Associations of Thrombotic-Hemostatic Factors with Cardiovascular Disease

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Abstract: Cardiovascular disease (CVD) remains a leading cause of global morbidity and mortality despite identification of major cardiovascular (CV) risk factors and risk reduction *via* appropriate interventions. During the last years several markers have been studied as potential predictors of CV events. Hemostatic and thrombotic factors such as fibrinogen, homocysteine, factor VII, von Willebrand, tissue plasminogen activator, plasminogen activator inhibitor - 1, D-dimer and lipoprotein (α) have been found to be closely related to CVD. Many epidemiological studies have indicated that raised levels of these factors are associated with higher incidence of CVD, while some others have yielded conflicting results. As a consequence, it remains obscure whether they contribute to prediction of future CV events on top of conventional risk factors. Although data suggest that most of them are somehow implicated in CVD pathophysiology, it is not clearly defined yet whether treatment of abnormal levels leads to CV risk reduction. As a result measurement and treatment of these factors are justified only in exceptional cases. Further investigation is required in order to conclude whether and which of these factors may claim a position in everyday clinical practice.

Keywords: Cardiovascular disease, hemostatic factors, thrombotic factors, review.

INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of global morbidity and mortality. In 2004, CVD accounted for 17.1 million deaths worldwide [1]. According to the last WHO report, it is believed that by 2030, as many as 23.4 million people will die annually due to CV causes [2].

The identification of major cardiovascular (CV) risk factors was an advance of pivotal importance in terms of primary prevention [3]. Individual risk assessment was enabled, and through interventions on modifiable risk factors, CV risk reduction can be achieved [3]. However, CV events occur even in subjects without these established risk factors. This, in conjunction with the growing burden of CVD as well as the in-depth understanding of atherosclerosis pathophysiology have led to the quest of novel risk factors in order to enhance primary and secondary prevention. During the last years, several markers have been studied and proposed as predictors of CV events. These include inflammatory markers, hemostatic – thrombotic factors, lipid-related and various other factors. This review will focus on the relationship of hemostatic and thrombotic factors and CVD.

1. Fibrinogen (Fib)

Plasma Levels Determinants

Fib is a key component of the blood coagulation system and an acute phase reactant. Fib is produced by the liver and is a large soluble glycoprotein found in the plasma, consisting of two identical subunits. Each subunit is comprised of three polypeptide chains alpha, beta and gamma linked to each other by disulfide bonds [4].

Plasma Fib levels are determined by both genetic and environmental factors. Advancing age, smoking, obesity, hypertension, dyslipidemia, physical inactivity, menopause, low socio-economic status, oral contraception, female sex and black race are associated with elevated Fib levels [4]. The relationship between smoking and Fib levels is dose-dependent according to the number of cigarettes smoked [5]. This effect is reversible upon smoking cessation [5]. On the other hand there are some factors related to lower Fib levels such as moderate alcohol consumption, hormone replacement therapy, regular exercise and weight reduction [4].

Fib & CVD

Elevated Fib levels were first reported to correlate with CVD and coronary heart disease (CHD) in particular, almost 60 years ago [6-8]. During the following decades, numerous epidemiologic studies showed a definite relation of Fib to CVD [9-17]. The causality still remains uncertain. The first meta-analysis which recognized Fib levels as an independent CV risk factor included six prospective epidemiologic studies. Elevated levels were associated with subsequent myocardial infarction (MI) or stroke [odds ratio in the upper vs. lower tertile varying between 1.8 (95% CI 1.2-2.5) and 4.1(95% CI 2.3-6.9)] [18]. A latter meta-analysis of 22 studies – including the former six – confirmed the previous findings [19]. It was also emphasized that raised plasma Fib levels are associated with increased CV risk in healthy as much as in high-risk individuals [19]. A recent meta-analysis of 31

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prospective studies including 154, 211 apparently healthy individuals showed that long-term increases in plasma Fib levels of 1 g/L are associated with an approximate doubling of risk of major CVD [20].

