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COMMENT

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Lessons from PROMINENT and prospects for pemafibrate

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Abstract

The neutral result of the PROMINENT trial has led to questions about the future for pemafibrate. This commentary discusses possible reasons for the lack of benefit observed in the trial. There were, however, indicators suggesting therapeutic potential in microvascular ischaemic complications associated with peripheral artery disease, with subsequent analysis showing reduction in the incidence of lower extremity ischaemic ulceration or gangrene. Reassurance about the safety of pemafibrate, together with emerging data from PROMINENT and experimental studies, also suggest benefit with pemafibrate in non-alcoholic fatty liver disease (alternatively referred to as metabolic dysfunction-associated steatotic liver disease) and microangiopathy associated with diabetes, which merit further study.

Keywords PROMINENT trial, Pemafibrate, Type 2 diabetes mellitus, Diabetic retinopathy, Peripheral artery disease

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For decades, there has been controversy about the role of triglyceride (TG)-rich lipoproteins (TRLs) and their remnants-for which plasma TGs are a surrogate biomarker-in atherosclerotic cardiovascular disease (ASCVD). Observational data from prospective cohort studies showed an association between elevated TGs and ASCVD [1–4]. Additionally, in high-risk patients (including those with type 2 diabetes mellitus [T2DM]) and well controlled levels of low-density lipoprotein cholesterol (LDL-C), residual cardiovascular risk was higher in those with high versus lower TG levels [5–7]. Genetic studies have helped to disentangle vascular risk attributable to elevated TG levels from that attributable to low levels of high-density lipoprotein cholesterol (HDL-C) showing that elevated levels of TRLs were independently linked with increased coronary heart disease risk whereas low HDL-C was not [8, 9]. The advent of Mendelian randomization design further helped to establish elevated TRLs as a likely causal factor in ASCVD [3].

Demonstrating that lowering TGs with a conventional fibrate (a peroxisome proliferator-activated receptor

alpha [PPARα] agonist) reduced cardiovascular events in high-risk patients has been challenging. While early trials suggested benefit from fibrate monotherapy [10, 11], later trials in patients receiving contemporary evidence-based therapy including a statin (unplanned drop-in of about 20% in the Fenofibrate Intervention and Event Lowering in Diabetes [FIELD] study and as planned in the Action to Control Cardiovascular Risk in Diabetes [ACCORD] study) were not positive [12, 13], in part confounded by issues with trial design and patient selection [13]. Post hoc analyses did, however, suggest that patients with elevated TG levels or mixed dyslipidaemia (high TG levels and low HDL-C]) derived benefit from fibrate therapy [14–16], although the limitations inherent in such post hoc analyses should be borne in mind.

Given that conventional fibrates have relatively weak PPARα agonistic potency, and the potential for reversible elevation in serum creatinine (with fenofibrate) [17, 18], as well as liver enzyme elevation especially in combination with a statin [19], alternative PPARα agonists were sought that may offer improved selectivity and potency for PPARα and better tolerability. The result was the selective peroxisome proliferator-activated modulator-α (SPPARMα) pemafibrate, which has shown greater potency for PPARα activation (>2,500 times versus fenofibric acid, the active form of fenofibrate) and improved specificity for PPARα over conventional fibrates [20–22]. In phase II/III trials in Japanese and European patients with dyslipidaemia pemafibrate in combination with a statin was effective in lowering TG levels (by up to 50%) irrespective of pre-existing renal dysfunction [23, 24], with only minor changes in serum creatinine (less than with fenofibrate) [13, 24, 25], as well as reduction in liver enzymes, compared with increases in studies with fenofibrate [24, 25]. Based on this favourable risk/benefit profile, pemafibrate was selected to test the rationale that lowering TG levels reduces cardiovascular risk in the PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) trial [26].

The PROMINENT study

PROMINENT was a well-designed, large, randomized, placebo-controlled multinational study. The investigators were careful to ensure inclusion of an appropriate patient population with elevated TGs and low HDL-C to avoid criticism as in past fibrate trials [27]. Thus, PROMINENT planned to include ~ 10,000 high-risk patients with the mixed dyslipidaemia of T2DM, defined by TG levels of 200–499 mg/dL (2.26–5.64 mmol/L) and low HDL-C (≤ 40 mg/dL or 1.03 mmol/L), who were randomized to treatment with pemafibrate (0.2 mg twice daily) or matching placebo. The average expected follow-up period was 3.75 years. Patients were required to receive either moderate-to-high intensity statin therapy or meet specified LDL-C criteria. At baseline, median TGs were 271 mg/dL (3.1 mmol/L), median LDL-C was 78 mg/dL (~ 2.0 mmol/L) with almost all patients on a statin (69% on high-intensity statin treatment), and about one-third of the cohort were high-risk primary cardiovascular prevention patients.

