PLTP activity is a risk factor for subsequent cardiovascular events in CAD patients under statin therapy: the Athero*Gene* Study

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Abstract Phospholipid transferprotein (PLTP) mediates both net transfer and exchange of phospholipids between different lipoproteins. Although many studies have investigated the role of PLTP in atherogenesis, the role of PLTP in atherosclerotic diseases is unclear. We investigated the association of serum PLTP activity with the incidence of a combined endpoint (myocardial infarction and cardiovascular death) and its relation to other markers of atherosclerosis in 1,085 patients with angiographically documented coronary artery disease (CAD). In the median follow-up of 5.1 years, 156 patients had suffered from the combined endpoint of myocardial infarction or cardiovascular death including 47 of 395 patients who were on statins at baseline. In Kaplan-Meyer analyses serum PLTP activity was not associated with the combined endpoint in all patients. However, in the subgroup of patients receiving statins at baseline, PLTP was shown to be a significant predictor of cardiovascular outcome ($P = 0.019$), and this also remained stable in univariate ($P = 0.027$) and multivariate cox regression analyses ($P = 0.041$) including potential confounders (classical risk factors, HDL cholesterol (HDL-C), and others). We showed in our study that, under statin treatment, high plasma PLTP activity was related to fatal and nonfatal cardiovascular events in CAD patients.—Schlitt, A., S. Blankenberg, C. Bickel, K. J. Lackner, G. H. Heine, M. Buerke, K. Werdan, L. Maegdefessel, U. Raaz, H. J. Rupprecht, T. Munzel, and X-C. Jiang. **PLTP activity is a risk factor for subsequent cardiovascular events in CAD patients under statin therapy: the Athero*Gene* Study. *J. Lipid Res.* 2009.** 50: **723–729.**

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Atherogenesis is initiated by the interaction of cholesterol-rich lipoproteins with the arterial wall (1). Many processes have been implicated in early atherogenesis, including lipoprotein oxidation (2), lipoprotein retention and aggregation, endothelial alteration, macrophage chemotaxis and foam cell formation, and smooth muscle cell migration and alteration (1, 3). However, subendothelial retention and aggregation of LDL particles have emerged as the primary pathogenic processes (1, 4).

Primary and secondary intervention trials in patients with coronary atherosclerosis have shown that treatment with 3-hydroxy-3-methylglutaryl CoA reductase inhibitors (statins) reduces the relative risk of major coronary events by approximately 30%, demonstrating a greater benefit for patients with a higher baseline risk (5). Whether the benefit of statin therapy can completely explained by reducing LDL cholesterol (LDL-C) levels or whether other nonlipid- or lipid-associated effects may influence thrombus formation, inflammatory response, endothelial function, and plaque stability has been the subject of several publications (6–8). Recent clinical trials have demonstrated that high-dose statin therapy provides cardiovascular benefits beyond those of conventional statin therapy among patients with unstable and stable coronary artery disease (CAD). Thus, current guidelines recommend the use of high-dose statin therapy in patient populations at an increased risk for cardiovascular events with an optional therapeutic goal of LDL-C below 70 mg/dl (9–13).

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The plasma phospholipid transfer protein (PLTP) is primarily involved in HDL metabolism. PLTP mediates net transfer and exchange of phospholipids between lipoproteins (14). PLTP can also cause convert HDL_3 into larger and smaller particles in a time- and concentration-dependent fashion (15). Because there are two forms of PLTP in human plasma, one being catalytically active and the other not, activity measurement of PLTP is more relevant than its mass measurement (16–18).

Genetic mouse models have played a crucial role in elucidating the role of PLTP. In PLTP transgenic mice, PLTP overexpression increases the influx of phospholipids and secondarily of cholesterol into HDL, leading to an increase in pre-β-HDL particles (19–21). PLTP gene knockout mice have provided the first in vivo evidence of a crucial role for PLTP-mediated lipid transfer in the maintenance of lipoprotein levels (22, 23). Moreover, PLTP's proatherogenic potency has been demonstrated in atherogenic mouse models: PLTP deficiency resulted in markedly decreased atherosclerosis, due in part to decreased production and lower levels of apoB-containing lipoproteins (24) and increased bioavailability of vitamin E in atherogenic lipoproteins (25). PLTP overexpression resulted in markedly increased atherosclerosis, due in part to decreased HDL levels (26) and increased VLDL secretion (27).

