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Review

Plasminogen activator inhibitor 1 in acute coronary syndromes

Marin Pavlov[a,*,1], Ivana Ćelap[b,1]

[a] Department of Cardiology, Sestre milosrdnice University Hospital Centre, Vinogradska cesta 29, 10000 Zagreb, Croatia
[b] Department of Clinical Chemistry, Sestre milosrdnice University Hospital Centre, Vinogradska cesta 29, 10000 Zagreb, Croatia

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ABSTRACT

Plasminogen activator inhibitor 1 (PAI-1) is the main regulator of endogenous fibrinolysis, overriding the impact of other constituents of fibrinolysis. In plasma, it can be found in three forms: active, latent and inactive. There are numerous commercially available tests, analysing the activity of PAI-1 or the antigen level, with variable correlations between the two. PAI-1 has been extensively studied regarding incidence and outcomes of acute coronary syndromes, and showed positive association with both in numerous studies. Higher PAI-1 has been associated with worse short- and long-term outcomes. Studies are more consistent in the primary percutaneous coronary intervention era. Higher rise of PAI-1 within the first 24 h of acute myocardial infarction has been linked to some of its high-risk features. The circadian pattern of PAI-1 kinetics has been previously described, and the mechanisms behind this phenomenon and its impact on the incidence of acute coronary syndromes are well known. Further investigations are needed to test the safety and efficacy of PAI-1 as a pharmacological target in cardiovascular diseases.

1. Introduction

Plasminogen activator inhibitor 1 (PAI-1) is a single-chain glycoprotein comprised of 379 amino acids with a molecular weight of 47 kDa [1]. It is the main regulator of endogenous fibrinolysis. It shares common features with other serine protease inhibitors such as *suicide* inhibition by forming 1:1 stoichiometric complex [2,3]. Its main substrate is tissue plasminogen activator (tPA), a serine protease responsible for cleaving zymogen plasminogen to plasmin, the final effector of endogenous fibrinolysis. In active form, PAI-1 exhibits rapid and spontaneous conversion to a latent form, while sustaining capability of re-activation upon different stimuli, principally related to vascular injury [4]. In this way, high fibrinolysis inhibition is retained in areas of acute thrombus formation, ensuring localised conditions for clot stabilisation and persistence. PAI-1 is predominantly stored in alpha-granules of platelets, although de-novo synthesis of the active form within platelets via translationally active mRNA has been documented [5]. Other sites of production include vascular endothelial and smooth muscle cells, macrophages, and adipocytes [6]. Low plasma concentrations of PAI-1, despite a high biosynthesis rate, are thought to be sustained by its short biological half-life (8–10 min) [1].

Acute coronary syndromes are a group of acute occlusive vascular disorders, initiated by rupture or erosion of atherosclerotic coronary artery plaque, accompanied by subsequent acute thrombosis. The group consists of ST elevation myocardial infarction (STEMI) and non-ST elevation acute coronary syndromes (comprised of non-ST elevation myocardial infarction (NSTEMI), and unstable angina – a syndrome with no resultant myocardial necrosis) [7,8]. The distinction between the two is still established by persistent changes in electrocardiogram (ECG), which are suggestive of occlusive (for ST elevation) and sub- or non-occlusive (for non-ST elevation) lesions in affected coronary artery. Both require urgent treatment, with the main goal of establishing patency of coronary artery. Ideally, this involves timely percutaneous coronary intervention (PCI), thus limiting the size of the resultant myocardial ischemia and necrosis.

Here, we summarize the methods for PAI-1 detection, available data on its role in acute coronary syndromes, and its circadian pattern.

2. Methods of detection

PAI-1 testing is a complex task and should be performed in a specialised clinical laboratory. The clinical significance of PAI-1 levels is still a matter of debate, making this marker rarely used in everyday practice. Due to complex physiology of PAI-1 and a variety of available analytical methods, direct comparison of the results from different sources is challenging. Accuracy of the test depends on various

* Corresponding author.
E-mail address: marin.pavlov@gmail.com (M. Pavlov).
[1] Both addresses are permanent.

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preanalytical and analytical conditions. Promoter region indel polymorphism (rs1799889) of the SERPINE1 gene, a variation that alters PAI-1 antigen concentration and activity, will not be discussed here.

