Review

Fibrinogen: biochemistry, epidemiology and determinants

S. KAMATH and G.Y.H. LIP

From the Haemostasis Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham, UK

Introduction

Plasma fibrinogen is an important component of the coagulation cascade, as well as a major determinant of blood viscosity and blood flow. Increasing evidence from epidemiological studies suggests that elevated plasma fibrinogen levels are associated with an increased risk of cardiovascular disorders, including ischaemic heart disease (IHD), stroke and other thromboembolism.1,2 This increase in plasma fibrinogen levels may promote a prothrombotic or hypercoagulable state, and may in part explain the risk of stroke and thromboembolism in conditions such as atrial fibrillation (AF).

Nevertheless, the relationship between hyperfibrinogenemia, atherosclerosis and thrombosis is complicated. As the process of thrombogenesis is very closely related to atheroma formation (atherogenesis), it follows that specific thrombogenic factors such as fibrinogen (with important effects on blood rheology) may play key roles in the process of atherosclerotic lesion formation, with subsequent effects on cardiovascular diseases (Figure 1). However, knowledge about the precise determinants of plasma fibrinogen levels in health and disease is as yet incomplete, and many paradoxes are still present. For example, it is known that plasma fibrinogen is higher in Black than in White patients,3 but (in the UK at least) coronary artery disease is less common in Blacks than in White patients, while hypertension and stroke are conversely more common.4,5 Plasma fibrinogen is also influenced by many factors: it increases with age, body mass index, smoking, diabetes and post menopause and is related to fasting serum insulin, low-density-lipoprotein (LDL) cholesterol lipoprotein(a) and leukocyte count. Conversely, it decreases with moderate alcohol intake, physical activity, increased high-density-lipoprotein (HDL) cholesterol, and with hormone replacement therapy (HRT).6–8

We review the biochemistry, epidemiology, and genetic and extrinsic influences on plasma fibrinogen levels, as well as the close association between plasma fibrinogen and various vascular disorders.

Search strategy

We performed a search using electronic databases (MEDLINE, EMBASE, DARE), using the search terms ‘fibrinogen’ in combination with either ‘biochemistry’, ‘epidemiology’, ‘pathophysiology’, ‘atherosclerosis’, ‘genetics’, ‘coronary artery disease’ or ‘ischaemic heart disease’, ‘genetics’, ‘smoking’, ‘alcohol’, etc., to cover the range of subheadings addressed in the review. In addition, the reference lists from papers were scrutinized, and abstracts from national and international cardiovascular meetings were studied to identify further studies, published or unpublished. The influence of growth in early life on fibrinogen concentrations in adulthood, and interventions to reduce fibrinogen, were not considered for this review.

Pathophysiology

Fibrinogen is a soluble glycoprotein found in the plasma, with a molecular weight of 340 kDa.9 It
comprises of three pairs of non-identical polypeptide chains (alpha, beta and gamma chains) linked to each other by disulphide bonds. Fibrinogen has a biological half-life of about 100 h and is synthesized predominantly in the liver. As a clotting factor, fibrinogen is an essential component of the blood coagulation system, being the precursor of fibrin. However, at the ‘usual’ plasma levels of 1.5 to 4.5 g/l, its concentration far exceeds the minimum concentration of 0.5–1 g/l necessary for haemostasis.

Fibrinogen plays a vital role in a number of physiopathological processes in the body, including inflammation, atherogenesis and thrombogenesis. Nevertheless, our understanding of the mechanisms leading to the atherothrombogenic action of fibrinogen is fragmentary. Proposed mechanisms include the infiltration of the vessel wall by fibrinogen, haemorrheological effects due to increase in blood viscosity, increased platelet aggregation and thrombus formation. Furthermore, plasma fibrinogen is also a prominent acute-phase reactant. It augments the degranulation of platelets in response to adenosine diphosphate (ADP), when taken up by the α granules. Thus, elevated concentrations of fibrinogen, perhaps secondary to inflammation or infection (Chlamydia pneumoniae or Helicobacter pylori) implicated in cardiovascular risk may operate, in part, by increasing the reactivity of platelets.

Fibrinogen and inflammation

The process of inflammation is primarily mediated by its interaction with leucocytes through the surface receptors of the latter termed ‘integrins’. The 2 main receptors for fibrinogen on the surface of leukocytes include Mac-1 (CD11b/CD18, alpha M beta 2) and alpha X beta 2 (CD11c/CD18, p150, 95). Leukocytes (both monocytes and myelocytes) can specifically induce MAC–1 receptor to bind fibrinogen. The ability of MAC–1 receptor to bind fibrinogen results from the maturational changes occurring in the receptor during the process of cell differentiation, and is not seen in a resting leucocyte. The site on fibrinogen that interacts with MAC-1 is not shared by other integrins. Fibrinogen is also a ligand for Intercellular Adhesion Molecule-1 (ICAM-1), and enhances monocyte-endothelial cell interaction by bridging the Mac-1 on monocytes to ICAM-1 on endothelial cells. Thus, ICAM-1 behaves as a cell surface ligand for alpha L beta 2 and alpha M beta 2 (MAC-1) integrins, and has a key role in leukocyte adhesion to the vascular endothelium. Furthermore, fibrinogen upregulates and increases the concentration of ICAM-1 proteins on the surface of endothelial cells, resulting in increased adhesion of leukocytes on the surface of endothelial cells, even at high shear rates in flow conditions. Moreover, the fibrinogen binding to ICAM-1 on
the endothelial cells also mediates the adhesion of platelets. The interaction of fibrinogen and cells expressing ICAM-1 is associated with cellular proliferation.20

Fibrinogen, on binding to its integrin receptor on the surface of leukocytes also facilitates a chemo-tactic response, thus playing a vital role in the process of inflammation.21 One of the proposed mechanisms by which fibrinogen induces pro-inflammatory changes in leukocytes includes an increase in the free intracellular calcium and increased expression of neutrophil activation markers. These processes result in an increase in phagocytosis, antibody-mediated leucocyte toxicity and delay in apoptosis.22

Fibrinogen is also involved in the facilitation of both cell–cell interaction and the interaction of cell and extracellular matrix such as collagen.13,23 Thus, as explained above, fibrinogen is an important mediator of cell–cell interaction, adhesion and inflammation.

