Value of serum pregnancy-associated plasma protein A for predicting cardiovascular events among patients presenting with cardiac chest pain

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Abstract

Background: Pregnancy-associated plasma protein A (PAPP-A) has been suggested as a candidate marker for the identification of unstable plaques in coronary arteries. We assessed the value of PAPP-A for predicting short-term cardiovascular events in a large cohort of patients presenting with cardiac chest pain.

Methods: We included consecutive patients who presented to a teaching hospital in Germany with chest pain of cardiac origin confirmed by coronary angiography. We analyzed PAPP-A levels from serum samples drawn within 30 minutes after arrival in the emergency department or in the catheterization laboratory. Patients were followed for 90 days or until death for major adverse cardiovascular events, defined as the combined outcome of stent thrombosis, myocardial (re)infarction, ischemic stroke or cardiovascular-related death.

Results: A total of 2568 patients (mean age [± standard deviation (SD)] 68 ± 11 years; 74% male) presented with cardiac chest pain: 55% had stable angina and 45% had acute coronary syndrome. The PAPP-A levels ranged from 4 to 2154 mIU/L (median 14.0 mIU/L, interquartile range 9.3–25.2 mIU/L). Major adverse cardiovascular events occurred in 203 patients (7.9%). The mean PAPP-A level was higher among patients who had an event than among those who did not (62 ± 156 v. 21 ± 23 mIU/L, $p < 0.001$). In a multivariable analysis, PAPP-A remained a significant independent predictor of the primary outcome within 90 days (hazard ratio per 1 SD increase in PAPP-A level 1.96, 95% confidence interval 1.74–2.21). The optimal prognostic cutoff value was a PAPP-A level of 34.6 mIU/L.

Interpretation: Higher levels of serum PAPP-A were independently associated with an increased short-term risk of cardiovascular events in patients presenting with cardiac chest pain. Further studies are required to validate the use of PAPP-A in routine clinical practice to predict future cardiovascular events.

Competing interests: See end of article.

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Coronary artery disease is the leading single cause of death in the Western world.[1] Patients with coronary artery disease cycle between asymptomatic phases, episodes of progressive angina and acute coronary syndromes.[2] Cardiac troponin levels have a high sensitivity and specificity in the diagnosis of non-ST-segment elevation myocardial infarction.[3–5] However, a large number of patients at risk of major coronary events do not present with myocardial necrosis and cannot be identified by troponin elevations. Markers of plaque instability may be helpful in this regard.

An interesting candidate for the identification of unstable plaques is the zinc-binding metalloproteinase pregnancy-associated plasma protein A (PAPP-A).[6–8] It was identified in 1972 in blood samples from pregnant women,[9] and it is widely used in the screening for fetal trisomy.[10,11] However, the term "pregnancy-associated plasma protein A" is misleading, because the peptide is not secreted only during pregnancy. Interest in cardiovascular applications first arose in 2001, when it became clear that the peptide is abundantly expressed in eroded and ruptured, but not in stable, atherosclerotic plaques.[12] Several authors have later pursued the idea that PAPP-A might help to stratify the risk of major adverse cardiovascular events in patients with coronary artery disease. However, earlier studies were limited by sample size or by the number of clinical events.

We sought to evaluate the value of PAPP-A for predicting major adverse cardiovascular

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events in a large sample of 2568 consecutive patients who presented with cardiac chest pain.

Methods

Patient selection

We evaluated consecutive patients who presented with chest pain to the University Hospital Tübingen, Germany, between December 2007 and April 2009. A cardiac cause of chest pain was assumed unless proven otherwise and was confirmed with coronary angiography.

Clinical evaluation

All patients underwent coronary angiography within 24 hours after arrival, either for suspected acute coronary syndrome or as part of an elective admission in patients with stable angina. Acute coronary syndrome was defined according to the joint guidelines of the American Heart Association and the American College of Cardiology,[13] with a diagnostic threshold for troponin I of 0.04 ng/mL or higher. Stable angina pectoris was defined as symptoms of angina pectoris without progression and with stable intensity and a troponin I level below 0.04 ng/mL before cardiac catheterization.

