EnM
ENDOCRINOLOGY AND METABOLISM

Original Article

Endocrinol Metab 2016;31:120-126
http://dx.doi.org/10.3803/EnM.2016.31.1.120
pISSN 2093-596X · eISSN 2093-5978

Effect of Pitavastatin Treatment on ApoB-48 and Lp-PLA$_2$ in Patients with Metabolic Syndrome: Substudy of PROspective Comparative Clinical Study Evaluating the Efficacy and Safety of PITavastatin in Patients with Metabolic Syndrome

Hyo-Sun Lee[1], Chang Hee Jung[2], Sung Rae Kim[3], Hak Chul Jang[4], Cheol-Young Park[1]; PROPIT Study Team

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul; [2]Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul; [3]Department of Endocrinology, College of Medicine, The Catholic University of Korea, Seoul; [4]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea

Background: Apolipoprotein (Apo) B-48 is an intestinally derived lipoprotein that is expected to be a marker for cardiovascular disease (CVD). Lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$) is a vascular-specific inflammatory marker and important risk predictor of CVD. The aim of this study was to explore the effect of pitavastatin treatment and life style modification (LSM) on ApoB-48 and Lp-PLA$_2$ levels in metabolic syndrome (MS) patients at relatively low risk for CVD, as a sub-analysis of a previous multi-center prospective study.

Methods: We enrolled 75 patients with MS from the PROPIT study and randomized them into two treatment groups: 2 mg pitavastatin daily+intensive LSM or intensive LSM only. We measured the change of lipid profiles, ApoB-48 and Lp-PLA$_2$ for 48 weeks.

Results: Total cholesterol, low density lipoprotein cholesterol, non-high density lipoprotein cholesterol, and ApoB-100/A1 ratio were significantly improved in the pitavastatin+LSM group compared to the LSM only group ($P \leq 0.001$). Pitavastatin+LSM did not change the level of ApoB-48 in subjects overall, but the level of ApoB-48 was significantly lower in the higher mean baseline value group of ApoB-48. The change in Lp-PLA$_2$ was not significant after intervention in either group after treatment with pitavastatin for 1 year.

Conclusion: Pitavastatin treatment and LSM significantly improved lipid profiles, ApoB-100/A1 ratio, and reduced ApoB-48 levels in the higher mean baseline value group of ApoB-48, but did not significantly alter the Lp-PLA$_2$ levels.

Keywords: Apolipoprotein B-48; Lp-PLA$_2$; Metabolic syndrome; Pitavastatin

Received: 25 July 2015, **Revised**: 3 August 2015, **Accepted:** 4 August 2015
Corresponding author: Cheol-Young Park
Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongno-gu, Seoul 03181, Korea
Tel: +82-2-2001-1869, **Fax:** +82-2-2001-1588, **E-mail:** cydoctor@chol.com

INTRODUCTION

With an increasing prevalence worldwide, metabolic syndrome (MS) has become a leading health concern [1]. MS is associated with a 2-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality [2]. Dyslipidemia is one diagnostic criteria for the MS and these lipid abnormalities are recognized risk factors for cardiovascular disease (CVD) [3]. Statins decrease significant CVD risk in patients with MS by reducing low density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels and possibly by decreasing inflammation [4].

Apolipoprotein B (ApoB) is the main structural surface protein found on all β lipoproteins and is known to cause atherosclerosis [5]. Of two type of ApoB, ApoB-48 is an intestinally derived lipid with a chylomicron remnant that increases in postprandial hyperlipidemia, a known risk factor of coronary artery disease (CAD) [6]. The effect of statins on hepatic ApoB-100 is well known [7], but the direct effect of statins on intestinal ApoB-48 is less well understood.

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2), an emerging biomarker of cardiovascular risk, is an inflammatory enzyme expressed in macrophages of atherosclerotic plaques and carried in the circulation predominantly bound to LDL-C [8,9]. Recently, analysis of data from 32 prospective studies linked LP-PLA_2 activity directly with the risk of CVD [10]. Previous studies report that increased Lp-PLA_2 activity is associated with MS and incident fatal and non-fatal CVD [11]. High Lp-PLA_2 activity is observed in subjects with the MS and associated with several lipid-related risk factors such as ApoB [12].