Finally, there is evidence that fibrinogen facilitates the biomaterial-provoked inflammatory response.24 Interaction with the biomaterial results in conformational changes within the fibrinogen molecule and conversion into ‘proinflammatory’ fibrinogen, resulting in the exposure of the epitope that interacts with the MAC-1 receptor for macrophages.24,25

**Fibrinogen and atherogenesis**

There seems to be little doubt that fibrin deposition can both initiate atherogenesis and contribute to the growth of plaques.26,27 Fibrinogen and its metabolites appear to cause endothelial damage and dysfunction by a number of mechanisms.28 Many human atherosclerotic lesions, showing no evidence of fissure or ulceration, can contain a large amount of fibrin, which may either be in the form of mural thrombus on the intact surface of the plaque, in layers within the fibrous cap, in the lipid-rich core, or diffusely distributed throughout the plaque. This phenomenon may be compounded by the decrease in arterial intimal fibrinolytic activity and plasminogen concentration observed in cardiovascular disease.26

It has been proposed that once in the arterial intima, fibrin stimulates cell proliferation by providing a scaffold along which cells migrate, and by binding fibronectin, which stimulates cell migration and adhesion.29 Fibrin degradation products, which are present in the intima, may stimulate mitogenesis and collagen synthesis, attract leukocytes, and alter endothelial permeability and vascular tone. In the advanced plaque, fibrin itself may be involved in the tight binding of LDL and accumulation of lipid, resulting in the lipid core of atherosclerotic lesions.26 However, it cannot be overemphasized that many of these observations are only associations, and a definite causal role for fibrinogen cannot be fully demonstrated.

**Fibrinogen and thrombogenesis**

Thrombogenesis is regulated by a fine balance between the coagulation and fibrinolytic pathways (Figure 2). Subsequent to vessel wall trauma, tissue thromboplastin is released from the sub-endothelium. Tissue thromboplastin in turn triggers the extrinsic pathway of coagulation by activating factor VII to VIIa. Contact of blood with the foreign surface initiates the intrinsic pathway of coagulation, by activating factor XII to XIIa, as well as platelets. Platelet aggregation, however, does not confer adequate stability, and therefore activation of the coagulation pathway is also necessary.

The final common pathway of the coagulation cascade involves the activation of factor X to Xa, and the subsequent activation of prothrombin to thrombin. Thrombin, which is a protease enzyme, facilitates the cleavage of fibrinogen into fibrin monomers, which link to each other both sideways and end-to-end to form fibrin polymers. Activated factor XIII facilitates the cross linkage of fibrin polymers to form a stable fibrin clot.

Fibrinogen is also involved in the final common pathway of platelet aggregation. Fibrinogen cross-links the platelets by binding the glycoprotein IIb-IIIa receptor on the platelet surface.30 This has become more relevant with the advent of glycoprotein IIb-IIIa receptor inhibitors, which block this final common pathway of platelet binding.

**Determining plasma fibrinogen levels**

The available methods of determining fibrinogen can be classified into two groups, ‘functional’ and ‘direct’. The first category involves tests based on the determination of the coagulation time, which in turn is proportional to the fibrinogen concentration. The most widely used method for the functional fibrinogen assay in most clinical laboratories is the Clauss method, which records the time taken to reach the coagulation end point, (i.e. the formation of a clot). An adequate calibration procedure is indispensable for reliable fibrinogen measurements, whatever the method used, as variation between the declared and measured fibrinogen concentrations can exceed 30%.31 The second group of tests quantifies fibrinogen molecules directly, either immunologically, gravimetrically or precipitation (by heat or salting.
However, the latter tests do not provide information about the coagulability (functional ability) of the fibrinogen.

The Expert Committee on Biological Standardization of the World Health Organization, on proposal by Fibrinogen Sub-Committee of the Standardization and Scientific Committee of the International Society on Thrombosis and Haemostasis, has recently established the 2nd International Standard for Fibrinogen, Plasma (code 98/612) the potency of which is 2.19 mg/ampoule by the automated Clauss assay.32 Although a number of different fibrinogen assays are available, the total clottable protein assay, which was used to establish the 2nd International Standard for fibrinogen is the recommended gold standard.32

Indeed, one of the barriers to cross-study comparisons are the differences due to the different methods for the determination of fibrinogen. The Clauss assays are generally reproducible between centres, analysers and reagents,31 but it is important to note that the normal reference interval must be determined for each laboratory for each assay, and is not a general value (Table 1), although the widely accepted normal reference value for fibrinogen is between 1.5 and 4.5 g/l.

These differences may be of relevance to clinical research. For example, Smith et al.33 reported levels of clottable fibrinogen to be 13.9% higher in patients with peripheral artery disease compared to controls \( (p = 0.001) \), but nephelometric levels to be 14.9% higher \( (p < 0.001) \), a difference which may be trivial. However, although levels defined by the Clauss method failed to correlate with the degree of femoro-popliteal atherosclerosis \( (r = 0.06) \), nephelometric levels did correlate with extent of disease \( (r = 0.2, \ p < 0.01) \).34 Another epidemiological study reported a correlation coefficient of 0.62 between the nephelometric and Clauss methods for fibrinogen.35 While this is statistically significant \( (p < 0.001) \), it could be argued that this is methodologically of poor significance since, in an ideal world, a correlation coefficient >0.9 would be expected if the assays do indeed measure the same molecule. Indeed, the association with ischaemic heart disease was ten-fold more significant using the nephelometric assay \( (p < 0.001) \) than with the Clauss assay \( (p < 0.01) \). The same group later reported nephelometric levels of fibrinogen to be 9.3% higher in those men who, after a ten year interval, went on to suffer an incidence of ischaemic heart disease.36 This figure is remarkably close to the difference of 9.5% in Clauss-defined levels between those suffering or free of a coronary event in the PROCAM study.37 Thus, despite the close agreement between these prospective studies, doubts as to the precise and comparative value of each method remain.38

**Epidemiological studies**

Several epidemiological studies have provided prospective data on plasma fibrinogen levels in relation to cardiovascular disease (Tables 1 and 2). According to these studies, the risk of developing a...
Table 1  Mean fibrinogen concentration in different epidemiological studies

