Fibrinogen: An Important Risk Factor for Atherothrombotic Diseases

E. Ernst

Epidemiological follow-up studies have suggested that fibrinogen is a major, primary cardiovascular risk factor. Cross-sectional results also show associations between fibrinogen and cardiovascular risk factors or diseases. Clinical cohort studies demonstrate that fibrinogen might also be a secondary risk factor. The determinants of the plasma level of fibrinogen in health and disease are known only incompletely. Our understanding of the mechanisms involved in the atherogenic actions of fibrinogen is similarly fragmentary. These might include blood coagulation, blood rheology, platelet aggregation, direct effects on the vascular wall, and the acute phase response. Thus, many questions are yet to be answered. Nevertheless, the data available at present strongly suggest that fibrinogen represents a major, independent cardiovascular risk factor. Fibrinogen should be considered for screening programmes aimed at identifying individuals at risk.

Key words: fibrinogen; atherothrombosis; risk factors; coagulation; haemorheology; myocardial infarction; stroke.

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Introduction

Research over the last four decades has identified several important predictors of atherothrombotic events. Knowledge of these now 'accepted' risk factors is widespread and its application to clinical practice may have prompted a considerable reduction of cardiovascular mortality and morbidity, particularly in the U.S. It is tempting, therefore, to forget that our understanding is still incomplete. Only about 30% of all cardiovascular events can be extrapolated on the basis of 'accepted' risk factors (1). It would seem to follow that additional ones exist. Fibrinogen has been proposed as a potential candidate (2).

Human fibrinogen is a long protein of 340,000 daltons molecular mass which is synthesized predominantly in the liver. It consists of three different polypeptide chains. 80-90% of the body's fibrinogen is found in the blood plasma. Normal plasma levels range from 2 to 4.5 g/l; the molecule's half-life is 3-6 days. Fibrinogen synthesis is believed to be under the feedback control of its plasma degradation products and cytokines produced by activated macrophages.

Fibrinogen is an acute phase protein, a clotting factor and has numerous other functions (3): co-factor for platelet aggregation, determinant of the rheological behaviour of blood, and stimulant of smooth muscle cell migration and proliferation. This review is aimed at summarizing the data to suggest that fibrinogen represents a major risk factor for atherothrombotic diseases.

Epidemiological Evidence

Prospective Analyses

Early clinical studies stimulated epidemiological investigations of the possibility of a link between fibrinogen and cardiovascular pathology. The first such investigation was the Northwick Park Heart Study from the U.K.: 1510 white men aged 40–64 years were randomly recruited and tested for a range of clotting factors, including fibrinogen. At 4 years' follow-up, 49 individuals had died, 27 from cardiovascular diseases (4). There was a significant association between cardiovascular deaths and fibrinogen, which was independent of other risk factors and stronger than the association for total cholesterol.

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Other causes of death were not related to fibrinogen levels. Fifteen of the 25 patients who died of ischaemic heart disease belonged to the high tertile of fibrinogen (<3.2 g/l). At 10 years' follow-up (5), 109 men had suffered a first coronary event. Multiple regression analyses showed an association between fibrinogen and ischaemic heart disease, which was again independent of other risk factors. Approximately half of all the incident coronary events occurred in the high tertile of fibrinogen.

About 2000 men aged 45-64 years were recruited for the Speedwell Study (6). Baseline fibrinogen was positively associated with prevalent ischaemic heart disease. The study was later expanded into the Caerphilly/Speedwell Study, involving more than 4700 men (7). Its baseline data revealed a significant association of smoking with fibrinogen. (In fact virtually all studies have confirmed this inter-relationship. The effect of smoking is considered in more detail below). The prospective evaluation of the Speedwell/Caerphilly Study with an average follow-up of 5.1 and 3.2 years, respectively, included a total of 251 major coronary events (8). A multivariate analysis demonstrated that fibrinogen was an independent risk factor for ischaemic heart disease. Its predictive power was comparable to, if not stronger than that of accepted coronary risk factors like total cholesterol, blood pressure or body mass index.

