D-dimer, plasmin-antiplasmin complex and matrix metalloproteinase-2 as markers of cardiovascular events in patients with stable coronary disease

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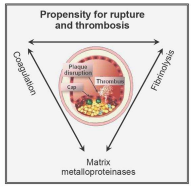
ATHEROTHROMBOSIS AND HIGH-RISK PLAQUE



• **Atherothrombosis** is a complex disease in which cholesterol deposition, inflammation, and thrombus formation play a major role.

• **Matrix metalloproteinases (MMPs) activation** modifies the architecture of the plaque and may directly participate in the process of fibrous cap destabilization and rupture.

• **Plaque rupture** is the most common trigger of arterial thrombosis, the main cause of ACS, ischemic stroke and sudden cardiac death.

• The thrombotic response to plaque rupture depends on state of activation of platelets, **coagulation and fibrinolysis**.

~ **Elevations in circulating levels of hemostatic activation markers and MMPs may reflect the propensity for atherothrombotic events.**
~ **However, only few prospective studies (ARIC, 2001; Caerphilly, 2005; AtheroGene, 2006, etc.) have demonstrated the predicative role of hemostatic markers.**
~ **Hemostatic markers have not been yet taken in account for current clinical risk scores.**

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AIM OF THE STUDY

To investigate prospective associations between markers of fibrinolytic function, circulating matrix metalloproteinases and thrombotic events in patients with stable coronary artery disease.

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STUDY DESIGN

Inclusion

1.Outpatients aged≥ 35 yrs
2.Documented CAD (at least 1 criteria):
– Stable angina, Class II – III
– ACS > 2 months ago
– PCI/CABG > 2 months ago
3.No thrombotic events within last two months
4.Therapy: according to current evidence-based guidelines

At admittance

1. Assessment for classic risk factors
2. Assessment for coronary, cerebrovascular and peripheral arterial disease
3. Blood collection and storage at -60°C until analyses
- markers of fibrinolytic function:
D-dimer;
Plasminogen activator inhibitor [PAI-1] activity;
Tissue plasminogen activator [tPA] / PAI-1 complex;
Plasmin-antiplasmin complex [PAP]
- circulating MMPs:
Total MMP-9 and free MMP-2

End points

follow-up ~ 3-7 years

Major arterial thrombotic events:
- CV death
- acute coronary syndrome
- ischemic stroke or transient ischemic attack
- peripheral arterial thrombosis

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STUDY POPULATION
(risk factors profile)

Classic CV risk factors were common in pts with stable symptomatic CAD

Gender (male/female), n	503 (387/116)
Age, yrs (M±m)	59,4 ± 0,4
Arterial hypertension, n (%)	427 (84,9%)
Hyperlipidemia*, n (%)	405 (80,5%)
Smoking status: • ex-smoker, n (%) • current smoker, n (%)	 183 (36,4%) 118 (23,5%)
Obesity (BMI> 30 kg/m^2), n (%)	167 (33,2%)
Diabetes mellitus, n (%)	93 (18,5%)
Atrial fibrillation, n (%)	36 (7,2%)
Renal impairment (creatinine clearance < 60 ml/min), n (%)	269 (53,6%)

* Serum cholesterol > 5,2 mmol/l and/or current intake of lipid lowering drugs

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STUDY POPULATION
(affected vascular beds)

Coronary artery disease (inclusion criteria)	**503 (100%)**
• Stable angina, functional class II – III	378 (75,1%)
• Previous ACS (> 2 month ago)	407 (80,9%)
• Previous coronary procedures:	
– PCI	333 (66,2%)
– CABG	64 (12,7%)
• Signs of heart failure (NYHA II – III)	35 (6,96%)
• Left main / 3-vessel coronary disease	95 (18,9%)
Coexisting with cerebrovascular disease (CVD)	**93 (18,5%)**
• Previous ischemic stroke / TIA (> 2 months ago)	32(6,4%)/16(3,2%)
• Carotid artery stenosis > 50%	62 (12,3%)
• Carotid surgery/angioplasty > 2 months ago	12 (2,4%)
Coexisting with peripheral arterial disease (PAD)	**123 (24,4%)**
• ABI <0,9	107 (21,3%)
• Intermittent claudication, Fontaine stage II-III	47 (9,3%)
• Peripheral surgery / angioplasty > 2 months ago	6 (1,2%)
Polyvascular disease (CAD + CVD + PAD)	**40 (7,9%)**