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Method</th>
<th>n</th>
<th>Mean fibrinogen (g/l) Without CHD</th>
<th>With CHD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northwick Park Heart Study (Meade et al. 1986)</td>
<td>Gravimetry</td>
<td>1511</td>
<td>2.90</td>
<td>3.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Framingham (Kannel et al. 1987)</td>
<td>Spectrophotometry</td>
<td>1315</td>
<td>2.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goteborg (Wilhelmsen et al. 1984)</td>
<td>Spectrophotometry</td>
<td>792</td>
<td>3.30</td>
<td>3.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leigh (Stone et al. 1985)</td>
<td>Nephelometry</td>
<td>297</td>
<td>3.13</td>
<td>3.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PROCAM (Heinrich et al. 1991)</td>
<td>Clauss</td>
<td>2187</td>
<td>2.62</td>
<td>2.86</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Copenhagen (Moller et al. 1991)</td>
<td>Gravimetry</td>
<td>438</td>
<td>2.73</td>
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<td>Caerphilly (Yarnell et al. 1985)</td>
<td>Nephelometry</td>
<td>134</td>
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</tr>
<tr>
<td>Speedwell (Baker et al. 1982)</td>
<td>Nephelometry</td>
<td>226</td>
<td>2.97</td>
<td>2.87</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Clauss</td>
<td>223</td>
<td>4.02</td>
<td>4.39</td>
<td>&lt;0.01</td>
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</tbody>
</table>


Table 2  Plasma fibrinogen levels according to endpoints in epidemiological studies

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Person-years</th>
<th>Number of events</th>
<th>Fibrinogen level according to end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northwick Park Heart Study (Meade et al. 1986)</td>
<td>15 110</td>
<td>128</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IHD deaths</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IHD non-fatal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All IHD end points</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other deaths</td>
</tr>
<tr>
<td>Northwick Park Heart Study (Meade et al. 1986)</td>
<td>15 110</td>
<td>128</td>
<td>2.9</td>
</tr>
<tr>
<td>Gothenburg Study (Wilhelmsen et al. 1984)</td>
<td>10 692</td>
<td>130</td>
<td>None</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>MI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stroke</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other deaths</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>3.3</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.3</td>
</tr>
<tr>
<td>Leigh Study (Stone et al. 1985)</td>
<td>2168</td>
<td>40</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.0</td>
</tr>
<tr>
<td>Framingham Study (Kannel et al. 1987)</td>
<td>15 780</td>
<td>404</td>
<td>16 events/1000/year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 events/1000/year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>26 events/1000/year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.7–3.1</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;3.1</td>
</tr>
<tr>
<td>Caerphilly and Speedwell Studies (Yarnell et al. 1991)</td>
<td>20 325</td>
<td>251</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IHD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.1</td>
</tr>
<tr>
<td>Munster Heart Study (Assmann et al. 1996)</td>
<td>4045</td>
<td>15</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any event</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.3</td>
</tr>
<tr>
<td>GRIPS (Cremer et al. 1996)</td>
<td>26 195</td>
<td>107</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.0</td>
</tr>
</tbody>
</table>

GRIPS, Gottingen Risk, Incidence and Prevalence Study; IHD, Ischaemic Heart Disease; MI, myocardial infarction. Adapted from reference 39.
A cardiovascular event such as IHD or stroke is 1.8 to 4.1 times higher in subjects with fibrinogen levels in the top third than in those with levels in the lower third. Preliminary evidence also suggests that reducing fibrinogen levels in patients with high baseline levels and coronary disease may be beneficial.

A meta-analysis of the six prospective epidemiological studies with samples representative of the general population, concluded that plasma fibrinogen was an independent cardiovascular risk factor, the results being uniform despite the diversity of study designs, sample compositions, follow-ups and end-point criteria. In this meta-analysis of 92,147 person-years experience, all prospective studies showed that plasma fibrinogen was associated with subsequent myocardial infarction (MI) or stroke. The odds ratio for the events in the upper vs. lower tertile varied between 1.8 (95% CI 1.2–2.5) in the Framingham study and 4.1 (95% CI 2.3–6.9) in the Gottingen risk incidence and prevalence study, with a summary odds ratio of 2.3 (95% CI 1.9–2.8). Furthermore, there was uniform, continuous increase in risk from the lowest to highest tertile. Plasma fibrinogen was associated with ‘true’ risk factors such as diabetes, hypertension and hypercholesterolemia in the studies included in this meta-analysis. However, even when these factors were included in the multivariate analysis, the association between plasma fibrinogen and cardiovascular disease remained statistically significant, suggesting that fibrinogen is an independent cardiovascular risk factor.

In another meta-analysis, which included 22 studies (13 prospective, 5 cross-sectional, and 4 case-control) trying to determine the role of fibrinogen as a cardiovascular risk factor, the overall estimate of risk of cardiovascular events in subjects with plasma fibrinogen levels in the higher tertile, was twice as high as that of subjects in the lower tertile (OR 1.99; 95% CI 1.85–2.13). High plasma fibrinogen levels were associated with an increased risk of cardiovascular disease in healthy as much as in high-risk individuals.

Thus, there is strong and unequivocal evidence from epidemiological studies that plasma fibrinogen levels are independently related to the presence of, and the subsequent development of, vascular disease. Principal findings from some of the pivotal epidemiological studies are summarized below.

The Northwick Park Heart Study (NPHS)
In this study, out of 1511 White men aged between 40 and 64 years, 109 subsequently experienced a first major IHD event. Elevated levels of plasma factor VII coagulant activity and fibrinogen were associated with increased IHD risk. Indeed, elevations of one standard deviation in factor VII activity, fibrinogen, and cholesterol were associated with increases in the risk of an episode of IHD within 5 years of 62%, 84%, and 43%, respectively, demonstrating that the association between haemostatic markers and IHD to be stronger than that for cholesterol.

Gothenburg study
In a random sample of 792 men aged 54 years, MI occurred in 92 men, stroke in 37, and death from causes other than MI or stroke in 60 during 13.5 years of follow-up. Plasma fibrinogen was an independent risk factor for MI and stroke on univariate analysis. On multivariate analysis, plasma fibrinogen was still statistically significant for stroke risk.

Leigh General Practice Study
In the Leigh General Practice Study, 505 men aged 40–69 years and free from IHD, diabetes and hypertension were recruited from one general practice in the UK. After a mean follow-up of 7.3 years, 40 cases of MI occurred. On multivariate analysis, plasma fibrinogen proved to be the strongest predictor of adverse cardiovascular events, with an OR of 21:1 when those with high levels (> 3.5 g/l) were compared to those with low levels (< 2.9 g/l) of fibrinogen.

Framingham Study
In the Framingham Study, the risk of developing cardiovascular disease was significantly related to plasma fibrinogen levels. In both sexes, cardiovascular and stroke risk increased progressively in relation to antecedent fibrinogen values over the 1.8–4.5 g/l range. As in NPHS, the influence of plasma fibrinogen on cardiovascular risk was much more pronounced in younger men. The impact of plasma fibrinogen levels on cardiovascular disease was comparable with the major risk factors, such as blood pressure, haematocrit, adiposity, cigarette smoking and diabetes; and was still an independent predictor of coronary artery disease on multivariate analysis.