Despite a well-argued rationale, supported by strong observational, genetic, and mechanistic evidence [3, 27], PROMINENT was terminated early after full recruitment (n=10,497) on the advice of an independent data and safety monitoring board for reasons of futility. Despite lowering TGs by 26% (placebo-corrected), treatment with pemafibrate did not reduce major adverse cardiovascular events, a composite of nonfatal myocardial infarction, ischaemic stroke, coronary revascularization, or death from cardiovascular causes (hazard ratio 1.03, 95% confidence interval [CI], 0.91 to 1.15), with no apparent effect modification in any prespecified subgroup [26].

PROMINENT did provide further insights into the safety of pemafibrate. Overall, pemafibrate did not differ significantly from placebo with respect to the incidence of adverse events, including infections and musculoskeletal complications. There was a slight excess in the incidence of investigator-reported adverse renal events with pemafibrate versus placebo (1463 vs. 1347 patients, p=0.004), with increases in both chronic kidney disease (CKD, 180 vs. 117 patients, p<0.001) and acute kidney injury (160 vs. 106 patients, p=0.001). Pemafibrate treatment was also associated with a small increase in median serum creatinine and decrease in estimated glomerular filtration rate, although both returned to baseline levels similar to that of the placebo group after discontinuation of treatment [26]. Similar findings have been reported with fenofibrate in the ACCORD and FIELD trials [12, 18], although another study suggested that long-term fenofibrate may delay impairment in renal function in T2DM patients [17]. The underlying mechanisms to explain the differences in impact on kidney function between pemafibrate and fenofibrate, as well as the drug-induced elevation of serum creatinine, are not fully understood.

Compared with placebo, the pemafibrate treatment group had an increase in the number of patients with investigator-reported venous thromboembolism events (71 vs. 35, p<0.001), pulmonary embolism (40 vs. 19, p=0.008), and deep-vein thrombosis 45 vs. 19, p=0.001) [26]. Similarly, the FIELD trial reported a significant increase in pulmonary embolism with fenofibrate versus placebo (0.7%vs. 1.1%, p=0.022) [12], in line with some previous reports [28, 29] suggesting possible caution in patients with a history of thromboembolic events. On the other hand, PROMINENT reported a decrease in investigator-reported non-alcoholic fatty liver disease

(NAFLD) events [26], consistent with previous reports [30]. To overcome issues associated with the terms 'non-alcoholic' and 'fatty', the nomenclature metabolic dysfunction-associated steatotic liver disease (MASLD) as advocated by expert consensus [31] has been adopted in this review.

The reasons why pemafibrate failed to show significant benefit on cardiovascular events are uncertain. One factor may relate to the intensity of background statin therapy in PROMINENT. TG lowering with pemafibrate was less than that anticipated based on phase II/III clinical trials in patients treated with less intense statin regimens [21, 24, 26] (~45% to >50%%) [23, 32]. Subgroup analyses of PROMINENT showed that the TG-lowering response with pemafibrate was attenuated with high-intensity statin treatment compared with less intense statin regimens (TG reduction by 24.6% versus 28.5% for patients on a moderate-intensity statin and 34.3% on low intensity or no statin). As statins decrease both LDL-C and TG in patients with hypertriglyceridaemia, with efficacy dependent on baseline levels of each lipid parameter [33], the TG-lowering effects of high-intensity statin treatment are likely to have impacted TG-lowering with pemafibrate in this subgroup. Indeed, while there was no evidence of heterogeneity in treatment effects when analysed according to statin intensity groups, among 2,636 patients on a moderate-intensity statin, incidence rates for the primary endpoint appeared to favour pemafibrate treatment (incidence rates 3.63 vs. 3.90 on placebo), although this was not statistically significant [26].