2.1. Preanalytics

The preanalytical testing phase, which includes patient preparation for blood sampling, time of specimen collection, blood collection technique, sample handling, and storage conditions, highly impacts the test result. Blood should be drawn after an overnight fast, ideally between 7:00 and 9:00 AM. Studies have shown that physical activity, caffeine intake, and smoking change PAI-1 levels (to be avoided at least 2 h before blood sampling). Venous blood is drawn into a 3.2% buffered sodium citrate tubes, avoiding extended tourniquet application (to prevent activation of endothelial cells, thus inducing fibrinolysis). Blood is collected up to the mark and the tube should be gently inverted a few times [9]. Specimens with high haematocrit levels should be collected in tubes with reduced amount of citrate. Samples should be transported at room temperature, within 4 h, and double centrifuged for 15 min at 1500*g* to ensure platelet free plasma [10]. Double centrifugation is recommended for samples stored for a later analysis. Described process is common for PAI-1 analysis on automated coagulation analysers. However, comprehensive instructions on sample type, handling, and storage conditions are usually provided by the manufacturer. Biological factors influencing PAI-1 levels, such as age, stress, pregnancy, inflammation, and obesity, should be determined in the preanalytical phase, due to the limited diagnostic value of PAI-1 detection in such circumstances [10,11].

2.2. Analytics

Analytical technique used for the determination of PAI-1 depends on its intended use. Total PAI-1 antigen immunoassay is a frequently used method. This test measures all of the plasma PAI-1 forms: active, latent and inactive/coupled with tPA or urokinase plasminogen activator (uPA). Although differences between immunoassay designs of different manufacturers exist, the basic principal is this: microplate is coated with PAI-1 specific monoclonal antibody which binds to PAI-1 from patient sample. Subsequently, anti-PAI-1 antibody labelled with peroxidase is added. Finally, after the addition of a chromogen substrate a colour develops. Absorbance is directly proportional to the concentration of PAI-1 in the sample. This type of test provides reliable quantification of PAI-1 antigen concentration. Tests with higher sensitivity at lower levels of antigen concentration also exist [12]. The results are not affected by tPA-PAI-1 complexes, and are specific for PAI-1 (other plasminogen activator inhibitors are not detected). However, antigen assays cannot detect qualitative defects, and cannot distinguish between active and latent PAI-1 forms. Results are reported as ng/mL, usually ranging between 5 and 40 ng/mL.

Functional PAI-1 assays are based on the determination of an active form of PAI-1. Two different methods are used, immunoassay and chromogenic assay. Designs of the functional PAI-1 immunoassays vary, as for PAI-1 antigen. Shortly, microplate is coated with active tPA or uPA, which binds active PAI-1 from the patient's blood sample. The next step is the addition of PAI-1 specific monoclonal antibody labelled with peroxidase. Finally, the addition of a peroxidase substrate to the reaction results in a coloured end product. The colour intensity of the end product is proportional to PAI-1 activity in the sample. Chromogenic activity assay is usually a three step method. In the first step, known excess concentration of tPA or uPA is added to the patient plasma sample, to bind with active PAI-1 from the sample. In the second step, residual plasminogen activator catalyses the conversion of plasminogen to plasmin, allowing plasmin to cleave chromogen substrate. Absorbance of the sample is proportional to PAI-1 activity. However, the results obtained in this way can be to some extent affected by other plasminogen activator inhibitors (particularly plasminogen activator inhibitor-2, a protein naturally occurring during pregnancy) [13]. Sensitivity of these tests is often scarce at very low levels, and some manufacturers declare values of zero to be within the reference range [14]. Results obtained in functional assays are reported as U/mL.

2.3. Postanalytics

Most manufacturers report inter-assay coefficient of variation of under 10% for both antigen and activity determination. Although the data on biological variation are outdated and need major revision, studies have shown that PAI-1 exhibits considerable intra-individual (47.2%) and inter-individual (70.9%) variability [15]. Thus, analytical precision of current methods has limited contribution in reference change value (111%). Results obtained by different kits could not be fully adjusted even by using reference plasma to calibrate the analyser [16]. In an analysis of 17 available PAI-1 tests, the following issues emerged: (a) interference by another inhibitory factor in plasma, (b) suboptimal results in acid or Stabilyte plasma, (c) sensitivity to endogenous tPA levels, (d) focus on the assessment of elevated PAI-1 levels and underperformance at very low levels [13]. The latter is of particular significance when these tests are used to exclude PAI-1 deficiency as a cause for delayed surgical or posttraumatic bleeding.