The causal relevance of elevated Fib levels with disease was assessed in a latter meta-analysis [21]. Approximately one third of the variation in Fib levels was explained by age, sex and cohort [21]. An additional 7% was accounted for by established risk factors [smoking, body mass index (BMI), high density lipoprotein (HDL)-cholesterol] and a further 10% was explained by inflammatory markers [notably C - reactive protein – (CRP)] [21]. Furthermore, high plasma Fib concentration has been independently associated with subclinical CVD in the subsequent decade [22] and premature development of CHD in young individuals aged 25-37 and < 45 years respectively [23]. Among blood viscosity major determinants, Fib emerged as the only remaining significantly associated with CV events and total mortality after adjustment for conventional risk factors [24, 25]. Finally, some studies have reported that Fib levels also correlate with the severity of the underlying CHD [26].

Fib & Peripheral Arterial Disease (PAD)

Studies on atherosclerosis in vascular grafts of PAD patients suggested an important role of Fib in PAD [27, 28]. Subsequent epidemiological data demonstrated an independent association of Fib with future PAD development [29-36] and the severity of disease [37, 38]. This association seems to be stronger among diabetic patients [39]. Furthermore, high plasma concentration has emerged as the strongest predictor of coronary death and all – cause CV mortality in patients with PAD [40].

Besides a potential pathogenetic role in PAD [41, 42], Fib is also significantly associated with the development of restenosis at the site of percutaneous transluminal angioplasty (PTA) [43, 44]. Resolution of critical limb ischemia results in a decrement of Fib levels, without reaching values seen in population controls [44]. This finding implies that elevated Fib is probably a causal factor and not just a consequence of tissue ischemia.

Additional Predictive Value

It remains unclear whether Fib provides additional predictive value to conventional risk factors regarding future CV events. The Caerphilly Study concluded that Fib has the potential to increase the prediction of CHD and ischemic stroke in middle-aged men, on top of conventional risk factors [45], confirming previous findings [19]. Another study showed that high Fib levels remain independently predictive of the risk of mortality after adjustment for the Framingham score [46]. However, this study included individuals examined in a high-risk preventive cardiology clinic, so the possibility of bias cannot be excluded. In a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) on hypertensive patients, Fib emerged as a strong independent predictor of Framingham CHD and stroke risk ($p<0.0001$), the number of individual risk factors and Pocock cardiovascular death risk ($p<0.0001$) [47]. Nevertheless, the AtheroGene Study showed that Fib, even though predictive for future cardiovascular risk in patients with documented CHD, did not provide any further information on top of that obtained from models including traditional risk factors [48]. Similarly, in the Edinburgh Artery Study, even though Fib was significantly associated with incident CVD after adjustment not only for conventional CVD risk factors but also for a measure of subclinical disease (ankle brachial index), very little prognostic information individually over and above traditional risk factors assessment was provided [49]. Finally, in the PRIME Study, Fib lost its significance as predictor for MI and coronary death after adjustment for conventional risk factors and inflammatory markers [50].

Fib & CVD Pathophysiology

Fib has been detected in plaques and it is thought to promote atherosclerosis [51, 52]. Except for its role in the coagulation cascade being the precursor of fibrin, Fib exhibits a number of other functions. It stimulates platelet aggregation, increases blood viscosity, promotes smooth muscle proliferation and migration and regulates cell adhesion and chemotaxis [3, 53]. These may be the mechanisms through which Fib participates in vascular disease. Furthermore, the effect of elevated Fib levels on atherosclerosis may be mediated by inflammation through its role as an acute phase reactant [54].

Fib-Lowering Strategies

High Fib levels can be reduced through lifestyle interventions. Smoking cessation is associated with a decrement of approximately 0.15 g/L in plasma Fib [55]. Moderate alcohol consumption [56], regular exercise [57] and loss of excess body weight [58] are also accompanied by reduction in circulating Fib.

Several medications have been reported to possess Fib-lowering properties. This effect is more evident with bezafibrate [58-60], fenofibrate [61, 62] and ciprofibrate [63], but not with gemfibrozil [61, 64]. Other drugs with a Fib-lowering effect are angiotensin converting enzyme inhibitors (ACEI) [65], angiotensin receptor blockers (ARB) [66], β-blockers [66, 67] and ticlopidine [68]. Despite significant reductions sporadically reported in some pravastatin studies [69-71], Fib-lowering action of statins is disputable [72]. Studies on PAD patients showed that the use of vasodilators [73], rheological [74] and thrombolytic [75, 76] agents leads to reduced Fib levels, usually accompanied by clinical improvement.