In the Gothenburg Study, fibrinogen, blood pressure, total cholesterol, and smoking habits were quantified in a random sample of 792 men all of them born in 1913 (9). After a mean follow-up period of 13.5 years, there were 92 cases of myocardial infarction, 37 strokes, and 60 deaths from non-cardiovascular causes. Univariate analyses identified smoking, cholesterol, and fibrinogen as risk factors for myocardial infarction, while blood pressure and fibrinogen were risk factors for stroke. In a multivariate analysis the association between fibrinogen and cardiovascular events weakened, but was still statistically significant for stroke. The study was recently extended to a 21 years' follow-up, where 119 myocardial infarctions, 81 strokes and 333 deaths of other causes had occurred (10). Again fibrinogen was positively associated to the coronary heart disease incidence in the univariate analysis, while in the multivariate evaluation stroke and total mortality were significantly associated with fibrinogen.

In a much smaller prospective study 297 men aged 40-69 years and initially free of coronary heart disease, were recruited from one general practice in the U.K. (11). After a mean follow-up period of 7.3 years, 40 cases of heart infarction had been registered. Fibrinogen was positively correlated with its incidence. In hypertensive patients the incidence was six times higher when fibrinogen levels exceeded 3.5 g/l compared to the subpopulation with values below this threshold. Multivariate analyses showed that the predictive power of all variables in descending order were: fibrinogen, age, systolic blood pressure, total cholesterol, obesity, number of cigarettes smoked per day, VLDL.

The tenth biennial examination of the Framingham Study analysed the inter-relation of fibrinogen with smoking in detail. It confirmed a dose-dependent increase in fibrinogen with smoking (12). During a 14 years follow-up period, the risk of cardiovascular disease in men and women increased as a function of initial fibrinogen levels. The age-adjusted incidence in male smokers with high fibrinogen levels was doubled compared to a low-fibrinogen subgroup. As in the Northwick Park Heart Study (4, 5), the effect was more pronounced in younger males. Using the same data, fibrinogen was demonstrated to be a risk factor for coronary heart disease independent of smoking or other accepted factors (13). In women, the magnitude of the fibrinogen-mediated risk declined with age. Fibrinogen was also a risk factor for stroke in men, but not in women. The relative impact of fibrinogen was comparable to those of blood pressure, obesity, smoking and diabetes. A more recent analysis of the Framingham material (14) revealed that in men the fibrinogen risk ratio was greatest for stroke and smallest for peripheral arterial disease. For women the risk ratio was greatest for coronary heart disease.

The PROCAM Study (15) examined 1674 men aged 40-65 years without a history of myocardial infarction or stroke. Fifteen cardiovascular events were observed during 2 years of follow-up. Ten of these fell into the high fibrinogen tertile. When this trial was extended to 2817 men, also followed for 2 years, 55 coronary events had occurred. Twenty-nine were in the upper fibrinogen tertile, while 10 were in the lowest (16).

The Finnish KIHD Study also included fibrinogen (17) in its 3 years' follow-up. At this point 51 myocardial infarctions had been registered. Baseline fibrinogen differed only numerically but not significantly in the event and non-event populations. The relative hazard for fibrinogen was 1.48. This analysis was aimed at factors other than fibrinogen, and only one single cut-off value was used.

The above data are highly suggestive but also show some weaknesses. For instance, most of the above studies either do not consider LDL-cholesterol in their multivariate models or quantify this variable by inadequate methods. As LDL-cholesterol is one of the strongest predictors of coronary heart disease known to date, previous results might have over-estimated the predictive power of fibrinogen. The GRIPS Study (18), a prospective cohort study of 5239 men aged 40-60 years initially free of cardiovascular disease, overcame this drawback. 107 myocardial infarctions had occurred after 5 years of follow-up. Fibrinogen was a strong predictor in an univariate model. Its average level (±SD) was 3.6±0.8 g/l in the non-event and 4.2±1.0 g/l in the event group. Using a multivariate regression model, which accounted for LDL-cholesterol, the relationship weakened, yet remained statistically significant. In the final model the rank order of predictors was as follows: LDL-cholesterol, familial disposition, Lp(a), HDL-cholesterol, fibrinogen, age, smoking, glucose and blood pressure.

