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Elevated baseline plasma phospholipid protein (PLTP) levels are an independent predictor of long-term all-cause mortality in patients with diabetes mellitus and known or suspected coronary artery disease

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STRUCTURED ABSTRACT

Objectives—To investigate the long-term prognostic significance of baseline plasma PLTP levels in a group of well-characterized male patients with diabetes mellitus and known or suspected coronary artery disease referred for coronary angiography.

Background—PLTP is a plasma protein that mediates net transfer and exchange of phospholipids between lipoproteins. It has been implicated in the pathogenesis of atherosclerosis and elevated plasma levels have been reported in patients with diabetes mellitus.

Methods—Baseline plasma PLTP levels were measured in 154 male patients with diabetes mellitus who were referred for coronary angiography and followed prospectively for the development of all-cause mortality for 5 years.

Results—After adjustment for a variety of baseline clinical, angiographic and laboratory parameters, plasma PLTP levels (analyzed as a continuous variable) were an independent predictor of all-cause mortality at 5 years (HR, 1.55; 95% CI, 1.22–2.00; P=0.0009). Furthermore, in 3 additional multivariate models that also included a wide variety of contemporary biomarkers with established prognostic efficacy (i.e., ST2, GDF-15, Cystatin C, Fibrinogen, and NT-proBNP), PLTP remained an independent predictor of all-cause mortality at 5 years.

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Conclusions—Elevated baseline plasma levels of PLTP are associated with an increased risk of long-term all-cause mortality in patients with diabetes and known or suspected coronary disease. Furthermore, this association is independent of a variety of clinical, angiographic, laboratory variables, including a whole host of contemporary biomarkers with established prognostic efficacy.

Keywords

PLTP; phospholipid transfer protein; biomarkers; acute coronary syndrome; prognosis; mortality; diabetes mellitus

Introduction

Phospholipid transfer protein (PLTP) is an 81 kDa monomeric protein that belongs to a family of lipid transfer/lipopolysaccharide-binding proteins, including cholesterol ester transfer protein (CETP), lipopolysaccharide-binding and bactericidal/permeability increasing protein (1–3). Besides phospholipids, PLTP also efficiently transfers diacylglycerol, alpha-tocopherol, cerebroside, and lipopolysaccharides (4). Thus, plasma PLTP is a non-specific lipid transfer protein. A number of basic investigations have implicated PLTP in the pathogenesis of atherosclerosis (5–7), and clinical studies have also, in general, supported a pro-atherogenic role for PLTP as well (8–11). Furthermore, elevated plasma PLTP levels have been shown to be independently associated with the presence of left ventricular (LV) systolic function (12), a common accompaniment of atherosclerosis.

In addition to a pro-atherosclerotic role, PLTP activity has also been demonstrated to be increased in patients with diabetes mellitus (13–15), a condition closely associated with both atherosclerosis (16) and LV systolic dysfunction (17). Plasma PLTP levels are also elevated in patients with insulin resistance and obesity (18–20), two conditions that are closely related to the development of diabetes. Furthermore, elevated PLTP levels in patients with diabetes mellitus have been proposed as a possible explanation for the accelerated atherosclerosis seen in this disorder (21). However, despite the published associations between PLTP levels and both atherosclerosis and diabetes mellitus, there have no studies that have specifically examined the prognostic significance of baseline plasma PLTP levels in patients with diabetes mellitus. Accordingly, the objective of the current study was to investigate the long-term prognostic utility of baseline plasma PLTP levels in a well-characterized cohort of male patients with diabetes mellitus and either known or suspected coronary artery disease referred for coronary angiography. Specifically, the objective of this study was to examine the utility of PLTP for the prediction of all-cause mortality at 5 years in the context of well-established covariates known to be associated with poor outcomes, such as the extent of coronary artery disease, the presence of congestive heart failure and myocardial infarction, poor renal function, older age and well-established prognostic biomarkers such as NT-proBNP, Fibrinogen, Cystatin C, GDF-15, and ST2.