There are not available any specific Fib-lowering drugs yet. It remains unclear whether a reduction of Fib plasma concentration has a certain beneficial impact on clinical outcome. The development of such drugs would allow the conduction of randomized controlled trials evaluating the actual effect of Fib reduction on cardiovascular disease.

2. Homocysteine (Hcy)

Hcy is a thiol-containing amino acid and is an intermediate product in the metabolism of one of the essential amino acids, methionine [77]. Plasma levels of Hcy are determined by diet [78], genetic factors [77], renal function [79] and certain drugs [80]. Normal plasma concentrations range from 5 to 15 μmol/L [81]. Hcy levels from 15 to 30 μmol/L are classified as moderate hyperhomocysteinemia (hyper-Hcy), from 30 to 100 μmol/L as intermediate and levels higher than 100 μmol/L as severe hyper-Hcy [81]. Moderate hyper-Hcy is a frequent condition in the general population ranging from 5 to 10% among healthy adults [82] and from 20 to

40% among patients with MI [83], stroke [83] and venous thromboembolism [84] depending on the folate content of their diet.

Deficiency in folate, vitamin B_6 and B_{12}, smoking, lack of physical exercise, coffee consumption, increasing age, male gender and menopause have been associated with elevated concentrations of Hcy [78, 85, 86]. Chronic alcoholism is often accompanied by moderate hyper-Hcy [87] while moderate alcohol consumption is associated with reduced Hcy levels [88]. Several disease entities (such as end-stage renal failure, inflammatory bowel disease and hypothyroidism) are frequently accompanied by hyper-Hcy [89-91]. Finally, plasma Hcy is determined by genetic alterations in enzymes and molecules involved in Hcy metabolism [84, 92].

Hcy and CVD

The detection of atherosclerotic lesions in individuals with inborn errors of Hcy metabolism provided the first evidence for a possible connection of Hcy with CVD [93]. Since then, the association of hyper-Hcy with CVD has been repeatedly demonstrated in both animal [94] and prospective human studies [83, 95, 96]. Data indicate a graded correlation between Hcy levels and the risk or severity of CVD [97].

The first large meta-analysis, including 27 studies, showed that an increment of 5 μmol/L in Hcy levels leads to a rise of CHD risk proportional to that caused by an elevation of 20 mg/dl in total cholesterol [98]. It was suggested that a reduction of Hcy levels through higher folate intake may prove protective against atherosclerosis [98]. Furthermore, two prospective cohort studies found that high plasma Hcy levels were a strong predictor of mortality in patients with CHD [99] and those with aortic valve stenosis [100]. Nevertheless, a latter meta-analysis of prospective studies suggested that the value of elevated Hcy as a predictor of CHD and stroke in healthy populations is only modest [83]. A 25% reduction in Hcy levels (about 3 μmol/L) was associated with an 11% (OR, 0.89; 95% CI, 0.83-0.96) lower CHD risk and 19% (OR, 0.81; 95% CI, 0.69-0.95) lower stroke risk, after adjustment for conventional risk factors [83].

Another large meta-analysis of 72 genetic and 20 prospective studies concluded that the relationship between Hcy and CVD is causal [95]. It was suggested that lowering Hcy levels by 3μmol/L (by increasing folic acid intake) would reduce the risk of CHD by 16%, deep vein thrombosis by 25% and stroke by 24% [95]. Finally, in some studies raised Hcy levels emerged as a strong predictor of adverse clinical outcomes in patients with acute coronary syndromes (ACS) [101-103].

Pathophysiology

Hyper-Hcy is implicated in CVD pathophysiology *via* more than one way [104]. It is associated with, increased oxidative stress status, augmented thrombogenicity, activation of inflammatory processes, impaired endothelial function, enhanced platelet aggregation and adhesion, altered gene expression (due to DNA methylation) and increased vascular smooth muscle cells proliferation [77, 104].

Treatment

Folic acid, vitamin B_6 and vitamin B_{12} are required for Hcy metabolism [77]. Mediterranean diet, including food rich in B-vitamins and folic acid, is associated with lower plasma Hcy [105,106]. Administration of folic acid and B-vitamins reduces Hcy plasma concentrations in the general population [107,108]. Intake of 400 μg of folic acid (dose equal to RDA) daily is associated with a 25-30% reduction of HCy levels [107]. Co-administration with B_{12} (0.02-1 mg/day) offers an additional 7% reduction [108].