These prospective studies are summarized in Table 1. In this summary the Leigh and the KIHD Studies have been excluded: the former because the sample was not representative of the general population; the latter because its analysis of fibrinogen was too rough to yield interpretable results. It can be seen that in spite of con-
Fibrinogen and Atherothrombotic Diseases

Table 1. Descriptive data on epidemiological follow-up studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>n</th>
<th>Mean follow-up (years)</th>
<th>Patient years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northwick Park</td>
<td>1511</td>
<td>105</td>
<td>10</td>
<td>15,110</td>
</tr>
<tr>
<td>Gothenburg</td>
<td>792</td>
<td>113</td>
<td>13.5</td>
<td>10,692</td>
</tr>
<tr>
<td>Framingham</td>
<td>1315</td>
<td>202</td>
<td>12</td>
<td>15,780</td>
</tr>
<tr>
<td>Caerphilly/Speedwell</td>
<td>4860</td>
<td>231</td>
<td>4.2</td>
<td>20,325</td>
</tr>
<tr>
<td>PROCAM</td>
<td>1674</td>
<td>15</td>
<td>2.4</td>
<td>4045</td>
</tr>
<tr>
<td>GRIPS</td>
<td>5239</td>
<td>107</td>
<td>5</td>
<td>26,195</td>
</tr>
<tr>
<td>Total</td>
<td>15,391</td>
<td>773</td>
<td>6.0</td>
<td>92,147</td>
</tr>
</tbody>
</table>

N = individuals included. n = number of events during follow-up.

Table 2. Results from a meta-analysis.

<table>
<thead>
<tr>
<th>Events/1000/year</th>
<th>Overall odds-ratio (95% conf. interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L, M, H</td>
<td>2.3</td>
</tr>
<tr>
<td>5.5, 7.2, 12.4</td>
<td>(1.9-2.8)</td>
</tr>
</tbody>
</table>

All studies from Table 1 have been expressed as tertiles (low = L, medium = M, high = H). Odds ratios have been calculated comparing L with H and averaged.

Cross-Sectional Analyses

According to one MONICA study centre (20), fibrinogen was increased in male and female smokers. Blood viscosity (strongly influenced by fibrinogen) was closely correlated with 'accepted' risk factors. In another centre (21) plasma viscosity was raised in males with hypercholesterolaemia, untreated hypertension or in smokers, as well as in females with hypercholesterolaemia or obesity. In the Scottish Heart Health Study, 8824 men and women were examined. Women had higher fibrinogen levels than men (22). Fibrinogen was positively associated with age, smoking, cholesterol and body mass index and negatively linked to alcohol consumption. Female menopause also coincided with higher fibrinogen levels. A Danish study (23) of 439 men aged 51, showed positive associations of fibrinogen with low social class, physiological variables, smoking, physical inactivity, low HDL-cholesterol, low physical fitness and high LDL-cholesterol. The baseline data from the Caerphilly Study (24) demonstrated that leisure physical activity is associated with lower fibrinogen levels (0.3 g/l on average). This effect was extrapolated to amount to as much as 8% of reduction in ischaemic heart disease.

The largest (n = 15803) epidemiological study to include fibrinogen is the ARIC Study (25). Its baseline data showed fibrinogen to be 0.22 g/l higher in blacks compared with whites. It also confirmed higher values in women compared to men. Fibrinogen was furthermore increased with age, smoking, body size, diabetes, fasting serum insulin, LDL, Lp(a), total leucocyte count and menopause. It was decreased with ethanol intake, exercise, HDL and postmenopausal female hormone use.

These epidemiological studies are of adequate sample size (several thousand participants and several hundred major cardiovascular events) and sample composition (several random samples of the population, different genetic, occupational, social and geographical backgrounds). Thus, they leave little doubt as to a strong link between fibrinogen and atherothrombotic diseases and demonstrate that fibrinogen is an important, independent risk factor. Its relative impact is roughly as strong as that of total cholesterol or other 'accepted' risk factors. Fibrinogen is also related to most other risk factors. Table 3 summarizes the most important inter-relationships. Theoretically, these inter-relationships could suggest that its relation to atherothrombotic end-points is indirect, merely caused by associations with true risk factors. This line of thought is, however, largely invalidated by the fact that most of the above studies did consider such 'confounders' and fibrinogen remained of significant predictive value. Therefore, the cumulative data suggest that fibrinogen represents one mechanism by which various other risk factors lead to atherothrombotic events.

