Epidemiology of thrombotic-hemostatic factors and their associations with cardiovascular disease

Thomas A Pearson, James LaCava, and Henry FC Weil

ABSTRACT Abundant evidence proves that thrombosis is involved in the acute presentation of coronary, cerebrovascular, and peripheral vascular diseases. However, the role of thrombotic factors in the development of the atherosclerotic lesions themselves has been more difficult to prove. This difficulty has been due, at least in part, to several methodologic issues in the study of hemostatic factors and cardiovascular disease (CVD). These include the possibility that associations between CVD and hemostatic factors may not be causal but rather due to confounding by other factors, acting as part of an extended causal pathway or requiring interaction with other risk factors or atherosclerotic disease, or may result from disease rather than causing the disease. In addition, several challenges remain in the measurement of hemostatic factors. Nonetheless, a growing number of studies have examined the association of CVD with coagulation factors (fibrinogen, factor VII, factor VIII, and platelet aggregability) and fibrinolytic factors [tissue plasminogen activator, plasminogen activator inhibitor 1, lipoprotein(a), and plasminogen or global fibrinolytic activity]. Of these, only for fibrinogen is there significant, strong, and consistent evidence of a causal association. Given the preliminary nature of these associations, any association between dietary factors and hemostatic factors other than fibrinogen is difficult to invoke as evidence for a deleterious effect of diet on CVD risk via thrombogenic mechanisms. Am J Clin Nutr 1997;65(suppl):1674S–825.

KEY WORDS Atherosclerosis, cardiovascular disease, coronary artery disease, thrombosis, coagulation factors, fibrinolytic factors, lipoprotein(a), fibrinogen, risk, diet

INTRODUCTION

The role of hemostatic factors in the etiology of cardiovascular disease (CVD) is currently being defined. The database available to link hemostatic factors with CVD stands in stark contrast with the rich database available for several other risk factors, particularly serum lipids and lipoproteins. With this proviso, a general and probably oversimplified model of disease causation can still be proposed to organize the discussion (Figure 1). In this model, clinical disease entities caused by thrombotic occlusions or emboli in the coronary, cerebrovascular, or peripheral arterial systems can be linked to the process of thrombosis at the site of an atherosclerotic plaque that has become unstable and developed a fissure in its cap. The model emphasizes the dependence on the presence and destabilization of an atherosclerotic plaque in order for the thrombotic predisposition to manifest itself, thereby explaining the lack of clinical events in people with an apparent predisposition to thrombosis but a lack of atherosclerosis. The model also seeks to explain why some individuals develop extensive atherosclerosis and related disease syndromes (eg, angina pectoris and intermittent claudication) but may not have the thrombotic predisposition leading to myocardial infarction and other acute cardiovascular syndromes. The model also allows for the role of coagulation factors in the process of atherogenesis itself. Factors in both the coagulation and fibrinolytic pathways must be considered to describe the predisposition to thrombosis as a balance between the propensity to form and lyse clots.

This paper summarizes current evidence for the model in Figure 1, working backward from the clinical event. First, the well-established evidence for the involvement of thrombosis in atherosclerosis and CVD will be briefly reviewed. Second, methodologic problems that may be present in clinical and epidemiologic studies of the association between thrombotic predisposition and clinical events will be discussed. The clarification of these issues will allow the development of criteria for inclusion or exclusion of studies in the literature as evidence for the associations between hemostatic factors and disease. Finally, studies linking hemostatic factors and clinical cardiovascular events will be examined, including ecologic, cross-sectional and case-control, and prospective studies. A fuller description of the model in Figure 1 will then serve as the background for studies of the effect of dietary constituents on coagulation and fibrinolytic factors as possible mechanisms through which diet can be related to CVD.

EVIDENCE FOR INVOLVEMENT OF THROMBOSIS IN CVD

Two distinct mechanisms have been invoked to describe possible roles for hemostatic factors in CVD: involvement of thrombotic factors in the development of atherosclerotic plaques and involvement of thrombotic factors in the thrombosis process.

