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STATE-OF-THE-ART PAPER

Prognostic Value of Plasma Fibrinolysis Activation Markers in Cardiovascular Disease

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The pivotal role of hypoactive endogenous fibrinolysis in the occurrence of thrombotic cardiovascular events is now well-recognized. To evaluate the diagnostic and prognostic role of impaired fibrinolysis, plasma fibrinolysis markers have been investigated in large prospective studies in both healthy individuals and patients with established coronary disease. Antigen and activity levels of components of the fibrinolytic system were measured by immunoassays, which replaced earlier global fibrinolysis tests. This review covers 45 studies in nearly 50,000 subjects, examining the association between plasma markers of fibrinolysis and coronary artery disease, to establish the usefulness of these markers in predicting future cardiovascular events. The predictive value of plasma levels of tissue-type plasminogen activator, platelet activator inhibitor-1, plasmin-antiplasmin complex, D-dimer, thrombin activatable fibrinolysis inhibitor, and lipoprotein(a) for major adverse cardiac events is highly variable and conflicting, especially after adjusting for conventional risk factors, judging from the published data in the last decade. The value of fibrinolysis activity markers is very limited in aiding diagnosis and risk stratification in the individual patient, on the basis of the weak prognostic values obtained in some studies and the lack of power in others. The physiological limitations of such markers in reflecting endogenous fibrinolysis is discussed. The emerging novel global assays of fibrinolysis will require large-scale clinical trials before their prognostic power or superiority to multiple biomarker measurements can be evaluated. (J Am Coll Cardiol 2010; 55:2701–9) © 2010 by the American College of Cardiology Foundation

Scope of This Review

The measurement of plasma markers of fibrinolysis dates back more than 20 years. This review covers the last 10 years, from 1999 to July 2009. Earlier findings were reviewed by Lijnen and Collen (1) and Hoffmeister et al. (2). A new review is timely, because a number of new fibrinolysis markers have been discovered and a large number of clinical studies have been carried out with improved, more sensitive immunoassays.

This review covers 45 prospective studies in nearly 50,000 subjects, examining the association between plasma markers of fibrinolysis and coronary artery disease (CAD), to establish the usefulness of these markers in predicting future cardiovascular events. Of the prospective studies, only those that have evaluated the results by multivariate regression analysis and calculated relative risk are shown in Table 1.

Significance of Endogenous Fibrinolysis in Acute Coronary Syndromes (ACS)

Endogenous fibrinolysis is a protective mechanism against lasting arterial thrombotic occlusion, which would otherwise lead to permanent tissue damage. Because arterial thrombogenesis is an active, ongoing, and dynamic process, a healthy endogenous fibrinolytic system can prevent the build-up of thrombus before complete occlusion occurs or break up the occlusive thrombus before lasting tissue damage ensues.

Until the early 1980s, coronary artery spasm and diminished myocardial oxygen supply were regarded as the fundamental mechanisms of myocardial infarction (3,4). Coronary artery thrombosis as the major pathogenic mechanism of sudden death from ischemic heart disease was disputed mainly because autopsy studies reported a very low incidence of identifiable coronary thrombus. By performing early autopsies, with improved techniques, the British pathologist Dr. Michael Davies first reported coronary thrombi in 74 of 100 subjects who died of ischemic heart disease and, of all these, only 5 subjects had no acute arterial lesion (5). Similar findings were reported by others, showing that the infarct-related artery was occluded in 90% of cases within the first 6 h of acute myocardial infarction (AMI), whereas this fell to 57% by 12 to 24 h (6). Growing evidence from cases of spontaneous lysis of arterial thrombi further supported the pathology findings and provided an explanation for the failure of earlier studies to detect thrombi at late autopsies (7–10).

Over the last decade, increasing evidence has emerged to support the assumption that AMI is a failure of timely

