Fibrinogen: A New Major Risk Factor for Cardiovascular Disease

A Review of the Literature

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During the last decade, several epidemiological studies have reliably demonstrated that plasma fibrinogen is a strong and independent risk factor for cardiovascular disease that is at least as important as more traditional risk factors for the disease. The deleterious effects of this protein seem to be mediated through its role in hemorrheology, hemostasis, and the atherogenic process itself. According to prospective epidemiological studies, the risk of developing a cardiovascular event such as ischemic heart disease 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. Epidemiological studies, clinical trials, pathophysiology, and therapeutical possibilities are reviewed in this paper.

Key words. Fibrinogen; cardiovascular diseases; stroke; coronary disease; drug therapy. (*J Fam Pract 1994; 39:468-477*)

Cardiovascular disease (CVD) is the major cause of mortality in developed countries. Decades ago, several conditions were identified as cardiovascular risk factors in epidemiological studies: sex, age, high cholesterol level, cigarette smoking, high blood pressure, and glucose intolerance. On an individual basis, however, these traditional risk factors proved to be poor predictors of the likelihood of CVD.[1] There may have been other risk factors that had not yet been identified: there was reason to suspect that clotting factors were involved in the development of CVD.

In 1953, the medical and scientific community was shocked by a report on the autopsies performed on United States soldiers killed in action in Korea.[2] The report revealed that 42% of those soldiers had luminal coronary atherosclerotic narrowing ranging between 10% and 100% despite their average age of 22.1 years. Three percent had plaques causing complete occlusion of one or more coronary vessels, yet all of them were asymptomatic. This study showed that the slow progression of atherosclerotic plaques could completely occlude coronary lumen without leading to angina or death because of the gradual development of compensatory collateral blood flow. Conversely, it was found that in most autopsies on patients who died of myocardial infarction (MI), thrombi were responsible for abrupt arterial occlusion on a disrupted middle-sized plaque.[3-5] Fibrinogen and its derivatives were present in the plaque itself, fibrin being a main component.[6-8]

New epidemiological studies that included hematologic variables were designed. Some early studies, such as the Framingham Study, added fibrinogen later because it was recognized as a potential factor in the development of CVD.[9,10] The role of fibrinogen in the development of CVD has been fully confirmed by the results of all relevant studies conducted during the last 10 years[9-15]: the level of plasma fibrinogen is an independent, major risk factor for CVD with at least as great a predictive value as traditional risk factors.

Epidemiological Prospective Studies

Göteborg Study

In the Göteborg Study,[11] a random sample of 792 men, aged 54 years at recruitment, were followed during a 13.5-

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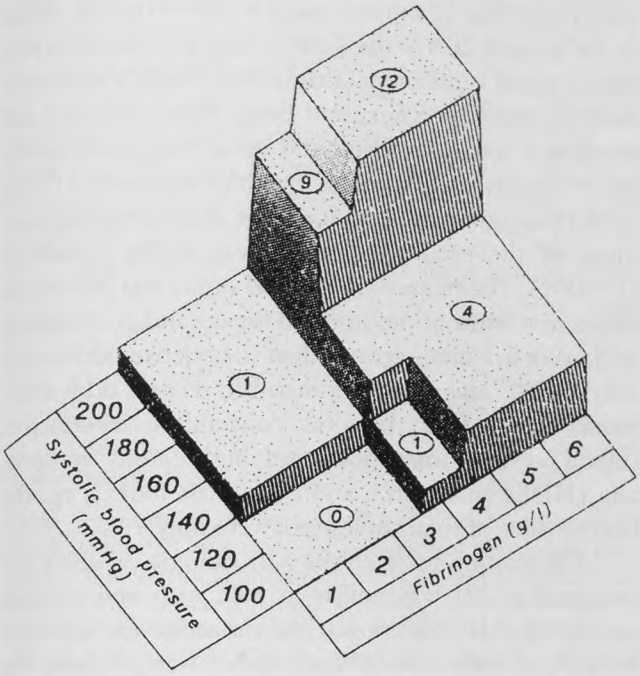