All patients underwent echocardiography within 48 hours after initial presentation. The degree of left ventricular impairment was classified according to the left ventricular ejection fraction: severe impairment (left ventricular ejection fraction < 35%), moderate impairment (35%–44%), mild impairment (45%–59%) or no impairment (≥ 60%).

All patients were followed up by telephone interview or outpatient office visit for 90 days or until death. No patient was lost to follow-up.

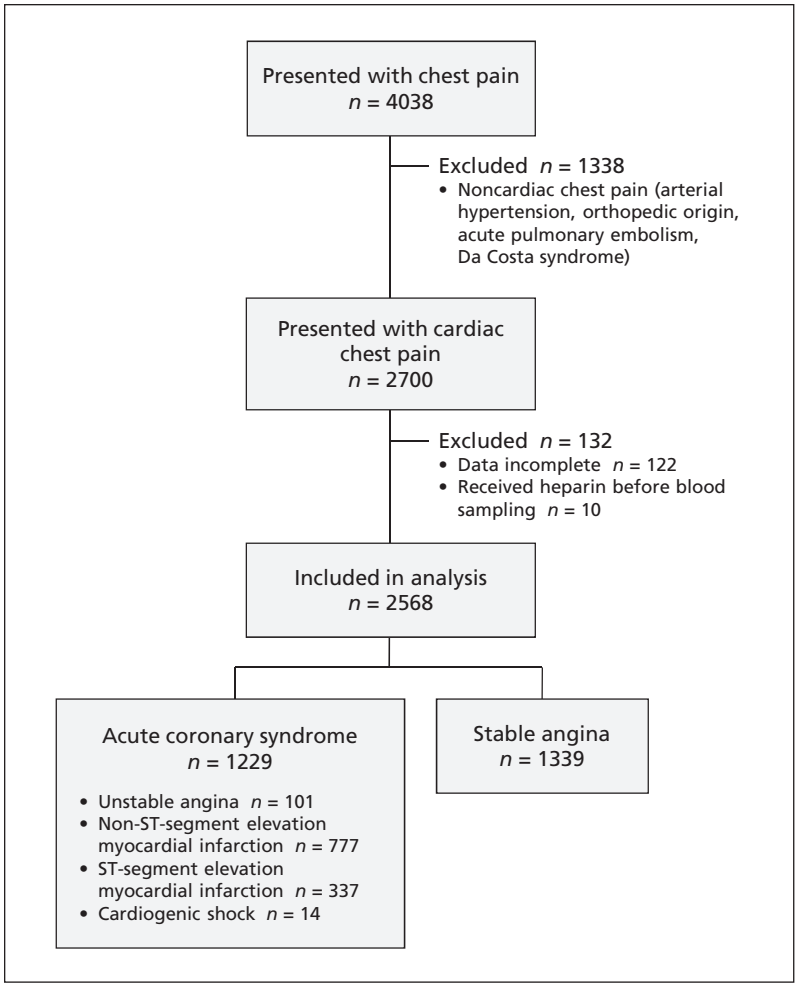

Figure 1: Selection of patients.

Biochemical analysis

Venous blood was drawn from an antecubital vein for routine clinical assessments and as part of a prospective biomarker research project. For our study, we excluded patients who had blood samples collected after the administration of heparin, because PAPP-A is known to interact with heparin.[14] Serum samples were immediately centrifuged and stored at –80°C for later analysis.

We analyzed serum values of creatine kinase, C-reactive protein and creatinine using standard laboratory assays. Troponin I was analyzed using a highly sensitive assay (Troponin I-Ultra assay on the ADVIA Centaur immunoanalyzer, Siemens AG, Eschborn, Germany). If more than one measurement was available for the entire hospital stay, the respective peak values were entered into the analysis. For PAPP-A assessment, an additional blood sample was filled into 5-mL pyrogen-free serum vials. Blood samples for PAPP-A analysis were drawn within 30 minutes after arrival to the emergency department or in the catheterization laboratory, whichever came first. PAPP-A serum values were analyzed using an automated immunofluorescent assay (Kryptor PAPP-A automated immunofluorescent assay, Thermo Fisher Scientific, BRAHMS GmbH, Hennigsdorf, Germany). The functional assay sensitivity (interassay coefficient of variance < 3%) is 4 mIU/L. According to the manufacturer, the normal serum value in men and nonpregnant women is < 14 mIU/L. Physicians involved in caring for the patients or who performed follow-up investigations were unaware of the respective PAPP-A serum values.

