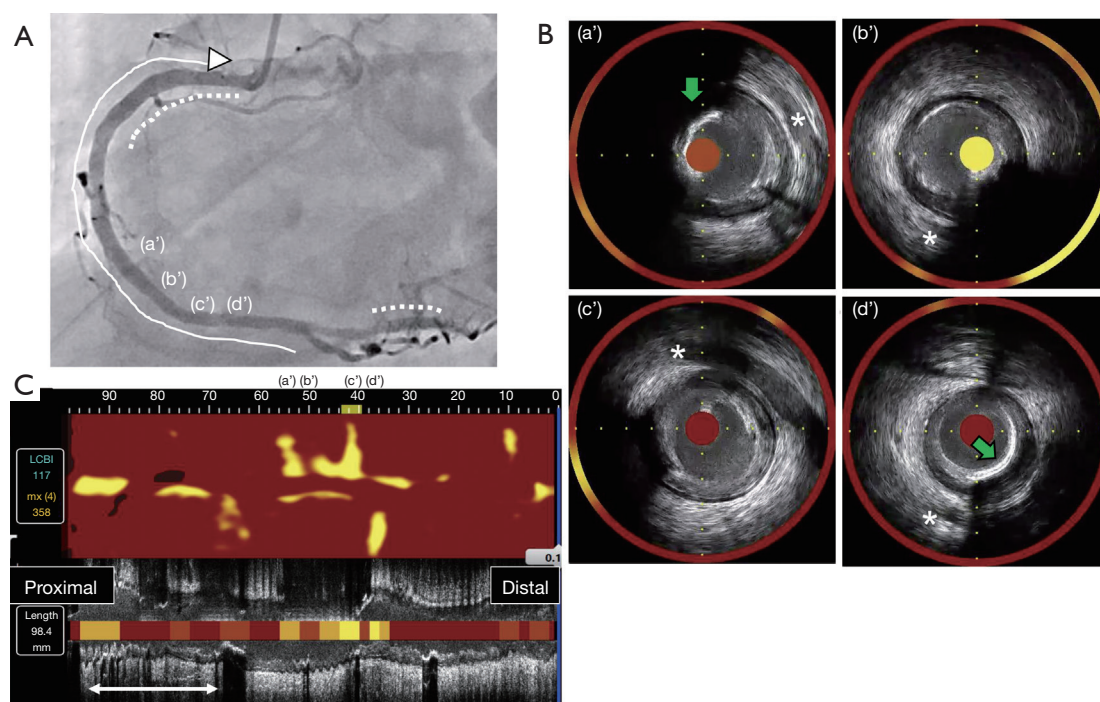
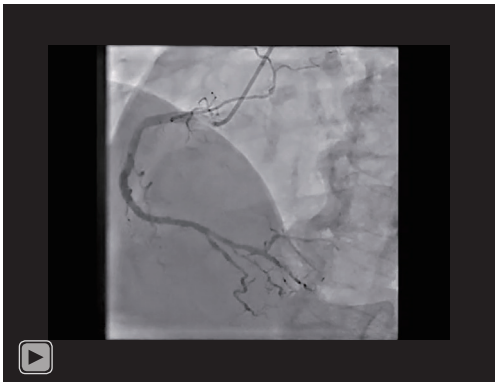
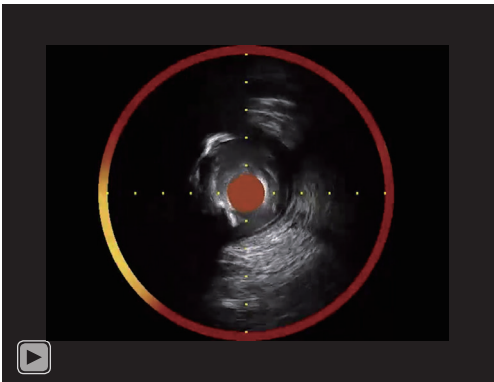


Figure 5 Evaluation of right coronary artery with NIRS/IVUS imaging in 2021. (A) Angiographic findings of right coronary artery in 2021 was not different from that in 2020. (a'-d') corresponds to cross-sectional images in (B) and chemogram in (C). White dotted-lines indicate the implanted drug-eluting stents. While arrow was the imaged segment by NIRS/IVUS. (B) Matched cross-sectional images revealed the formation of plaque calcification (green arrows) and a reduction of yellow signal (a'-d'). (C) $\text{MaxLCBI}_{4\text{mm}}$ in this untreated segment lowered to 358. Asterisks showed cardiac veins which were landmarks for matching IVUS imaging in 2020 and 2021. Double heads white arrow indicates the segment receiving stent. NIRS/IVUS, near-infrared spectroscopy and intravascular; $\text{MaxLCBI}_{4\text{mm}}$, maximum 4-mm lipid-core burden index.



Video 3 Coronary angiography of right coronary artery in 2021.



Video 4 NIRS/IVUS images of right coronary artery in 2021. NIRS/IVUS, near-infrared spectroscopy and intravascular.