The influence of low baseline LDL-C levels in PROMINENT (median 78 mg/dL or ~2.0 mmol/L) also merits discussion [34]. Pemafibrate treatment reduced remnant cholesterol by 43.6% (25.6% after correction for placebo) [26], but in contrast to phase II/III trials [24], did not lower levels of small dense LDL (sdLDL), as estimated by Sampson's Equation [35, 36]. A recent study in 1,508 T2DM patients (over 50% on a statin) and 670 controls showed that the slope of the regression curve between sdLDL and TG flattened at lower LDL-C levels, implying that rigorous control of LDL-C might minimize the inhibitory effect of pemafibrate on sdLDL production [37]. The underlying mechanisms are not defined, although it has been suggested that lower LDL-C concentrations may attenuate the involvement of TG in sdLDL generation, or alternatively, activation of hepatic TG lipase and promotion of sdLDL generation by pemafibrate treatment may counteract the decrease in sdLDL-C due to lower TG [36].

Some have suggested that the neutral results of PROMINENT may relate to the small increases in LDL-C and apolipoprotein B100 (apoB) with pemafibrate, although differences between the groups subsequently declined, and were similar after 30 days washout at study close [26]. While evidence supports apoB as a predictor of coronary heart disease (CHD) risk, this may be an oversimplification as it is an indirect measure of the total concentration of all apoB-containing particles which differ substantially by class. Although apoB is strongly correlated with LDL, it may fail to adequately capture variations in other apoB containing lipoproteins present at much lower concentration. The composition of LDL particles also merits consideration, with a recent prospective study showing a positive association between mean TG molecules per LDL particle and CHD risk but no associations with other lipid fractions or lipid particles [38]. Thus, LDL-TG rather than TG plasma concentration may represent a better biomarker of cardiovascular risk in the setting of hypertriglyceridaemia with well controlled LDL-C levels. Alternatively, absolute mass changes in remnant cholesterol, LDL-C, and apoB may be more relevant, with both higher total atherogenic cholesterol and higher apoB explaining the results of PROMINENT [39].

Increases in LDL-C levels are not unique to pemafibrate. REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial) also showed a median 3.1% increase in LDL-C levels with high-dose icosapent ethyl (*supplement to publication*), but treatment was associated with 25% reduction in the primary composite endpoint (cardiovascular death, myocardial infarction, stroke, coronary revascularization, or unstable angina requiring hospitalization) [40]. Similarly, increases in LDL-C have been reported with the sodium-glucose cotransporter 2 (SGLT2) inhibitors, of the order of 4–5 mg/dL or ~10% increase from baseline with empagliflozin or canagliflozin [41–44]. In a meta-analysis of 60 randomized controlled trials with SGLT2 inhibitors, increases in total and LDL cholesterolwere similar (0.09 and 0.08 mmol/L), varying slightly by drug dose and ethnicity [45]. However, given the beneficial effects of this drug class in reducing cardiovascular death in T2DM patients [41–43], these modest lipid changes are unlikely to be clinically relevant. The mechanism(s) of this increase in LDL-C is uncertain, possibly involving both delayed LDL clearance from the circulation and increased plasma lipoprotein lipase activity [46]. While this finding aligns with the proposed explanation of enhanced lipolysis of TRLs increasing LDL-C levels with pemafibrate, it does not explain the neutral effect on cardiovascular outcomes observed in PROMINENT.

The above discussion focuses on potential factors influencing the efficacy of pemafibrate on cholesterol-related residual risk. However, evidence from an analysis of three major multinational trials that investigated the effect of TG-lowering on cardiovascular outcomes in high-risk patients receiving contemporary statin treatment, i.e., PROMINENT, REDUCE-IT, and STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk

with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia) has underlined the importance of residual inflammatory risk. In this analysis, residual inflammatory risk (as measured by high-sensitivity C-reactive protein [hsCRP]) was a stronger predictor of cardiovascular outcomes than residual cholesterol risk [47]. This is relevant to the PROMINENT patient population, which was characterized by high inflammatory risk (more than half of patients had hsCRP levels ≥ 2 mg/L) and implies that intervention targeting both cholesterol and inflammatory components is needed to sufficiently impact residual cardiovascular risk inT2DM patients.