However, data regarding the effect of Hcy lowering strategies on CVD are conflicting. A meta-analysis of eight randomised trials showed that folic acid supplementation significantly reduced the risk of stroke in primary prevention by 18% (RR 0.82, 95% CI 0.68-1.00; p=0.045) [109]. In addition, a population based cohort study in Canada and the United States demonstrated that folic acid fortification of food results in an improvement in stroke mortality [110]. Furthermore, Hcy lowering regimens significantly reduce CV risk in patients with cystathionine beta synthase deficiency despite imperfect biochemical control [111].

On the other hand, several secondary prevention trials have failed to confirm the beneficial effect of Hcy-lowering strategies on CVD clinical outcomes [112-114]. In some cases, this was attributed to deficiencies in the design of trials such as short treatment duration [115,116].

The Heart Outcomes Prevention Evaluation (HOPE) 2 trial indicated that lowering of Hcy with folic acid and vitamins B_6 and B_{12} did reduce the risk of overall stroke, but not stroke severity or disability [117]. This is consistent with overall evidence implying that the role for Hcy as a CV risk factor is stronger for stroke than for CHD, and possibly strongest for the primary prevention of stroke [117]. However, regardless the effect on CVD clinical outcomes, Hcy lowering has been associated with plaque regression. Several short-term intervention trials have reported improvement of carotid intima media thickness (cIMT) and flow-mediated dilation (FMD) by Hcy lowering strategies, while long-term Hcy lowering has not been found to significantly improve FMD or cIMT in people with a history of stroke [118].

Evidence so far can not justify pharmacological treatment with folate and B vitamins in general population [119]. Hcy-lowering treatment should be considered in cases of hyper-Hcy [104]. Reversal of the cause (eg. diet, hypothyroidism, drugs etc) is the best treatment for moderate and intermediate hyper-Hcy [104]. Howevere there is insufficient data to support that pharmacological treatment of moderate hyper-Hcy with folic acid alone or in combination with vitamins B_{12} and B_6, would definitely reduce CV risk. Nevertheless, it is indicated at least in certain cases and most patients respond well [120].

3. Factor VII (FVII)

FVII is an enzyme of the serine protease class. It is activated by tissue factor, transforming from a single chain zymogen into a two-chain form. FVII plays an important role in initiating the process of coagulation [121]. There is a positive correlation between FVII levels and BMI, blood pressure, age, postmenopausal status in women and plasma glu-

cose, insulin and triglyceride concentrations [122]. The association with hypertriglyceridemia is the most powerful one and remains strong and significant after adjustment for conventional risk factors [123].

Although there is evidence supporting an association of FVII with CVD, results from various studies are inconsistent. Elevated FVII levels have been repeatedly reported in CVD patients [124-127]. Northwick Park Heart Study (NPHS)-I demonstrated a dose-dependent relation between FVII concentrations and CHD events as well as total mortality [128] which was not observed in NPHS-II [129]. In addition, FVII antigen levels measured on admission emerged as an independent predictor of mortality and reinfarction in patients with acute MI [130]. On the contrary, the PROCAM study failed to confirm such a relation [131]. Interestingly, multivariate analysis of the Caerphily Prospective Study showed an inverse association of factor VIIc with CVD [45]. Although this may be a chance finding, a similar inverse association was observed in the NPHS-II [129]. As a result, the role of FVII in the development of CVD remains controversial.

4. von Willebrand (vW)

vW is a large glycoprotein secreted into the circulation by endothelial cells. Its levels are raised under conditions of endothelial damage. Therefore, its use as a marker of endothelial dysfunction has been suggested. vW release can be induced by a variety of stimuli such as hypoxia, inflammatory cytokines, histamine, thrombin, leukocyte elastase, endotoxin, exercise, adrenaline and vasopressin, both *in vitro* and *in vivo* [132].

vW has three important roles in hemostasis. First, activated vW binds to platelets mediating their aggregation and adhesion to the vascular wall, especially under conditions of high shear stress. Second, vW serves as a carrier protein for factor VIII. Third, vW binding to collagen in the subendothelial connective tissue leads to a structural change within the factor VIII– binding motif of VWF that lowers the affinity for factor VIII. Enhanced release of FVIII locally may promote fibrin clot formation. This is more important in cases of injury and denudation of endothelium as in ACS [132].