Therefore, the purpose of the present study was to evaluate the effect of pitavastatin and life style modification (LSM) treatment on ApoB-48 and Lp-PLA_2 levels in subjects with MS, using serum samples from the PROPIT (PROspective comparative clinical study evaluating the efficacy and safety of PITavastatin in patients with metabolic syndrome) trial.

METHODS

Trial design

The PROPIT trial was a 12-month, multicenter, prospective, randomized open label study at 10 clinical centers in Korea. The detailed protocol for PROPIT has been previously described [13]. Briefly, after screening, selected subjects with MS were randomized into two groups: the pitavastatin (2 mg daily)+intensive LSM group or the intensive LSM only group. Subjects with LDL ≥190 mg/dL or glycated hemoglobin (HbA1c) ≥8% at the 24-week (6-month) follow-up visit were withdrawn from the study because there was a drug-naïve arm in our study design. All subjects were trained for LSM with the same protocol at the time of enrollment by health professionals.

Study subjects

Between February 2008 and December 2010, 164 MS patients were enrolled in the PROPIT study. Among them, we randomly selected 37 and 38 subjects for the pitavastatin and LSM groups, respectively, after matching for age, sex, and body mass index.

Eligible patients were men and women aged 18 to 75 years with central obesity (waist circumference: men ≥90 cm, women ≥85 cm, according to guideline of the Korean Society for the Study of Obesity) [14] and impaired fasting glucose (fasting glucose ≥100 mg/dL), which are essential components of MS, and one or more of the followings components: (1) TG ≥ 150 mg/dL; (2) high density lipoprotein (HDL) for men ≤40 mg/dL, and for women ≤50 mg/dL; and (3) systolic blood pressure ≥130 mm Hg or diastolic blood pressure (DBP) ≥85 mm Hg. Selected subjects had no prior history of atherosclerosis or CVD. They were statin naïve, with no prior use of oral hypoglycemic agents.

The exclusion criteria were the use of statins within the preceding 3 months; uncontrolled hypertension (DBP ≥95 mm Hg); poorly controlled diabetes (HbA1c ≥8.0%); high cholesterolaemia (LDL ≥190 mg/dL or TG ≥400 mg/dL); a past medical history of coronary disease, atherosclerosis, malignancy or severe infective disease; renal dysfunction (creatinine ≥ 2.0 mg/dL) or hepatic dysfunction (aspartate aminotransferase or alanine aminotransferase ≥upper normal limit [UNL] × 2.5); uncontrolled hypothyroidism (thyroid-stimulating hormone ≥UNL ×1.5); creatine phosphokinase ≥UNL ×2; pregnancy or possible pregnancy; and lactation.

Measurement of plasma levels of ApoB-48 and Lp-PLA2

Plasma concentration of ApoB-48 was measured by enzyme-linked immunosorbent assay (ELISA) kit (product code: SEB-883Hu) which is a sandwich enzyme immunoassay for *in vitro* quantitative measurement of ApoB-48 in human serum, plasma, and other biological fluids. The plasma concentration of Lp-PLA_2 was determined by a commercially available Lp-PLA_2 ELISA kit (Uscn Life Science Inc., Houston, TX, USA).

Endpoint assessment

The primary end-point was the change from baseline in plasma

level of ApoB-48 and Lp-PLA$_2$ after the 12-month intervention. Secondary end-points included changes from baseline in lipid profiles (TG, HDL, non-HDL, and LDL), ApoB-100/A1 ratio and high molecular weight (HMW) adiponectin.

Statistical analysis

The data are presented as mean±standard deviation for continuous variables and as proportions (%) for categorical variables. Baseline clinical and biochemical characteristics between the two treatment groups were compared using two-sample *t* test for continuous variables and chi-square test for categorical variables. The changes of the primary end-point and other parameters from baseline within groups were analyzed using a paired *t* test, and the significance of the changes between the treatment groups were analyzed using a two-sample *t* test. In a separate analysis, changes from baseline in the levels of ApoB-48 and LpPLA$_2$ according to their baseline values (i.e., below and above median values) were compared using a Wilcoxon signed rank test, and differences in changes between the treatment groups was analyzed using a Mann Whitney *U* test. All statistical analyses were carried out with SPSS version 21.0 (IBM Co., Armonk, NY, USA). A two-tailed $P<0.05$ was regarded as statistically significant.