Study Design

The present study represents an analysis of the diabetic subpopulation of patients derived from a database of 389 patients. The database was generated at an urban Veterans

Administration (VA) Medical Center and was approved by the local IRB (22). All patients referred to the Cardiac Catheterization Laboratory for coronary angiography between January 13, 1999 and October 17, 2002 were eligible for inclusion in the database. Patients with active gastrointestinal bleeding or a hemoglobin concentration less than 8 g/dl were excluded. During the period of study enrollment, a total of 523 unique and consecutive patients underwent diagnostic coronary angiography. Of these 523 patients, 50 could not be enrolled because of an unexpected loss of key study personnel between January 29, 2001 and July 2, 2001. Of the remaining 473 patients, 84 were either unwilling or unable to provide informed consent. Thus, a total of 389 patients provided consent and constituted the total population from which the database was derived. Fasting blood was obtained from the patients at the time of angiography (but prior to the injection of contrast) for subsequent analysis. Clinical and demographic information was obtained on all patients by interview as well as review of the computerized medical records. Patients were followed prospectively for the occurrence of death (all-cause mortality).

The present analysis was performed on the 170 patients who constituted the diabetic cohort of the original database. Patients were classified as having diabetes mellitus if they had ever been treated with an insulin regimen or an oral hypoglycemic agent, or if they were documented to have a random glucose value of more than or equal to 200 mg/dl before the current presentation. Although the precise breakdown was not available, the vast majority of the patients were Type 2 diabetics.

Patients were divided into two groups based upon the median value of PLTP for the entire diabetic cohort. Summary statistics for the continuous variables (including the biomarkers) were presented as means $\pm$ SDs and medians with interquartile ranges, and comparisons between the two groups were performed with the nonparametric Wilcoxon rank-sum test. Log transformation was applied to the biomarkers to decrease the skewness and kurtosis of the data. Categorical data were summarized as frequencies and percentages, and comparisons between groups were performed with the Pearson chi square test or the Fisher's exact test if the number of observations per cell was <5 .

The predictors of all-cause mortality at 5 years were identified by univariate Cox regression. All of the variables (baseline characteristics) listed in Table 1 were studied by univariate analysis for their association with all-cause mortality. All biomarkers were analyzed as continuous variables, with the hazard ratios representing an increase of 1 SD in the respective log-transformed biomarker. Only those univariate predictors with $p < 0.05$ were subsequently entered into multivariate models. Multivariate Cox proportional hazard analyses were then performed as stepwise regressions with backward elimination to identify the independent predictors of all-cause mortality.

Time-to-event at 5 years was presented with Kaplan–Meier curves for the outcome of all-cause mortality. Comparison between the two groups defined by the median value of the entire diabetic cohort was performed with the log-rank test.

All analyses used two-sided tests with an overall significance level of $\alpha = 0.05$. All statistical analyses were performed using SAS (version 8) statistical software package (Cary, NC).

Measurement of PLTP activity

PLTP activity was measured with an assay kit (Cardiovascular Targets Inc., New York, NY, USA). The kit includes both donor and acceptor particles. Incubation of donor and acceptor particles with 3 μ l of human plasma results in 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 $3.3 \pm 0.5\%$. The linear range of PLTP activity in this assay was between 1 and 7 μ l of plasma. Three freeze-thaw cycles of plasma did not influence the assay. To validate the novel PLTP activity assay, we compared the results with those obtained by the classic radiolabeled method (23,24). There was a high degree of correlation between the 2 methods ($r = 0.90$, $p < 0.01$; $n = 30$). Laboratory personnel were unaware of the study individual assignment.

Measurement of Other Biomarkers

Commercially available kits were used to measure the plasma levels of high-sensitivity C-Reactive Protein (hs-CRP; Life Diagnostics, West Chester, PA, USA), N-Terminal-Pro-B-Type Natriuretic Peptide (NT-proBNP; Diagnostic Automation, Calabasas, CA, USA), Myeloperoxidase (MPO; Assay Designs, Ann Arbor, Michigan, USA), GDF-15 (R & D Systems, Minneapolis, MN, USA), ST2 (R & D Systems, Minneapolis, MN, USA), and Cystatin C (BioVendor, Asheville, NC, USA). Fibrinogen was measured using the Beckman Coulter ACL Advance (Beckman Coulter, Inc., Fullerton, California) with the method of clot curve analysis.