Clinical Evidence

Clinical studies to include fibrinogen are numerous. Only some recent and important findings with an emphasis on prospective data are selected for this review.

Table 3. The most important determinants of fibrinogen levels.

<table>
<thead>
<tr>
<th>Factors to increase fibrinogen</th>
<th>Factors to decrease fibrinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>Regular alcohol consumption</td>
</tr>
<tr>
<td>Age</td>
<td>Regular exercise</td>
</tr>
<tr>
<td>Black race</td>
<td>Weight reduction</td>
</tr>
<tr>
<td>Female sex</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Menopause</td>
<td>Fish consumption</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Female hormone use</td>
</tr>
<tr>
<td>Being overweight</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
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<tr>
<td>Arterial hypertension</td>
<td></td>
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<tr>
<td>Hyperlipoproteinemia</td>
<td></td>
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<tr>
<td>Physical inactivity</td>
<td></td>
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<tr>
<td>Stress</td>
<td></td>
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<tr>
<td>Inflammatory processes</td>
<td></td>
</tr>
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</table>

*Controversial.
Coronary Heart Disease

It has long been appreciated that an acute myocardial infarction leads to transient hyperfibrinogenemia (review (26)). Fibrinogen increases progressively with the severity of coronary atherosclerosis (27–29). This can be interpreted in terms of an acute phase response, yet fibrinogen (or plasma viscosity) remains high for years following an infarction (30). A prospective study investigated fibrinogen levels in 120 survivors of a myocardial infarction (31). Re-infarction exclusively occurred in cases where the initial fibrinogen level exceeded 0.75 g/l during the acute phase of the disease. In a prospective study, 1716 men were observed for 2 years who had suffered a myocardial infarction 6 months before (32). During this period 126 had suffered a second ischaemic event. Fibrinogen was significantly elevated in this subgroup. Statistically significant differences in fibrinogen also existed between patients who survived and those who died. The relative odds for death showed an approximately linear relationship with fibrinogen level. A more recent analysis of this data showed that smoking cessation had a positive influence on these patients' survival, an effect that appeared to be mediated by fibrinogen levels (33).

Stroke

Fibrinogen levels increase after an acute stroke (34). This has also been attributed to an acute phase reaction subsequent to brain tissue necrosis. However, plasma viscosity is significantly increased in TIA patients, suggesting that fibrinogen levels are elevated before the stroke (35, 36). In a prospective study of stroke survivors, fibrinogen was significantly higher in patients who suffered a second cardiovascular event during the subsequent 2 years (Table 4). The effect was independent of concomitant risk factors (37). These results are in accordance with data showing that patients with a progression of carotid artery lesions had significantly higher fibrinogen levels compared to those with non-progressing lesions in the angiogram (38).

Peripheral Arterial Disease

In peripheral arterial occlusive disease (PAOD), fibrinogen is significantly increased (39, 40). In claudicants fibrinogen is often highly abnormal in the absence of gross angiographic narrowing of the arteries, a finding that led to the concept of 'rheologic claudication' (40). Longitudinal data of PAOD patients showed that high fibrinogen was a predictor for re-occlusion of femoropopliteal vein grafts (41). Recently it was demonstrated that PAOD patients have a high incidence of variation of the beta-fibrinogen locus leading to elevated plasma levels (42).

Unspecified Mortality

Fibrinogen was measured in 142 geriatric patients and related to subsequent cardiovascular deaths (43). The patients were divided into individuals with fibrinogen levels lower or higher than 4.5 g/l. In the low-fibrinogen subgroup, 72% of individuals survived for more than 1 month and 68% survived for more than 1 year. In the high-fibrinogen group, these figures were 52% and 28%, respectively.

These clinical findings suggest that fibrinogen is elevated in overt atherothrombotic diseases. This might well be interpreted in terms of a haematological stress syndrome (40). Longitudinal data identify fibrinogen as a valuable prognostic indicator in several clinical situations. Thus, one might suspect that it also represents a risk factor for the sequelae of cardiovascular disease. This hypothesis, however, requires further testing.