Figure 1. Incidence of stroke (circled percentages) according to groups delineated by various combinations of systolic blood pressure and fibrinogen levels, in the Göteborg Study. From Wilhelmsen L. Svärdsudd K, Korsan-Bengtsen K, Larsson B, Welin L, Tibblin G. Fibrinogen as a risk factor for stroke and myocardial infarction. N Engl J Med 1984; 311:504. Reprinted with permission of The New England Journal of Medicine.

year period. Myocardial infarction occurred in 92 men, stroke in 37. The fibrinogen level, measured at the entry examination, was significantly higher in subjects who later had MI or stroke than in those without these endpoints. There appeared to be a "dose-response" relation: the higher the fibrinogen level, the higher the incidence of MI or stroke. Blood pressure, degree of smoking, and serum cholesterol level were also risk factors for MI, but only high blood pressure and the fibrinogen level proved to be significant risk factors for stroke. Fibrinogen appeared to be a stronger predictor than blood pressure, which is usually the traditional risk factor most closely associated with stroke.

The risk of stroke strongly depended on the levels of fibrogen and blood pressure (Figure 1). If the levels of these two risk factors were low, the probability of stroke was close to 0%. If one factor was high and the other low, the risk of stroke was 1% to 4%. If both factors were high, the risk was 12%. A group at high risk of stroke could be delineated by selecting subjects with systolic blood pressure of 180 mm Hg or higher and a fibrinogen concentration of 350 mg/dL (3.5 g/L) or more. The men identified as high risk according to these criteria represented 19% of the total study population. In this group, 1 in 10 had a stroke during the follow-up; ie, approximately one half of the stroke cases were found in that subgroup. Therefore, the positive predictive value of these risk factors for stroke was 50% in this subgroup.

Leigh Study

The Leigh Study[12] consisted of 297 men aged 40 to 69 years who were recruited from one general practice in the United Kingdom. They were initially free of ischemic heart disease (IHD), diabetes mellitus, and severe hyperlipidemia and hypertension already being treated by diet or drugs. During a mean observation period of 7.3 years, 40 of these men experienced initial heart attacks. Thirty of the heart attacks occurred in those who had plasma fibrinogen levels greater than 350 mg/dL (3.5 g/L), an incidence of 31%. The incidence was 5% among men whose concentration was lower than that level.

In the men who died of heart attacks, the plasma fibrinogen level was significantly higher than in those who did not have heart attacks (402 vs 313 mg/dL [4.02 vs 3.13 g/L], $P<.001$). The men who died as a result of their first heart attack had significantly higher mean fibrinogen levels than did the men who survived their first heart attack and lived to the end of the study (429 vs 369 mg/dL [4.29 vs 3.69 g/L], $P=.025$). These two subgroups did not differ with respect to any other variable.

In men with high cholesterol levels, the incidence of heart attacks in those with plasma fibrinogen levels in the top third was 6 times greater than the incidence of heart attacks in those with fibrinogen levels in the bottom third; in men with high systolic blood pressure, the incidence in the top fibrinogen third was 12 times greater than the incidence in the bottom third.

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, and very-low-density lipoprotein (VLDL) levels. The addition of plasma fibrinogen significantly increased the predictive power of the model ($P<.001$).

Northwick Park Heart Study

Among 1511 men aged between 40 and 64 at the time of recruitment for the Northwick Park Heart Study,[13] 109 subsequently experienced first major events of IHD during a mean follow-up interval of 10 years. Several tests of hemostatic function were conducted to investigate the thrombotic component of the disease. Elevation of one standard deviation in factor VII activity, fibrinogen, and cholesterol were associated with increases in the risk of IHD of 62%, 84%, and 43%, respectively, within 5 years. No association was found with the other hemostatic mea-

surements studied. Multiple regression analysis indicated independent association for factor VII in coronary death and for fibrinogen in fatal and nonfatal IHD. Cholesterol made no independent contribution to the risk. Cigarette smoking was not a significant predictor (P=NS) when fibrinogen (P<.001) was included in multiple regression analysis. Only age was more strongly associated with IHD than plasma fibrinogen level.