Munster Heart Study
In the Munster Heart Study (PROspective CArdiovascular Munster Study, PROCAM), plasma fibrinogen, factor VIIc, blood pressure, and lipid parameters were measured in 2781 healthy men aged 40–65 years. After 8 years of follow-up, 130
coronary events were observed, and the mean plasma fibrinogen level of the ‘event group’ exceeded that of the non-event group by 0.32 g/l. The incidence of coronary events among men within the upper tertile of plasma fibrinogen concentration was threefold higher than among men within the lower tertile. When fibrinogen and LDL concentration were considered together, there was a graded and dramatic eightfold increase in 8-year risk among men with both fibrinogen and LDL cholesterol in the higher tertiles, when compared to men with both of these parameters in the lower tertile.

Caerphilly and Speedwell studies
The Caerphilly and Speedwell collaborative heart disease studies were based on a combined cohort of 4860 middle-aged men from the general population. After a follow-up of 5.1 years in the Caerphilly study and 3.2 years in the Speedwell study, 251 major IHD events occurred. The age-adjusted relative odds of IHD for men in the top 20% of the distribution compared with the bottom 20% were 4.1 for fibrinogen, 4.5 for viscosity, and 3.2 for white blood cell count. Multivariate analysis showed that white blood cell count, fibrinogen and viscosity were independent risk factors for IHD.

European Concerted Action on Thrombosis and disabilities study (ECAT)
In the ECAT, plasma fibrinogen was a strong and independent risk factor for MI and sudden death, particularly in patients with pre-existing coronary artery disease, along with plasma von Willebrand factor (vWF) antigen (a marker of endothelial damage), and tissue plasminogen activator antigen (a marker of thrombolytic activity). In patients with coronary artery disease, the relationship of plasma fibrinogen levels to the incidence of acute coronary syndromes was stronger than that of low-density lipoprotein cholesterol. Fibrinogen (RR 1.31, 95% CI 1.07-1.61) had a stronger association with future coronary events than either vWF antigen (RR 1.24, 95% CI 1.00-1.53) or t-PA antigen (RR 1.29, 95% CI 1.04-1.60).

Gottingen Risk Incidence and Prevalence Study (GRIPS)
As with any other conventional risk factor, very occasionally studies have failed to provide the expected results associating fibrinogen with coronary artery disease. In the prospective GRIPS based on a sample of 6002 men aged 40-60 years, initially free of cardiovascular disease, plasma fibrinogen was an independent risk factor for the incidence of acute coronary events during the initial 5 years of follow-up, although this relationship was lost during the subsequent 5 years of follow-up. Similarly when adjusted for LDL, there was no significant association between plasma fibrinogen and the development of chronic coronary artery disease without acute MI. This could partly be attributed to the lack of reliable recommendations for the elevated plasma fibrinogen levels, and choosing different cut-off points.

Deyerminants of plasma fibrinogen levels
Plasma fibrinogen level is dependent upon both genetic and environmental factors.

Genetic influences
The evidence suggests that plasma fibrinogen levels are probably under substantial genetic control, as genetic polymorphisms account for some 20–51% of variations in plasma fibrinogen levels. The demonstration of such substantial genetic control further supports the view that plasma fibrinogen is a primary risk factor for atherothrombotic disorder rather than just a reflection of such disorder.

The fibrinogen locus comprises three genes coding for fibrinogen gamma (FGG), fibrinogen alpha (FGA), and fibrinogen beta (FGB), clustered in a region of approximately 50 kb on the long arm of chromosome 4q23-q32, the direction of transcription of the $\beta$ gene being in the opposite direction to that of the other two. Variation in the fibrinogen locus contributes to the individual differences in plasma fibrinogen levels. However, the precise molecular mechanism(s) underlying the genetic heritability of plasma fibrinogen concentration remain unclear.

The genetic influence on the fibrinogen beta-chain gene has been more extensively studied, because $\beta$-chain synthesis is the limiting step in the production of mature fibrinogen. In recent years, several polymorphisms have been identified in the fibrinogen chain genes that determine plasma levels of fibrinogen, mainly by restriction fragment length polymorphism (RFLP) and single-stranded conformation polymorphism (SSCP) analyses. For example, the BclI RFLP of the $\beta$ fibrinogen gene is associated with between-person differences in plasma fibrinogen levels. Similarly, van’t Hooft et al. demonstrated that the −455G/A and
-854G/A polymorphisms of the β fibrinogen gene have a significant impact on the plasma fibrinogen concentration. The -455G/A mutation in the promoter region of the β fibrinogen gene is one of the strongest genetic variations, associated with an increase in plasma fibrinogen in both genders in the general population.55,58

However, the results have been conflicting, and some studies have failed to demonstrate such relationships between these genetic polymorphisms and plasma fibrinogen levels. For example, Connor et al.59 found that plasma fibrinogen levels did not show any significant associations with the four fibrinogen polymorphisms examined, at the α (TaqI), β (BclI and HaeIII), and γ (KpnI/Sacl) fibrinogen loci. Humphries et al.49 found that the individuals with the genotype B1B1 had a mean fibrinogen of 2.74 g/l, while those with B2B2 had a mean plasma fibrinogen level of 3.69 g/l, a level previously associated with a strongly increased risk of IHD. Those heterozygous for the two alleles, with the genotype B1B2, had mean plasma fibrinogen levels of 2.98 g/l.

Despite the recognition that plasma fibrinogen levels are under a ‘significant’ degree of genetic control, the precise genes/alleles/polymorphisms that are responsible for the variation in levels between different populations, and the clinical significance, if any, still remains uncertain as much of the limited data are conflicting.