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bolic occlusion, embolization, or both at sites of the destabilized atherosclerotic plaques. Indeed, these mechanisms are not mutually exclusive and may both be active in the causation of clinical events (1).

Evidence that hemostatic factors are involved in atherogenesis is derived from several sources. Classical pathologists such as Rokitansky in 1844 and Duguid in the 1940s postulated that atherosclerosis was due, at least in part, to the incorporation of blood constituents. The Demonstration of fibrin (2, 3) and platelet components (4) within atherosclerotic plaques through use of immunologic and electron microscopy techniques provided direct evidence for this hypothesis. Additional studies in cell culture and animal models added to the evidence that thrombosis (particularly platelets) produces potent chemotactic substances and growth factors (1). Thus, in vivo evidence for an atherogenic role for coagulation factors exists but the relative importance of thrombosis compared with other atherogenic factors (eg, low-density lipoprotein) in the formation of atherosclerotic lesions is less well defined.

More established is evidence that acute cardiovascular syndromes involve thrombosis. Early pathologic studies in the 1940s and 1950s showed the association between myocardial infarction and coronary thrombosis, with transmural infarction associated with coronary thrombosis more often than subendocardial infarction (5, 6). Debate arose as to whether the coronary thrombus caused the infarction or developed after the infarction, as intracoronary thrombus was rarely found at autopsy and, when found, often appeared to be of more recent origin than the infarction itself (7).

This debate was settled by several convincing pieces of evidence suggesting that thrombosis plays a key role in acute cardiovascular events but may not be found in autopsy studies because of fibrinolytic activity and clot retraction (8). First, coronary arteriography performed within 6 h of the onset of pain identified a complete occlusion of the relevant coronary artery in 86% of patients, with the proportion dropping with longer intervals after infarction (9). Second, autoradiographic studies with radiolabeled fibrinogen suggested that thrombus formation preceded the infarction (10). Third, angioscopy with fiber optic technology made it possible to see plaque fissures and overlying thrombus in lesions causing unstable angina (11). Fourth, thrombolytic therapy for acute myocardial infarction was able to conclusively show that the coronary occlusions causing myocardial infarction were due to fresh thrombi, which can be lysed to reestablish patency of the occluded artery. At least nine trials have each randomly allocated > 1000 patients with a suspected acute myocardial infarction, showing significant reductions in mortality if thrombolysis is initiated within 6 h of the onset of pain (12).

Finally, antiplatelet and anticoagulation therapy (heparin and warfarin) have consistently been shown to reduce coronary and cerebrovascular events. In patients with evidence of vascular disease, long-term therapy with aspirin results in a 13% reduction in risk of death from CVD and a 25% reduction in risk of myocardial infarction (13, 14). Heparin anticoagulation in the acute setting and warfarin anticoagulation on a chronic basis have also been shown to reduce coronary events in patients surviving myocardial infarction (15–18). This impressive compendium of evidence has established the role of acute thrombosis at least in causing myocardial infarction, unstable angina, atherothrombotic stroke, and peripheral vascular disease (19). The evidence for a role of thrombotic factors in the development of atherosclerotic lesions is more tenuous.

**METHODODOLOGIC ISSUES IN THE STUDY OF THE ASSOCIATION BETWEEN HEMOSTATIC FACTORS AND CVD**

Methodologic issues relevant to studies of hemostatic factors must be discussed before any discussion of specific studies (Figure 2). The goal of these studies, using a variety of different designs, has been to define a causal pathway in which elevation (or depression) of hemostatic factors is causally linked to CVD. Unfortunately, the complex system of checks and balances that constitutes the hemostatic system necessitates extra caution when interpreting study results. When lacking experimental results, human observational studies must not only show significant associations between a hemostatic factor and CVD, but also show independence and specificity of the association, a temporal sequence in which the elevated factor preceeds the disease, a consistency of the association among studies and within subgroups of a single study, a strong association, and a biologically coherent mechanism of action (20). These criteria must be applied to studies in the current literature when assessing the evidence for causal association between hemostatic factors and disease.