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Abbreviations and Acronyms

ACS = acute coronary syndrome
AMI = acute myocardial infarction
CAD = coronary artery disease
ELISA = enzyme-linked immunoadsorbent assay
HR = hazard ratio
Lp(a) = lipoprotein(a)
MACE = major adverse cardiovascular event
OR = odds ratio
PAI = plasminogen activator inhibitor
PAP = plasmin-alpha2-antiplasmin complex
PCI = percutaneous coronary intervention
SR = spontaneous reperfusion
STEMI = ST-segment elevation myocardial infarction
TAFI = thrombin activatable fibrinolysis inhibitor
TAFI-Ag = thrombin activatable fibrinolysis inhibitor antigen
TPA = tissue-type plasminogen activator

spontaneous thrombolysis (11). Spontaneous reperfusion of the infarct-related artery was reported to occur frequently in patients with AMI and was associated with significant myocardial salvage (12). In 585 patients with ST-segment elevation myocardial infarction (STEMI), electrocardiographic or angiographic spontaneous reperfusion (SR) was observed in 15%, and those with SR had lower mortality, lower composite of death/shock/congestive heart failure, and significant reduction in death or reinfarction (13). In a recent study of 710 patients with STEMI undergoing primary percutaneous coronary intervention (PCI), SR was observed in 22% of patients and at 30 days was associated with significantly lower incidence of death, congestive heart failure, and recurrent ACS (14). It has been suggested that impaired fibrinolysis at the time of coronary angioplasty contributes to restenosis (15). Deficient local endothelial tissue-type plasminogen activator (TPA) release in patients with CAD indicates reduced local fibrinolytic capacity and might explain the increased risk of coronary thrombosis in this patient group (16). Recently, low plasma fibrinolytic potential, found in 10% of the population, was found to increase the relative risk of arterial thrombosis 2-fold (17).

Assessment of Overall Fibrinolytic Status by Biomarkers

The mechanism and elements of the fibrinolytic system have been reviewed recently, and are shown in simplified schematic in Figure 1 (18,19). Thrombin converts the inactive proenzyme plasminogen to active plasmin. Plasmin degrades the cross-linked fibrin into soluble degradation products by the tissue-type (TPA) and the urokinase type plasminogen activators. It is TPA that is mainly responsible for the dissolution of fibrin formed in the circulation. This fibrinolytic system can be inhibited either by antagonizing plasmin through alpha 2-antiplasmin or by specific plasminogen activator inhibitors (PAI). There are 3 types of PAI described so far; of these, physiologically the most important inhibitor is PAI type 1 (PAI-1). The thrombin activatable fibrinolysis inhibitor (TAFI) is another important

Table 1 Studies Using Multivariate Analysis to Demonstrate Either NS or Significant Predictive Value of Plasma Fibrinolysis Marker Levels for MACE

D-Dimer		TPA		PAI-1		PAP		TAFI		Lp(a)	
NS	HR	NS	HR	NS	HR	NS	HR	NS	HR	NS	HR
198 (38)	2.5,* 5,201 (41)	198 (38)	2.1,† 207 (27)	198 (38)	3.3,* 44 (63)	1,057 (52)	3.1,† 146 (41)	44 (63)	3.4, 554 (55)	142 (39)	1.1,* 5,732 (64)
142 (39)	4.0, 458 (42)	142 (39)	3.2,† 106 (30)	142 (39)	4.2, 249 (32)		5.0,† 200 (51)	598 (54)	1.7,† 1,668 (58)	144 (70)	2.5, 397 (69)
555 (50)	2.0,‡ 304 (26)	133 (25)	3.5,‡ 304 (26)	64 (40)	5.5, 60 (33)		2.0, 6,391 (43)	327 (56)	2.0,† 159 (61)	520 (34)	3.1,† 144 (65)
2,860 (28)	1.3,† 1,256 (31)	2,398 (31)	12.1,‡ 226 (29)	3,209 (37)	5.3,* 520 (34)						3.9,‡ 663 (66)
3,209 (37)	11.0,† 214 (46)		1.2,* 2,860 (28)	92 (30)	1.24,† 1,256 (31)						1.7,‡ 876 (67)
358 (44)	1.8,‡ 871 (49)		1.5,* 1,344 (36)	146 (41)	2.67,† 25,167 (35)						1.2, 897 (68)
6,391 (43)	1.3,† 1,057 (52)		1.1, 3,582 (24)								
3,582 (24)	1.5, 897 (68)										
397 (69)	6.4,* 257 (47)										
395 (28)											
10	9	4	7	6	6	1	3	3	3	3	6

Numbers are presented as n with the number of the relevant reference shown in parentheses. Significance (where given in the citation): *0.05 > p > 0.02; †0.02 > p > 0.001; ‡p < 0.001.
HR = hazard ratio; Lp(a) = lipoprotein(a); MACE = major adverse cardiovascular event; NS = not significant; PAI = plasminogen activator inhibitor; PAP = plasmin-alpha2-antiplasmin complex; TAFI = thrombin activatable fibrinolysis inhibitor; TPA = tissue-type plasminogen activator.