RESULTS

Baseline patient characteristics

All subjects were patients with MS, obesity and prediabetes, and all were statin naïve, with no prior use of oral hypoglycemic agents. The two groups of patients were well-matched according to lipid profile, blood glucose level and the pattern of life style including the frequency of exercise, alcohol consumption and smoking. The mean body mass index and fasting plasma glucose level were around 27 kg/m^2 and 115 mg/dL, respectively. The number of subjects with coronary heart disease family history, insulin resistance (homeostasis model assessment of insulin resistance), and inflammation state (high-sensitivity C-reactive protein) did not differ between groups. Baseline characteristics of the study subjects are summarized in Table 1.

Table 1. Baseline Characteristics of Subjects in the Sub-Analysis

Variable	Pitavastatin+LSM (n=37)	Only LSM (n=38)	P value
Age, yr	52.9±8.5	52.0±9.1	NS[a]
Male sex	22 (59.5)	25 (65.8)	NS[b]
BMI, kg/m^2	26.8±2.2	27.1±3.6	NS[a]
WC, cm	91.8±4.4	94.3±6.5	NS[a]
SBP, mm Hg	129.6±10.1	126.3±11.1	NS[a]
DBP, mm Hg	80.7±6.6	80.8±7.3	NS[a]
Exercise, time/wk			NS[b]
>3	15 (40.5)	18 (47.4)	
1–3	10 (27.0)	6 (15.8)	
Never	12 (32.4)	14 (36.8)	
Current smoker	10 (27.0)	12 (31.6)	NS[b]
Alcohol habits, time/wk			NS[b]
≥3	14 (37.8)	17 (44.7)	
<3	14 (37.8)	11 (28.9)	
Never	9 (24.3)	10 (26.3)	
CHD family history	9 (24.3)	9 (23.7)	NS[b]
FPG, mg/dL	114.1±11.1	116.5±14.9	NS[a]
Total cholesterol, mg/dL	223.6±28.7	215.5±26.5	NS[a]
HDL-C, mg/dL	49.2±9.6	46.9±10.0	NS[a]
LDL-C, mg/dL	144.7±19.8	136.1±24.0	NS[a]
Non-HDL-C, mg/dL	174.4±28.8	168.6±24.4	NS[a]
TG, mg/dL	162.4±50.6	175.8±72.9	NS[a]
hs-CRP, mg/dL	0.15±0.16	0.19±0.32	NS[a]
HOMA-IR	2.9±1.2	3.5±1.7	NS[a]

Values are expressed as mean±SD or number (%).
LSM, life style modification; NS, not significant; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; FPG, fasting plasma glucose; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance.
[a]The *P* values are computed from two-sample *t* test; [b]The *P* values are computed from v2-test.

Changes in metabolic parameters, apolipoprotein, and Lp-PLA$_2$ in both groups after 12 months of treatment

After the 12 months of treatment, LDL-C and non-HDL cholesterol (HDL-C) were significantly reduced in the pitavastatin +LSM group compared with those in the LSM only group (Table 2). TG level was significantly lower in the pitavastatin +LSM group but slightly higher in LSM only group, but the differences were not significant (TG change: –24.7±54.1 mg/dL vs. 2.7±98.1 mg/dL, P=0.143).

The ApoB-100/A1 ratio was also significantly lower in both groups, but was much greater in the pitavastatin+LSM group (ApoB-100/A1 ratio change: –0.21±0.16 vs. –0.05±0.12, $P<0.001$).