The role of PLTP in human atherosclerosis remains controversial. We have previously shown that *high* plasma PLTP activity is a risk marker for CAD (28). In contrast, a recently published study indicated that *low* PLTP activity was a risk factor for peripheral atherosclerosis (29). Furthermore, we found that serum PLTP activity was higher in hemodialysis patients than in matched controls, presenting as a further aspect of uremic dyslipidemia in end-stage kidney disease. However, PLTP activity was not related to survival in this patient group (30). Thus, the significance of PLTP involvement in atherogenesis is still an open issue.

In order to further investigate the role of PLTP in atherosclerosis, we measured plasma PLTP levels in 1,085 patients with angiographically proven CAD and its relationship to clinical outcome.

METHODS

Study population

Between November 1996 and July 2000, we recruited 1,085 patients suffering from symptoms of CAD (599 patients with stable angina [SAP]; 486 with acute coronary syndrome [ACS]) admitted to the II. Medical Department of the Johannes Gutenberg-University, Mainz, Germany, or the Hospital of the German Federal Armed Forces, Koblenz, Germany, for diagnostic coronary angiography. The sole inclusion criterion was the presence of a stenosis >30% in at least one major coronary artery. The study is described in detail elsewhere (31). Exclusion criteria were lack of CAD as defined above and evidence of significant concomitant disease, in particular severe valvular heart disease, known cardiomyopathy, neoplastic disease, inflammatory disease, or a febrile condition. Patients completed a questionnaire about smoking habits, history of diabetes mellitus, hypertension, hyperlipoproteinemia, current drug use, and family history of premature CAD (documented in one first-degree relative before age 65). Diabetes mellitus was diagnosed in patients who had previously undergone dietary treatment or received additional oral antidiabetic or insulin medication or who had a current fasting blood sugar level >125 mg/dl. Patients who received antihypertensive treatment or had a blood pressure >160/90 mmHg in repeated measurements under standardized conditions were defined as hypertensive.

Patients were followed up for a median of 5.1 years. The majority of the patients were invited for follow-up investigations and interviews and presented at our clinic. Patients that were not able or did not want to present at the clinic represents a small number. They were interviewed by telephone by trained medical staff. Approximately 2% of patients were lost to follow-up (lost to follow-up patients were found in all PLTP-quartiles). Totally, cardiovascular death or nonfatal myocardial infarction occurred in 156 patients. Information about the cause of death or clinical events was obtained from hospital or general practitioner charts. However, it was not possible in this subgroup of patients to get reliable information about medical treatment (statin intake) or other variables (active smoking) at the time of (fatal) events.

In general, study patients were of German nationality and were inhabitants of the Rhein-Main Area. The study was approved by the ethics committee of the University of Mainz. Participation was voluntary, and each study subject gave written informed consent.

Laboratory methods

Blood was drawn from all subjects under standardized conditions after a fasting period and before coronary angiography was performed. Plasma lipid levels [total cholesterol, Roche Diagnostics, Mannheim, Germany; HDL cholesterol (HDL-C), Rolf Greiner Biochemica, Flacht, Germany; LDL-C, calculated according to the Friedewald formula; triglycerides, Roche Diagnostics] were determined immediately. C-reactive protein (CRP) was determined by a highly sensitive, latex particle-enhanced immunoassay (detection range of 0–20 mg/l); the between-day imprecision of this assay (n = 21) was 2.14% and 1.44% at mean levels of 1.90 mg/l and 4.33 mg/l (Roche Diagnostics).

PLTP activity was measured by using an assay kit (Cardiovascular Target, Inc., New York, NY), as described previously (28). Basically, the kit includes donor and acceptor particles. Incubation of donor and acceptor with 3 μl of human plasma results in the PLTP-mediated transfer of fluorescent phospholipid, which is present in a self-quenched state when associated with the donor. The transfer is determined by the increase in fluorescence intensity as the fluorescent lipid is removed from the donor and transferred to the acceptor. The interassay coefficient of variation of the PLTP activity was 3.3 ± 0.5%. The linear range of PLTP activity in this assay was between 1 μl and 7 μl of plasma. Three freeze-thaw cycles of plasma did not influence the assay. To validate this PLTP activity assay, we compared the results with those obtained by the classic method. The two methods were well correlated ($r = 0.90$, $P < 0.01$, n = 30) (14, 29).