An alternate way in which a hemostatic factor may be spuriously related to disease is through confounding, in which both disease and the hemostatic factor are related because of their mutual association with a common third risk factor rather than being directly related to each other (number 2 in Figure 2). For example, factor VII concentrations are associated with body mass index, diabetes, hyperinsulinemia, and, in particu-
A potentially important issue in studies of hemostatic factors is prevalence-incidence bias. This would be particularly important in cross-sectional or case-controlled studies, although short-term prospective studies may not be immune to this problem. One issue is that many hemostatic factors are acute-phase reactants; that is, their concentrations acutely change after major insults such as surgery, infection, trauma, or myocardial infarction. Fibrinogen, lipoprotein(a) [Lp(a)], and several other factors are elevated after such stresses. Thus, the relevance of elevations of hemostatic factors in acute cases compared with control subjects becomes difficult or impossible to interpret. Likewise, an elevated concentration of a factor may fall in response to these insults. Recently, it was suspected that people with asymptomatic atherosclerotic disease may have elevations in concentrations of acute-phase reactants, such as C-reactive protein (23). This has been attributed to the inflammatory component now considered to be an important part of the vascular biology of atherosclerosis (24). Inflammation and subclinical thrombosis may be an ongoing process in atherosclerosis, leading to responses of the hemostatic system. D-Dimer concentrations, as measures of ongoing fibrinolysis, are elevated in the presence of carotid atherosclerosis (25). Such mechanisms may also explain apparently paradoxical relations between fibrinolytic factors and later disease. Ridker et al (26), for example, found elevated concentrations of t-plasminogen activator (t-PA), a measure of the endogenous fibrinolytic system, to be related to disease, explaining the results as evidence for the activation of the fibrinolytic system years in advance of the clinical presentation of the vascular disease.

Various issues concerning the measurement of hemostatic factors are relevant. One issue is whether the key components of the hemostatic system have been identified and are currently being quantified. For example, considerable debate persists whether concentrations of activated factor VII or concentrations of total factor VII zymogen are the best predictors of disease (27, 28). Several studies have identified significant intrapersonal variation in hemostatic factors related to intradividual factors, methods of sample collection, and variability of the assay (21, 29). Finally, nonconcurrent, prospective studies assume that concentrations and activities persist long term in samples stored at −70 °C or below. The extent to which variability and other artifacts are introduced by freezing and storage is poorly understood. For example, a recent report suggests that Lp(a) concentrations fall after extended storage at −70 °C (30). These issues become important because the potential to predict an increased risk of CVD involves distinguishing among individuals whose high values often fall within the normal range (31).

**EVIDENCE FOR ASSOCIATION OF SPECIFIC COAGULATION FACTORS WITH CVD**

Components of the coagulation system that have been studied for associations with CVD include fibrinogen, factor VII, factor VIII, and platelet aggregability. Components of the fibrinolytic system that have been studied for associations with CVD include t-PA, plasminogen activator inhibitor 1 (PAI-1), Lp(a), and plasminogen and global fibrinolytic activity.
Fibrinogen

Ernst and Resch (32), Eliasson (33), and Folsom et al (34) recently reviewed the association between fibrinogen concentrations and other risk factors and high risk states (Table 1). Additionally, there may be a familial or genetic determinant of fibrinogen concentrations, with at least one polymorphism of fibrinogen explaining a portion of the variability of fibrinogen concentrations (35–37). This long list of possible associations leads to the conclusion that any association between fibrinogen and CVD will need to be examined carefully to ensure that the association is not confounded by the many established risk factors on the list (most notably age, cigarette smoking, high-density-lipoprotein cholesterol, low-density-lipoprotein cholesterol, diabetes, obesity, and physical activity). Conversely, fibrinogen may be part of the causal pathway through which these factors act.