Ethics approval

The study design was approved by the Clinical Ethics Committee of the University Hospital Tübingen, and all patients provided written informed consent.

Outcome measure

The primary outcome measure was a combined outcome of stent thrombosis, myocardial (re)infarction, ischemic stroke or cardiovascular-related death.

Statistical analysis

Data are expressed as mean ± standard deviation (SD). Normal distribution was assessed using the Kolmogorov–Smirnov test, and non-normally distributed data were log-transformed to achieve normal distribution. We used the χ^2 test, Student unpaired *t*-test, and analysis of variance with the Fisher predicted least significant difference (post hoc) test to compare differences between groups. Univariable regression analyses were performed to assess factors that independently predicted PAPP-A levels. The association of baseline variables with survival was assessed by means of Cox proportional hazard analysis (single predictor and multivariable analysis). Hazard ratios (HRs) and 95% confidence intervals (CIs) for risk factors and significance level for χ^2 (likelihood ratio test) were calculated. For variables that were included twice in the unadjusted model (as log and continuous variables), the variable with the higher level of significance in the unadjusted model, as judged by the χ^2 value, was chosen for the multivariable model. To estimate the influence of risk factors on the occurrence of the primary outcome at 90 days, we constructed Kaplan–Meier cumulative survival curves for illustrative purposes and compared them using the log-rank test. The optimal prognostic cut-off value was defined as the highest product of sensitivity multiplied by specificity. In all analyses,

Table 1: Baseline characteristics of 2568 patients presenting with cardiac chest pain

Parameter	Primary diagnosis; no. (%) of patients or mean ± SD			*p* value†
	All *n* = 2568	Stable angina *n* = 1339	Acute coronary syndrome *n* = 1229	
Age, yr	68.4 ± 11.2	68.4 ± 9.9	68.3 ± 12.4	0.7
Male sex	1905 (74.2)	1025 (76.5)	880 (71.6)	0.005
BMI,* kg/m^2	*n* = 1336 27.7 ± 4.6	*n* = 662 28.2 ± 4.8	*n* = 674 27.3 ± 4.5	< 0.001
Left ventricular impairment				
None	1259 (50.8)	750 (57.9)	509 (43.0)	< 0.001
Mild	577 (23.3)	282 (21.8)	295 (24.9)	
Moderate	402 (16.2)	160 (12.4)	242 (20.4)	
Severe	242 (9.8)	103 (8.0)	139 (11.7)	
Coronary artery disease	*n* = 940	*n* = 547	*n* = 393	0.4
No. of affected coronary vessels per patient	2.3 ± 0.8	2.3 ± 0.8	2.3 ± 0.8	
Underwent coronary intervention	919 (97.7)	526 (96.2)	393 (100.0)	< 0.001
Type of intervention performed				
PTCA only	18 (2.0)	17 (3.2)	2 (0.5)	< 0.001
Bare metal stent	790 (86.0)	503 (95.6)	286 (72.7)	
Drug-eluting stent	79 (8.6)	3 (0.6)	76 (19.3)	
Both types of stents	31 (3.4)	3 (0.6)	29 (7.4)	
C-reactive protein, mg/L	*n* = 1998 37 ± 63	*n* = 876 14 ± 30	*n* = 1122 56 ± 74	< 0.001
Creatine kinase, U/L	*n* = 2272 521 ± 1259	*n* = 1106 145 ± 246	*n* = 1166 877 ± 1666	< 0.001
Troponin I, μg/L	*n* = 2553 16.6 ± 60.7	*n* = 1339 0.8 ± 7.3	*n* = 1214 33.7 ± 84.5	< 0.001
Creatinine, μmol/L	*n* = 2326 110.2 ± 73.1	*n* = 1160 105.0 ± 66.2	*n* = 1166 115.4 ± 79.0	< 0.001