Advancing age is associated with higher vW levels [132]. This may be explained by age-related arterial stiffness leading to increased vW endothelial secretion [133]. Furthermore, vW release is induced by inflammatory cytokines and raised levels accompany several inflammatory disorders [132, 134]. A positive correlation between vW and CRP has been reported in large clinical studies [135, 136]. Type 2 diabetes mellitus (DM), insulin resistance, smoking, hypercholesterolemia and hypertension are also associated with elevated vW levels [137-139]. Moreover, vW plasma levels have been inversely associated with flow mediated dilation [140]. Thus, it has been suggested that vW increase is a result of impaired NO production. Finally, as much as 75% of the variance of vW plasma levels is attributed to genetic factors [132].

Studies have failed to establish vW as a strong predictor of CHD events in the general population. Most of them have demonstrated weak associations of vW levels with the risk of CHD, turning into insignificant after adjustment for conventional risk factors [23, 30, 135, 137, 141-143]. A large prospective study yielded encouraging results showing a moderately significant association between vW and CHD even after adjustment for baseline values of classical risk factors (OR in the top vs. the bottom third 1.82, 95% CI 1.37-2.41) [144]. Moreover, the PRIME study showed a 3.04-fold increase in the risk of MI and coronary death in patients with plasma vW levels in the highest vs. the lowest quartile (95% CI, 1.59 to 5.80) [145].

Interestingly, the association of vW levels with CVD is stronger with ischemic stroke [146] and PAD [147]. In addition, vW seems to be more closely related to CVD risk in high-risk populations such as diabetic, hypertensive or cardiovascular patients [48,144,148]. Furthermore, several studies including MI survivors have described an association of raised vW levels with reinfarction or/and mortality risk [149-152]. Another interesting aspect of the vW case is the typical time-related increase of its levels during an acute cardiovascular event. This increase has been shown to be an independent predictor of short-term adverse clinical outcome in these patients [153,154]. Finally, vW has been reported to be independently associated with surrogates of atherosclerosis (cIMT and microalbuminuria) [155]. Therefore, it was suggested that vW might represent a valuable systemic biomarker of subclinical atherosclerosis.

In conclusion, current data does not support the use of vW levels as a predictor of CVD in clinical practice. Further data on the value of vW in the prediction of CVD events other than CHD, especially stroke, are required.

5. Tissue Plasminogen Activator (tPA), Plasminogen Activator Inhibitor-1 (PAI-1)

tPA is a glycoprotein, produced and released mainly by vascular endothelial cells. It is a serine proteinase that mediates the transformation of plasminogen to plasmin, playing a key role in the process of fibrinolysis. PAI-I is produced by the liver, adipose tissue and possibly the endothelium. It is a member of the superfamily of serine proteinase inhibitors [156]. It forms a complex with tPA and inactivates it in order to prevent excessive fibrinolysis and its hazardous complications. Free active tPA is difficult to measure in plasma. Therefore, measurements usually concern circulating tPA antigen values. This is mostly a measure of complex formation between these two factors. High tPA antigen values reflect low tPA activity [156].

Multiple factors can modify t-PA and PAI-1 levels. Regular physical exercise and moderate alcohol consumption promote fibrinolysis, increasing tPA activity and decreasing PAI-1 and tPA antigen levels [157]. Fibrinolytic capacity can be seriously diminished by smoking, atherosclerosis, advancing age, heavy or binge alcohol intake and obesity [157-159]. BMI and waist/hip ratio correlate positively with t-PA and PAI-1 antigen values, while estrogen is inversely associated with tPA and PAI-1 antigen values [157].

Insulin, free fatty acids, triglycerides and both oxidized and glycated low density lipoprotein (LDL) (all raised in IR/type 2 DM) as well as lipoprotein (Lp) (α) and inflammatory mediators may induce PAI-1 expression through apparently independent signalling pathways [121, 122, 160]. Activation of the renin - angiotensin system (RAS) also increases

PAI-1 expression. This effect is primarily mediated by angiotensin type-1 receptor [161], but there is evidence indicating that renin augments PAI-1 expression too [162].

t-PA release is stimulated by factors such as substance P, bradykinin, cytokines [e.g. tumor necrosis factor (TNF) –α] [156]. Finally, there is a genetic influence on fibrinolysis [121]. Certain polymorphisms are associated with higher tPA and PAI-1 levels [121].

tPA, PAI-1 and CVD

tPA antigen and PAI-1 have been positively associated with CV events [45,122,137,163,164]. In some studies, however, these associations failed to arise as independent of other CV risk factors [165]. The two most frequently studied genetic variants of tPA and PAI-1, have been reported to correlate with increased CV risk, but findings were not further confirmed [166-168].