HMW adiponectin increased in both groups, but there was no significant difference between the two groups. We evaluated the

Table 2. Changes of Metabolic Parameters after 12 Months Intervention in Both Groups

Variable	Pitavastatin+LSM (*n*=37)			LSM only (*n*=38)			*P* value[a]
	Baseline	12 months	Change	Baseline	12 months	Change	
TC, mg/dL	223.6±28.7	178.2±25.9	–45.4±34.7[b]	215.7±26.8	215.7±22.7	0±22.5	<0.001
TG, mg/dL	162.4±50.6	137.7±54.2	–24.7±54.1[b]	175.8±72.9	179.6±106.6	2.7±98.1	NS
HDL-C, mg/dL	49.2±9.6	49.9±9.0	0.7±6.2	47.2±10.0	49.2±8.5	2.0±7.3	NS
LDL-C, mg/dL	144.7±19.8	103.0±24.5	–41.7±29.6[b]	135.8±24.3	134.1±22.3	–1.7±23.2	<0.001
Non-HDL-C, mg/dL	174.4±28.8	138.4±28.7	–46.0±34.4[b]	168.6±24.4	166.5±22.8	–2.0±21.2	<0.001
ApoB-100/A1 ratio	0.75±0.17	0.55±0.18	–0.21±0.16[b]	0.71±0.18	0.66±0.13	–0.05±0.12[b]	<0.001
Adiponectin, μg/mL	2.40±0.997	3.37±1.47	0.965±1.38[b]	3.15±1.87	3.67±1.76	0.519±1.14[b]	NS
HMW-adiponectin, μg/mL	2.20±1.30	2.61±1.70	0.404±1.01[b]	2.20±1.30	3.06±2.77	0.775±1.07[b]	NS
ApoB-48, μg/mL	5.64±1.55	5.36±1.75	–0.272±2.17	5.98±3.20	6.36±2.62	0.382±4.05	NS
Lp-PLA$_2$, μg/mL	1.20±0.262	1.25±0.251	0.048±0.225	1.21±0.241	1.33±0.316	0.116±0.288[b]	NS

Values are expressed as mean±SD.
LSM, life style modification; TC, total cholesterol; TG, triglyceride; NS, not significant; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; ApoB-100, apolipoprotein B100; ApoA1, apolipoprotein A1; HMW, high molecular weight; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$.
[a]Comparison of the changes between the groups by two-sample *t* test; [b]*P*<0.05 by paired *t* test.

Table 3. Changes from Baseline in the Levels of ApoB-48 and Lp-PLA$_2$ according to Their Baseline Values (i.e., Below and Above Median Values)

Variable	Pitavastatin+LSM (*n*=37)			LSM only (*n*=38)			*P* value[a]
	Baseline	12 months	Change	Baseline	12 months	Change	
Below median, μg/mL							
ApoB-48	4.54 (4.02–4.89)	4.64 (3.83–6.35)	0.15 (–0.65 to 2.09)	4.57 (4.11–4.94)	5.46 (4.70–6.11)	0.68 (0.21–1.70)	0.234
Lp-PLA$_2$	1.02 (0.86–1.17)	1.12 (0.94–1.38)	0.16 (0.00–0.30)	1.02 (0.91–1.11)	1.22 (1.14–1.30)	0.19 (0.10–0.33)	0.331
Above median, μg/mL							
ApoB-48	6.09 (5.62–7.30)	5.07 (4.67–5.75)	–0.88 (–2.51 to –0.65)[b]	6.41 (5.64–7.70)	5.99 (5.11–6.63)	0.14 (–1.69 to 0.67)	0.045[b]
Lp-PLA$_2$	1.44 (1.27–1.48)	1.40 (1.27–1.56)	–0.03 (–0.15 to 0.11)	1.34 (1.29–1.44)	1.44 (1.15–1.54)	0.06 (–0.18 to 0.15)	0.598

Values are expressed as median (interquartile range). The values corresonding to the median of baseline apoB-48 and Lp-PLA$_2$ are 5.42 and 1.23 μg/mL, respectively.
ApoB-48, apolipoprotein B48; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; LSM, life style modification.
[a]Comparison of the changes between the groups by Mann-Whitney *U* test; [b]*P*<0.05 by Wilcoxon signed rank test.

change of Lp-PLA$_2$ and ApoB-48 levels before and after intervention. Pitavastatin+LSM did not significantly affect ApoB-48 levels in subjects overall, but when we evaluated changes from baseline in ApoB-48 level according to baseline values (i.e., below and above median values), pitavastatin+LSM significantly reduced ApoB-48 levels in the group with above median baseline value of ApoB-48. There was no effect of pitavastatin+LSM on Lp-PLA$_2$ in either group (Table 3).