In summary, the take-home message from PROMINENT is that pemafibrate does not reduce cardiovascular events in T2DM patients with elevated TG and low HDL-C and well controlled LDL-C levels on intense statin therapy. Although there may be benefit when LDL-C is less tightly controlled, evidence that residual inflammatory risk is a stronger predictor of cardiovascular outcomes than cholesterol residual risk, especially in T2DM patients [47], argues for combination therapy targeting both components of risk.

Does PROMINENT suggest new prospects for pemafibrate?

The lack of a positive outcomes trial does not signal the end of the road for pemafibrate. Emerging data from PROMINENT suggest potential benefit with pemafibrate on complications of peripheral artery disease (PAD), as well as MASLD events (referred to as NAFLD in the trial), both of which have unmet clinical needs. In patients with T2DM, PAD tends to occur earlier and is often more severe and diffuse in than in nondiabetic patients, with the underlying pathophysiology driven by both progression of atherosclerotic disease and microvascular damage (mostly peripheral neuropathy) from chronic hyperglycaemia. In PROMINENT, pemafibrate treatment was associated with a clinically-relevant 13% relative reduction in new or worsening PAD events (hazard ratio 0.87, 95% CI 0.69–1.09) [26]. A secondary analysis [48] evaluated treatment effects on complications of PAD, i.e., incident lower ischaemic extremity ulceration or gangrene, defined as the new occurrence of lower extremity ulceration (leg or foot) or gangrene with diagnostic testing indicative of new or worsening obstructive PAD. Incidence rates (per 1000 person-years) for this composite outcome were 2.1 in the pemafibrate group vs. 3.4 in the placebo group, resulting in a 37% relative reduction in risk (hazard ratio, 0.63; 95% CI 0.41–0.95; $p=0.03$), as well as 53% reduction in the risk of gangrene (hazard ratio 0.47, 95% CI 0.25–0.87; $p=0.01$), and a lower incidence of ulcer (not statistically significant) [48]. These findings suggest novel therapeutic potential for pemafibrate in a setting with an unmet need for preventive therapies for distal small vessel ischaemic complications associated with PAD. Thus, while the combination of high-intensity statin therapy with pemafibrate may obscure the added advantage of pemafibrate in preventing macrovascular events, such as cardiovascular events, it does not seem to affect its efficacy in addressing microvascular complications as shown by this exploratory analysis of PROMINENT. This distinction in outcomes could be attributed to the lipid-independent mechanisms of action associated with pemafibrate.

For severe limb ischaemia caused by occlusive PAD, however, surgical treatment involving autologous vein grafts is the main therapeutic option, but graft failure is common within the first postoperative year [49, 50]. Insights into the cellular and molecular mechanisms that underlie vein graft failure could offer new therapeutic targets. In a recent study using a combination of proteomics, network analysis, and high-resolution ultrasonography in an experimental vein graft disease model, PPARα activation mediated by pemafibrate suppressed the development of vein graft failure and arteriovenous fistula lesions [51]. Although preliminary, these promising data merit further study and extrapolation to a clinical setting.

PROMINENT also hinted at possible benefit with pemafibrate in MASLD. Pemafibrate significantly reduced any hepatic adverse event (incidence per 100 person-years, 1.35 vs. 1.64, hazard ratio 0.83, 95% CI 0.69–0.99, $p=0.04$), as well as investigator-reported MASLD events (referred to as NAFLD in the trial) (incidence per 100 person-years 0.95 vs. 1.22, hazard ratio 0.78, 95% CI 0.63–0.96, $p=0.02$) [26]. Although absolute event numbers were small, these findings warrant further analysis. Other studies have shown that pemafibrate treatment decreased markers of liver dysfunction and non-invasive surrogates for liver fibrosis [52–55]. In a randomized placebo-controlled trial, treatment with pemafibrate reduced liver stiffness assessed by magnetic resonance elastography, although there was no significant reduction in liver fat [56]. With MASLD recognized as among the most prevalent chronic diseases globally, especially in low-to-middle income countries [57], these findings with pemafibrate are encouraging. An ongoing trial is investigating combination treatment with pemafibrate and an SGLT2 inhibitor in patients with non-alcohol related steatohepatitis and liver fibrosis, the more severe presentation of MASLD, with results anticipated in 2025 (ClinicalTrials.gov Identifier NCT05327127).