A meta-analysis of 13 prospective studies examined the relationship between tPA antigen values and CHD [165]. Seven of these studies included samples from the general population, while the rest referred to patients with diagnosed CHD or PAD. Adjustment for baseline values of conventional risk factors led to reductions of odds ratios adjusted for age and sex only [odds ratio of 2.18 (95% CI 1.77-2.69) in the top third vs. bottom third reduced to 1.47 (95% CI 1.19-1.81) for the former seven studies and odds ratio of 3.23 (95% CI 1.71–6.09) reduced to 1.32 (95% CI 0.70–2.50) for the latter six] [165]. The role of PAI-1 in predicting coronary events has been partly attributed to its association with insulin resistance [169-171].

Several studies have reported low t-PA and, more frequently, high PAI-1 values in PAD patients [172]. Impaired fibrinolysis appears to play a role in the future development of PAD in patients with type 2 DM [173]. Interestingly, the grade of fibrinolysis impairment has been reported to correlate with the severity of claudication [174]. Finally, PAI-1 activity measured 24 and 48 hours after PTA in PAD patients emerged as the only significant predictor of restenosis [175].

Impaired Fibrinolysis and Pathophysiology of CVD

The causal relationship between impaired fibrinolysis and atherogenesis has not been fully addressed. It is hypothesized that these two processes cooperate and interact resulting in vascular damage [158]. Increasing coronary atheroma burden has been associated with diminished coronary release of active tPA as well as an increase in PAI-1 plasma concentrations in cigarette smokers, implying a direct link between atherosclerosis and impaired acute fibrinolytic capacity [158]. The proposed responsible mechanisms are chronic endothelial cell injury, impairment of the L-arginine nitric oxide pathway and depletion of endothelial cell tPA stores due to chronic stimulation and upregulation of the release [158].

PAI-1 is highly expressed in atherosclerotic lesions [176]. Its raised levels limit fibrinolysis and facilitate thrombosis [177]. Moreover, high PAI-1 levels attenuate migration of vascular smooth muscle cells at sites of vascular injury [178]. This results in the formation of vulnerable, acellular atheromatic plaques, the rupture of which can trigger an ACS [178]. Furthermore, it has been shown that overexpression of PAI-1 in transgenic mice facilitates the formation and persistence of microthrombi containing clot-associated mitogens [179]. Atherothrombosis is favoured and coronary clots may develop, giving rise to coronary events in the absence of typical atherosclerotic background such as hypertension and hyperlipidemia [180].

It has been suggested that levels of tPA and PAI-1 may be more closely related to the presence and severity of atherosclerosis rather than to an upcoming CV event [180]. The association of tPA/PAI-I with subclinical atherosclerosis has been described as one of intermediate significance (compared with the respective relation of fibrinogen to subclinical atherosclerosis which is described as strong) [181].

Strategies to Improve Fibrinolytic Capacity

Normal function of the fibrinolytic system is affected by multiple factors. Proper modification of these factors can prove helpful in terms of impaired fibrinolysis. This may be achieved through either lifestyle intervention measures or pharmacologic agents or both. Regular physical exercise, moderate alcohol consumption, smoking cessation, weight loss (by regular exercise or/and dietary modifications), amelioration of hypertriglyceridemia (either by dietary changes or treatment with gemfibrozil) are accompanied by favourable effects on fibrinolysis [157]. It has been suggested that the rise in tPA activity through exercise is propionate to exercise intensity but temporary [182,183].

The effect of n-3 PUFA intake on fibrinolysis remains unclear. Studies have yielded inconsistent results, demonstrating either improvement [184] or impairment [185] or even no effect [186] on fibrinolysis.

Lipid lowering agents, pharmacologic inhibition of the RAS [161], improvement of insulin sensitivity and glucose metabolism [187,188] can reduce raised PAI-1 and enhance impaired fibrinolysis. Treatment with ACEI is associated with reductions in PAI-1 levels and a lower incidence of ischemic CV events [189]. This effect is augmented by co-administration of spironolactone [190]. Statins also favour fibrinolysis increasing t-PA and reducing PAI-1 levels [191-193]. This is only merely attributed to their lipid – lowering action. Statins appear to modify signalling pathways [inhibit Rho family proteins and activate phosphatidylinositol (PI)-3 kinase/Akt] which are implicated in inflammation mediated induction of PAI-1 expression [194].