Framingham Study

In 1968, at the 10th Biennial Examination, measurements of fibrinogen were taken in 1315 participants of both sexes (ranging in age from 47 to 79 years) in the Framingham Study[9] because of the suspected importance of fibrinogen level as a CVD risk factor. After 18 years of follow-up, there was a 30% increase in cardiovascular risk per one standard deviation of fibrinogen level [58 mg/dL (0.58 g/L)] in both sexes (P<.001); 30% for men and 40% for women in coronary heart disease (P<.001, both); and 20% for men (P=NS) and 30% for women (P<.01) in cardiac failure. The figures were even higher for peripheral arterial disease but were not significant, probably because of the small sample size with this less common disease. A rise in the incidence of stroke, including transient ischemic attack, was significantly associated with fibrinogen level measured 12 years earlier in men (P<.001). At the 18-year follow-up, the risk was twice as high among subjects with fibrinogen levels in the upper third (>310 mg/dL [>3.1 g/L]) as the risk in the lower third (<265 mg/dL [<2.65 g/L]) in both sexes, but not significant, again probably because of the small sample size. The predictive value of fibrinogen diminished slightly but remained significant and thus independent after taking into account nine important cardiovascular risk factors. In men, there was no evidence of a declining impact of fibrinogen level with age.

Caerphilly and Speedwell Collaborative Heart Disease Studies

The relation of fibrinogen, viscosity, and white blood cell count to the incidence of MI was examined in 4641 men from a general population aged 45 to 59 years in the Caerphilly and Speedwell Collaborative Heart Disease Studies.[14] The follow-up was 5.1 years in Caerphilly and 3.2 years in Speedwell. The predictive power of a logistic model that included age, geographic area, preexistent IHD, smoking status, and hemostatic and rheologic factors was considerable. Only 10% of observed events occurred in the bottom 40% of the distribution of predictive risk, whereas nearly 80% occurred in the top 40%. There were more than 12 times as many events in the top 20% as in the bottom 20% of the distribution. This model was at least as good as the model that included total cholesterol, diastolic blood pressure, and body mass index but not fibrinogen levels, viscosity, and white blood cell count. When the latter hematologic variables were added to the model containing the traditional risk factors, the improvement of the predictive power was highly significant (P<.001). The relative odds of MI in the top 20% of the fibrinogen distribution, adjusted for age and geographical area, were 4.1 times greater than the relative odds in the lowest 20%. This is greater than the relative odds commonly reported for the more conventional risk factors (blood pressure, total cholesterol, high-density lipoprotein [HDL] cholesterol, and body mass index); eg, the relative odds of total cholesterol were only 1.7.

The relation between the hematologic variables and incidence of MI was similar in men with and without preexistent IHD. Fibrinogen and viscosity were not independent of each other. When either was put into the model alone, it showed a strong predictive power, and when both were entered, the joint effect was attributed equally to both.

Prospective Cardiovascular Münster Study

In 1981, fibrinogen was added as a potential heart disease risk factor in the Prospective Cardiovascular Münster Study[10] of 2116 men who were 40 to 65 years of age and free of MI or stroke. After 6 years of follow-up, fibrinogen was found to be an independent risk factor for coronary heart disease by means of a multiple logistic function analysis adjusted for age, blood pressure, smoking, diabetes mellitus, angina pectoris, family history of MI, total cholesterol, and HDL. Persons whose fibrinogen levels were in the upper third were at greater risk than were those whose fibrinogen levels were in the lowest third (61.5% and 16.4% of the events, respectively), no matter what the value of low-density lipoprotein (LDL) cholesterol (Figure 2). The effect of LDL cholesterol seemed to be limited by the level of fibrinogen. When the latter was in the lower third, the incidence remained low and did not vary according to LDL. More than 29% of the events occurred among subjects with LDL in the upper third and concurrent high fibrinogen levels; less than 5% occurred among subjects with LDL in the upper third and a low level of this clotting factor.

These results are preliminary and correspond to a subgroup of the original sample of 19,698 subjects. This study is expected to produce additional important data in the coming years.