DISCUSSION

We conducted a sub-analysis of the PROPIT study to evaluate the effect of combined therapy with a statin and LSM on lipid profiles, ApoB-48 and Lp-PLA$_2$ in MS patients. In our study, pitavastatin treatment significantly improved lipid profiles and reduced ApoB-48 levels in the higher mean baseline value group of ApoB-48, but did not significantly alter the Lp-PLA$_2$ levels.

Insulin resistance is a major component of MS and represents major complications associated with atherogenic dyslipidemia [15]. Atherogenic dyslipidemia in MS patients is characterized by low HDL-C and high TG levels. TGs are associated with TG-rich lipoproteins (TRLs), and chylomicron remnants have been implicated as significant risk factors for atherosclerosis

[6,16]. The small intestine regulates lipid metabolism in fed and fasting states and plays a central role in lipid homeostasis [17,18]. Since the small intestine consists of insulin sensitive tissue, lipid synthesis pathways in the small intestine are also influenced by insulin resistance. ApoB-48 is present only in intestinally derived lipoproteins such as chylomicron and chylomicron remnants. High ApoB-48 levels suggest delayed metabolism of TRLs, which are commonly associated with insulin resistance and abdominal obesity [19]. In our study showed that pitavastatin+LSM did not change the level of ApoB-48 in subjects overall, but the level of ApoB-48 was significantly lower in the higher mean baseline value group of ApoB-48.

Some previous studies report that plasma level of ApoB-48 could be a marker of new onset as well as chronic CAD [20,21]. Therapeutically, statins are most commonly used to reduce dyslipidemia via inhibition of endogenous hepatic cholesterol synthesis (inhibition of 3-hydroxy-3-methylglutaryl CoA reductase). Because the effect of statins on the intestine is relatively unknown, some other investigators have examined the effect of statins on levels of ApoB-48. Dane-Stewart et al. [22] reported that 80 mg/day of atorvastatin significantly lowered ApoB-48 levels in 10 normolipidemic patients with CAD. Lamon-Fava et al. [23] also documented that atorvastatin at both 20 and 80 mg/day significantly lowered ApoB-48 in the fed state in nine patients with combined hyperlipidemia.

There were some differences between our study and prior studies. Previously, the effect of statins on ApoB-48 was measured in the post-prandial setting by meal challenge test, because ApoB-48 reflects TG-rich remnant lipoproteins which are risk factors for CVD and increase in postprandial hyperlipidemia. In our study, we measured ApoB-48 in the fasting condition, and so the change of ApoB-48 level after intervention was lower than in prior studies. However, some studies report that a high fasting serum concentration of ApoB-48 also may be a risk factor for CAD [20,24]. Although the change of ApoB-48 in the fasting state was smaller than in the fed state, we thought that it was important to measure ApoB-48 in the fasting state.

Lp-PLA_2, also known as low density associated platelet-activating factor acetylhydrolase, is released from the macrophages of atherosclerotic plaques into circulation [25]. Lp-PLA_2 hydrolyzes oxidized phospholipids on LDL to lysophosphatidylcholine and oxidizes fatty acids, and lysophosphatidylcholine activates several second messengers with potentially atherogenic effects [26]. Several investigations report that Lp-PLA_2 is a cardiovascular risk marker independent of, and in addition to, traditional risk factors [27,28]. As an important predictor of CVD, Lp-PLA_2 has received attention as a potential new therapeutic target. The advent of some novel pharmacological inhibitors of this enzyme such as darapladib and varespladib may help to reduce the risk of CAD [29]. A previous study revealed that darapladib, when added to statins, prevents necrotic core expansion and offers great benefit in the reduction of plaque formation [30]. Some researchers have investigated the effect of statins on Lp-PLA_2 activity. Winkler et al. [31] reported that 80 mg/day of fluvastatin for 8 weeks decreased the activity of Lp-PLA_2 by 22.8% in subjects with type 2 diabetes. Schaefer et al. [32] also reported that 40 mg/day of atorvastatin reduced mean Lp-PLA_2 values by 26% over 36 weeks in 84 patients who had coronary heart disease and LDL-C levels >130 mg/dL. In contrast to previous studies, pitavastatin (2 mg/day) treatment did not reduce Lp-PLA_2 levels in our study.