**Extrinsic influences**

There is evidence that plasma fibrinogen level and its associated cardiovascular risk may be dependent upon an interaction between environmental and intrinsic (genetic) factors (Table 3) rather than just the latter. For example, there is a dose-response effect between the number of cigarettes smoked and plasma fibrinogen level, as well as an inverse relationship with time since cessation of smoking.60 Moderate drinking may lower plasma fibrinogen concentration, and if fibrinogen is a causal risk factor for cardiovascular disease, it may be one of the variables that explain the protective effect of moderate alcohol consumption on cardiovascular disease.61

The observation of extrinsic influences on plasma fibrinogen levels suggests that elevated plasma fibrinogen levels may be modifiable through appropriate lifestyle changes. Furthermore, there is evidence that strategies that lower the cardiovascular

<table>
<thead>
<tr>
<th>Table 3 Factors influencing plasma fibrinogen levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors associated with raised fibrinogen</td>
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</tr>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Black race</td>
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<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Obesity</td>
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<tr>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Elevated cholesterol</td>
</tr>
<tr>
<td>Menopause</td>
</tr>
<tr>
<td>Oral contraception</td>
</tr>
<tr>
<td>Stress</td>
</tr>
</tbody>
</table>

**Table 4 Role of fibrinogen in hypertension**

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Age (years)</th>
<th>Fibrinogen association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. 1990</td>
<td>4515 M, 4309 F</td>
<td>40–59</td>
<td>SBP: ( r = 0.13 ) (M); ( r = 0.01 ) (F)</td>
</tr>
<tr>
<td>Moller et al. 1991</td>
<td>439 M</td>
<td>51</td>
<td>SBP: NS in regression analysis</td>
</tr>
<tr>
<td>Lowe et al. 1992</td>
<td>477 M, 438 F</td>
<td>25–64</td>
<td>DBP: ( r = 0.12 ) (M); ( r = 0.14 ) (F)</td>
</tr>
<tr>
<td>Smith et al. 1992</td>
<td>1264 M and F</td>
<td>25–64</td>
<td>DBP: ( r = 0.03 ) (M); ( r = 0.07 ) (F)</td>
</tr>
<tr>
<td>Folsom et al. 1993</td>
<td>1933 M, 2260 F</td>
<td>18–30</td>
<td>SBP: ( r = 0.02 ) (M); ( r = 0.12 ) (F)</td>
</tr>
<tr>
<td>Fowkes et al. 1993</td>
<td>809 M, 783 F</td>
<td>55–74</td>
<td>DBP: ( r = 0.23 ) (M); ( r = 0.17 ) (F)</td>
</tr>
<tr>
<td>Eliasson et al. 1994</td>
<td>776 M, 807 F</td>
<td>25–64</td>
<td>SBP: ( r = 0.22 ) (M); ( r = 0.09 ) (F)</td>
</tr>
<tr>
<td>de Boever et al. 1995</td>
<td>745 M</td>
<td>35–59</td>
<td>DBP: ( r = 0.14 ) (M); ( r = 0.23 ) (F)</td>
</tr>
</tbody>
</table>

Adapted from: Lee AJ. The role of rheological and haemostatic factors in hypertension. J Hum Hypertens 1997; 11:767–76. \( r = \) correlation coefficient.
lar risk may also lower plasma fibrinogen levels.\textsuperscript{62} Nonetheless, whether these measures translate to clinically relevant benefits remain uncertain, as the mediator(s) of the beneficial effects may be due to mechanisms (e.g. endothelial function, lipids, etc.), or combinations of mechanisms, other than the reduction of plasma fibrinogen \textit{per se}. Some of the more important extrinsic influences on plasma fibrinogen levels are discussed below.

**Gender**

The second World Health Organization \textit{ Monitoring Trends and Determinants in Cardiovascular Disease} (MONICA) Augsburg survey found the crude fibrinogen values to be consistently higher in women than in men of all ages, irrespective of pregnancy or the use of oral contraceptives.\textsuperscript{63–67} Plasma fibrinogen levels are higher in women than in men, even after accounting for confounding factors, as observed in the Goteborg MONICA survey.\textsuperscript{7} Furthermore, this pattern was observed even among healthy adolescents in the Florence Teenager Study.\textsuperscript{64} However, occasional studies have failed to demonstrate a significant gender difference in plasma fibrinogen levels between men and women.\textsuperscript{65} It should also be noted that amongst the prospective epidemiological studies, only the Framingham study included women; thus the influence of plasma fibrinogen on cardiovascular risk amongst women still needs to be more strongly established.

**Age**

Plasma concentrations of fibrinogen generally increase with age.\textsuperscript{63,65,68,69} This age-related increase in plasma fibrinogen may be due to a slower rate of disposal of fibrinogen, rather than an increased production rate.\textsuperscript{70}

**Body mass index and body habitus**

Plasma fibrinogen concentration has been positively correlated with body mass index, the waist circumference, the hip circumference and waist-to-hip ratio in both sexes.\textsuperscript{63,69,71} Indeed, plasma fibrinogen level is significantly higher amongst patients with a body mass index of $> 30$ kg/m$^2$, compared to those with body mass index $< 25$ kg/m$^2$,\textsuperscript{72} and rises with higher quartiles of skin fold thickness.\textsuperscript{73} Moreover, weight reduction can reduce plasma fibrinogen. For example, Ditschuneit \textit{et al.}\textsuperscript{71} reported that in patients who were extremely overweight and had high plasma fibrinogen levels, a reduction in weight (mean $\pm$ SEM $20 \pm 3$ kg) correlated with a decrease in plasma fibrinogen levels ($0.33 \pm 0.1$ g/l).

Surgical treatment of morbid obesity may have a long-term beneficial effect on mortality from cardiovascular and thromboembolic disease, as demonstrated by the reduction of the decrease in prothrombotic factors, including fibrinogen.\textsuperscript{74} In a study by Primrose \textit{et al.}\textsuperscript{74} haemostatic and fibrinolytic factors were measured before and again 6 and 12 months after surgery (vertical gastric stapling with or without jejuno-ileal bypass) in 19 patients suffering from morbid obesity. This resulted in a mean decrease in body weight of 64 kg at 12 months, accompanied at 12 months by significant reductions in median concentrations of serum cholesterol (from 5.3 mmol/l to 3.6 mmol/l); factor VII (from 113% of normal to 99%); fibrinogen (from 3.5 g/l to 2.8 g/l); and plasminogen activator inhibitor-1 activity (from 21 IU/ml to 6.3 IU/ml).

**Metabolic syndrome**

‘Metabolic syndrome’ is characterized by the presence of three or more of the following metabolic markers: high-density lipoprotein-cholesterol $< 1.13$ mmol/l; triglycerides $\geq 1.80$ mmol/l; glucose $\geq 5.5$ mmol/l; diastolic blood pressure $\geq 90$ mm Hg. Obesity, poor cardiorespiratory fitness and the metabolic syndrome are all closely linked to each other. Furthermore, these may be related to the development of haemorrheological abnormalities (such as increased fibrinogen) associated with the metabolic syndrome. Plasma fibrinogen increases with a number of components of the metabolic syndrome, independent of major confounders.\textsuperscript{75} The age-adjusted OR for hyperfibrinogenaemia ($\geq 3.47$ g/l) was non-significantly higher at 1.69 (95% CI 0.87–3.27; $p = 0.119$) for subjects with the metabolic syndrome when compared with those with no metabolic abnormalities.\textsuperscript{73}

**Physical exercise**

**Acute exercise**

Changes in the plasma fibrinogen levels have been reported after acute exercise, especially when post-
exercise raw data were corrected for the contraction of plasma volume. However, the results reported from various studies have been conflicting, due to differences in the populations studied, exercise protocols, testing procedures, and the analytical methods used for the assessment of plasma fibrinogen. Moreover, whether exercise-induced blood hypercoagulability in vitro corresponds to in vivo thrombin generation and fibrin formation is unknown.