Results

In total, 170 men were enrolled in the study. However, PLTP values were available for only 154 of these patients. Baseline characteristics of the study population stratified by the median PLTP value of the group (i.e., <17.44 pmol/ μ l/h vs ≥ 17.44 pmol/ μ l/h) are listed in Table 1. Higher baseline levels of PLTP were associated with higher baseline levels of NT-proBNP and the presence of myocardial infarction on presentation. There was also a trend towards higher baseline levels of PLTP being associated with a history of prior CABG and more extensive coronary artery disease, consistent with the existing literature (8).

Five-year follow-up data were available for all patients. For the 154 patients in whom baseline PLTP values were available, there were a total of 52 deaths at 5 years. The following baseline variables were significant univariate predictors ($p < 0.5$) of all-cause mortality at 5 years: CAD extent, CHF on presentation, MI on presentation, older age, estimated GFR using MDRD, Metformin use, TZD use, Cystatin C, NT-proBNP, Fibrinogen, ST2, GDF-15 and PLTP. Together with PLTP (analyzed as a continuous variable), all baseline clinical, laboratory and angiographic variables that were significant

for their association with all-cause mortality with $p < 0.05$ were entered into 4 different multivariate models. All 4 models included PLTP in the selection of covariates, as it was significant on univariate analysis and the focus of the investigation. Model 1 included only “clinical variables” in the selection that were significant on univariate analysis (the presence of CHF on presentation, the presence of MI on presentation, the extent of angiographically-defined coronary artery disease, estimated GFR using the MDRD formula, Metformin use, and TZD use). Models 2–4 included the same clinical variables as in Model 1, but also included “biomarkers” that were significant on univariate analysis for their association with all-cause mortality. Model 2 included the traditional biomarkers NT-proBNP and Fibrinogen. Model 3 included Cystatin C in addition to NT-proBNP and Fibrinogen. Model 4 included the novel biomarkers GDF-15 and ST2, but did not include NT-proBNP, Fibrinogen, or Cystatin C. In all 4 multivariate models, PLTP emerged as an independent predictor of all-cause mortality at 5 years, with a hazard ratio ranging between 1.38 and 1.63.

Using the median of PLTP for the entire group as a prespecified cut-off point (i.e., < 17.44 pmol/ul/h vs ≥ 17.44 pmol/ul/h), Kaplan-Meier curves were derived for the outcome of all-cause mortality at 5 years (Figure 1). Kaplan-Meier plots demonstrated an increase in all-cause mortality for patients whose plasma PLTP levels were greater than or equal to the median value, compared with those patients whose baseline values were less than the median value. Specifically, the mortality rates at 5 years for the 2 groups were 46.75% and 20.78%, respectively ($p = 0.0011$ by log-rank test).

Discussion

The most significant finding of our study was that elevated baseline plasma levels of PLTP were strong and independent predictors of all-cause mortality in a population of high risk male patients with diabetes mellitus and either known or suspected coronary artery disease referred for coronary angiography. Importantly, this association with mortality persisted even after adjustment for a wide variety of clinically significant covariates, including well-established contemporary biomarkers with proven prognostic efficacy. To our knowledge, this is the first report on utility of plasma PLTP levels for the prediction of mortality in patients with diabetes mellitus.

PLTP is a plasma protein that mediates net transfer and exchange of phospholipids between lipoproteins. Although much of the original research on PLTP focused on its positive role in high-density lipoprotein (HDL) metabolism, more recent investigations have instead demonstrated that PLTP is in fact a pro-atherosclerotic protein (18). Indeed, basic investigations in transgenic mice have supported this paradigm (6,7,25,26), and this construct has been further bolstered by a number of clinical studies in humans (8–11). In one such study, PLTP activity was shown to be positively and independently related to coronary artery disease (8). In another analysis done in 3 European populations using a gene score based on several single nucleotide polymorphisms of PLTP, it was found that cardiovascular disease was lower in those subjects with a lower overall PLTP gene score (10). More recently, the Framingham Heart Study found that higher PLTP activity was associated with a significantly increased risk of cardiovascular disease, although this association was

confined to men (11). Finally, PLTP activity has also been shown to be independently associated with the presence of LV systolic dysfunction (12), which is common in patients with atherosclerosis.