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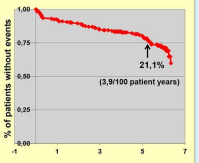
OCCURRENCE OF MAJOR THROMBOTIC EVENTS IN PATIENTS WITH STABLE CAD
(mean follow-up period = 5,4 years)

End point	No of events
CV death	**25**
• Sudden death	19
• Fatal MI	6
Non-fatal events	**81**
• ACS (ST-elevation)	18
• ACS (non-ST-elevation)	37
• Ischemic stroke	10
• Transient ischemic attack	14
• Peripheral arterial thrombosis	2
All thrombotic events	**106 21,1%**

Cumulative incidence of events



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CLINICAL VARIABLES AND RISK OF THROMBOTIC EVENTS IN PATIENTS WITH STABLE CAD
(initial stepwise selection procedure)

Variable	OR*	95% CI	p
Angina severity: class II-III vs class I	1,6	1,1-2,4	0,01
Previous myocardial infarction	1,3	0,9-1,8	0,1
Left main / 3-vessel coronary disease	1,45	1,0-2,1	0,05
Previous ischemic stroke / TIA	1,6	1,0-2,5	0,05
Peripheral arterial disease	1,3	0,9-1,7	0,1
BMI ≥ 31,6 кг/м^2	1,6	1,1-2,3	0,02
Renal impairment (creatinine clearance < 60 ml/min)	1,5	0,95-2,2	0,06

* Adjusted for age and sex

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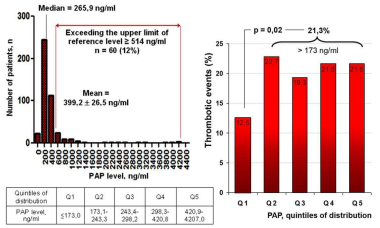
PLASMIN-ANTIPLASMIN LEVELS AND FREQUENCY OF THROMBOTIC EVENTS IN PATIENTS WITH STABLE CAD, n=503



Quintiles of distribution	Q1	Q2	Q3	Q4	Q5
PAP level, ng/ml	≤173,0	173,1-243,3	243,4-298,2	298,3-420,8	420,9-4207,0

Thrombotic events were observed more frequently in four upper quintiles of PAP distribution

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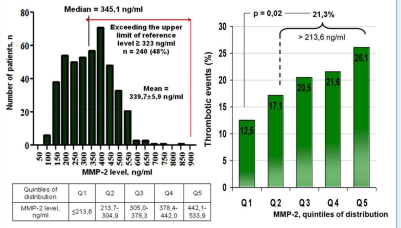
MMP-2 LEVELS AND FREQUENCY OF THROMBOTIC EVENTS IN PATIENTS WITH STABLE CAD, n = 503



Quintiles of distribution	Q1	Q2	Q3	Q4	Q5
MMP-2 level, ng/ml	≤213,6	213,7-304,9	305,0-378,3	378,4-442,0	442,1-533,9

Thrombotic events were observed more frequently in four upper quintiles of MMP-2 distribution

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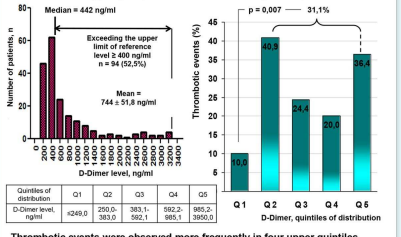
D-DIMER LEVELS AND FREQUENCY OF THROMBOTIC EVENTS
(group of pts without recent PCI*, n=179)



Quintiles of distribution	Q1	Q2	Q3	Q4	Q5
D-Dimer level, ng/ml	≤249,0	250,0-383,0	383,1-592,1	592,2-985,1	985,2-3950,0

Thrombotic events were observed more frequently in four upper quintiles of D-Dimer distribution

* D-dimer level was elevated in most pts with recent PCI (<10 days) due to fibrin deposition at vascular access site. Therefore, these pts were not included in analysis.