Novel insights from preclinical studies

There are also intriguing insights suggesting a possible beneficial role for pemafibrate in several settings with unmet clinical needs, notably diabetic eye disease [58]. One area of interest is in diabetic retinopathy, especially

given evidence of benefit with fenofibrate in the FIELD and ACCORD trials, specifically in reduction in retinopathy progression, as shown by 31% reduction in first laser treatment in FIELD [59] and 40% reduction in progression, as assessed by the Early Treatment Diabetic Retinopathy Study Severity Scale in ACCORD [60].

Table 1 Potential of pemafibrate for therapeutic areas of unmet need in diabetes patients

Indication	Clinical or preclinical evidence?	Citation	Summary of evidence
PAD complications	Clinical	[26] [48]	PROMINENT: • 13% relative reduction in new or worsening PAD events • 37% relative reduction in lower ischaemic extremity ulceration/ gangrene
NAFLD (MASLD)	Clinical	[26] [52–55]	• PROMINENT: Reduced any hepatic adverse event ($p=0.04$), and investigator-reported NAFLD (MASLD) events ($p=0.02$) • Other trials: decreased markers of liver dysfunction and non-invasive surrogates for liver fibrosis
Diabetic retinopathy	Preclinical	[62, 63] [64, 65]	• Inhibited retinal inflammation, vascular leukostasis and leakage (ocular ischaemia) • Protected retinal function (diabetic retinopathy) • Suppressed retinal pathological neovascularization (oxygen-induced retinopathy)
Chronic kidney disease	Preclinical Clinical	[67] [68]	• Suppressed increases in plasma creatinine and blood urea nitrogen levels, decreased renal fibrosis and inhibited upregulation of inflammatory mediators in animal models • Efficacy and safety in patients with renal insufficiency
Abdominal aortic aneurysm (AAA)	Preclinical	[73]	• Prevented fatal aortic rupture, in part due to anti-oxidative and anti-inflammatory effects (model of angiotensin-II-induced AAA)

AAA Abdominal aortic aneurysm; *PAD* peripheral artery disease; *MASLD* metabolic dysfunction-associated steatotic liver disease; *NAFLD* non-alcoholic fatty liver disease

Moreover, a meta-analysis of large cardiovascular trials showed that fenofibrate treatment reduced the need for retinal laser treatment by over 20% versus placebo [61]. Given a role of PPARα activation in this indication, and the higher specificity of pemafibrate for PPARα [20], suggests potential benefit with pemafibrate, although there are so far no data from PROMINENT. However, there are encouraging findings from preclinical models. Oral administration of pemafibrate inhibited retinal inflammation and retinal vascular leukostasis and leakage in a mouse model of carotid artery occlusion-induced ocular ischaemia [62], and in an experimental rat model of diabetic retinopathy improved systemic metabolism, protected retinal function [63], and improved inner retinal dysfunction [64]. Pemafibrate also suppressed retinal pathological neovascularization in a mouse model of oxygen-induced retinopathy [65], and suppressed choroidal neovascularization, an important cause of age-related macular degeneration [66]. These findings suggest a rationale for further study.

Beyond these effects, there are experimental data that suggest therapeutic potential for renal protective effects of pemafibrate in CKD patients. In an adenine-induced mouse model of CKD, administration of pemafibrate suppressed increases in plasma creatinine and blood urea nitrogen levels, decreased renal fibrosis and inhibited upregulation of inflammatory mediators such as interleukin-6 [67]. Clinical studies have demonstrated the efficacy and safety of pemafibrate in CKD patients with a wide range of renal insufficiency [68], and in a case study in patients with IgA nephropathy [69].An ongoing trial, PROFIT-CKD (Pemafibrate, open-label, Randomized cOntrolled study to evaluate the renal protective eFfect In hyperTriglyceridemia patients with Chronic Kidney Disease) aims to assess renal protective effects of pemafibrate in CKD patients, with change in urine protein/creatinine ratio over 12 months as study outcome [70]. Prevention of abdominal aortic aneurysm (AAA) rupture, which so far lacks effective preventive treatments beyond surgical approaches, is another area of interest with pemafibrate, given beneficial effects on inflammation and oxidative stress (Table 1).