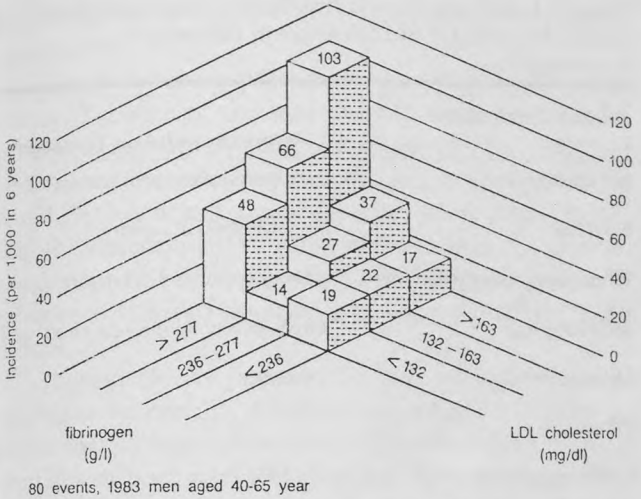

Figure 2. Incidence of coronary heart disease according to groups delineated by various combinations of low-density lipoprotein cholesterol and fibrinogen levels, in the Prospective Cardiovascular Münster (PROCAM) Study. From Assmann G, Schulte H. Results and conclusions of the Prospective Cardiovascular Münster (PROCAM) Study. In: Assmann G, ed. Lipid metabolism disorders and coronary heart disease. 2nd ed. Munich, Germany: MMW-Medizin Verlag, 1993:19–67. Reprinted with permission of G. Assmann, ed.

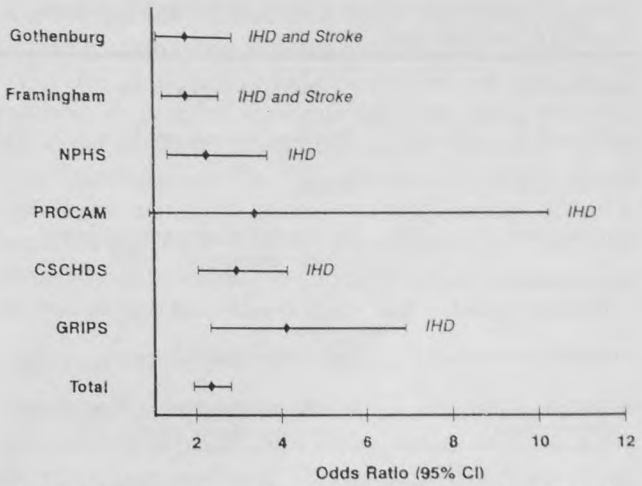

Figure 3. Meta-analysis of prospective epidemiological studies. Odds ratios (95% confidence intervals) for cardiovascular events in persons with fibrinogen levels in the upper third as compared with the lower third. IHD denotes ischemic heart disease; NPHS, the Northwick Park Heart Study; PROCAM, the Prospective Cardiovascular Münster Study; CSCHDS, the Caerphilly and Speedwell Collaborative Heart Disease Studies; GRIPS, the Göttingen Risk, Incidence, and Prevalence Study. Reproduced with permission, from Ernst E, Resch KL. Fibrinogen as a cardiovascular risk factor: a meta-analysis and review of the literature. Ann Intern Med 1993; 118:959.

Göttingen Risk, Incidence, and Prevalence Study

The Göttingen study was based on a random population sample of 5239 men who were 40 to 60 years old and initially free of CVD. After 5 years of follow-up, fibrinogen was identified as a strong predictor of MI. Using a multivariate regression model, fibrinogen proved to be a better predictor than traditional risk factors, with the exception of family history. The rank order of prediction for risk factors (in descending order) was: LDL, family history, lipoprotein a (Lp a), HDL, fibrinogen level, age, smoking, glucose, and blood pressure.