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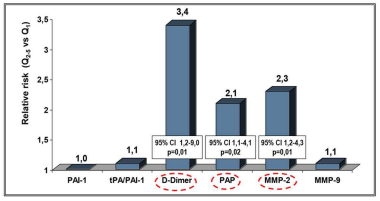
COMPONENTS OF FIBRINOLYTIC SYSTEM, CIRCULATING MMPs AND RISK OF THROMBOTIC EVENTS
Univariate analysis (age- and sex-adjusted)



On univariate analysis (age- and sex-adjusted), only D-dimer, PAP and MMP-2 were significantly associated with risk of TE.
Other estimated variables (PAI-1, TPA/PAI-1, MMP-9) have no prognostic impact.

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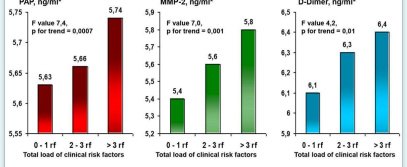
PLASMIN-ANTIPLASMIN COMPLEX, MMP-2, D-Dimer AND TOTAL LOAD OF CLINICAL RISK FACTORS
(regression model)



Plasma levels of PAP, MMP-2 and D-Dimer were strongly associated with total load of conventional factors, which have prognostic impact in our study (i.e., severity of angina, history of MI, multivessel coronary disease and other comorbidity). Other estimated variables (PAI-1, TPA/PAI-1, MMP-9) have no significant relations to clinical risk factors.**

* levels of hemostatic factors were logarithmically transformed because the distribution was skewed
** see picture № 7

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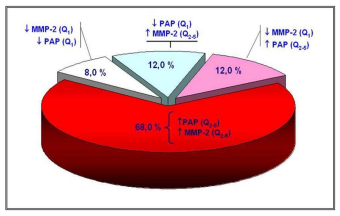
• **Simultaneous activation of fibrinolysis (↑PAP) and increase of circulating MMP-2 observed in 68% of pts with stable CAD**



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HEMOSTATIC PREDICTORS OF THROMBOTIC EVENTS IN PATIENTS WITH STABLE CAD
(Cox proportional hazards model)

Variable	RR*	95% CI	p
↑ MMP-2 - Q II -V > 213,7 ng/ml	2,1	1,1 – 4,1	0,02
↑ PAP - Q II -V > 173,1 ng/ml	1,8	0,9 – 3,5	0,07
↑ MMP-2 + ↑ PAP	**3,6**	**1,1 – 11,5**	**0,03**
↑ D-Dimer (in pts without recent PCI) - Q II -V ≥ 250,0 ng/ml	3,1	1,1 – 8,7	0,03

*** Adjusted for age, sex and clinical risk factors**

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CONCLUSION

1. The 5,4-years incidence rate of major thrombotic events in pts with stable CAD was 21,1% (3,9/100 patient years).
2. Plasma levels of activation markers of blood coagulation, fibrinolysis and MMPs were significantly associated with total load of clinical factors, which had prognostic impact in our study, i.e. severity of angina, history of MI, multivessel coronary disease and other comorbidity.
3. Independent hemostatic predictors of major thrombotic events in patients with stable CAD were: PAP (adjusted RR = 1.8; 95% CI 0.9-3.5, p=0,07), MMP-2 (adjusted RR = 2.1; 95% CI 1.1-4.1, p=0,02), and D-Dimer levels (adjusted RR = 3.1; 95% CI 1.1-8.7, p=0,03).
4. Elevation of both MMP-2 and PAP was associated with the highest risk of thrombotic events (RR = 3.6; 95% CI 1.1-11.5, p=0,03). This fact may be due to joint activation of fibrinolysis and MMPs in most pts (68%) with stable CAD.

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Declaration of interest: The authors have declared that no competing interests exist.