A strong case can be made for a causal relation between fibrinogen concentrations and CVD manifesting as ischemic heart disease, stroke, or peripheral vascular disease (32, 38–44). Although several case-control studies might be criticized because of fibrinogen’s role as an acute-phase reactant, the evidence establishing fibrinogen as a risk factor is primarily based on seven prospective studies with strikingly consistent results (Table 2). Dose-response relations between risk and tertiles of fibrinogen were identified in each study. Most studies adjusted for major risk factors and found the association to persist. A meta-analysis of the odds ratio for CVD endpoints yielded a risk estimate of 2.3 (95% CI of 1.9–2.9) for fibrinogen concentrations at the highest compared with lowest tertiles (32). The strength of this association was therefore similar to those of established risk factors (total cholesterol, blood pressure, etc).

However, several cautionary notes are justified. First, only the Framingham Study included women, with some differences in associations with stroke (41). Second, no study included African Americans, who have higher fibrinogen concentrations. Third, no study adjusted for all the possible confounding factors found in Table 1. However, the major risk factors were usually included within multivariate models in several of the studies. Fourth, most studies did not explore interactions between fibrinogen and other risk factors to identify subgroups with potentially extraordinary risk (22). Finally, fibrinogen, as an acute-phase reactant, may be persistently elevated in the ongoing inflammation that is part of the atherosclerotic disease process. An elevated fibrinogen value may be related to later CVD events through a prevalence-incidence bias rather than a causal mechanism (26). This latter mechanism remains a plausible alternative explanation of the data.

It appears safe to conclude that in whites, the relation between fibrinogen and CVD events is strong, significant, temporally established, independent, consistent, and biologically plausible. The size and consistency of the relation make interesting the general lack of explorations to modify fibrinogen concentrations as a means to prevent CVD events, though alteration of associated conditions listed in Table 1 may reduce both the concentration of fibrinogen and the risk for disease.

Table 1

<table>
<thead>
<tr>
<th>Higher fibrinogen concentrations</th>
<th>Lower fibrinogen concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regions with high CVD incidence</td>
<td>Regions with low CVD incidence</td>
</tr>
<tr>
<td>Winter season</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td></td>
</tr>
<tr>
<td>Black race</td>
<td></td>
</tr>
<tr>
<td>Low socioeconomic status</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Menopause</td>
<td></td>
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<tr>
<td>Obesity</td>
<td></td>
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<tr>
<td>Diet rich in carbohydrates</td>
<td></td>
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<tr>
<td>Systolic blood pressure</td>
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<tr>
<td>Total or LDL cholesterol</td>
<td></td>
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<tr>
<td>Triacylglycerol concentration</td>
<td></td>
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<tr>
<td>Lipoprotein(a)</td>
<td></td>
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<tr>
<td>Serum insulin</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
</tr>
<tr>
<td>Inflammation or infection</td>
<td></td>
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</table>

Factor VII

Factor VII can be measured in various ways, including measuring zymogen mass, factor VII activity, and factor VII antigen. The strongest risk factor correlations with factor VII (as measured by mass or activity) are with serum lipids. The direct association with serum triacylglycerol concentrations, even when measured in young adults free of CVD, has been especially consistent and strong for both mass and activity assays (45–52). The association with serum total and low-density-lipoprotein cholesterol in these patients is also positive, but perhaps less consistent (21, 38, 39, 46–48, 51–53). Factor VII concentrations have also increased with serum glucose concentrations (45, 54), blood pressure (39), body weight (45, 55), age (56, 57), and postmenopausal status in women (58). In many instances, these univariate associations may be confounded by associations with other coronary risk factors (eg, triacylglycerol concentrations confounding the glucose–factor VII association). After adjustment, the triacylglycerol–factor VII association continued to be strong and significant (45). In any case, any associations between factor VII and disease should take these risk factor correlations into account.