For detection of PLTP, samples were placed on ice immediately and within 30 min were centrifuged at 4,000 rpm for 10 min, divided into aliquots, and frozen at −80°C until analysis.

Statistical analysis

Demographic and clinical variables of cases and controls were compared by the Chi-square test for categorical and *t*-test for continuous variables between patients receiving and not receiving statin therapy at baseline. Because of skewed distribution of triglyceride, HDL-C, and Hs-CRP levels, median values were presented and the Mann-Whitney test applied to assess these variables. We aimed to evaluate any evidence of an association be-

TABLE 1. Patient baseline characteristics

Variable	All patients	Statins at baseline	No statins at baseline	*P*
Patients (n)	1,085	395	690	
Age, years	61.1 ± 10.1	60.3 ± 10.2	61.6 ± 10.0	0.683
Sex, % male	74.7	74.7	74.8	0.971
BMI, kg/m^2	27.2 ± 3.7	27.3 ± 3.8	27.1 ± 3.7	0.883
Smoking (ever smoked), %	37.2	36.2	37.8	0.603
Diabetes, %	21.7	19.5	22.9	0.190
Hypertension, %	71.1	74.9	69.9	0.074
Family history of CAD, %	38.2	40.5	36.8	0.228
ACS, %	44.8	35.9	49.9	<0.001
LVEF, %[a]	62.4 ± 14.7	63.5 ± 14.3	61.7 ± 14.9	0.494
Beta blocking agents intake, %	59.7	68.6	54.6	<0.001
ACE inhibitors intake, %	48.1	54.2	44.6	0.002
Aspirin intake, %	87.6	93.2	84.5	<0.001
Total-cholesterol, mg/dl	220 ± 46	216 ± 49	221 ± 44	0.164
LDL-C, mg/dl	142 ± 40	138 ± 45	144 ± 37	0.003
HDL cholesterol, mg/dl[b]	47 (39/57)	48 (38/58)	46 (39/56)	0.449
Triglycerides, mg/dl[b]	140 (102/192)	145 (106/199)	138 (99.5/189)	0.121
Hs-CRP, mg/l[b]	4.46 (1.94/12.51)	3.50 (1.50/9.06)	5.13 (2.25/14.09)	<0.001

ACS, acute coronary syndrome; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; LDL-C, LDL cholesterol. Categorical variables are presented as percentage of patients, and *P* values were obtained by Chi-square test; continuous, normally distributed variables are presented as mean ± SD, and *P* values were obtained by *t*-test.

[a] Left ventricular ejection fraction (LVEF) was determined in 902 patients.

[b] Skewed distributed variables are presented by median (25%/75%-interquartiles), statistical comparison by Mann-Whitney-test.

tween PLTP and CAD in models that assumed linear and nonlinear effects. We thus divided patients into quartiles. Survival was analyzed by the Kaplan-Meyer method and log-rank test. In all survival analyses, the endpoint comprised a combined endpoint of death of cardiovascular causes and nonfatal myocardial infarction. Data on patients who died of other causes were censored at the time of death. Hazard ratios and 95% confidence intervals (CIs) were reported with 2-tailed probability values. $P < 0.05$ was considered significant. All analyses were carried out using SPSS 11.5 software.

RESULTS

Baseline data

Baseline data of our patients according to statin intake at baseline are specified in **Table 1**. Classical risk factors were not different; however, ACS was more frequently found in patients not under statin therapy at baseline. Hs-CRP and LDL-C were increased in these patients, whereas β-blocking agents, ACE inhibitors, and aspirin

TABLE 2. Patient characteristics stratified by quartiles of phospholipid transferprotein (PLTP)