Immunoassays, both antigen and functional, as opposed to chromogenic assay, are not affected by interferences such as haemolysis, lipemia, and icteria [17]. On the other hand, clinical value of PAI-1 antigen assay is limited due to inconsistencies in correlation to functional studies. Simultaneous PAI-1 activity determination is suggested in order to improve the interpretation of the test results [14].

Functional assays bear a potential as diagnostic and prognostic tests. However, due to the rapid conversion from active to latent form, and coupling with tPA, additional efforts in assay design are needed in order to improve reproducibility of in vivo conditions.

Chromogenic assays for active PAI-1 determination are the most suitable tests for high-throughput laboratories. Automated methods on the robust analysers show the lowest analytical imprecision, but can be affected by various exogenous and endogenous interfering substances (use of heparin, levels of α1-antiplasmin, tPA) [18,19].

3. PAI-1 and acute coronary syndromes

Numerous studies investigated the role of PAI-1 in the development and the outcome of the whole cardiovascular disease spectrum. Given the number of available tests, differences in treatment throughout the decades, issues regarding timing of specimen collection, and different end-points measured, the heterogeneity of the studies is extensive. Results are equivocal, and whether PAI-1 is a causing agent or just an innocent bystander is not yet clear.

3.1. Incidence

Studies investigating predictive value of PAI-1 levels on incidence of acute coronary syndromes and death show inconsistent results. Majority of studies with small sample sizes, studies with univariate analyses, and limited adjustment analyses, revealed positive correlations [20–24]. Conversely, after the role of PAI-1 in insulin resistance (IR) syndrome in last two decades of 20th century was clarified, several larger studies included adjustments for components of IR. In a large prospective observational study, a part of European concerted action on thrombosis and disabilities angina pectoris (ECAT) study [25] which included over 3000 patients with angina pectoris, PAI-1 activity and antigen levels were found to be predictive of myocardial infarction (MI) and sudden cardiac death in two-year follow-up. However, after adjusting for parameters reflecting IR, predictive value was lost. Detailed analysis comparing various fibrinolytic factors in men surviving MI (560 patients) compared to healthy subjects (646 controls) was

published by Meltzer et al. [26]. Increased risk of MI was observed in men with higher PAI-1 levels (odds ratio (OR) of 1.7; 95% confidence interval (CI) 1.2–2.3). After adjusting for markers of inflammation, the association was still significant (OR 1.5; 95% CI 1.1–2.1), however after adjusting for constituents of IR, the significance of the association was lost (OR 1.1; 95% CI 0.8–1.6). Folsom et al. reported similar results on 326 patients who developed coronary heart disease during mean follow-up of 4.3 years, compared to a random sample of 720 cases [27]. PAI-1 antigen level was predictive of outcome after adjusting for age, sex, and race. The significance was lost after additional atherosclerosis risk factors were added in the model.

In disagreement with these studies, Tofler et al. presented data of 10-year follow-up of Framingham Heart Study offspring cohort (3203 participants) with the inclusion in the fifth examination cycle [28]. PAI-1 antigen levels were predictive of adverse cardiovascular events (not only acute coronary syndrome) in an independent manner. Hazard ratio of 1.9, 1.9 and 2.6 ($p = 0.006$) was found for inter-quartile elevations in PAI-1, after adjusting for 10 covariates.

Therefore, despite certain large-sample studies in which PAI-1 did not endure multivariate analyses, particularly when corrected for the elements of IR, abundant data on the role of PAI-1 in progression and development of acute cardiac events exist. As the main regulator of endogenous fibrinolysis, elevated PAI-1 could diminish the capability of the fibrinolytic system to prevent fibrin deposition in vessel walls and thrombus formation [29]. In addition to being an acute phase reactant, PAI-1 is a marker of endothelial injury and may represent a pathway by which other risk factors exert their effect on vascular wall. Normal vascular remodelling is also impaired by PAI-1 through the influences on integrin expression and cellular migration processes [30,31]. This proposes even the causative role of PAI-1 in destabilisation of coronary lesions, and further supports the research of pharmacological measures for PAI-1 reduction.