Note: BMI = body mass index, PTCA = percutaneous transluminal coronary angioplasty, SD = standard deviation.
*BMI values were available for 1336 patients (662 with stable angina and 674 with acute coronary syndrome).
†For comparison between patients with stable angina and those with acute coronary syndrome (analysis of variance, Student *t*-test or χ^2 test).

a value of $p < 0.05$ was considered significant. Statistics were calculated using StatView 5.0 software for Windows (Abacus Concepts, Berkley, California).

Results

Of 4038 consecutive patients presenting with chest pain, 2700 were confirmed by coronary angiography to have cardiac chest pain (Figure 1). Inclusion criteria were met by 2568 of these patients. The median time between onset of chest pain and hospital admission was 2.5 hours.

The patients' clinical characteristics are presented in Table 1; their medical history and use of medications are provided in Table 2. A total of 1339 (52.1%) patients were classified as having stable angina and the remainder as having acute coronary syndrome. The precise diagnoses are shown in Figure 1. We detected significant differences between patients with stable angina and those with acute coronary syndrome in terms of body mass index (BMI), and serum levels of C-reactive protein, troponin I, creatine kinase and creatinine ($p < 0.001$ in each case). The impairment of left ventricular function was significantly more pronounced in patients with acute coronary syndrome than in those with stable angina ($p < 0.001$).

Serum levels of PAPP-A were available for all of the patients. The mean level was 24.6 ± 50.2 mIU/L (range 4.1–2154.4 mIU/L), and the median was 14.0 mIU/L (interquartile range 9.3–25.2 mIU/L). The broadness of the range of PAPP-A values was driven by one patient, whose level was 2154 mIU/L. The remaining patients had serum levels between 4.1 and 276.2 mIU/L. The PAPP-A values did not differ significantly between male and female patients (25.0 ± 56.4 mIU/L and 23.5 ± 25.6 mIU/L, respectively; $p = 0.97$). Patients who had acute coronary syndrome presented with slightly higher serum levels of PAPP-A than patients with stable angina (24.8 ± 28.5 v. 24.4 ± 64.0 mIU/L; $p = 0.01$). Serum levels of PAPP-A tended to increase with increasing degree of left ventricular dysfunction; however, this finding was driven mainly by patients with severely impaired left ventricular function (mean PAPP-A 30.3 ± 35.3 mIU/L among patients with left ventricular ejection fraction < 35% v. 22.8 ± 26.0 mIU//L among those with an ejection fraction ≥ 60%;

Table 2: Medical history and medication use

Variable	% (no.) of patients			
	All patients $n = 2568$	Stable angina $n = 1339$	Acute coronary syndrome $n = 1229$	p value*
Medical history				
Family history of heart disease	21.1 (533/2526)	23.7 (315/1329)	18.2 (218/1197)	< 0.001
Hypertension	80.9 (2044/2527)	82.4 (1095/1329)	79.2 (949/1198)	0.04
Atrial fibrillation	12.5 (312/2499)	12.5 (164/1313)	12.5 (148/1186)	0.99
Hyperlipidemia	65.3 (1649/2526)	72.2 (960/1329)	57.6 (689/1197)	< 0.001
Diabetes mellitus	33.5 (847/2526)	33.9 (450/1328)	33.1 (397/1198)	0.7
Current smoker	39.4 (995/2524)	38.9 (517/1328)	40.0 (478/1196)	0.6
Previous MI	7.0 (65/926)	6.9 (37/534)	7.1 (28/392)	0.9
Previous revascularization	11.3 (105/926)	12.9 (69/534)	9.2 (36/392)	0.07
Medication use				
ASA	65.5 (1537/2345)	75.2 (933/1241)	54.7 (604/1104)	< 0.001
Clopidogrel	28.8 (675/2343)	32.9 (408/1240)	24.2 (267/1103)	< 0.001
ACE inhibitor or ARB	59.8 (1402/2345)	68.4 (849/1241)	50.1 (553/1104)	< 0.001
Beta-blocker	65.0 (1522/2343)	74.1 (920/1241)	54.6 (602/1102)	< 0.001
Statin	54.5 (1277/2344)	65.6 (814/1240)	41.9 (463/1104)	< 0.001
Calcium-channel blocker	18.4 (239/1300)	20.2 (127/630)	16.7 (112/670)	0.1
Diuretic	38.3 (498/1300)	40.6 (256/630)	36.1 (242/670)	0.09
Aldosterone antagonist	2.8 (36/1299)	3.3 (21/630)	2.2 (15/669)	0.2