Several case-control studies have sought to define the association between factor VII and CVD. This study design can yield spurious results if disease processes raise or lower factor VII concentrations. Nonetheless, three case-control studies of patients surviving myocardial infarction have shown higher factor VII concentrations in these patients than in control subjects (43, 59, 60). Similarly, patients with arteriographically defined coronary stenoses had higher factor VII concentrations (27). These data, though far from conclusive by themselves, support the factor VII–disease link.
TABLE 2
Seven prospective studies of fibrinogen and cardiovascular disease *

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>Duration of follow-up</th>
<th>Endpoints</th>
<th>Association</th>
<th>Independence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northwick Park (38), 1986</td>
<td>1151 men</td>
<td>10.0</td>
<td>Ischemic heart disease</td>
<td>Positive</td>
<td>Yes</td>
</tr>
<tr>
<td>Gothenburg (39), 1984</td>
<td>792 men</td>
<td>13.5</td>
<td>MI, stroke</td>
<td>Positive</td>
<td>Yes</td>
</tr>
<tr>
<td>Leigh (40), 1985</td>
<td>297 men</td>
<td>7.3</td>
<td>MI</td>
<td>Positive</td>
<td>Yes</td>
</tr>
<tr>
<td>Framingham (41), 1987</td>
<td>554 men</td>
<td>12.0</td>
<td>Ischemic heart disease, stroke</td>
<td>Positive</td>
<td>Yes</td>
</tr>
<tr>
<td>Caerphilly and Speedwell (42), 1991</td>
<td>4860 men</td>
<td>5.1</td>
<td>Ischemic heart disease</td>
<td>Positive</td>
<td>Yes</td>
</tr>
<tr>
<td>Prospective Cardiovascular Munster Study (43), 1991</td>
<td>1674 men</td>
<td>2.0</td>
<td>Ischemic heart disease</td>
<td>Positive</td>
<td>Yes</td>
</tr>
<tr>
<td>Göttingen (44), 1992</td>
<td>5239 men</td>
<td>5.0</td>
<td>MI</td>
<td>Positive</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Modified from Ernst and Resch (32). MI, myocardial infarction.

Much of the interest in factor VII as a cardiovascular risk factor is derived from the prospective study at Northwick Park, England (38, 61). Dose-response relations in 1151 white men, aged 40–64 y, were seen between factor VII concentrations and all ischemic heart disease, fatal ischemic heart disease, and nonfatal myocardial infarction as well as total mortality (38). These results were adjusted for age, fibrinogen, cholesterol, and blood pressure. The associations did not appear to be as strong as those for fibrinogen but appeared stronger than those for serum total cholesterol. This single prospective study of incident cases of coronary artery disease remains the major evidence for indictment of factor VII as a cardiovascular risk factor. One additional prospective study, the PLAT Study, examined patients with preexisting vascular disease in the coronary, cerebrovascular, and peripheral circulations (62). On univariate analysis, factor VII predicted atherothrombotic events in patients with prior myocardial infarction or peripheral vascular disease. However, on multivariate analysis, factor VII was not independently associated with CVD events after adjustment for age, factor VIII, and fibrinogen concentrations.

Factor VIII and other coagulation factors

Relatively less is known about the relation between factor VIII and established CVD risk factors. Factor VIII concentrations appear to increase with age and increase rapidly in women after menopause (45). Factor VIII does not appear to be associated with smoking, body weight, or alcohol consumption. Studies linking factor VIII and CVD can only be described as preliminary. The PLAT Study of patients with established CVD in various circulations remains perhaps the best evidence for factor VIII as a CVD risk factor (62). In that study, factor VIII concentrations measured by biological assay were univariate predictors of vascular disease events (myocardial infarction, sudden death, cardic death, stroke, transient ischemic attacks, or acute peripheral occlusions and ischemia) in patients with prior myocardial infarction, transient ischemic attacks, and peripheral vascular disease. Multivariate analyses showed associations to be independent only in the myocardial infarction group, after adjustment for fibrinogen and factor C concentrations.