	First quartile PLTP	Second quartile PLTP	Third quartile PLTP	Fourth quartile PLTP	
Patients (n)	271	272	271	271	*P*
Range PLTP, pmol/μl/h	<17.8	⩾17.840–24.9	⩾24.9–31.169	⩾31.169	
Age, years	61.1 ± 9.9	62.1 ± 10.2	60.6 ± 10.1	60.8 ± 10.3	0.282
Sex, % male	71.2	77.2	74.5	76.0	0.408
BMI, kg/m^2	27.2 ± 3.7	27.1 ± 3.7	27.1 ± 3.7	27.3 ± 3.9	0.886
Smoking (ever smoked), %	39.3	33.8	37.6	38.1	0.584
Diabetes, %	22.1	24.6	19.2	20.7	0.460
Hypertension, %	70.8	72.4	70.8	72.7	0.941
ACS, %	49.1	46.7	42.1	41.3	0.209
LVEF, %[a]	61.9 ± 15.1	61.8 ± 14.4	62.8 ± 14.5	63.0 ± 14.8	0.772
Statins intake, %	38.7	33.8	40.2	32.8	0.202
Total-cholesterol, mg/dl	220 ± 45	218 ± 49	220 ± 43	221 ± 47	0.775
LDL-C, mg/dl	141 ± 39	141 ± 43	142 ± 37	143 ± 42	0.951
HDL cholesterol, mg/dl[b]	49 ± 14	49 ± 15	48 ± 15	50 ± 16	0.524
Triglycerides, mg/dl[b]	165 ± 107	160 ± 103	170 ± 100	164 ± 91	0.689
Hs-CRP, mg/l[b]	15.2 ± 28.9	14.7 ± 27.9	14.5 ± 28.6	10.9 ± 29.7	0.389

ACS indicates acute coronary syndrome; BMI, body mass index. Categorical variables are presented as percentage of patients, and *P* values were obtained by Chi-square test; continuous variables are presented as mean ± SD, and *P* values were obtained by ANOVA.

Cox regression analyses of serum PLTP activity stratified by quartiles in univariate (model 1) and multivariate models (model 2 included the classical risk factors: age, sex, BMI, smoking, diabetes mellitus, arterial hypertension, family history of CHD and left ventricular ejection fraction, HS-CRP, and HDL-C) in patients without statins at baseline (3A) and with statins at baseline (3B).

[a] Left ventricular ejection fraction (LVEF) was determined in 902 patients.

[b] Because of skewed distribution, log transformation was applied and antilog values are presented.

were used more often by patients who had been receiving statin therapy at baseline (Table 1).

In **Table 2**, patient characteristics are stratified in comparison to PLTP-quartiles. We found no significant differences for all variables (see Table 2), although there seemed to be a nonsignificant trend for less-ACS patients in the higher quartiles of PLTP ($P = 0.209$) and for a decrease of Hs-CRP also in the higher quartiles of PLTP ($P = 0.389$). Moreover, statin intake at baseline was also not different in comparison of PLTP-quartiles ($P = 0.202$, see Table 2).

Cardiovascular risk and serum PLTP activity

Figure 1 demonstrates serum PLTP activity divided into quartiles in relation to the incidence of the combined endpoint (myocardial infarction and cardiovascular death) in the total cohort (Fig. 1A), in patients not receiving statins at baseline (Fig. 1B) and in patients receiving statins at baseline (Fig. 1C). The Kaplan-Meyer survival analyses showed that serum PLTP activity was not associated with the combined endpoint in the total cohort ($P = 0.672$ by log rank test, Fig. 1A) or in the subgroup of patients not receiving statins at baseline ($P = 0.373$ by log rank test, Fig. 1B). However, among the patients under statin treatment at baseline, a higher proportion of individuals who had suffered myocardial infarction and died of cardiovascular causes were found in the upper quartiles ($P = 0.019$ by log rank test, Fig. 1C).

For further evaluation, univariate (model 1) and multivariate (model 2) Cox-regression analyses were performed in the subgroup of patients under statin therapy at baseline (**Table 3**). The univariate Cox regression analysis showed that PLTP activity was significantly related to the combined endpoint ($P = 0.027$ for all quartiles). This also remained significant in the multivariate Cox regression analyses including potential confounders (age, sex, body mass index, smoking, diabetes mellitus, arterial hypertension, family history of CHD, acute coronary syndrome, left ventricular ejection fraction, HDL-C, and HS-CRP, $P = 0.041$).

Finally, we investigated the influence of statin treatment at baseline on cardiovascular outcome and found a nonsignificant increase of cardiovascular events in patients without statins at baseline (15.6% in patients without