Conclusion

The fibrates have had a chequered history in clinical outcomes studies, and PROMINENT has provided another twist to this story. While some have claimed that PROMINENT represents the 'swan song of the fibrates' [71], further data emerging from this trial, together with experimental studies, suggest otherwise. In particular, the possibility of favourable effects on diabetic-related microangiopathy suggests that the SPPARMα agonist pemafibrate may offer new opportunities to addressing the largely unmet clinical need of residual

microvascular risk, specifically in PAD complications, as well as in MASLD (NAFLD) [72]. The answers await further research driven by the fine details emerging from PROMINENT.

Abbreviations

AAA	Abdominal aortic aneurysm
ACCORD	Action to Control Cardiovascular Risk in Diabetes trial
ApoB	Apolipoprotein B100
ASCVD	Atherosclerotic cardiovascular disease
CHD	Coronary heart disease
CI	Confidence interval
CKD	Chronic kidney disease
FIELD	Fenofibrate Intervention in Event Lowering in Diabetes trial
HDL-C	High-density lipoprotein cholesterol
hsCRP	High-sensitivity C-reactive protein
LDL-C	Low-density lipoprotein cholesterol
MASLD	Metabolic dysfunction-associated steatotic liver disease
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
PAD	Peripheral arterial disease
PROFIT-CKD	Pemafibrate, open-label, Randomized cOntrolled study to evaluate the renal protective eFfect In hyperTriglyceridemia patients with Chronic Kidney Disease
PROMINENT	Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) trial
sdLDL-C	Small dense LDL-C
SGLT2	Sodium-glucose cotransporter 2
SPPARMα	Selective peroxisome proliferator-activated modulator-α
T2DM	Type 2 diabetes mellitus
TG	Triglyceride
TRL	Triglyceride-rich lipoprotein

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable for this comment. All patients in the PROMINENT study gave written informed consent. The study was approved at participating centres by the responsible institutional review board or ethics committee, as applicable, and by regulatory authorities in the 24 countries where the trial was conducted.

Consent for publication
Not applicable.

Competing interests
J-CF and JF-N report personal fees for consultancy from Kowa Company, Ltd. SY reports grants and personal fees from Kowa Company, Ltd., Otsuka Pharmaceutical Co., Ltd., Shionogi & Co., Ltd., Bayer Yakuhin, Ltd., MSD K.K., Takeda Pharmaceutical Company, Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Astellas Pharma Inc., Daiichi-Sankyo Company, Ltd., Astra Zeneka K.K., Kaken Pharmaceutical Co., Ltd., grants from Nippon Boehringer Ingelheim Co., Ltd., National Institute of Biomedical Innovation, Kyowa Medex Co., Ltd., Mochida Pharmaceutical Company, Ltd., Hayashibara Co., Ltd., Teijin Pharma Limited and Kissei; and personal fees from Ono Pharmaceutical Company, Ltd., Skylight Biotec, Inc., Pfizer, Astellas Amgen, Sanofi, and Aegerion In addition, M Yamashita has a patent PCT/JP2016/074402 (Assisting Method for the Diagnosis of Type III Hyperlipidemia) pending to Fujirebio & Osaka University, a patent PCT/JP2017/038766 (Method for Selecting Subject Needing Treatment for Dyslipidemia and Reagent for Such Selection) pending to Osaka University & Kyowa Medex Co., Ltd., and a patent PCT/JP2017/038715 (Method for Measuring Oxidized High-Density Lipoprotein) pending to Osaka University & Kyowa Medex Co.PL reports a research grant from Novartis and honoraria as a scientific advisory board member for Dalcor Pharmaceuticals, and provides unpaid consultancy for Amgen, AstraZeneca, Ionis Pharmaceuticals, Kowa Pharmaceuticals, Pfizer, Sanofi-Regeneron, XBiotech Inc., Corvidia Therapeutics, IFM Therapeutics, Olatec Therapeutics, Medimmune and Esperion Therapeutics.KY reports grants and personal fees from Kowa Pharmaceutical Co, Astellas, AstraZeneca, MSD, Sanofi, Takeda, Pfizer, Mochida, and personal fees from Kowa Company, Astellas-Amgen Biopharm, and Bayer.TK is the recipient of a research grant from Kowa Company. YT reports research grants from the Alcon Research Institute, Manpei Suzuki Diabetic Foundation, Oguchi Foundation, and Kowa Life Science Foundation. PMR reports grants from Kowa, Inc, Novartis, and Pfizer. AZ reports honoraria for lectures from Abbott, Amgen, Sanofi and Mylan. MPH reports no conflict of interest.

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