Platelet aggregability

In vitro aggregability studies have been performed since the 1960s with a wide variety of techniques such as platelet adhesiveness and aggregability to a variety of aggregating agents (ADP, thrombin, collagen, and epinephrine). In many instances, several different aggregating agents were used, expanding the number of independent variables and the chance of spurious associations. Studies have been performed on acutely ill patients, with potential influences of acute illness, health behaviors (eg, smoking), and drugs (eg, aspirin, heparin, and β-blockers) on platelet function. Considerable laboratory-to-laboratory variation exists in the ability to perform these tests with good precision. Therefore, the older, case-control literature is exceptionally difficult to sort out. In 1985 no established method of in vitro platelet aggregability or platelet function could characterize patients at high risk of thrombosis (63).

Nonetheless, these measures of platelet aggregability have been used in correlational studies to identify risk factors associated with assay results. Aggregability appears to increase with age, is greater in women than men, and is higher in whites than blacks (63). Diabetes appears to predispose to increased aggregability (64). Cigarette smoking gives inconsistent results (63), with most studies suggesting increased aggregation in smokers (65, 66). Elevated low-density-lipoprotein cholesterol appeared to be associated with heightened aggregability in some studies (67) but not in others (63). Platelet aggregability appears to have a diurnal cycle with a peak from 0600 to 1200, correlating with the peak occurrence of myocardial infarction (68).

Studies linking platelet aggregability and CVD have included ecological studies of regions with high compared with low prevalence of CVD, such as regions of France and Scotland and other regions in the United Kingdom (69–72). In general, these studies have been difficult to interpret, given the vast differences in a panoply of genetic and behavioral conditions that occur among geographically and culturally distinct groups, as well as questions regarding the validity of measures of platelet aggregability as real predictors of cardiovascular events.

Many cross-sectional and case-control studies have identified associations between platelet aggregability and myocardial infarction (73–78) or stroke (79–82). Again, the interpretation of these results is made difficult by influences of acute symptoms on aggregability, despite the absence of atherosclerotic disease (83). Also, most studies consisted of clinical populations in an acute setting. One population-based, cross-sectional study was performed on 1811 men in the Caerphilly Study (84). When divided by the quintile of ADP-induced platelet aggregation, a dose-response relation with prior myocardial
infarction or ischemia on electrocardiogram was observed. No relation was observed with collagen-induced aggregation. The results were not adjusted for several other risk factors associated with platelet aggregability.

Finally, a prospective study of spontaneous platelet aggregability was performed in patients surviving myocardial infarction (85). In those with spontaneous platelet aggregability, 46.2% had cardiac death or recurrent infarction during the 5-y follow-up period compared with 14.9% of those without spontaneous aggregability. These results remained significant after adjustment for other prognostic variables. Additional studies of spontaneous platelet aggregability are warranted to determine whether this method is more reliable in detecting high-risk patients.

EVIDENCE FOR ASSOCIATION OF FIBRINOLYTIC FACTORS WITH CVD

Lipoprotein(a)

Lp(a) is included, at least briefly, in the discussion of fibrinolytic factors because of its proposed role as an antifibrinolytic compound. Briefly, this is based on several pieces of evidence from in vitro studies. First, parts of the Lp(a) molecule, apolipoprotein(a), have a high degree of homology with plasminogen but cannot be activated into a fibrinolytic enzyme (86, 87). However, Lp(a) can competitively inhibit plasminogen through its binding sites on streptokinase, t-PA, endothelial cells, platelets, and fibrin (88, 89). Thus, associations between Lp(a) concentrations and CVD have been hypothesized to be due to this ability to inhibit the fibrinolytic system (88, 89). Two objections exist to this line of reasoning. First, Lp(a) contains apolipoprotein B and lipids and appears to be capable of oxidative modification and promotion of smooth muscle cell proliferation (90). Therefore, any association between Lp(a) and vascular disease may be due to its atherogenic actions rather than its prothrombotic actions. Second, there is no direct evidence from human subjects of an antifibrinolytic role for elevated concentrations of Lp(a) in causing CVD syndromes.