Summary of Studies

Six of these epidemiological prospective studies were included in a recent meta-analysis[16] covering a total of 92,147 person-years. The risk of a cardiovascular event (ischemic heart disease, stroke) in subjects with fibrinogen levels in the upper third as compared with those in the lower third varied from 1.8-fold in the Framingham Study (95% confidence interval [CI], 1.2 to 2.5) to 4.1 in the Göttingen Study (95% CI, 2.3 to 6.9), with a summary risk of 2.3 (95% CI, 1.9 to 2.8). This cumulative data analysis reasserts that fibrinogen is a strong, independent cardiovascular risk factor (Figure 3).

Only the Framingham Study has published results that included women. Future trials will contribute more data on the role of fibrinogen in the development of heart disease in women.

Other Studies

Over the last 2 decades a number of studies relevant to the role of fibrinogen levels in cardiovascular disease have been undertaken, with the following findings:

Subjects with a previous atherothrombotic event. Among survivors of a stroke[17] or MI,[18] fibrinogen levels, measured after the acute phase, are significantly higher in those who experience a fatal recurrence of the event as compared with those who survive a recurrence, and the levels are higher in the latter group than in those without a second event. Death has a nearly linear relationship with levels of fibrinogen, independent of age. Fibrinogen measured in the acute phase of MI also showed predictive value for the recurrence of a cardiac event in the subsequent fortnight.[19]

Subjects with impaired blood flow. The following conclusions were drawn from several studies: (1) Patients suffering from angina have higher fibrinogen levels than do controls in either sex. The levels are even higher for those showing two or more indicators of angina (determined by chest pain questionnaire and electrocardiogram) as compared with those with only one. The values

Table 1. Processes for Which Plasma Fibrinogen Has Been Found To Be Predictive

Angina at rest	Occlusion of bypass grafts
Stable angina	Transient ischemic attack
Unstable angina	Stroke
Cardiac failure	Severity and progression of carotid atheromatosis
Myocardial infarction (fatal and nonfatal)	Cardiovascular event in stroke survivors
Myocardial reinfarction	Intermittent claudication
Severity of coronary atheromatosis	Severity and progression of peripheral arterial occlusive disease

are higher (in descending order) for angina at rest, unstable angina, and stable angina. Among men, the risk increases linearly with fibrinogen concentration after adjustment for 10 other coronary risk factors.[20,21] (2) Fibrinogenemia is increased in patients with intermittent claudication. The severity of the disease and the progression of the peripheral circulatory disturbance correlate with plasma concentration.[20,22–24] (3) In elderly patients, cerebral blood flow, as determined by the ^{133}Xenon inhalation, had an inverse correlation with fibrinogen but not with age.[25]

Atherosclerosis. Persons with carotid atherosclerosis or carotid atherosclerosis progression have higher levels of fibrinogen than those without these disorders.[26,27] Patients with coronary atherosclerosis have increased levels of fibrinogen as compared with controls; the severity of the process, as measured by the extent of atheroma and the number of vessels affected, is strongly associated with its concentration.[21,28–31]

Bypass grafts. The occlusion of bypass grafts is a common complication following reconstructive vascular surgery. In a 2-year prospective study, plasma fibrinogen concentration was identified as the most important predictor of graft occlusion, followed by smoking. LDL cholesterol above the median did not correlate with a higher occlusion rate.[32]

Table 1 displays processes for which plasma fibrinogen has been found to be predictive.

Determinants of Fibrinogenemia

Fibrinogen is a large plasma protein widely known for its role in coagulation. It is considered one of the acute-phase proteins because of its increase in response to inflammation associated with tissue injuries. Baseline values, therefore, should not be assessed when the patient is experiencing acute inflammation. Baseline determinations,

Table 2. Circumstances and Risk Factors That Have Been Found Associated with Differences in Fibrinogen Concentration

Associated with High Fibrinogen	Associated with Low Fibrinogen
Inflammation	Estrogen replacement therapy
Smoking	Regular physical activity
Winter respiratory infections	Chronic ethanol intake
Increasing age	High-density lipoprotein cholesterol
Menopause	Japanese
Pregnancy	
Oral contraceptive drugs	
Hypertension	
Low-density lipoprotein cholesterol	
Glucose intolerance	
Black race	
Low socioeconomic class	
Cold weather	
Inactivity	
Adiposity	
Stress	

however, can be made in subjects with chronic inflammation, which raises fibrinogen levels, because increased levels convey damage and risk independent of the cause of the rise.