Note: ACE = angiotensin-converting enzyme, ARB = angiotensin-receptor blocker, ASA = acetylsalicylic acid, MI = myocardial infarction.
*χ^2 test for comparison of patients with stable angina and those with acute coronary syndrome.

p_{trend} = 0.003). In simple regression analysis, PAPP-A levels correlated slightly with serum values of creatine kinase (r = 0.065, p = 0.002) and troponin I (r = 0.04, p = 0.046), but not with age, BMI, creatinine level or C-reactive protein level (p > 0.3 in each case). Effects of patients' comorbidities and medication use on serum levels of PAPP-A are presented in Table 3.

A total of 203 (7.9%) of the patients had 245 primary outcome events during the 90 days of follow-up: stent thrombosis (58 events), myocardial (re)infarction (98 events), ischemic stroke (18 events) and cardiovascular-related death (71 events). Patients who experienced a primary outcome had a mean PAPP-A level of 62.0 ± 156.4 mIU/L, as compared with 21.4 ± 22.8 mIU/L among those who did not (p < 0.001). No difference in outcome was detected between patients with stable angina and any of the subgroups of patients with acute coronary syndrome (p_{trend} = 0.09).

Several dichotomized and continuous variables were investigated to determine their potential to predict the primary outcome within 90 days of follow-up (Table 4). In the single predictor Cox proportional hazard analysis, the presence of left ventricular dysfunction (dichotomized), the presence of acute coronary syndrome (dichotomized), PAPP-A (dichotomized or continuous), C-reactive protein (dichotomized or continuous), creatine kinase (dichotomized), troponin I (dichotomized or continuous) and creatinine (dichotomized or continuous) all predicted major adverse cardiovascular events, whereas sex, age, BMI, number of affected coronary vessels and attributes from the patients' medical history did not (all $p \geq 0.05$, Table 4). After adjustment for predictors of the primary outcome that were clinically important in the single-predictor model, PAPP-A remained a significant independent predictor of major cardiovascular events (adjusted HR per 1 SD increase in log PAPP-A 1.96, 95% CI 1.74–2.21). Other significant predictors in the adjusted model were a history of diabetes mellitus (adjusted HR 1.49, 95% CI 1.06–2.10) and a history of atrial fibrillation (adjusted HR 0.52, 95% CI 0.29–0.94) (Table 4).

PAPP-A remained the strongest predictor of major cardiovascular events when we restricted the analysis to patients with stable angina (adjusted HR per 1 SD increase in log PAPP-A 2.15, 95% CI 1.81–2.56) and when we restricted it to patients with acute coronary syndrome (adjusted HR per 1 SD increase in log PAPP-A 1.91, 95% CI 1.48–2.46). In the multivariable model including the entire cohort, no material change was noted when we analyzed separately the outcomes myocardial (re)infarction (adjusted HR per 1 SD increase in log PAPP-A 1.89, 95% CI 1.60–2.24), ischemic stroke (adjusted HR per 1 SD increase in log PAPP-A 2.15, 95% CI 1.51–3.06) and cardiovascular-related death (adjusted HR per 1 SD increase in log PAPP-A 2.06, 95% CI 1.70–2.49). This finding could not be verified with regard to the outcome stent thrombosis, for which only the presence of left ventricular dysfunction (adjusted HR 2.05, 95% CI 1.05–3.99) and a medical history of diabetes (adjusted HR 3.33, 95% CI 1.78–6.22) proved to be independently predictive.