Acute exercise may cause a rise in plasma fibrinogen levels in patients with some vascular disease states. For example, in patients with chronic AF exercised to exhaustion, plasma fibrinogen rose significantly within 20 minutes with a simultaneous alteration in fibrinolytic activity (i.e., reduced PAI). In another study, in patients with stable chronic heart failure exercised to exhaustion, plasma fibrinogen level increased significantly within 20 minutes. These observations may contribute to the thromboembolic risk associated with these disease states.

**Regular exercise**

Regular exercise over a span of few weeks or months has shown a reduction in plasma fibrinogen levels both in healthy and diseased individuals. In healthy individuals, strenuous exercise over a period of 4 weeks lowers plasma fibrinogen levels, equivalent to a difference of about 15% in the risk of IHD. In one study, a 12-week exercise-training programme in patients with mild hypertension resulted in a significant decrease in plasma fibrinogen and an improvement in overall coronary risk profile. Regular physical exercise may also be beneficial in reducing overall coronary risk profile by decreasing the blood pressure and plasma fibrinogen levels in otherwise healthy individuals; Nevertheless, plasma fibrinogen levels return to baseline values after resumption of sedentary activity.

Furthermore, in the Caerphilly Prospective Heart Disease Study, plasma fibrinogen concentrations were lowered by 0.24 g/l in the third of men who were the most active in leisure activities. Overall, the average decrease achieved by regular endurance exercise over several months was around 0.4 g/l. Men with low level of social activities and activities at home had a higher plasma fibrinogen concentration, when compared to those with high levels of activity.

Therefore, the available evidence would suggest that regular exercise over a period could exert its beneficial influence on cardiovascular events through a beneficial effect on plasma fibrinogen levels.

**Seasonal differences**

Cardiovascular disorders, cerebrovascular disorders, associated risk factors and mortality all show a seasonal variation, with a peak during winter season, especially among the elderly. Correspondingly, plasma fibrinogen levels show a seasonal variation, with the peak in winter, both in normal healthy adults and in patients with cardiovascular disorders. For example, the Rotterdam Study found a seasonal difference of 0.34 g/l (95% CI 0.29–0.39) and the difference was more pronounced in subjects aged 75 years or older. In the latter group, the difference between winter and the summer months ranged as high as 23%.

Seasonal variation in plasma fibrinogen levels with a rise in winter could be due partly to the observed seasonal variations in the known vascular risk factors, and partly to the factors described below.

**Vitamin C and infection**

It has been suggested that a lower dietary intake of vitamin C and/or an increase in upper respiratory infections (with its associated acute phase response) in the winter seasons might be the underlying cause for the raised levels of acute-phase reactants, especially fibrinogen. Furthermore, plasma fibrinogen levels correlate with various markers of respiratory infection, such as neutrophil count, C-reactive protein, self-reported cough and coryza. However, the studies have generally yielded inconsistent results.

An increase in dietary vitamin C of 60 mg/day (contained in approximately one orange) was associated with a decrease in plasma fibrinogen concentrations of 0.15 g/l, equivalent to a decline of approximately 10% in risk of IHD. Nonetheless, it remains to be seen as to whether treatment of the infections results in decrease in plasma fibrinogen levels and whether decreasing the fibrinogen levels results in decreased cardiovascular morbidity and mortality.

Organisms such as *Chlamydia pneumoniae* and *Helicobacter pylori* are implicated in the pathogenesis of coronary artery disease. Fibrinogen may be implicated in the complex interaction of these infectious agents and coronary artery disease. Antibodies to *C. pneumoniae* are significantly increased in patients with stroke and severe essential hypertension, but there was no apparent association between these titres and plasma fibrinogen levels. Fibrinogen is also thought to be an
intermediary in the apparent link between *H. pylori* infection and coronary artery disease but once again, studies have yielded inconsistent results. The recent STAMINA (South Thames Trial of Antibiotics in Myocardial Infarction and Unstable Angina) study showed that although antibiotic treatment failed to reduce plasma fibrinogen levels significantly, it significantly reduced adverse cardiac events in patients with acute coronary syndromes; however, the effect was independent of *H. pylori* or *C. pneumoniae* seropositivity. Furthermore, in a recent meta-analysis of all published prospective studies, *C. pneumoniae* antibody titres were not predictive of CHD in the general population. Therefore, the question of whether these infections increase the cardiovascular risk and if so, whether fibrinogen is an intermediary, is still far from clear.

**Psychosocial factors**

Adult plasma fibrinogen concentration is determined by various factors operating throughout life. The available data suggest that the inverse relation between socio-economic status and coronary artery disease may be partly explained by differences in plasma fibrinogen levels.

In a cross-sectional study of civil servants in London, aged 45–55 years, measures of childhood environment (adult height, father’s social class, and participant’s education) were inversely associated with adult plasma fibrinogen concentration in both sexes. Lower socio-economic status (as shown by employment grade) was also associated with higher plasma fibrinogen concentrations, which were not accounted for by measures of childhood circumstances. Control over work, assessed by personnel managers and self, was also inversely related to plasma fibrinogen levels.

Furthermore, the results of the Stockholm Heart Epidemiology Programme (SHEEP) study suggest that adverse job characteristics might also be related to plasma fibrinogen concentrations, particularly in female workers. Low self reported control over the job, inferred high demand, and inferred job strain were significantly associated with increased plasma fibrinogen concentration.

**Hormonal status**

Both cross sectional and longitudinal studies demonstrate that oral contraceptive (OC) pill use results in a significant rise in plasma fibrinogen levels, an effect that seems to be strongest in OCs with a high oestrogen concentration. Furthermore, there are positive and significant interactions between OC use and smoking in their effects on haemostatic variables, including fibrinogen. Conversely, plasma fibrinogen level returns to normal on discontinuation of the OC pill, usually within about 3 months.