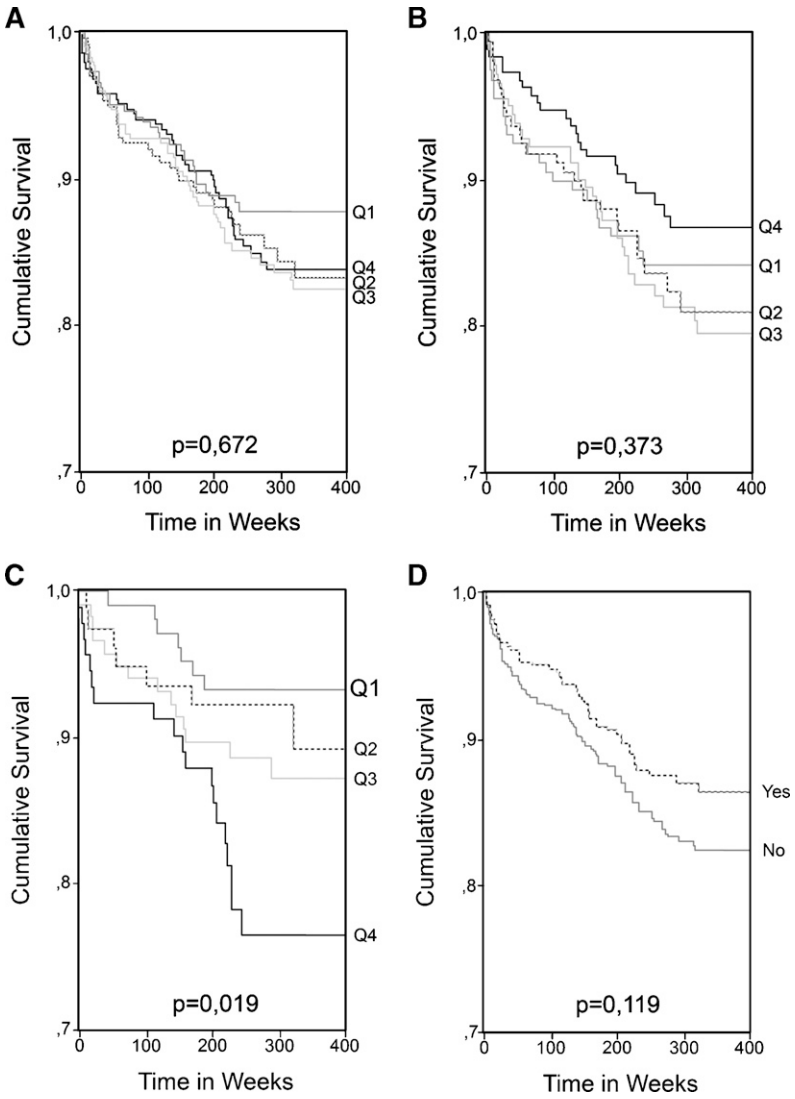

Fig. 1. Kaplan-Meyer survival plots for combined endpoint (cardiovascular mortality and myocardial infarction) after stratifying patients for phospholipid transferprotein (PLTP) levels (A–C) and after stratifying for statin treatment (D). A: PLTP in quartiles, all subjects. B: PLTP in quartiles, patients not receiving statins at baseline. C: PLTP in quartiles, patients receiving statins at baseline. D: Statin treatment, all subjects.

TABLE 3.

	Model 1					Model 2			
	Events (%)	Exp(B)	Lower CI	Upper CI	*P*	Exp(B)	Lower CI	Upper CI	*P*
a. PLTP activity (pmol/μl/h)					0.296[a]				0.460[a]
Q1 (<17.8)	26 (24.3)								
Q2 (>17.8–24.9)	29 (27.1)	0.990	0.583	1.681	0.970[b]	0.891	0.453	1.750	0.737[b]
Q3 (>24.9–31.2)	30 (29.0)	1.131	0.672	1.906	0.643[b]	1.317	0.706	2.459	0.386[b]
Q4 (>31.2)	21 (19.6)	0.667	0.375	1.185	0.167[b]	0.408	0.408	1.668	0.592[b]
b. PLTP activity (pmol/μl/h)					0.027[a]				0.041[a]
Q1 (<17.8)	7 (14.9)								
Q2 (>17.8–24.9)	9 (19.1)	1.384	0.485	3.945	0.543[b]	2.207	0.510	9.555	0.290[b]
Q3 (>24.9–31.2)	13 (27.7)	1.809	0.730	4.483	0.200[b]	3.090	0.822	11.617	0.095[b]
Q4 (>31.2)	18 (38.3)	3.298	1.386	7.846	0.007[b]	5.663	1.540	20.827	0.009[b]

Cox regression analyses of serum PLTP activity stratified by quartiles in univariate (model 1) and multivariate models (model 2 included the classical risk factors: age, sex, BMI, smoking, diabetes mellitus, arterial hypertension, family history of CHD and left ventricular ejection fraction, HS-CRP, and HDL-C) in patients with statins at baseline. CI, confidence interval.