Figure 2 shows the Kaplan–Meier survival curves for patients with PAPP-A below and above the best prognostic cut-off of 34.6 mIU/L, adjusted for all variables shown in the multivariable model in Table 4 (adjusted HR 5.28, 95% CI 3.81–7.31).

Adjusting the main clinical model for the variables that were available only for a limited number of patients (BMI, previous myocardial infarction and previous revascularization) did not change the results with regards to PAPP-A. After adjustment for BMI, PAPP-A remained a significant predictor of the combined primary outcome (adjusted HR per 1 SD increase in log PAPP-A 2.13, 95% CI 1.83–2.49), with BMI also being

Table 3: Serum PAPP-A levels by attributes of medical history and medication use

Factor	Serum PAPP-A level, mean ± SD		p value*
	Factor absent	Factor present	
Medical history			
Family history of heart disease	24.3 ± 54.8	26.0 ± 30.3	0.04
Hypertension	24.4 ± 25.8	24.7 ± 54.8	0.2
Atrial fibrillation	25.2 ± 53.6	21.7 ± 22.8	0.2
Hyperlipidemia	23.3 ± 26.5	25.4 ± 59.6	0.6
Diabetes mellitus	25.2 ± 58.4	23.6 ± 29.4	0.1
Current smoker	24.8 ± 61.2	24.4 ± 27.2	0.1
Medication use			
ASA	24.6 ± 29.0	24.7 ± 60.5	0.2
Clopidogrel	24.9 ± 58.9	24.4 ± 27.6	0.4
ACE inhibitor or ARB	24.4 ± 29.7	24.9 ± 62.5	0.96
Beta-blocker	25.3 ± 30.3	24.4 ± 60.4	0.04
Statin	26.9 ± 71.7	22.9 ± 25.2	0.2
Calcium-channel blocker	27.0 ± 70.6	26.0 ± 32.9	0.8
Diuretic	27.7 ± 80.3	25.4 ± 27.9	0.97
Aldosterone antagonist	26.8 ± 66.2	27.5 ± 24.9	0.3

Note: ACE = angiotensin-converting enzyme, ARB = angiotensin-receptor blocker, ASA = acetylsalicylic acid, PAPP-A = pregnancy-associated plasma protein A, SD = standard deviation.
*Student *t*-test.

independently predictive (adjusted HR per 1 kg/m^2 increase 0.94, 95% CI 0.89–0.99). Adjusting the main model for the number of affected coronary vessels, history of myocardial infarction and previous revascularization showed that the primary diagnosis of acute coronary syndrome, the presence of left ventricular dysfunction, a history of diabetes, a history of atrial fibrillation, a C-reactive protein level above the optimal cut-off and PAPP-A were all predictive of the combined primary outcome (adjusted HR per increase in 1 SD of log PAPP-A 1.95, 95% CI 1.57–2.42). The number of affected coronary vessels, history of myocardial infarction and previous revascularization were not predictive in this model.

Interpretation

Our study showed that PAPP-A was an independent predictor of the combined primary outcome of stent thrombosis, myocardial (re)infarction, ischemic stroke and cardiovascular-related death within 90 days among patients presenting with cardiac chest pain. This finding remained true when we restricted the analysis to include either patients with stable angina or those with acute coronary syndrome.

Similar to other metalloproteinases, PAPP-A could be involved in the processing of the extracellular matrix of arterial plaque and in the weakening of the fibrous cap.[15] However, whether PAPP-A acts in a proinflammatory

Table 4: Association of serum PAPP-A level and other clinical variables with major adverse cardiovascular events within 90 days after presentation with cardiac chest pain