Recently, however, a serial arteriographic study identified patients with progression of coronary stenoses over a short time (an average of 66 d) (91). Elevated Lp(a) concentrations were observed in 67% of patients with rapidly progressive lesions compared with only 33% of patients without progression. The nature of this evidence is indirect because of the inability to discern whether the rapid progression is due to atherogenesis or thrombosis. However, Lp(a) concentrations were the sole predictors of such rapid progression, which likely has at least some thrombotic component.

Although some controversy and inconsistency in the association between the Lp(a) concentrations and CVD persist, many studies have linked clinical events with this lipoprotein (92). However, in lieu of more direct evidence for a role of Lp(a) in the fibrinolytic system, only the preceding brief discussion will be provided in this portion of the review.

Plasminogen activator inhibitor 1

PAI-1 is a serine protease inhibitor with a high affinity for t-PA. Thus, elevated concentrations, at least theoretically, may inhibit the fibrinolytic system. PAI-1 concentrations have been associated with several risk factors (Table 3) (33). In general, PAI-1 is positively correlated with the risk factors associated with the metabolic syndrome X, namely obesity, high triacylglycerol concentrations, low high-density-lipoprotein cholesterol, hyperglycemia, hyperinsulinemia, and low amounts of physical activity, in a dose-responsive fashion (93). Several lines of evidence point to the key role of abdominal obesity in causing elevated PAI-1 concentrations. First, PAI-1 concentrations appear to be related to both body mass index and waist-to-hip ratio in several cross-sectional studies (94–97). Second, PAI-1 concentrations decrease when insulin concentrations decrease, suggesting a role for the hyperinsulinemia associated with abdominal obesity as a direct cause of the PAI-1 elevation (95). Finally, weight loss does not change D-dimer or fibrinogen concentrations, but PAI-1 concentrations are substantially reduced with large weight reductions in both men and women (96). Thus, obesity and associated metabolic conditions appear closely linked to elevations in PAI-1.

The direct evidence for an association of PAI-1 concentrations with CVD is much more limited, however. One issue is the apparent transient increase in PAI-1 activity during episodes of cardiac ischemia, suggesting that disease activity may increase PAI-1 concentrations rather than vice versa (97). This questionable cause-and-effect relation then makes difficult the interpretation of several case-control and cross-sectional studies that have identified higher PAI-1 concentrations in patients with myocardial infarction than in control subjects (98, 99). More convincing is the prospective study of Hamsten et al (100), who measured PAI-1 concentrations in 109 survivors of myocardial infarction and followed the subjects for 3 y (100). PAI-1 concentrations were independently predictive of reinfarction after adjustment for degree of coronary disease, left ventricular dysfunction, and serum lipids. Patients with both recurrent infarctions and nonrecurring coronary disease had high concentrations of PAI-1 compared with control subjects, raising the issue that PAI-1 concentrations may have simply been a measure of the intensity of ongoing disease activity.

### Table 3

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Univariate association of PAI-1 activity and t-PA activity in the MONICA: Northern Sweden Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factor</td>
<td>PAI-1 activity</td>
</tr>
<tr>
<td>Age</td>
<td>+ (P &lt; 0.001,</td>
</tr>
<tr>
<td>Body mass index</td>
<td>- (P &lt; 0.001)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>- (P &lt; 0.001)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>+ (P &lt; 0.01)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>- (P &lt; 0.001)</td>
</tr>
<tr>
<td>Triacylglycerol</td>
<td>+ (P &lt; 0.001)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>+ (P &lt; 0.01)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>+ (P &lt; 0.01)</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>+ (P &lt; 0.001)</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>+ (P &lt; 0.001)</td>
</tr>
<tr>
<td>Smoking</td>
<td>0</td>
</tr>
<tr>
<td>Physical activity</td>
<td>- (P &lt; 0.001)</td>
</tr>
<tr>
<td>Menopause</td>
<td>+ (P &lt; 0.05)</td>
</tr>
</tbody>
</table>