Even though these cumulative clinical and epidemiological results are consistent, there are several problems with their interpretation. 'Normal' values for fibrinogen are poorly researched at present. Most authors consider them to range from 2 to 4.5 g/l. The normal range might need to be redefined in the light of the above new data. The average values of the 'at-risk-individuals' in the above trials are within this range. Clearly, it is also not possible to give a true normal range when no universally accepted method for the measurement exists. It is well known that absolute readings vary according to the technique of measurement (44). However, as long as one centre adheres to one method and employs adequate quality control, this problem cannot be conceived to have influenced the above findings. Nevertheless, standardization of measurement is an urgent task for the future.

Another problem could be a considerable degree of seasonal variation reported recently (45). Others (46, 47) have not confirmed this phenomenon, but nonetheless short- and long-term dependency should be considered in more detail.

Table 4. Results from a 2 years follow-up study on stroke survivors.

<table>
<thead>
<tr>
<th>Parameter (dimension)</th>
<th>Matched pairs for CVRF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Re-event*</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>4.0 (3.6–4.3)</td>
</tr>
<tr>
<td>Plasma viscosity (mPaxs)</td>
<td>1.33 (1.30–1.36)</td>
</tr>
<tr>
<td>Blood viscosity (mPaxs)†</td>
<td>36.5 (34.2–36.8)</td>
</tr>
</tbody>
</table>

CVRF = cardiovascular risk factors.
*Data presented as means and 95% confidence intervals.
†Measured at 0.7 s/l and standardized for haematocrit of 0.45 (l/l).
Determinants of the Fibrinogen Plasma Level

Associations With Other Risk Factors
A genetic determination of fibrinogen levels seems to exist (48, 49). However, it does not fully account for its large physiological variability. Some reports have demonstrated that fibrinogen levels increase with age (50–52). Others have suggested that fibrinogens (or plasma viscosity) are not age-dependent (53). This apparent contradiction may be due to confounding by disease status: in elderly subjects there is a relatively higher prevalence of unrecognized diseases associated with elevated fibrinogen, causing spuriously high mean values. If strict criteria for health are applied, individuals with hidden diseases are excluded and the age-dependence disappears (53).

Fibrinogen levels are elevated in patients with type II hyperlipoproteinaemia (54), familial hypercholesterolaemia (55), and with hypertriglyceridaemia (56). In a large population sample, plasma viscosity correlated positively with total cholesterol and apoprotein B (57). The baseline data from the GRIPS Study (18) showed that fibrinogen levels are associated positively with total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol but not with Lp(a).

Smoking is known to increase fibrinogen levels in healthy individuals (see above). The effect is dose-related (58) and reversible upon cessation of smoking (59). There is a significant correlation between fibrinogen and carboxy haemoglobin levels (60). Plasma viscosity was found to be raised in male but not in female smokers (61). Therefore, the relation between fibrinogen and smoking has to be carefully considered when interpreting the CVD incidence data, and most studies did this using multivariate logistic regression analyses. The most detailed analysis of the inter-relation of fibrinogen with smoking and CVD is probably the one from Framingham (12–14). It estimated that 50% of the cardiovascular harm done by chronic smoking is mediated through its effect of rising fibrinogen. This fascinating hypothesis seems worthy of further investigation.

In patients with essential hypertension, fibrinogen levels are higher than in normotensive controls (62). Similarly, plasma viscosity is elevated in hypertensive subjects, and blood pressure readings are positively correlated with plasma viscosity (63). Even when hypertension is only mild, patients have higher fibrinogen levels than normotensive controls (64).

Fibrinogen is raised in diabetes (65). Patients with microvascular involvement have higher fibrinogen levels than diabetics free from such complications. The Framingham data revealed a correlation between blood sugar levels and fibrinogen (66). Fasting glucose correlates with fibrinogen even in normal individuals (21). In diabetics with albuminuria, fibrinogen is higher than in diabetics without this complication (67) and fibrinogen has been shown to be an independent predictor of vascular complications in type II diabetes (68).