Most circumstances and risk factors related to CVD have been associated with fibrinogen levels[33,34] (Table 2). Multiple regression analyses showed that the predictive power of this protein diminished partially after adjusting for those variables but remained statistically significant and is, therefore, independent. At least part of the influence of such conditions on CVD is mediated through elevation of fibrinogen level. In the case of smoking, one fourth to one half of its effect might be attributable to fibrinogenemia.[35] These two risk factors are so closely related that in multivariate analysis of some studies, the coefficient for smoking became substantially reduced and was no longer statistically significant when fibrinogen level was included in the model.[13,35] Plasma fibrinogen levels are significantly higher in cigarette smokers than in nonsmokers.[11,13,14,27,34,35] When smoking is discontinued, fibrinogen levels decrease irrespective of the duration of the habit, and after some years, they are similar to those of patients who have never smoked. This decrease is

comparable to the drop in CVD risk resulting from smoking cessation.[36,37]

Family history of premature heart disease implies an increased chance of the subject developing it,[38,39] independent of commonly accepted risk factors.[39-41] In those persons, significant increases in fibrinogenemia have been found.[20] That fibrinogen levels seem to be primarily genetically determined[42,43] may indicate that the genetic component of fibrinogen concentrations may be a contributor to the likelihood of inheriting premature heart disease.

Among elderly people, the rates of mortality and morbidity (especially infectious diseases) are higher in winter than in summer months, with seasonal variations in the rates of both fatal and nonfatal MI and stroke. This tendency is partially explained by the increase in fibrinogen induced by winter respiratory infections through activation of the acute-phase response.[44] A reported 23% increase in fibrinogen levels during the coldest 6 months is inversely related to core body and environmental temperature.[45] Both infections and cold may be responsible for seasonal variation in plasma fibrinogen sufficient to increase the risk of MI and stroke in winter. As with LDL cholesterol and hypertension, recognized personal and environmental factors that influence fibrinogen levels account for only a small part of the variability in fibrinogen levels across a given population.[46]

Pathophysiology

There are several potential ways in which fibrinogen promotes CVD.

Hemorrheology

Fibrinogen hinders blood flow and oxygen delivery through diminishing erythrocyte deformability, furthering red cell aggregation and augmenting plasma and blood viscosity.[47] This process potentiates the hemodynamic effects of atheromatosic stenoses and leads to clinically overt ischemia (ie, angina and intermittent claudication). In microcirculation, distortability of red blood cells and plasma viscosity are the main factors determining blood flow resistance.[48] After a thrombotic event, these factors play a relevant role in maintaining blood flow through a collateral supply to the zone in penumbra and thereby reducing the volume of infarcted tissue.[49]

Hemostasis

The basis for fibrinolytic therapy is that intraluminal thrombosis is the prevailing mechanism leading to sudden death, atherothrombotic stroke, and MI. Vessel injuries or plaque disruptions activate platelets that expose a receptor for fibrinogen, which binds them to each other, resulting in platelet aggregation. Fibrinogen, which is converted to fibrin, is essential for the final step of the coagulation cascade. The concentration of plasma fibrinogen bears a positive relation to the amount of fibrin settled in the clot.[50,51] An increased fibrinogen level may contribute substantially to a hypercoagulable state.

Atherogenesis

Fibrinogen contributes to the atherosclerotic process itself, as fibrinogen and fibrin are important constituents of the atheromatous plaque. Their pattern of deposition correlates with that of LDL.[8,52,53] Fibrinogen but no LDL can be detected in the uninvolved intima surrounding the lesion, which suggests that its deposition precedes that of LDL and that once fibrin has formed within this layer, it binds LDL, serving as a scaffold.[54] Fibrinogen induces a dose-dependent migration of smooth muscle cells from the media and their proliferation,[54,55] which plays an important role in atherogenesis. Fibrinogen and some of its degradation derivatives trigger a variety of other mechanisms thought to be relevant in atherogenesis.[56] Studies in rodents demonstrate that a few days after the formation of thrombi in limited endothelial injuries (similar to mechanical injuries caused by hemodynamic forces thought to initiate atherosclerosis in humans), the thrombi become indistinguishable from fibrous atherosclerotic plaques.[57] Mural and intraluminal thrombosis (a dynamic and repetitive process) is fundamental in the development and progression of atheromatous plaque, particularly in rapidly progressive plaques.[5,58] Fibrinogen and LDL have a synergic effect in promoting atherosclerosis, although it is possible that fibrinogen and its derivatives play a more important role than LDL in the development of atherosclerotic lesions.