[a] All quartiles.

[b] First quartile.

statins vs. 12.1% in patients with statins at baseline, $P = 0.119$, see Fig. 1D).

DISCUSSION

In the present study, serum PLTP activity was not related to the combined endpoint in the patient group as a whole or in the subgroup of patients not receiving statins at baseline. However, we demonstrated that PLTP was a significant predictor for a combined endpoint including nonfatal myocardial infarction and death of cardiovascular causes in CAD patients under statin therapy according to Kaplan-Meyer and univariate Cox regression analyses. This remained stable in the multivariate Cox regression analysis including potential confounders related to outcome and/or related to PLTP activity, such as HDL-C, Hs-CRP, and left ventricular ejection fraction.

Statins (3-hydroxy-3-methylglutaryl CoA reductase inhibitors) are potent inhibitors of cholesterol biosynthesis. Large clinical trials have demonstrated the beneficial effects of statins in the primary and secondary prevention of coronary heart disease. However, the overall clinical benefits observed with statin therapy appear to be greater than what might expect from changes in lipid profile alone, suggesting that the beneficial effects of statins might extend beyond those related to serum cholesterol levels. Indeed, experimental and clinical evidence indicates that some of the cholesterol-independent or pleiotropic effects of statins involve improving or restoring endothelial function, enhancing the stability of atherosclerotic plaques, and decreasing oxidative stress and vascular inflammation (32).

It is well known that plasma PLTP function involves much more than phospholipid transfer and exchange among the lipoproteins. PLTP deficiency contributes to reduced systemic inflammation in mice (33–35). Indeed, PLTP deficiency increased (25), while PLTP overexpression decreased the antioxidant potential in mouse models (36). Although PLTP seems to be involved in human atherogenesis, it is unclear under which circumstances high or low PLTP activity increases or decreases initiation or progression of atherosclerotic diseases (28, 30).

The relationship between statin treatment and PLTP activity is unknown and published results are controversial. In a recent study in patients with type 2 diabetes, atorvastatin treatment resulted in a decrease in PLTP activity and an increase in PLTP mass, leading to a substantial change in mass-adjusted activity, which was related to apoE metabolism (37). In contrast, serum PLTP activity showed no significant changes in patients with type IIb hyperlipidemia after simvastatin treatment compared with controls (38). Moreover, combined treatment with simvastatin and niacin over 12 months did not alter PLTP activity in patients with low HDL and cardiovascular disease (39). These differing results in humans may be explained by the different effects of statins on PLTP activity as shown in a study comparing the effect of pravastatin and simvastatin on PLTP activity in plasma and cerebrospinal fluid in mice (40). We recently reported that PLTP activity was independent of current statin treatment (25.0 ± 9.6pmol/μl/h in patients receiving and 25.6 ± 9.9pmol/μl/h in patients not receiving statin therapy at baseline, $P = 0.350$) (28).

What could be the link between statin treatment and the prognostic value of plasma PLTP activity? PLTP activity and statin treatment are closely related to inflammation, lipoprotein oxidation, and reverse cholesterol transport (6–8, 34–35, 41). As these mechanisms are involved in progression of atherosclerotic diseases, they are related to clinical outcome of these patients (1–4). As a consequence, it is reasonable to find comparable effects of PLTP and statin treatment. We showed in our study that, under statin treatment, high plasma PLTP activity is related to fatal and nonfatal cardiovascular events in CAD patients, independent of other markers such as Hs-CRP or HDL-C. Thus, on one hand we hypothesize that in the statin-treated group, PLTP activity elevation may indicate that, except for lowering levels of cholesterol, statin treatment does not improve the anti-flammation and anti-oxidation properties or even

affect reverse cholesterol transport (42). On the other hand, another interpretation of the results of our study is that the benefical effects of statins are blunted in patients with high PLTP activity, which means that high PLTP activity could be one confounder for less-beneficial effect of statin treatment.

However, this analysis is descriptive and the interpretation and is limited by missing data about laboratory (e.g., PLTP activity) and clinical parameters (e.g., smoking) at follow-up especially in case of events. Our data are hypothesis generating; further prospective trials are warranted to elucidate the exact connection between statin treatment and PLTP activity.

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