Fibrinogen is also raised in obese individuals and increases with skin fold thickness (69). The normalization of overweight is associated with a reduction in fibrinogen levels (70).

Dietary Influences
Diets low in fat and rich in carbohydrates, lower fibrinogen slightly (71). Diets containing large amounts of n-3 and n-6 polyunsaturated fatty acids may reduce fibrinogen if taken for long periods of time (72–74), so apparently does moderate alcohol intake (16).

Other Influences
Fibrinogen is related to social class (75), which has in part been attributed to different levels of emotional stress (76, 77). Several controlled trials have shown that fibrinogen levels increase in women taking oral contraceptives (78). Recently it has been demonstrated that fibrinogen is lowered in adults who have had low infant weight (79). It also has been demonstrated to be higher in individuals with poor dental health (80).

The long list of determinants in Table 3 confirms the above epidemiological results to a large extent. It seems obvious that we have to elucidate the pathophysiological mechanisms behind these associations in much more detail in order to better comprehend the control of fibrinogen synthesis in health and disease.

Pathophysiological Mechanisms
The mechanism(s) by which fibrinogen may promote atherothrombosis are still not fully understood. Fibrinogen strongly affects haemostasis, blood rheology, platelet aggregation and endothelial function. A hypercoagulable state would seem to favour the thrombotic aspects of atherothrombosis. This could well be fibrinogen's most important role: it certainly is the most obvious. Fibrinogen represents the major determinant of plasma viscosity and induces reversible red cell aggregation. Both phenomena significantly limit blood's fluidity. Blood rheology might act at various levels, by reducing flow, by predisposing to thrombosis, or by enhancing atherogenesis (2, 76).

Platelet hyperaggregation plays an accepted role in the genesis of an atherosclerotic lesion. Fibrinogen binds to receptors on the platelet membrane which, in turn, is a precondition for aggregation in vivo (81). Furthermore, fibrinogen is also integrated directly into arteriosclerotic vascular lesions where it is converted to fibrin and fibrinogen degradation products; it binds low-density lipoproteins and sequesters more fibrinogen. Both fibrinogen and fibrinogen degradation products have been demonstrated to stimulate smooth muscle proliferation and migration (82, 83). By these effects it seems to be involved in the early stages of plaque formation.

The fact that fibrinogen is an acute phase reactant also deserves consideration. Atherosclerosis bears similarities to an inflammatory process (84). For instance, white cell counts are significantly elevated in the presence of active atherosclerosis (25). Thus, it is
Ann Med 26

Ann exist. 

In the above clinical and epidemiological findings are the result of complex interactions between these and possibly other mechanisms which we still need to understand more completely.

Can Fibrinogen Be Lowered Pharmacologically?

The final test for the hypothesis that fibrinogen is a cardiovascular risk factor would be a randomized trial to therapeutically lower it in patients and determine the subsequent atherothrombotic events. An essential pre-condition for doing so would be the availability of a drug which reduces fibrinogen levels both safely and selectively. Regrettably no such substance is known to date. The list of medications that have been shown to decrease fibrinogen in various clinical settings is sizeable (Table 5). All of these are known primarily for other pharmacological actions on the cardiovascular system. Fibrates are a good example: they have been reported to induce relatively large fibrinogen reductions (up to 44%). Yet, fibrates primarily reduce blood lipids which makes them unsuitable for a trial of the independent fibrinogen effect. Thus, the value of reducing fibrinogen in an attempt to reduce the cardiovascular risk is unknown (88), and the ultimate test for the validity of the above hypothesis is hardly feasible and may remain so for quite some time.

Conclusions

A link between fibrinogen and atherothrombotic diseases is indisputable and plausible. Prospective trials indicate that a plasma fibrinogen level in excess of around 3.5 g/l is a powerful, independent risk factor for brain and/or heart infarction. Clinical findings suggest that fibrinogen may also be a secondary risk factor. At present some, but probably not all determinants of the fibrinogen level in health and disease are known. The time appears to be right to test the hypothesis of fibrinogen as a cardiovascular risk factor by intervention trials, yet the ideal drug to lower fibrinogen alone has not been found. Future research of atheriothrombotic diseases should consider fibrinogen and attempt to solve the long list of open questions.

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