6. D-dimer

D-dimer is the product of cross-linked fibrin primary degradation [195]. Therefore, its levels represent a measure of ongoing fibrin turnover, reflecting activated coagulation and fibrinolysis [195]. Increasing age and female sex have been correlated with higher D-dimer levels [196-198].

D-dimer has been consistently associated with incident CVD [30, 40, 199-201]. Substantially elevated D-dimer levels have been reported in patients with ACS [202-204]. A meta-analysis of six prospective studies yielded a combined OR of 1.7 for CHD in individuals in the top vs. those in the bottom third baseline D-dimer values (95% CI, 1.3 to 2.2) [199]. In the Caerphilly study, D-dimer was found to have the potential to increase the prediction of CHD or ischemic stroke in middle-aged men in addition to conventional risk factors [45]. Both pathological and clinical studies have in-

dicated significant correlations between D-dimer and the severity of atherosclerosis, especially in terms of PAD [147, 197, 205]. Thus, it is suggested that local degradation of cross-linked fibrin may be involved in the progression of atherosclerosis.

A relationship between D-dimer and inflammation has also been postulated. D-dimer levels have been repeatedly associated with CRP and IL-6 [199, 200, 206, 207]. In fact, it appears that the combination of D-dimer and CRP is an even more powerful predictor of CVD [207].

These associations may derive from the effect of D-dimer (and other fibrin degradation products) on secretion of IL-6, which, in turn, stimulates hepatic synthesis of acute-phase proteins including CRP [206]. The predictive value of CRP for CVD is attenuated when classic risk factors such as age and smoking are included in multivariate analyses [135, 207]. In contrast, adjustment for these factors has little effect on the association of D-dimer with CV risk, since D-dimer is only weakly related to them [206, 207].

Nevertheless, there is inadequate evidence implying that D-dimer levels provide additional predictive value on top of that obtained from established risk factors. Thus, the use of D-dimer levels in CV risk assessment remains unjustified.

7. Lipoprotein (α) [Lp(α)]

Lp(a) is a particle that resembles LDL in terms of its lipid composition and apolipoprotein (apo) B 100 [208]. The unique component of Lp(α) is its apo(α) moeity, a glycoprotein similar to plasminogen, bound to apo B100 with a disulfide bond [208]. The biological function of Lp(α) remains elusive, even though a role in wound healing has been suggested [209]. Concentrations of Lp(α) are not related to those of other lipoproteins and apolipoproteins or factors known to influence them such as diet and exercise. Lp(α) levels are largely under genetic control. They vary widely among individuals, depending on the size of the apo (α) isoform present [208]. Raised Lp(α) levels have been found in patients with chronic renal failure, nephrotic syndrome, DM, cancer and hypothyroidism and menopausal women. Finally, Lp(α) may increase as part of the acute phase response. In contrast, Lp(α) values are lower in liver failure and hyperthyroidism [208].

Lp(α) is considered highly atherogenic. Plasma levels exceeding 20 to 30 mg/dL have been associated with increased CV risk [210]. It has been suggested that Lp(α) may be more atherogenic when carrying small apo (α) isoforms (defined as <22 kringle-4 repeats) than larger ones [211].

Lp(α) binds to endothelial cells, macrophages, platelets and to the subendothelial matrix and promotes proliferation of vascular smooth muscle cells and chemotaxis of monocytes. Also, Lp(α) is thought to compete with plasminogen for binding to plasminogen receptors, fibrinogen, and fibrin (due to their structural homology) [208]. Therefore, it may inhibit clot fibrinolysis at sites of tissue injury, in favour of atherothrombosis. Furthermore, Lp(α) induces the production of PAI-1 and inhibits the secretion of t-PA by endothelial cells. Finally, it represents a rich source of cholesterol at sites of vascular injury. All these properties of Lp(α) support its role in atherothrombosis [208].

The importance of Lp(α) regarding the incidence of CVD has been extensively studied. A meta-analysis of 27 prospective studies demonstrated a clear association between Lp(α) and CHD. The combined analysis yielded an OR of 1.6 (95% CI 1.4 to 1.8) in the top vs. the bottom third of baseline Lp(α) [212].