Variable	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
Male sex	1.23 (0.88–1.71)	1.11 (0.73–1.69)
Age, per year increase	1.00 (0.99–1.02)	1.01 (0.99–1.02)
BMI, per unit increase	0.96 (0.91–1.00)	
Left ventricular dysfunction present	1.70 (1.27–2.27)	1.32 (0.93–1.89)
Acute coronary syndrome diagnosed	1.36 (1.03–1.79)	0.82 (0.54–1.27)
Coronary artery disease, per 1 increase in no. of affected coronary vessels	0.99 (0.74–1.32)	
Only PTCA performed during current admission	0.64 (0.09–4.60)	
Stent implantation performed during current admission	3.45 (0.48–24.82)	
Previous MI	1.77 (0.88–3.55)	
Previous revascularization	1.62 (0.89–2.94)	
Family history of heart disease	1.01 (0.72–1.42)	1.08 (0.71–1.64)
Hypertension	0.88 (0.62–1.23)	1.04 (0.68–1.61)
Atrial fibrillation	0.73 (0.46–1.18)	0.52 (0.29–0.94)
Hyperlipidemia	0.89 (0.67–1.19)	0.91 (0.64–1.30)
Diabetes mellitus	1.27 (0.96–1.69)	1.49 (1.06–2.10)
Current smoker	1.09 (0.82–1.44)	1.14 (0.79–1.65)
log PAPP-A, per 1 SD increase	1.99 (1.79–2.21)	1.96 (1.74–2.21)
PAPP-A above optimal cutoff (> 34.6 mU/L)	5.30 (4.02–6.98)	
log C-reactive protein, per 1 SD increase	1.24 (1.06–1.45)	
C-reactive protein above optimal cutoff (> 41.2 mg/L)	1.75 (1.28–2.40)	1.43 (0.97–2.13)
log Creatine kinase, per 1 SD increase	1.12 (0.98–1.29)	
Creatine kinase above optimal cutoff (> 207 U/L)	1.51 (1.13–2.02)	0.95 (0.60–1.52)
log Troponin I, per 1 SD increase	1.19 (1.05–1.36)	
Troponin I above optimal cutoff (> 2.07 μg/L)	1.70 (1.28–2.25)	1.47 (0.89–2.44)
log Creatinine, per 1 SD increase	1.20 (1.07–1.36)	
Creatinine above optimal cutoff (> 88.4 μmol/L)	1.43 (1.07–1.92)	1.23 (0.86–1.76)

Note: BMI = body mass index, CI = confidence interval, HR = hazard ratio, MI = myocardial infarction, PAPP-A = pregnancy-associated plasma protein A, PTCA = percutaneous transluminal coronary angioplasty, SD = standard deviation.
*Adjusted for all other variables in the table. For variables that were included twice in the unadjusted model (as log and continuous variables), the variable with the higher level of significance in the unadjusted model, as judged by the χ^2 value, was chosen for the multivariable model.

sense or exerts inflammatory suppressor activity is unclear.[15] Also unclear is whether insulin-like growth factor-1, whose availability is increased by PAPP-A, is an anti- or a pro-atherogenic molecule. The fact that only a minority of studies have shown a correlation between PAPP-A and C-reactive protein values casts further doubt on the argument that PAPP-A plays a role in inflammatory reactions.[16] Such a correlation was not noted in our study.

Our findings support the results of earlier studies that suggested PAPP-A as a marker of unstable atherosclerotic plaques, the first of which was published in 2001.[12] In a study by Cosin-Sales and colleagues involving 396 patients with stable angina, 289 of whom had significant coronary artery disease, patients who had complex lesions had higher serum PAPP-A levels than those who did not.[17] Lund and colleagues[18] found that a PAPP-A level above the cut-off of 2.9 mIU/L and a C-reactive protein level above the cutoff of 2.0 mg/L predicted cardiovascular death, myocardial infarction or the need for revascularization within 6 months of follow-up. Heeschen and colleagues analyzed PAPP-A levels in 547 patients with angiographically validated acute coronary syndrome and 644 heterogenous patients presenting with acute chest pain.[19] They found that PAPP-A (optimal cut-off 12.1 mIU/L) was an independent predictor of adverse outcomes in both subgroups of patients.