3.2. Outcomes

First studies of the prognostic value of PAI-1 in MI patients originate from pre-PCI era. Hamsten et al. reported an association between PAI-1 activity determined 3 to 6 months after MI, and a recurrent fatal- or non-fatal MI during 3-year follow-up [32]. The association persisted in multiple regression models. Study reporting similar results in both univariate and multivariate analyses of long-term outcome in relation to PAI-1 activity was published by Malmberg et al. [33]. In the same decade, Jansson et al. reported no correlation between PAI-1 activity 3 months after MI and 10-year survival [34]. Gray et al. found higher PAI-1 activity, but not antigen levels, in patients with re-infarction within 3 days from thrombolysis for acute MI [35]. In a similar study design, Nordt et al. found no correlation between PAI-1 antigen and activity measured at multiple time-points, and intra-hospital re-infarction [36]. Sane et al. reported similar results, with the activity measured at the baseline only [37]. In the same study, lower PAI-1 antigen levels correlated with greater patency of infarct-related artery at coronary angiogram 90 min after thrombolysis, signifying the role of endogenous hypofibrinolysis in thrombolysis-resistant thrombi.

Studies from PCI era are somewhat more consistent. Collet et al. showed that higher PAI-1 antigen level rise relates to worse short-term outcome, an association that persisted in multivariate analysis along with final thrombolysis-in-myocardial-infarction (TIMI) flow [38]. In this study on predominantly acute STEMI patients, with substantial penetration of primary PCI, PAI-1 was measured on admission and after exactly 24 h, thus avoiding common issues regarding circadian variations. Associations with occurrence of heart failure, peak troponin I values, and inverse association with left ventricular ejection fraction were also observed. Akkus et al. reported PAI-1 and CRP levels as the only predicting variables of death in MI complicated with cardiogenic shock, with other covariates in multivariate analysis being age, gender, STEMI, and early invasive treatment [39]. Interestingly, in this study, no difference was found in PAI-1 levels across the groups of patients with cardiogenic shock, with and without heart failure. However, only one PAI-1 sample was analysed within 6 h of admission, which is a possible explanation for this lack of association. Soeki et al. found higher PAI-1 antigen levels in patients with first MI compared to the control group (patients with chest pain and no coronary artery disease) [40]. The difference was significant in samples obtained at admission, as well as after 28 days. PAI-1 antigen levels at both time points were not associated to worse outcome, a finding also reported by other authors [41,42]. On the contrary, Sargento et al. found higher PAI-1 activity values at discharge in transmural MI patients who experienced a cardiac event during one-year follow-up [43]. In the same study, PAI-1 activity was significantly lower 6 months after discharge in all patients. Recently, we showed that the rise in PAI-1 activity in an early phase of acute STEMI treated with primary PCI is associated with worse 5-year outcome [44]. In the higher PAI-1 activity rise group, mortality of 50.0% was observed, as opposed to 8.2% in the lower rise group, with Kaplan-Meier survival curves separating within first post-STEMI year. Similar to some of the findings by Collet et al., higher PAI-1 rise was observed in patients with high-risk features, such as worse final TIMI flow, anterior myocardial wall infarction, left anterior descending artery as infarct-related artery, females, patients with occurrence of heart failure, and larger extent of myocardial necrosis. Contrary to the study by Prisco et al., who found no difference in PAI-1 activity prior and after primary PCI [41], we reported a significant rise in activity within the first 24 h of treatment. Sinković et al. published comparable data on short-term outcome in patients with non-ST elevation acute coronary syndrome [45]. Interestingly, in both studies, similar cut-off value for outcome prediction was proposed (Pavlov: 3.7 U/mL, Sinković 4.0 U/mL). The only available study that compared STEMI to NSTEMI was published by Rott et al., who found higher PAI-1 antigen levels in STEMI patients [46]. In a recent meta-analysis, despite the heterogeneity of the studies included, Jung et al. successfully showed an association between PAI-1 antigen levels and major adverse cardiovascular events in patients with known coronary artery disease (not uniformly post-MI patients) [47].