There were several differences between our study and previous studies in Lp-PLA_2 as well. Previous studies evaluated the effect of statins on Lp-PLA_2 activity in subjects at high risk for CVD due to previous coronary disease or diabetes mellitus. However, this study excluded subjects at high risk for CVD (uncontrolled hypertension [DBP ≥95], poorly controlled diabetes [HbA1c ≥8.0%], or high cholesterolemia [LDL ≥190 mg/dL or TG ≥400 mg/dL]). Possibly because we focused on patients at relatively low risk for CVD, the effect of pitavastatin on the change of Lp-PLA_2 was lower than in previous studies. Another difference compared to other studies was the dosage of statin. Pitavastatin 2 mg shows similar effects to atorvastatin 10 mg in improving lipid profiles [33]. Prior studies investigating the effect of statins on the level of Lp-PLA_2 used a higher dosage of statin sufficient to reduce the level of Lp-PLA_2. We thought that the dosage of pitavastatin in present study was not enough to change the levels of Lp-PLA_2. In addition, we measured the mass concentration of Lp-PLA_2 by commercial assay. The median value of Lp-PLA_2 has varied widely in prior epidemiologic studies, making it difficult to use this assay for clinical purposes. It has been suggested that a measure of Lp-PLA_2 activity might serve as a more reproducible and representative biomarker of enzyme functions [34]. If we measured Lp-PLA_2 activity with Lp-PLA_2 mass concentration, we would have more accurate results for the effect of pitavastatin on Lp-PLA_2.

Some important limitations of this study deserve mention. First, it was a sub-study with a relatively small number of subjects. Accordingly, the plasma levels of ApoB-48 and Lp-PLA_2 had wide standard deviations and statistical power was reduced. The strength of this study was that it is the first inter-

ventional study that investigated the effect of pitavastatin on the level of ApoB-48 and Lp-PLA$_2$.

In conclusion, pitavastatin+LSM in MS patients at relatively low risk for CVD significantly reduced ApoB-48 levels in the higher baseline mean value group of ApoB-48, but did not significantly alter Lp-PLA$_2$ levels. Further studies with modified dosage and larger populations are needed to evaluate the effects of pitavastatin treatment on Lp-PLA$_2$ and ApoB-48.

CONFLICTS OF INTEREST

This study was supported by JW Pharmaceutical, Seoul, Republic of Korea. The sponsor participated in the study design, data collection and analysis of the data, but not in writing the manuscript and the decision to submit the manuscript for publication.

ACKNOWLEDGMENTS

We thank other investigators for their cooperation in this study. The full list of other investigators for this study is as follows: PROPIT Study Team Sung Hee Choi (Seoul National University Bundang Hospital, Seongnam, Korea), Soo Lim (Seoul National University Bundang Hospital, Seongnam, Korea), Ji A Seo (Korea University Ansan Hospital, Ansan, Korea), Jung Hyun Noh (Inje University Ilsan Paik Hospital, Goyang, Korea), Ji Oh Mok (Soonchunhyang University Bucheon Hospital, Bucheon, Korea), Ki Young Lee (Gachon University Gil Medical Center, Incheon, Korea), Jong Sook Park (Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea), Dae Jung Kim (Ajou University Hospital, Suwon, Korea), and Chang Beom Lee (Hanyang University Guri Hospital, Guri, Korea).