In addition to being associated with atherosclerosis, PLTP activity has also been shown to be increased in patients with diabetes mellitus. Indeed, a fairly large number of studies have consistently shown that plasma PLTP levels are elevated in patients with diabetes mellitus and those with insulin resistance (13–15,27–31), and that high PLTP activity may be responsible for the accelerated atherosclerosis seen in this disease (21). However, there are no studies that have specifically examined the prognostic utility of baseline plasma PLTP levels in patients with diabetes mellitus. In the current study, we report for the first time that elevated baseline plasma levels of PLTP predict the subsequent development of long-term mortality in high-risk diabetic male patients referred for coronary angiography. Using 4 different multivariate models that included a whole host of covariates known to predict adverse events in patients with and without diabetes, as well as other biomarkers with established prognostic efficacy, baseline PLTP levels emerged as independent predictors of the individual hard endpoint of all-cause mortality at 5 years. We believe that the consistency of the various multivariate models with respect to the predictive power of PLTP is a testimony to the validity of the findings.

The mechanism(s) by which elevated plasma levels of PLTP independently predict long-term mortality in male patients with diabetes mellitus remains unknown. Clearly, the known association of PLTP with both atherosclerosis and LV systolic dysfunction, two powerful predictors of adverse outcomes, could explain its relationship with mortality. Importantly, however, is it not known whether elevated PLTP levels predict mortality, presumably through its association with atherosclerosis, in a non-specific manner and across a broad population of patients, or whether there are unique implications of elevated PLTP levels in patients with diabetes mellitus. It is noteworthy that in a large study of patients with documented coronary artery disease, baseline PLTP levels predicted adverse cardiovascular events only in the subgroup of patients treated with a statin (9). Similarly, in another small study, baseline PLTP levels did not predict mortality in patients on hemodialysis (32). Along the same lines, and as already stated, a recent analysis from the Framingham Heart Study found that PLTP was associated with significantly increased cardiovascular disease in men, but not women (11). Thus, in contrast to biomarkers such as hs-CRP or NT-proBNP, which have predictive efficacy in a broad population of patients and across the full spectrum of risk, the predictive power of PLTP may in fact be limited to specific high-risk groups, such as those with diabetes mellitus. Concordant with the findings of the Framingham Heart Study, our study consisted only of male patients.

There are several limitations to the present study. First, it was conducted exclusively in men, and as such, the results cannot be extrapolated to women. This is particularly relevant since, as already stated, another study similarly found an association between PLTP and cardiovascular disease that was restricted to men. Second, the size of our population was small, and the study was not designed with *a priori* calculations with respect to sample size or statistical power. As such, the findings need to be confirmed in larger and prospectively designed studies. Third, given the relatively small number of patients in our study, we were

unable to perform meaningful subgroup analyses designed to examine whether the prognostic utility of PLTP was in any way related to underlying risk. Clearly, PLTP levels were higher in those diabetic patients who had myocardial infarction as their index diagnosis. Along the same lines, and for the same reasons, we were not able to perform sub-analyses based on left ventricular function or the extent of coronary artery disease. Finally, the observations derived from this study do not allow us to draw conclusions regarding causality. Indeed, given the discordant biologic effects of PLTP, it is unknown whether PLTP represents a risk marker or a risk factor (or perhaps both) for the development of future cardiovascular events.

In conclusion, we found that baseline plasma PLTP activity was a predictor of long-term all-cause mortality in a group of high risk male patients with diabetes mellitus referred for coronary angiography. Importantly, this association with long-term mortality was independent of other well-established predictors of adverse outcomes, including other biomarkers with proven prognostic efficacy. PLTP may thus represent a novel biomarker for risk stratification in high-risk diabetic patients with known or suspected coronary artery disease.

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ABBREVIATIONS

eGFR	estimated glomerular filtration rate
MI	myocardial infarction
CAD	coronary artery disease
CABG	coronary artery bypass graft surgery
CHF	congestive heart failure
LV	left ventricular
EF	ejection fraction
BMI	body mass index
hs-CRP	high-sensitivity C-Reactive Protein
NT-proBNP	N-Terminal-Pro-B-Type Natriuretic Peptide
MPO	myeloperoxidase
GDF-15	Growth Differentiation Factor 15
ACE-I	angiotensin converting enzyme inhibitor
ARB	angiotensin receptor blocker
TZD	Thiazolidinediones

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- PLTP is a plasma protein that mediates net transfer and exchange of phospholipids between lipoproteins.
- PLTP has been implicated in the pathogenesis of atherosclerosis and elevated plasma levels have been reported in patients with diabetes mellitus.
- Elevated plasma levels of PLTP are associated with an increased risk of long-term all-cause mortality in patients with diabetes mellitus and known or suspected coronary disease that is independent of a variety of clinical, angiographic, laboratory variables.