Both the menopausal status and HRT have independent effects on plasma fibrinogen levels. The increases in factor VIIc, fibrinogen, and cholesterol levels with the menopause would increase the risk of fatal IHD in postmenopausal women by about 40%, compared with the risk in premenopausal women of the same age. However, lower plasma viscosity and plasma fibrinogen levels are found in women on HRT (both with oestrogen-progestrone combinations and oestrogen monotherapy). Theoretically therefore, the use of HRT may exert a protective effect by reducing plasma fibrinogen levels.

However, evidence for the influence of menopause and/or HRT on plasma fibrinogen has not been unequivocal. For example, Conard et al. (1997) reported a significant increase in plasma fibrinogen levels with oral oestrogen HRT. Moreover, the only study on the effect of HRT on haemostatic factors following surgical menopause (patients aged 43 ± 6.5 years) did not find any significant difference in the levels of plasma fibrinogen among patients, prior to the surgery and following oopherectomy while taking HRT.

Interestingly, in the Postmenopausal Estrogen/ Progestin Interventions (PEPI) study, which was a three-year, double-blind, placebo-controlled trial of HRT on risk factors in 875 postmenopausal women, a lower baseline plasma fibrinogen level was significantly associated with venous thromboembolic events among subjects who subsequently received HRT.

Many questions relating to the interaction between hormonal status, fibrinogen and cardiovascular disorders remain unanswered. The available data are inconsistent, and vary with regard to populations and type of hormone preparation studied.

**Smoking**

Available evidence suggests that cigarette smoking is strongly associated with increased plasma fibrinogen levels, and the adverse cardiovascular effects of smoking may partly be mediated through an increase in plasma fibrinogen levels. Indeed, each cigarette smoked per day increases mean plasma fibrinogen by 0.35 g/l.

Similar data are available from epidemiological studies. In the Framingham study, plasma fibrinogen values were significantly higher in smokers than in
non-smokers, with a dose-dependent increase with smoking in both sexes; ex-smokers had values as low as those of non-smokers. Over 10 years of follow-up, the risk in both sexes increased progressively in relation to antecedent plasma fibrinogen values over the 1.8–4.5 g/l range. In the second MONICA Augsburg survey, the impact on the population plasma fibrinogen level was most pronounced for age in both sexes, followed closely by body mass index and cigarette smoking. In the MUNSTER Heart Study, smoking-related adverse changes in plasma fibrinogen were of greater magnitude in men than in women. A switch from cigarette to cigar smoking is also associated with a large increase in plasma fibrinogen levels, in keeping with the observation that cigar smokers remain at an increased risk of IHD.

Passive smoking is not free of risk either, and may increase the risk of coronary heart disease partly by increasing plasma fibrinogen concentrations. On average, plasma fibrinogen concentrations were 0.86 g/l higher in women exposed to cigarette smoke outside the home and 1.12 g/l higher in women exposed both in and outside the home, when compared to women unexposed in either location. These effects of passive smoking were about 40–60% of that of current active smoking. Furthermore, smoking could have an acute effect on plasma fibrinogen levels. For example, post-MI patients who smoked within the previous 24 h had significantly higher plasma fibrinogen levels than patients who refrained from smoking for 24 h.

How does smoking alter plasma fibrinogen levels? Smoking results in an inflammatory reaction, probably of the pulmonary bronchi and alveoli and the blood vessels of the lung parenchyma, as evidenced by an increase in the levels of C-reactive protein. The resulting inflammation may increase the production of the cytokines, such as interleukin-6, which have major roles in the regulation of synthesis in the liver of acute-phase proteins, including fibrinogen. Thus increased plasma fibrinogen levels in smokers may reflect a chronic inflammatory state of the vascular wall, and may act as an intermediary in the enhanced coronary risk among smokers.

Smoking potentiates thrombosis at the dysfunctional endothelium, at least partly by increasing the concentration of plasma fibrinogen and altering the activity of platelets. All these pro-atherogenic effects of smoking to injure the endothelium are also observed, albeit to lesser extent, in passive smokers.

Alcohol

Moderate drinking appears to lower plasma fibrinogen concentrations. The so-called ‘French paradox’ may be at least partly explained in relation to the effects of alcohol on clotting factors. For example, in the DESIR Study (Data from an Epidemiological Study on the Insulin Resistance syndrome) of 4967 men and women aged 30–64 years, alcohol consumption was associated with plasma fibrinogen levels, with higher concentrations in those who were non-drinkers or who drank > 60 g of alcohol per day. This U-shaped association was stronger amongst men than women. Consumption of wine and spirits was also associated with changes in plasma fibrinogen levels, whereas consumption of beer or cider was not. In women, for example, 1 g of alcohol per day induces a 0.008 g/l decrease in the mean plasma fibrinogen, while in men the decrease was 0.004 g/l within the down slope of the U-shaped curve.

These findings are further supported by other studies. For example, a U-shaped relation between alcohol consumption and plasma fibrinogen levels was also found in the second MONICA Augsburg survey (1989–1990), especially amongst men. In the Scottish Heart Health Study, plasma fibrinogen was negatively associated with alcohol consumption in both sexes. Nevertheless, as with other factors, there have been occasional reports of failure to correlate alcohol with plasma fibrinogen, as in the Munster Arteriosclerosis Study (MAS).

The precise mechanisms by which alcohol influences plasma fibrinogen levels remain uncertain. Animal experiments have suggested that alcohol exerts its effects through the action on the genetic expression of plasma fibrinogen in the liver cells. On the other hand, alcohol can also result in high blood pressure and atrial fibrillation (AF), which are conditions associated with high plasma fibrinogen levels.

Fibrinogen: cause or effect?

As discussed above, epidemiological studies have established that elevated plasma fibrinogen levels are an independent and modifiable risk factor for coronary heart disease. Nonetheless, in patients with established vascular disease, the strength of the causal relationship needs to be addressed by relating plasma fibrinogen levels to disease severity, prognosis and treatments for the condition, as well as considering whether the pathophysiological mechanisms make this relationship plausible.
The clinical scenario

The concentration of plasma fibrinogen positively correlated with the severity of the underlying coronary heart disease in some studies.\textsuperscript{131–133} Plasma fibrinogen levels are higher in patients with unstable angina than in patients with stable angina, and higher in patients with severe vasospastic angina than in those with mild vasospastic angina and stable effort angina.\textsuperscript{133, 134} Nevertheless, a more recent study by Hoffmeister et al. failed to demonstrate a relationship between plasma fibrinogen levels and the severity of IHD in any of the three systems used to score the severity.\textsuperscript{135}