Lowering Fibrinogen

If one accepts that in epidemiological prospective studies and in diverse clinical conditions it has been proven that plasma fibrinogen concentration is an independent, powerful risk factor and that preconditions for causality have been reasonably fulfilled, it should be conceded that there is much more scientific foundation for decreasing fibrinogen levels than for utilizing platelet aggregation inhibitors.[59-61] Although no large intervention trial has been conducted to assess the actual benefit of fibrinogen reduction, several studies that involved reducing plasma fibrinogen levels by various methods (ie, fibrinolytics, extracor-

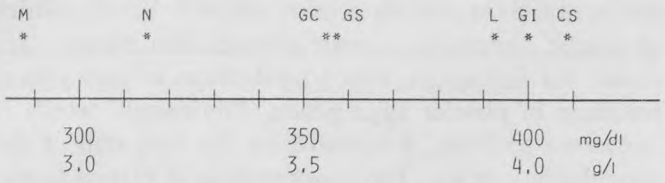

Figure 4. Mean plasma fibrinogen levels related to the onset of cardiovascular end-points, in the prospective epidemiological studies, are within traditional "physiologic" levels with a unique exception which slightly exceeds it. N denotes the Northwick Park Heart Study; M, the Prospective Cardiovascular Münster Study; GC, the Göteborg Study (coronary heart disease); GS, the Göteborg Study (stroke); GI, the Göttingen Risk, Incidence, and Prevalence Study; L, the Leigh Study; CS, the Caerphilly and Speedwell Collaborative Heart Disease Studies. In GI, L, and CS, a nephelometric assay was used to measure fibrinogen. Data from the Framingham Study were reported in a different way (rates of CVD by upper, middle, and lower thirds of fibrinogen level), so its mean level is not shown.

poreal fibrinogen precipitation, or oral drugs) have reported improvement in peripheral, cardiac, and cerebral ischemia.[62-66] In one study of patients suffering angina pectoris that was refractory to all conventional antianginal therapy,[67] administration of low doses of urokinase, a fibrinolytic enzyme, three times a week for 3 months reduced fibrinogen by 36%. This therapy led to the hemorrheological changes and clinical improvement that were theoretically expected on the basis of pathophysiologic knowledge: there were significant decreases in the number of daily attacks of angina (73%), daily nitrate consumption (78%), and ST-segment depression (27%), and improvement in working capacity (28%) and local or global perfusion (80%), as measured by SPECT myocardial scintigraphy.

The risk of CVD increases in direct relation to fibrinogen level. Mean level related to the occurrence of cardiovascular events in epidemiologic prospective studies is within the limits generally considered as "physiologic" (Figure 4),[9-15] suggesting that the traditionally accepted upper limit of normal (400 mg/dL [4.0 g/L]) may be considerably inadequate for evaluating cardiovascular risk. At present, the levels of reference have not been formally established. The adoption of fixed thresholds by committees of experts and the dissemination of the obtained consensus probably would result in a considerable advance, as would the standardization of the methods to assay fibrinogen.