Given its role in the fibrinolysis, it could be anticipated that PAI-1 plays a crucial role in the event of spontaneous reperfusion – a phenomenon in acute coronary syndromes in which ECG finding suggests occlusive syndrome, yet, patent (but stenotic) coronary arteries are found on angiography. However, both Haider et al. [48] (in patients treated with thrombolysis), and Huisse et al. [49] (in patients treated by PCI) found no difference in PAI-1 levels between the groups of patients with and without spontaneous reperfusion.

Although outcome studies, as opposed to incidence studies, are hindered by small sample sizes and limitations in multivariate analyses, certain conclusions can be drawn. Data suggest that PAI-1 dynamics in acute coronary syndromes resembles one of the slow evolving acute phase reactants. No correlation with outcome was observed in studies that measured PAI-1 on admission, and factors influencing PAI-1 levels were similar to the studies outside of acute coronary syndromes (such as abdominal obesity) [44]. Within 24 h, acute phase reactant feature of PAI-1 becomes evident, and association with outcomes at this time point is observed. This association is more consistent in studies involving invasive MI treatment strategies. Current studies provide no conclusion on the nature of this association. It is possible that PAI-1 lends its impact on outcomes from other clinically relevant variables (such as C-reactive protein, obtained level of reperfusion, final ejection fraction, or IR constituents, as in incidence studies). However, the majority of studies report PAI-1 to be an independent predictor of outcome in multivariate analyses. Therefore, there is a need for additional studies in order to elucidate whether the relation to outcomes is casual or causative. The fact remains that other markers of the atherosclerosis and factors related to MI outcome outperform PAI-1. However, if the causative relation is ascertained, PAI-1 could become an attractive pharmacological target.

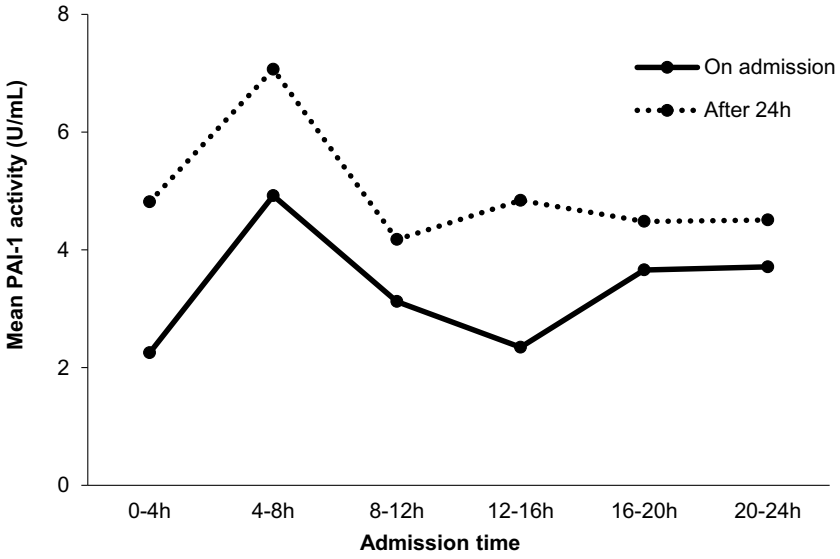

Fig. 1. Circadian pattern of plasminogen activator inhibitor 1 in ST elevation myocardial infarction patients (modified with permission according to M. Pavlov et al., Plasminogen activator inhibitor-1 activity and long-term outcome in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention: a prospective cohort study, Croat Med J. 59 (2018) 108–117).

Furthermore, PAI-1 plays a crucial role, not only during acute thrombotic incident, but also in post-MI fibrosis [50–52]. It is so to such extent that in studies on knock-out murine models, myocardial rupture and death was more common [53]. In addition, PAI-1 gene transcription is induced by acute phase cytokines, insulin, angiotensin II, and glucocorticoids [54]. Avoiding its rise in the early phase of acute coronary syndrome, while maintaining an operating level for supporting adequate post-MI healing should be the optimal goal. Although still in development, there is no PAI-1 antagonist/inhibitor currently available for clinical practice [55].