ORCID

Cheol-Young Park *http://orcid.org/0000-0002-9415-9965*

REFERENCES

1. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med 2006;119:812-9.
2. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol 2010;56:1113-32.
3. Austin MA, Rodriguez BL, McKnight B, McNeely MJ, Edwards KL, Curb JD, et al. Low-density lipoprotein particle size, triglycerides, and high-density lipoprotein cholesterol as risk factors for coronary heart disease in older Japanese-American men. Am J Cardiol 2000;86:412-6.
4. Lundbye JB, Thompson PD. Statin use in the metabolic syndrome. Curr Atheroscler Rep 2005;7:17-21.
5. McQueen MJ, Hawken S, Wang X, Ounpuu S, Sniderman A, Probstfield J, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. Lancet 2008;372:224-33.
6. Nakamura T, Kugiyama K. Triglycerides and remnant particles as risk factors for coronary artery disease. Curr Atheroscler Rep 2006;8:107-10.
7. Watts GF, Chan DC, Barrett PH, O'Neill FH, Thompson GR. Effect of a statin on hepatic apolipoprotein B-100 secretion and plasma campesterol levels in the metabolic syndrome. Int J Obes Relat Metab Disord 2003;27:862-5.
8. Kolodgie FD, Burke AP, Skorija KS, Ladich E, Kutys R, Makuria AT, et al. Lipoprotein-associated phospholipase A$_2$ protein expression in the natural progression of human coronary atherosclerosis. Arterioscler Thromb Vasc Biol 2006;26:2523-9.
9. Stafforini DM, Tjoelker LW, McCormick SP, Vaitkus D, McIntyre TM, Gray PW, et al. Molecular basis of the interaction between plasma platelet-activating factor acetylhydrolase and low density lipoprotein. J Biol Chem 1999;274:7018-24.
10. Lp-PLA(2) Studies Collaboration, Thompson A, Gao P, Orfei L, Watson S, Di Angelantonio E, et al. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. Lancet 2010;375:1536-44.
11. Tsimikas S, Willeit J, Knoflach M, Mayr M, Egger G, Notdurfter M, et al. Lipoprotein-associated phospholipase A$_2$ activity, ferritin levels, metabolic syndrome, and 10-year cardiovascular and non-cardiovascular mortality: results from the Bruneck study. Eur Heart J 2009;30:107-15.
12. Hirschler V, Merono T, Maccallini G, Gomez Rosso L, Aranda C, Brites F. Association of lipoprotein-associated phospholipase A$_2$ activity with components of the metabolic syndrome in apparently healthy boys. Cardiovasc Hematol Agents Med Chem 2011;9:78-83.
13. Choi SH, Lim S, Hong ES, Seo JA, Park CY, Noh JH, et al. PROPIT: a PROspective comparative clinical study evaluating the efficacy and safety of PITavastatin in patients with