A recent large case-control study demonstrated an independent and approximately continuous relationship between Lp(α) levels and risk of future CHD. Levels of Lp(α) were highly stable within individuals across many years and only weakly correlated with known risk factors [213]. Furthermore, a significant association of Lp(α) with premature CHD has been shown. Elevated Lp(a) levels appear to be common among individuals with a family history of premature CHD or in patients presenting with early-onset of CHD [214].

In the Edinburgh Artery Study, Lp(α) showed modest associations with MI events, but was significantly associated with stroke and PAD [30]. Another study including patients with acute MI showed that high Lp(α) levels were independently associated with an increased risk of developing events at 6 months and greater CV morbidity and mortality [215]. Interestingly, Lp(α) levels in diabetic coronary patients have been found to be low and not associated with the incidence of vascular events. In the same study, Lp(α) was a strong and independent predictor of vascular events in non-diabetic patients (standardized adjusted hazard ratio (HR) = 1.461 (1.121-1.904); p = 0.005) [216].

Some prospective studies have not confirmed the positive association of Lp(α) with CVD [217, 218]. This may be attributed to the variability in Lp(α) measurement assays as well as in the atherogenic potential of Lp(α) particles [219]. For, example, in African Americans, high Lp(a) levels are not usually associated with small apo(α) isoforms [220], explaining why elevated Lp(α) levels have not been consistently associated with increased CHD risk in this group of people [221].

Lp(α) is thought to interact with other risk factors and further increase CV risk. The presence of older age, low HDL, high LDL, hypertension have been accompanied by stronger associations of raised Lp(α) with CV risk [222].

The measurement of Lp(α) levels in combination with Fib, albumin and bilirubin levels may prove useful in the prediction of vascular events in high-risk populations [223]. However, routine use of Lp(a) in CVD risk assessment is not currently recommended not only because of the lack of a standardized assay, but also because of the limited therapeutic options in the treatment of elevated levels [224]. It has been suggested that the measurement of Lp(α) levels may be useful in subjects with a family history of premature CHD or in patients with premature CHD and those who develop CHD in the absence of conventional risk factors [225].

The most effective measure in treatment of high Lp(α) is apheresis. Niacin [226], trogens [227], fibrates [228] and some antihypertensive drugs [229] have been reported to exert a lowering effect on Lp(α) while statins [230] have no such action.

So far, there is no data showing that Lp(α) lowering is accompanied by a reduction of CV risk. As a result, Lp(α)

lowering strategies are not currently recommended in terms of primary or secondary prevention.

CONCLUDING REMARKS

Hemostasis and thrombosis play a crucial role in CVD pathophysiology. Elevated levels of thrombotic and hemostatic factors are commonly found in CVD patients. The role of most of them in the initiation and progression of atherosclerosis has been elucidated. Furthermore, their measurement may contribute to the prediction of upcoming CV events on top of conventional risk factors. Nevertheless, there is insufficient data supporting their use in the assessment of CV risk as part of routine clinical practice. Further studies are needed in order to confirm whether the treatment of these factors' raised levels has the potential to decrease CVD events.

ABBREVIATIONS

ACS	=	acute coronary syndromes
ACEI	=	angiotensin converting enzyme inhibitors
Apo	=	apolipoprotein
ARB	=	angiotensin receptor blockers
ASCOT	=	Anglo-Scandinavian Cardiac Outcomes Trial
BMI	=	body mass index
cIMT	=	carotid intima media thickness
CV	=	cardiovascular
CVD	=	cardiovascular disease
CHD	=	coronary heart disease
DM	=	diabetes mellitus
FVII	=	factor VII
Fib	=	fibrinogen
FMD	=	flow-mediated dilation
HDL	=	high density lipoprotein
Hcy	=	homocysteine
hyper-Hcy	=	hyperhomocysteinemia
LDL	=	low density lipoprotein
Lp(a)	=	lipoprotein (a)
PAD	=	peripheral arterial disease
PAI-1	=	plasminogen activator inhibitor - 1
PTA	=	percutaneous transluminal angioplasty
RAS	=	renin - angiotensin system
tPA	=	tissue plasminogen activator
TNF	=	tumor necrosis factor
vW	=	von Willebrand

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