To the best of our knowledge, there are no published data displaying significant correlation between drug therapy and PAI-1 levels in acute coronary syndrome patients. In our recent study on STEMI patients, PAI-1 activity was not affected by prior, concurrent, nor therapy given within first 24 h of treatment [44]. This included eptifibatide – a highly potent platelet activation inhibitor acting via integrin glycoprotein IIb/IIIa inhibition, and heparin, a drug previously described to influence the results of some of the PAI-1 tests [18,19]. Studies outside acute coronary syndromes showed inconsistent data, although some reported favourable effect of angiotensin-converting enzyme inhibitors and statins on PAI-1 levels [56], and even suggested PAI-1 could be the pathway for exhibiting the long-term beneficial effects of these drugs [57,58].

4. Circadian rhythm of fibrinolytic system

It has been well documented that the onset of acute coronary syndromes follows a circadian pattern, with the highest incidence in early morning hours. This pattern is determined by the daily rhythm of two main groups of triggers for acute coronary events: vascular (such as coronary artery tone, response to norepinephrine, peripheral resistance, blood viscosity) [59], and haemostatic. The latter is comprised of factors such as platelets number and activity, coagulation cascade factors concentration and activity, and fibrinolysis.

Endogenous fibrinolysis follows the same circadian pattern. Although tPA antigen levels are highest in the morning [60,61], activity assays indicate lowest values in the morning due to inhibition performed by PAI-1. High amplitude of PAI-1 antigen and activity levels are well known facts that have been consistently reproduced in numerous studies, with the highest values at 6:30 AM [61,62]. Possible purpose of such rhythm is to provide the highest capability for blood clotting during the hours that throughout the evolution were reserved for high demand physical activities, such as hunting [63]. Conversely, hyperfibrinolysis during evening and night hours has been linked to higher incidence of haemorrhagic events such as variceal bleeding [64]. Animal studies demonstrated that the mechanism behind the circadian rhythm is the direct control of core clock genes on PAI-1 promoter gene, an influence independent of behavioural and environmental factors [62].

In our recent study on acute STEMI patients, PAI-1 showed typical circadian pattern of activity values measured at presentation [44]. This pattern was maintained in samples obtained 24 h after admission, but with values consistently shifted towards higher activity levels (Fig. 1). The latter could indicate that not only incidence, but also outcomes of MI could be driven by fibrinolytic system circadian activity. Studies in this area are inconsistent, although associations (in univariate analyses) were found [65,66] (Table 1).

5. Conclusion

As the main regulator of fibrinolysis, PAI-1 has been extensively studied with regard to development and outcomes of acute coronary syndromes. Although there are some inconsistencies, the understanding of its pathophysiological role, association with incidence, the short, and long-term results of treatment are well documented. PAI-1 has been associated with high-risk features of acute coronary syndromes in numerous studies, and its circadian pattern mirrors the similar rhythm of symptom onset of acute MI. Even though investigations are still underway, PAI-1 has not yet been successfully targeted as a viable treatment option. Further studies are needed to ascertain its true potential, since both high and very low PAI-1 levels correlate with worse outcomes.

Conflicts of interest

No authors declared potential conflicts of interest.

Author contributions

Both authors confirm that they have contributed to the intellectual content of this paper and have met the following three requirements: (a) significant contributions to the conception and design, literature review, and analysis and interpretation of the obtained references; (b) drafting and revising the article for intellectual content; and (c) final approval of the published article.

Table 1
Studies on acute coronary syndrome patients examining plasminogen activator inhibitor 1 and its association with outcome (major adverse cardiovascular events only).