#n = 1558 men and women. Derived from Eliasson (33). PAI-1, plasminogen activator inhibitor 1; t-PA, t-plasminogen activator.
Finally, another approach correlates the extent of atherosclerosis measured noninvasively with PAI-1 concentrations. PAI-1 concentrations were measured in 457 case-control pairs in the Atherosclerosis Risk in Communities Study, with cases having increased intima-media thickness of the carotid arteries on ultrasound (25). A dose-response relation was observed between quartiles of PAI-1 concentration and the presence of carotid disease. At least two interpretations of these data are possible. First, PAI-1 concentrations relate to the extent of atherosclerotic disease as evidence of a hemostatic factor being related to atherogenesis rather than thrombosis. Second, PAI-1 concentrations may be indirectly related to disease, being activated by the disease process rather than being the cause of it. Prospective studies are needed to sort out these possibilities. Until then, the data linking PAI-1 and CVD can be summarized as intriguing but inconclusive.

**t-Plasminogen activator and other measures of fibrinolytic activity**

In general, t-PA activity is inversely related to PAI-1 activity because the two bind to form a complex in vivo. Thus, the association of t-PA with risk factors is generally opposite those for PAI-1, with the exception that both appear to increase with age (Table 3). One possible factor affecting t-PA concentrations may be physical activity, with global fibrinolytic activity generally increasing with physical activity (101). t-PA concentrations, but not PAI-1 concentrations, were increased with moderate exercise in a study comparing 14 inactive men with 12 men exercising at moderate amounts (102).

At first examination, studies linking t-PA activity and CVD have conflicting results. Hamsten et al (98) found lower t-PA activity in patients with myocardial infarction than in control subjects. Follow-up of infarction survivors also showed that low t-PA activity was prospectively associated with recurrent infarction at high levels of significance (100). Other studies showed the opposite: One case-control study of infarction survivors (99), another study using noninvasive measures of carotid atherosclerosis (25), and a follow-up study of patients with angina pectoris (103, 104) showed patients with atherosclerotic disease to have higher concentrations of t-PA and higher concentrations of d-dimer as evidence of ongoing fibrinolysis. Finally, a prospective follow-up of the Physicians Health Study found significantly higher t-PA concentrations in 88 persons with later cerebrovascular accidents than in 471 control subjects (26). These findings are difficult to rationalize. However, the activation of the coagulation system by the atherosclerotic disease process may elicit a response by the fibrinolytic system as the way in which fibrinolytic and anti-fibrinolytic factors can both be associated with disease. Studies that measure t-PA antigen may be measuring circulating t-PA–PAI-1 complexes, which are interpreted as evidence for reduced rather than increased fibrinolysis (22).

**SUMMARY**

Despite the solid evidence for thrombosis playing key roles in the pathogenesis of CVD, identifying specific hemostatic or fibrinolytic factors as causes of cardiovascular disease has been difficult except for fibrinogen. Even for fibrinogen, however, the exact causal pathway is not clear, possibly because of confounding, prevalence-incidence bias, or interaction with other risk factors. Many of the hemostatic factors are acute-phase reactants, making cross-sectional or even short-term prospective studies difficult to interpret. Factor VII and PAI-1 concentrations show promise as possible predictors of clinical events but lack the consistent, strong, independent associations with disease enjoyed by fibrinogen. Factor VIII, t-PA, and platelet aggregability studies provide even less consistency of results. Lp(a) also has promise but may not cause disease via the fibrinolytic system.

Given the inconsistency of findings, the search for additional coagulation factors or better ways to measure these variables should continue. In any discussion of dietary influences on thrombotic factors, however, there seems to be too little evidence to use hemostatic factors other than fibrinogen as surrogate measures of risk. In this context, any associations between dietary factors and hemostatic factors, with the possible exception of fibrinogen, are difficult to invoke as evidence for a deleterious effect of diet on CVD risk. Clearly, much more needs to be learned in this promising, but immature, field of inquiry.

**REFERENCES**