metabolic syndrome. Clin Endocrinol (Oxf) 2015;82:670-7.
14. Choi SH, Kim DJ, Lee KE, Kim YM, Song YD, Kim HD, et al. Cut-off value of waist circumference for metabolic syndrome patients in Korean adult population. J Korean Soc Study Obes 2004;13:53-60.
15. Ferrannini E, Natali A, Bell P, Cavallo-Perin P, Lalic N, Mingrone G. Insulin resistance and hypersecretion in obesity. European Group for the Study of Insulin Resistance (EGIR). J Clin Invest 1997;100:1166-73.
16. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2011;123:2292-333.
17. Haidari M, Leung N, Mahbub F, Uffelman KD, Kohen-Avramoglu R, Lewis GF, et al. Fasting and postprandial overproduction of intestinally derived lipoproteins in an animal model of insulin resistance. Evidence that chronic fructose feeding in the hamster is accompanied by enhanced intestinal de novo lipogenesis and ApoB48-containing lipoprotein overproduction. J Biol Chem 2002;277:31646-55.
18. Vine DF, Takechi R, Russell JC, Proctor SD. Impaired postprandial apolipoprotein-B48 metabolism in the obese, insulin-resistant JCR:LA-cp rat: increased atherogenicity for the metabolic syndrome. Atherosclerosis 2007;190:282-90.
19. Sato I, Ishikawa Y, Ishimoto A, Katsura S, Toyokawa A, Hayashi F, et al. Significance of measuring serum concentrations of remnant lipoproteins and apolipoprotein B-48 in fasting period. J Atheroscler Thromb 2009;16:12-20.
20. Mori K, Ishida T, Yasuda T, Monguchi T, Sasaki M, Kondo K, et al. Fasting serum concentration of apolipoprotein B48 represents residual risks in patients with new-onset and chronic coronary artery disease. Clin Chim Acta 2013;421:51-6.
21. Varbo A, Benn M, Tybjærg-Hansen A, Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. J Am Coll Cardiol 2013;61:427-36.
22. Dane-Stewart CA, Watts GF, Pal S, Chan D, Thompson P, Hung J, et al. Effect of atorvastatin on apolipoprotein B48 metabolism and low-density lipoprotein receptor activity in normolipidemic patients with coronary artery disease. Metabolism 2003;52:1279-86.
23. Lamon-Fava S, Diffenderfer MR, Barrett PH, Buchsbaum A, Matthan NR, Lichtenstein AH, et al. Effects of different doses of atorvastatin on human apolipoprotein B-100, B-48, and A-I metabolism. J Lipid Res 2007;48:1746-53.
24. Otokozawa S, Ai M, Diffenderfer MR, Asztalos BF, Tanaka A, Lamon-Fava S, et al. Fasting and postprandial apolipoprotein B-48 levels in healthy, obese, and hyperlipidemic subjects. Metabolism 2009;58:1536-42.
25. Racherla S, Arora R. Utility of Lp-PLA$_2$ in lipid-lowering therapy. Am J Ther 2012;19:115-20.
26. Wilensky RL, Macphee CH. Lipoprotein-associated phospholipase A(2) and atherosclerosis. Curr Opin Lipidol 2009;20:415-20.
27 Packard CJ, O'Reilly DS, Caslake MJ, McMahon AD, Ford I, Cooney J, et al. Lipoprotein-associated phospholipase A$_2$ as an independent predictor of coronary heart disease. West of Scotland Coronary Prevention Study Group. N Engl J Med 2000;343:1148-55.
28. Winkler K, Winkelmann BR, Scharnagl H, Hoffmann MM, Grawitz AB, Nauck M, et al. Platelet-activating factor acetylhydrolase activity indicates angiographic coronary artery disease independently of systemic inflammation and other risk factors: the Ludwigshafen Risk and Cardiovascular Health Study. Circulation 2005;111:980-7.
29. Garcia-Garcia HM, Serruys PW. Phospholipase A$_2$ inhibitors. Curr Opin Lipidol 2009;20:327-32.
30. Suckling KE. Phospholipase A$_2$ inhibitors in the treatment of atherosclerosis: a new approach moves forward in the clinic. Expert Opin Investig Drugs 2009;18:1425-30.
31. Winkler K, Abletshauser C, Friedrich I, Hoffmann MM, Wieland H, Marz W. Fluvastatin slow-release lowers platelet-activating factor acetyl hydrolase activity: a placebo-controlled trial in patients with type 2 diabetes. J Clin Endocrinol Metab 2004;89:1153-9.
32. Schaefer EJ, McNamara JR, Asztalos BF, Tayler T, Daly JA, Gleason JL, et al. Effects of atorvastatin versus other statins on fasting and postprandial C-reactive protein and lipoprotein-associated phospholipase A$_2$ in patients with coronary heart disease versus control subjects. Am J Cardiol 2005;95:1025-32.
33. Yokote K, Bujo H, Hanaoka H, Shinomiya M, Mikami K, Miyashita Y, et al. Multicenter collaborative randomized parallel group comparative study of pitavastatin and atorvastatin in Japanese hypercholesterolemic patients: collaborative study on hypercholesterolemia drug intervention and their benefits for atherosclerosis prevention (CHIBA study). Atherosclerosis 2008;201:345-52.
34. Mallat Z, Lambeau G, Tedgui A. Lipoprotein-associated and secreted phospholipases A$_2$ in cardiovascular disease: roles as biological effectors and biomarkers. Circulation 2010;122:2183-200.