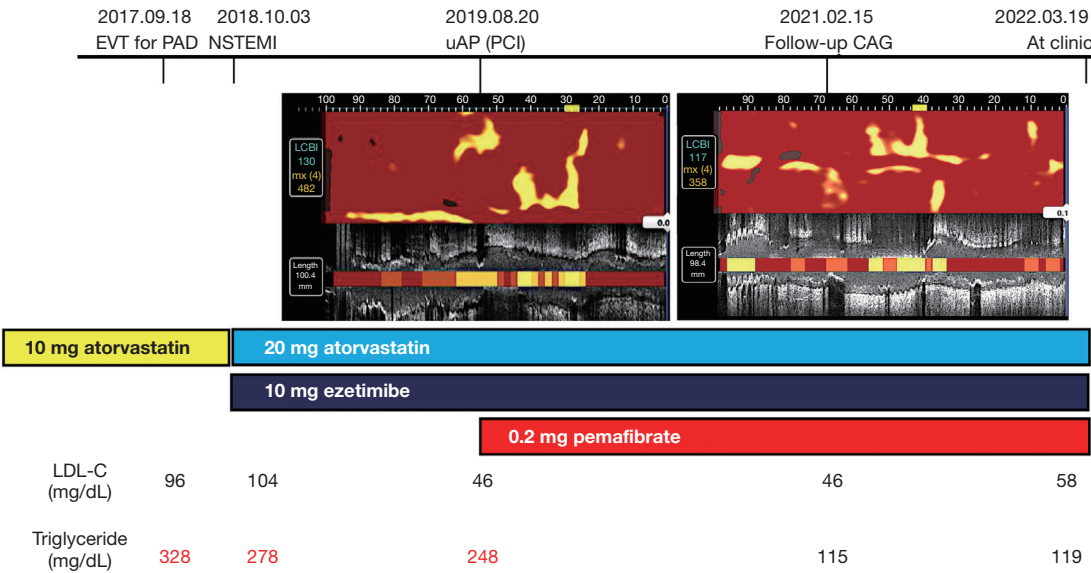


Figure 6 Timeline of this case. EVT, endovascular treatment; PAD, peripheral artery disease; NSTEMI, non-ST-elevation myocardial infarction; uAP, unstable angina pectoris; PCI, percutaneous coronary intervention; CAG, coronary angiography; LDL-C, low-density lipoprotein cholesterol.

with pemafibrate may induce the delipidation of coronary atheroma. MaxLCBI_{4mm} >400 at non-culprit segment has been reported to predict future cardiac events (4). A reduction of MaxLCBI_{4mm} in our case suggests plaque stabilization effect of pemafibrate which ultimately results in the prevention of future coronary events.

Plaque calcification under pemafibrate use is another intriguing observation. While statin promotes plaque calcification (5), it remains unknown whether plaque calcification was driven by statin and/or pemafibrate.

However, several mechanistic studies have reported an increased bone mineral density with the peroxisome proliferator activated receptor alpha agonist (6,7). The effect of pemafibrate on calcification requires further investigation.

The distance between NIRS imaging catheter and surface of plaque could affect MaxLCBI_{4mm}. We conducted serial NIRS imaging in this case. However, NIRS imaging catheter was not necessarily positioned at the exactly same location relative to evaluated plaques. Further refinement of

this imaging technique will be required for serial evaluation of MaxLCBI_{4mm}.

The strength of this case report is that serial NIRS/IVUS imaging allows to reveal anti-atherosclerotic effects of pemaifibrate *in vivo*. Currently, the PEMA-CORE study, a prospective randomized study using NIRS/IVUS and optical coherence tomography (OCT) is conducted to investigate the efficacy of pemaifibrate on coronary atherosclerosis in 300 patients with coronary artery disease who already received a statin (jRCTs031210067). This study is expected to further elucidate the efficacy of lowering triglyceride-rich lipoproteins with pemaifibrate on coronary atheroma progression and instability. The limitation of this study is that we did not conduct three-vessel NIRS/IVUS imaging in this case. It remains unknown how much anti-diabetic agents modulated coronary atherosclerosis.

Conclusions

In conclusion, a delipidation of coronary atheroma, accompanied by greater plaque calcification was observed after the commencement of pemaifibrate. This finding highlights potential anti-atherosclerotic benefit of pemaifibrate use in patients receiving a statin.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://cdt.amegroups.com/article/view/10.21037/cdt-22-401/rc>

Peer Review File: Available at <https://cdt.amegroups.com/article/view/10.21037/cdt-22-401/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://cdt.amegroups.com/article/view/10.21037/cdt-22-401/coif>). YK has received research support from Kowa, Nipro and Abbott, and honoraria from Nipro, Abbott, Kowa, Amgen, Sanofi, Astellas, Takeda and Daiichi-Sankyo. YK serves as an unpaid Editorial Board Member of *Cardiovascular Diagnosis*

and *Therapy* from September 2021 to August 2023. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Table S1 IVUS measures at the non-culprit segment of RCA

IVUS measures	2019	2021	Absolute change
Percent atheroma volume	59.4%	57.3%	−2.1%
Minimum lumen area	5.53 mm	6.13 mm	+0.6 mm

IVUS, intravascular ultrasound; RCA, right coronary artery.