Furthermore, raised plasma fibrinogen levels have prognostic implications, being a strong predictor of coronary heart disease, fatal or non-fatal, new or recurrent, and of death from an unspecified cause, for both men and women,\textsuperscript{136–138} and therefore, a predictor of accelerated coronary atherosclerosis. Furthermore, the beneficial effect of statins and fibrates in reducing coronary artery diseases events and mortality cannot entirely be explained by their beneficial effect on lipids. In addition to lipid lowering, the modification of thrombus formation and degradation, alteration in inflammatory response, plaque stabilization and improved endothelial function are thought to be responsible for additional reduction of morbidity and mortality due to cardiovascular events.\textsuperscript{139} Nonetheless, as explained below, although statins appear to improve thrombogenicity and endothelial dependent vasoresponsiveness, there is lack of convincing evidence of a reduction in plasma fibrinogen levels with statins, in contrast to the fibrates. For example, in the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT), the beneficial effect of bezafibrate on coronary events in young male survivors of MI, was attributed partly to the reduction in plasma fibrinogen levels, in addition to the beneficial effect on plasma lipid profile.\textsuperscript{140}

Fibrinogen is also associated with other well-known risk factors for cardiovascular disease, such as smoking, age, obesity, hypertension and diabetes.\textsuperscript{141} Elevation of plasma fibrinogen levels may therefore provide a mechanism for the risk factors to exert their effect. Certainly, the positive association between plasma fibrinogen levels and cardiovascular events is as strong as that for elevated cholesterol levels.\textsuperscript{142} Higher levels of plasma fibrinogen markedly increase the predictive power of high serum LDL cholesterol; conversely, low plasma fibrinogen levels are associated with low coronary risk, even when LDL is raised.\textsuperscript{143} Interestingly, plasma fibrinogen levels are also raised in people with family history of premature heart disease.\textsuperscript{126} Therefore, modification of cardiovascular risk factors may result in beneficial reduction of plasma fibrinogen levels and better cardiovascular outcome.

Fibrinogen as an acute-phase reactant

Plasma fibrinogen is an acute-phase protein, and is therefore likely to increase with inflammation or tissue necrosis. Interpretation of raised fibrinogen may be complicated by its behavior as an acute-phase reactant. For example, plasma fibrinogen concentrations are raised after acute stroke\textsuperscript{144} and acute MI,\textsuperscript{145} probably as an acute phase response. Nevertheless, measurement of plasma fibrinogen levels could potentially be more useful than those of other acute phase reactants such as C-reactive protein, as fibrinogen is probably more specific to vascular disease.

However, plasma fibrinogen strongly predicts cardiovascular events in patients with established atherosclerotic vascular disorders. Furthermore, it is raised even before the onset of acute stroke and acute MI in patients with transient ischaemic attack\textsuperscript{146, 147} and chronic stable angina pectoris,\textsuperscript{148} respectively. Therefore, though plasma fibrinogen is raised in the context of acute cerebrovascular and cardiovascular events, chronically raised plasma fibrinogen appears to be an independent risk factor for these events.

Genetic variation in plasma fibrinogen—a causal relationship?

Genetic variation in the fibrinogen gene may have implications in prognosis of patients with vascular disorders.\textsuperscript{149} For example, the data from the Edinburgh Artery Study provide evidence that a polymorphism of the P fibrinogen gene is associated with a varying risk of peripheral atherosclerosis: the −455AA genotype was associated with over twice the risk of PAD, compared with the −455GG genotype.\textsuperscript{150}

Furthermore, in subjects with AF, Thr312Ala polymorphism gives rise to an increased susceptibility for embolization of intra-atrial clot,\textsuperscript{149} and there was decreased survival in those possessing the A allele following stroke.\textsuperscript{149} Similarly, in some patients with deep venous thrombosis, variations in the fibrinogen genotype could predispose to the embolization of formed fibrin clot, resulting in pulmonary embolism.\textsuperscript{151}

It is important to appreciate that although several studies demonstrate a strong association between polymorphisms of the fibrinogen β-chain gene and plasma fibrinogen concentration, only a few have found a direct association between the former and
the risk of ischaemic heart disease. A substantial number of studies failed to find an association between polymorphisms in the fibrinogen gene and cardiovascular risk. For example, van der Bom et al. found that the −455G/A polymorphism was associated with increased plasma fibrinogen levels, but not with an increased risk for MI. These findings indicate that an increased plasma fibrinogen level due to this genetic factor may not increase the risk for MI. Similarly, Doggen et al. found that the TaqI, HaeIII and BclI polymorphisms in the fibrinogen gene were not associated with MI.

Therefore, many questions remain unanswered. Does a particular genetic polymorphism predispose to atherosclerotic disease? And if it does, is it mediated through raised fibrinogen or some associated mechanism? Some studies conducted on twins suggest that the environment, rather than genetic influences could have a greater influence on plasma fibrinogen levels.  

Conclusions

A definite association exists between fibrinogen and atherothrombogenesis. However, the nature of the link is unclear. Although epidemiological and clinical studies suggest that the link is causal, no definite evidence exists. Furthermore, plasma fibrinogen concentration is positively correlated with nearly all other cardiovascular risk factors, and may be a common mechanism by which these risk factors predispose to cardiovascular events. It appears that fibrinogen concentration and plasma viscosity are at least as predictive of coronary events as are cholesterol concentration, diastolic blood pressure and body mass index.

Encouragingly, plasma fibrinogen is partly a modifiable risk factor, and suitable lifestyle changes usually result in favourable decreases in plasma fibrinogen levels, although drug therapy has not been fully validated.

The relationship between genetic polymorphism in the fibrinogen gene and cardiovascular risk is very complex. Although polymorphisms in the fibrinogen gene could potentially augment the cardiovascular risk through increased fibrinogen levels, the effect appears to be antagonized by some unknown mechanism due to the same polymorphism. Therefore, polymorphisms of fibrinogen gene may modify the effect of external influences on the final phenotype (i.e. the vascular risk) rather than directly affecting the risk of the disease through plasma fibrinogen levels. In future, gene-environment interactions should be considered in evaluating the relevance of genetic variations on the risk of cardiovascular disease.

Future directions require determination of the ‘critically elevated’ fibrinogen threshold value, development of drugs that would specifically and safely decrease plasma fibrinogen levels and conduction of interventional trials to study the influence of lowering fibrinogen levels on overall cardiovascular risk profile. Meanwhile, plasma fibrinogen levels could potentially be considered for screening programmes to identify people at high risk of vascular events, and attempts should be made to strengthen the treatment of other risk factors in these patient groups.

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References