The difference between the optimal cut-off value in our study and the one calculated by Heeschen and colleagues is probably due to the difference in assays used and length of follow-up periods. Not all assays developed for the detection of PAPP-A in prenatal screening may be suitable for use in patients with coronary artery disease.[20] Indeed, antibodies used in assays for PAPP-A are all raised by immunization of mice with PAPP-A isolated from human pregnancy serum. However, unlike PAPP-A in patients with coronary artery disease, PAPP-A in pregnancy circulates as a complex with the proform of eosinophil major basic protein (proMBP). Qin and colleagues stated that assays using antibodies against only proMBP fail to detect PAPP-A in patients with acute coronary syndrome.[20] Although the assay used in our study was developed for use in prenatal screening, the fact that PAPP-A levels were detectable in all of the patients supports the view that the assay correctly identified PAPP-A levels in both patient subgroups.

Several authors have investigated the value of PAPP-A for predicting unstable atherosclerotic plaque using either single[16,17,21,22] or serial[23–25] measurements, even in patients receiving hemodialysis.[26] Studies have consistently shown higher PAPP-A levels in patients with acute coronary syndrome or multivessel coronary artery disease than in patients with stable angina or single-vessel disease.[20,27,28] Our study also showed higher levels in patients with acute coronary syndrome than in those with stable angina.

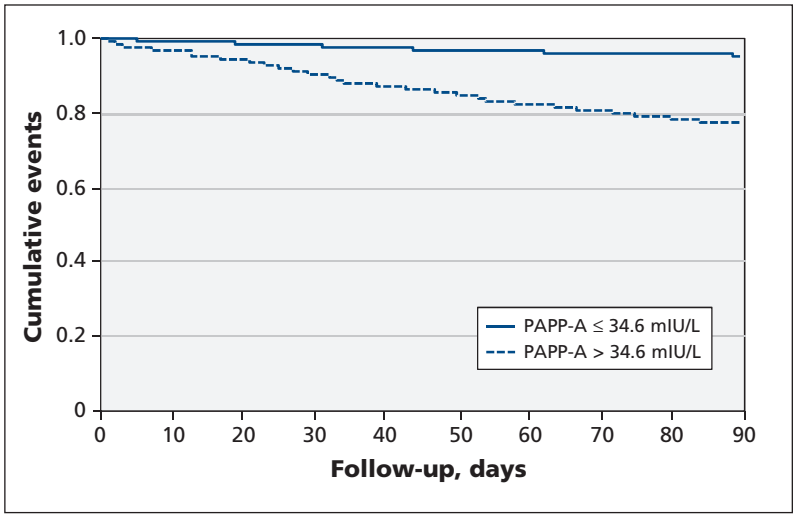

Figure 2: Kaplan–Meier curves for time to primary outcome (combined outcome of stent thrombosis, myocardial [re]infarction, ischemic stroke or cardiovascular-related death) among patients presenting with cardiac chest pain whose pregnancy-associated plasma protein A (PAPP-A) level was below or above the optimal prognostic cut-off value of 34.6 mIU/L (defined as the highest product of sensitivity times specificity).

Limitations

We analyzed PAPP-A values only from serum samples obtained at baseline. Follow-up samples were not available for our patients. We therefore cannot exclude that peak or follow-up PAPP-A values may have better (or worse) predictive value. In addition, not all patients who present with cardiac chest pain will eventually undergo cardiac catheterization; future studies need to show whether our findings can be applied to these patients as well. Further, we cannot exclude whether PAPP-A might be a better predictor of stent thrombosis if serum samples were drawn just after the procedure; however, in this case, the use of heparin may interfere with PAPP-A assessment. Even though PAPP-A had originally been suggested as a marker of unstable atherosclerotic plaques,[12] our study did not provide direct biological evidence of plaque instability. Another limitation is that we measured total PAPP-A, not the free form. Findings from a previous study suggested that the free form is a stronger predictor of cardiovascular diseases.[29] Although our study had a

large cohort, it was conducted in a single centre. A multinational, multicentre study is needed to validate our results.

Conclusion

Higher levels of serum PAPP-A were independently associated with an increased short-term risk of cardiovascular events in patients presenting with cardiac chest pain. Further studies are required to validate the use of PAPP-A in routine clinical practice to predict future cardiovascular events. If these studies are successful, PAPP-A measurements could play a role in reducing morbidity and mortality from coronary disease.

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