Author, year	Study type	Number of patients[a]	Type of initial event (as defined or interpreted)	Invasive treatment (%)	Follow-up period	Outcome (MACE only)	PAI-1 assay	PAI-1 measurement rhythm (time)	Association with outcome	
									Univariate analysis	Multivariate analysis
Hamsten [32], 1987	Cohort	109[b]	MI	Not reported	3 years	Fatal or non-fatal MI	Antigen, activity	3–6 months after MI	Yes $p < 0.01$ (33.0 + 13.5 vs. 20.5 + 16.0)	Yes $p = 0.008$
Sane [37], 1991	Cohort	386	STEMI	0% (all received thrombolysis)	2 years	Death + MI	Antigen, activity	Baseline	No	n.a.
Gray [35], 1993	Cohort	155	MI	0% (76,1% received thrombolysis)	3 days	MI	Antigen, activity	Prior to thrombolysis, daily for 3 days (8:00–8:30), evenings for 2 days (17:00–18:00)	Yes (for activity only) $p = 0.032$ (26.7 ± 6.4 vs 21.7 ± 6.3 U/mL)	n.a.
Malmberg [33], 1994	Case control	108/116	STEMI, Q wave infarction	Not reported	6 to 9 years	Cardiac death + MI + need for revascularisation	Activity	3–6 months after MI	Yes $p < 0.05$	Yes $p < 0.001$ for death
Jansson [34], 1998	Cohort	123	MI	Not reported	10.5 years	Death	Activity	3 months after MI	No	n.a.
Moss [67], 1998	Cohort	1045	MI	Not reported	26 months	Cardiac death + MI	Antigen	2 months after MI	No	No
Nordt [36], 1998	Cohort	31	STEMI	0% (all received thrombolysis)	1 year	MI	Antigen, activity	0, 1, 2, 12 h after thrombolysis, at discharge	No	n.a.
Wiman [68], 2000	Case control	86 & 133/261[c]	All MI	Not reported	3 months	MI	Activity	3 months after MI	No	
Bogaty [42], 2001	Case control	50/50/50[d]	MI, UA	Not reported	4 years	Fatal or non-fatal MI + UA	Antigen	At least 3 months after event (7:00–9:00)	No	n.a.
Prisco [41], 2001	Case control	54/48	STEMI	100%	18 months	MI + UA	Activity	Before and after PCI	No	n.a.
Ganti [69], 2002	Cohort	42	STEMI	Not reported	Intra-hospital	Death	Antigen	On admission	No	n.a.
Soeki [40], 2002	Case control	106/50	Q wave MI	66.3%[e]	50 months	Cardiac death + MI	Antigen	On admission & after 28 days (morning)	No	n.a.
Collet [38], 2003	Cohort	153	STEMI, Q wave infarction	77.1%	30 days	Death	Antigen	On admission and after 24 h	yes $p = 0.0001$ (values not reported)	yes p = 0.01 (values not reported)
Sargento [43], 2003	Cohort	88	Transmural MI	Not reported	1 year	Cardiac death + MI + UA	Activity	At discharge, after 6 and 12 months (8:30–9:30)	yes $p < 0.05$ (6.34 + 1.56 vs. 4.47 ± 1.84 U/mL)	n.a.
Sinković [45], 2004	Cohort	113	NSTEACS	8.8%/31.8%[f]	30 days	All-cause death + MI	Activity	On admission and every 12 h until 48 h	Yes $p = 0.042$ (4.2 ± 3.4 vs. 2.8 ± 2.4 U/mL)	n.a.
Akkus [39], 2009	Case control	60/60/60[g]	STEMI	100%	1 year	Death	Antigen	< 6 h from admission	Yes p = 0.038 for cardiogenic shock (130 vs. 52 ng/mL)	Yes $p = 0.038$ (OR 5.48)
Pavlov [44], 2018	Cohort	87	STEMI	100%	5 years	Death	Activity	On admission and after 24 h	Yes $p < 0.001$ (HR 8.92 for activity > 3.7 U/mL)	Yes $p = 0.018$ (HR 5.55 for activity > 3.7 U/mL)

HR = hazard ratio; MACE = major adverse cardiovascular event; MI = myocardial infarction; n.a. = not available; NSTEASC = non-ST elevation acute coronary syndrome; OR = odds ratio; PCI = percutaneous coronary intervention; STEMI = ST elevation myocardial infarction; UA = unstable angina

[a] For case control studies, number of cases/number of controls
[b] Male patients < 45 years
[c] Re-infarction & no re-infarction/healthy subjects
[d] Multiple acute coronary events/stable angina/no coronary artery disease
[e] Percutaneous transluminal coronary angioplasty
[f] Urgent/elective
[g] Cardiogenic shock/heart failure/no heart failure

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