Figure 1.

Kaplan-Meier curves for all-cause mortality stratified by the median value of PLTP for the diabetic group. At 5 years, the number of deaths in those patients whose baseline PLTP levels were below the median for the entire group was 16 (20.78%), whereas it was 36 (46.75%) in those whose baseline PLTP levels were at or above the median value for the entire group ($p = 0.0011$ by log-rank test).

Table 1

Baseline characteristics of the diabetes mellitus population stratified by the median value of group for PLTP (<17.44 vs ≥17.44 pmol/u/h)

Characteristics	Statistics	PLTP < 17.44 (N = 77)	PLTP ≥ 17.44 (N = 77)	p-value
Age	Mean(sd)	66.1(9.0)	65.7(9.6)	
	Median(25 th , 75 th)	67(57, 74)	67.7(57, 74)	0.9914
Race	Black	26(33.8)	24(31.2)	0.5866
	Hispanic	27(35.1)	23(29.9)	
	White	24(31.2)	30(39.0)	
Family history of premature coronary artery disease	Yes	18(23.4)	25(32.5)	0.2086
Hypertension	Yes	71(92.2)	71(92.2)	1.0000
Any history of tobacco use	Yes	63(81.8)	59(76.6)	0.4269
Active tobacco use	Yes	17(22.1)	25(32.5)	0.1478
CHF on presentation	Yes	21(27.3)	25(32.5)	0.4813
Atrial fibrillation	Yes	5(6.5)	2(2.6)	0.4422
Hyperlipidemia	Yes	51(66.2)	52(67.5)	0.8641
LV function	Normal (EF>=55%)	26(36.1)	22(30.1)	0.7655
	Mild decrease (EF 45–54%)	14(19.4)	19(26.0)	
	Moderate decrease (EF 31–44%)	18(25.0)	19(26.0)	
	Severe decrease (EF<=30%)	14(19.4)	13(17.8)	
Number of diseased coronary arteries	0	15(19.5)	9(11.7)	0.0791
	1	13(16.9)	14(18.2)	
	2	23(29.9)	13(16.9)	
	3	24(31.2)	35(45.5)	
	4	2(2.6)	6(7.8)	
Prior CABG	Yes	5(6.5)	12(15.6)	0.0719
MI on presentation	Yes	19(24.7)	32(41.6)	0.0260
ACS on presentation	Yes	35(45.5)	47(61.0)	0.0526
	Median(25 th , 75 th)	100.8(81, 123.4)	92.8(72, 120.5)	0.30008
BMI (kg/m ²)	Mean(sd)	30.1(5.9)	29.3(5.8)	