Fibrinogen-Lowering Therapy

A mild but probably relevant reduction of fibrinogenemia might be achieved by nonpharmacologic measures, such as avoiding obesity, sedentarism, cold, and, especially, smoking. Smoking cessation lowers plasma fibrinogen nearly 40 mg/dL (0.4 g/L) on average.[68] Although there is no oral pharmacologic treatment to specifically reduce the levels of fibrinogen, several drugs employed in cardiovascular therapy modify its concentration. Because of the possibility of external influences on plasma fibrinogen levels (eg, the onset of warmer weather), only trials with parallel control groups were considered in this paper. Bezafibrate,[69-74] a lipid-lowering drug widely used in Europe, consistently decreases fibrinogen concentration by an amount apparently superior to that of any other drug. Decreases are dependent on baseline values: approximately 25% for fibrinogen between 300 mg/dL (3.0 g/L) and 415 mg/dL (4.15 g/L), and approximately 45% for fibrinogen higher than 600 mg/dL (6.0 g/L). Fenofibrate[72] also seems to reduce fibrinogen levels, but more trials are needed to confirm this effect. Conversely, gemfibrozil[72,75] raises fibrinogen between 9% and 21%. Among HMG-Coa reductase inhibitors, results are disparate and no firm conclusions have been established. Neither simvastatin[69,72,76] nor pravastatin[72,77] seem to modify fibrinogenemia. In the only study found with a parallel control group, lovastatin[78] produced a minimal reduction (2%). Sulodexide,[79-81] an oral heparin-like glycosaminoglycan active agent, significantly decreases fibrinogen by a mean of 14%. Ticlopidine,[82-84] a potent antiaggregation agent that works by inhibiting fibrinogen binding to the specific membrane receptor of platelets, consistently diminishes fibrinogen levels by a mean of 13%.

A large intervention trial with a fibrinogen-lowering drug has not yet been conducted. In the future, it should be carried out in patients at risk for the purpose of determining subsequent cardiovascular outcome. At present, such a trial is difficult to design because of the lack of specificity of potential candidates until new drugs are developed. At this time, it is premature to indicate any drug treatment on the basis of its fibrinogen-lowering properties; however, when appropriate and available, fibrates possessing the "collateral" effect of diminishing fibrinogen perhaps should be the treatment of choice for hyperlipidemia. Based on the current literature, bezafibrate, which has an estimated 9 million patient-years of use since 1978, and is safe, economical, and of good compliance,[78,85,86] seems to be the most suitable drug for achieving this dual purpose. It consistently decreases fibrinogen by an amount large enough to theoretically transfer a patient from the "risk zone" to the "low-risk zone." In hypercholesterolemic patients, bezafibrate reduces LDL cholesterol by 20% to 30% and increases HDL in such a way that the cardiovascular risk quotient (total cholesterol: HDL cholesterol) decreases by 30% to 40%.[79,87,88] This reduction is similar to that obtained with lovastatin 20 mg[78]

orsimvastatin 20 to 40 mg.[88] Lipid profile and fibrinogen level could be simultaneously modified without augmenting costs or adverse reactions or worsening compliance.

Final Considerations

Although plasma fibrinogen has been firmly established as a powerful and independent CVD risk factor, it has not been well promoted as a screening test for atherothrombotic disease, and requests for this protein are still made only to prevent hemorrhagic risk.[89] In the light of present knowledge, it should be included in cardiovascular risk evaluation profiles[9,12,14,90,91] by incorporating it into the traditional model. The European Atherosclerosis Society in its new clinical guidelines[92] has included high fibrinogen level on its list of modifiable risk factors affecting treatment of dyslipidemias. Including fibrinogen level as a risk factor enables physicians to more accurately identify patients who require lipid-lowering measures, according to standard recommendations; ie, those who have a traditional risk factor and previously unrecognized hyperfibrinogenemia as a second risk factor. In the United States, the National Cholesterol Education Program has not yet delivered any information regarding this factor.[93]

As the preventive approach to atherosclerosis and its consequences must be multifactorial, hyperfibrinogenemia, which is directly involved in the genesis of atherosclerosis, ischemic chronic disease, and acute atherothrombotic arterial obstruction, probably should be modified.

Smoking causes increased fibrinogen levels, which in turn contribute to the development of CVD. Discussing the deleterious effects of excessive fibrinogen therefore could be used to motivate our patients to stop smoking.

Although there is evidence that fibrinogen plays a role in CVD, physicians should have access to a broader range of information about fibrinogen as a risk factor for CVD so that it can be included in risk assessment and possibly treatment decisions.

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