Characteristics	Statistics	PLTP < 17.44 (N = 77)	PLTP ≥ 17.44 (N = 77)	p-value
	Median(25 th , 75 th)	29.2(26.6, 34.6)	28.3(25.8, 31.9)	0.3184
hs-CRP (mg/L)	Mean(sd)	17(27.7)	32.2(54.2)	
	Median(25 th , 75 th)	7.3(3.8, 17.7)	9.2(4.9, 25.6)	0.1009
Fibrinogen (mg/dL)	Mean(sd)	387(116.6)	395.7(103.9)	
	Median(25 th , 75 th)	353(311, 428)	382(325, 460)	0.2911
Troponin I (ng/mL)	Mean(sd)	4.4(12.9)	13.3(40.9)	
	Median(25 th , 75 th)	0.3(0.2, 1.3)	0.3(0.2, 9.2)	0.2937
Serum creatinine (mg/dL)	Mean(sd)	1.2(0.4)	1.4(1.3)	
	Median(25 th , 75 th)	1.1(0.9, 1.3)	1.1(0.9, 1.3)	0.6228
NT-pro-BNP (ng/L)	Mean(sd)	1159(951)	1565(1188)	
	Median(25 th , 75 th)	764(549, 1437)	1050(689, 2334)	0.0273
eGFR by MDRD (mL/min 1.73 m ²)	Mean(sd)	76.3(19.8)	75.6(29.1)	
	Median(25 th , 75 th)	75(66, 90)	71(59, 92)	0.4394
Myeloperoxidase (ng/mL)	Mean(sd)	21.2(12.8)	21.5(15.0)	
	Median(25 th , 75 th)	17.4(12.7, 26.3)	16.1(13.2, 26.0)	0.8088
ST2 (ng/mL)	Mean(sd)	23.6(12.1)	27.6(16.4)	
	Median(25 th , 75 th)	19.9(16.1, 27.8)	22.6(16.0, 32.9)	0.2092
Cystatin-C (ng/mL)	Mean(sd)	1130(362)	1119(515)	
	Median(25 th , 75 th)	1045(900, 1253)	994(825, 1210)	0.1973
GDF-15 (ng/L)	Mean(sd)	1340(657)	1767(1290)	
	Median(25 th , 75 th)	1134(855, 1557)	1365(961, 2050)	0.0634
HbA1c (%)	Mean(sd)	8.0(1.8)	7.8(1.8)	
	Median(25 th , 75 th)	7.6(7.0, 9.0)	7.4(6.6, 8.7)	0.3124
Aspirin use	Yes	65(84.4)	64(83.1)	0.8270
Beta blocker use	Yes	61(79.2)	55(71.4)	0.2621
ACE-inhibitor use	Yes	53(68.8)	57(74.0)	0.4755
ARB use	Yes	10(13.0)	4(5.2)	0.0926
Statin use	Yes	49(63.6)	49(63.6)	1.0000
Fibrate use	Yes	5(6.6)	4(5.2)	0.7455

Characteristics	Statistics	PLTP < 17.44 (N = 77)	PLTP ≥ 17.44 (N = 77)	p-value
Insulin use	Yes	21(27.3)	21(27.3)	1.0000
Any oral hypoglycemic use	Yes	55(71.4)	49(63.6)	0.3018
TZD use	Yes	5(6.4)	3(3.9)	0.7192
Metformin use	Yes	27(35.1)	28(36.4)	0.8665

* Hyperlipidemia was diagnosed in patients who had been given lipid-lowering medication or had a history of total cholesterol levels > 240 mg/dL (22).

** Takes into account the left main, left anterior descending, left circumflex, and right coronary arteries (22).

Table 2

Multivariate Cox Regression Models for All-Cause Mortality at 5 Years

Variable	Model 1		Model 2		Model 3		Model 4	
	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)
PLTP	0.0009	1.55(1.22,2.00)	0.0002	1.63(1.26,2.10)	0.0013	1.54(1.18,2.00)	0.0140	1.38(1.07,1.77)
Age/10 y	0.0012	1.74(1.24,2.43)	0.0001	1.97(1.40,2.77)	0.0001	1.99(1.40,2.84)	0.0012	1.81(1.26,2.60)
MI on presentation	NS	-	NS	-	NS	-	NS	-
CHF on presentation	NS	-	NS	-	NS	-	NS	-
CAD extent	NS	-	NS	-	NS	-	NS	-
Estimated GFR	0.0018	0.62(0.46, 0.84)	NS	-	NS	-	NS	-
Metformin use	NS	-	NS	-	NS	-	0.0026	0.35(0.18,0.69)
TZD use	0.0116	3.28(1.31, 8.26)	0.0010	4.55(1.84,11.20)	0.0029	3.93(1.60,9.67)	NS	-
NT-proBNP			NS	-	0.0012	1.62(1.21,2.17)		
Fibrinogen			NS	-	NS	-		
Cystatin C					NS	-		
ST2							NS	-
GDF-15							<0.0001	1.91(1.47,2.49)

All variables included in the selection were significant predictors of all-cause mortality at 5 years on univariate analysis with $p < 0.05$ **Model 1** included only clinical and angiographic variables in the selection, along with PLTP**Model 2** is the same as Model 1, but also includes the biomarkers NT-proBNP and Fibrinogen**Model 3** is the same as Model 1, but also includes the biomarkers NT-proBNP, Fibrinogen and Cystatin C**Model 4** is the same as Model 1, but also includes the biomarkers ST2 and GDF-15.