Brief Reviews

Measuring Plasma Fibrinogen to Predict Stroke and Myocardial Infarction
An Update

Giulio Maresca, Anna Di Blasio, Roberto Marchioli, Giovanni Di Minno

Abstract—Plasma fibrinogen is a major determinant of platelet aggregation and blood viscosity. The decrease in plasma fibrinogen by bezafibrate is associated with a decrease in the risk of reinfections. To strengthen the predictive value of plasma fibrinogen with respect to cardiovascular risk, we performed a meta-analysis of studies conducted between 1984 and 1998. Emphasis has been put on the relationship between high levels of plasma fibrinogen and fatal and/or nonfatal cardiovascular events in both the general population and in patients with previous cardiovascular events. Twenty-two studies (13 prospective, 5 cross-sectional, and 4 case-control) addressing the association between fibrinogen plasma concentrations and cardiovascular disease were analyzed. The overall estimate of risk of cardiovascular event in subjects with plasma fibrinogen levels in the higher tertile, was twice as high as that of subjects in the lower one (odds ratio, 1.99; 95% confidence interval, 1.85 to 2.13). High plasma fibrinogen levels were associated with an increased risk of cardiovascular disease in healthy as much as in high-risk individuals. A metaregression showed no confounding effects attributable to selected characteristics of retrieved studies. A subgroup analysis (study design, follow up, mean fibrinogen levels, percentage of smokers, and mean age) allowed us to conclude that fibrinogen is an independent risk factor for cardiovascular disease; that it interacts with major determinants of myocardial and cerebrovascular ischemia; and that, in secondary prevention studies, it enhances by 8% the prediction of future events by established risk factors. Thus, fibrinogen measurements should be encouraged to refine the overall risk profiles of individuals and to better tailor preventive interventions. (Arterioscler Thromb Vasc Biol. 1999;19:1368-1377.)

Key Words: fibrinogen □ risk factor □ stroke □ myocardial ischemia □ meta-analysis

Stroke and myocardial infarction are major thrombotic complications of atherosclerosis and leading causes of morbidity and mortality in western countries. Many studies have established the involvement in atherosclerosis of blood lipids and lipoproteins, hypertension, diabetes mellitus, and smoking, as well as the active role of endothelial injury, smooth muscle cell proliferation, and inflammation. The role of hypercoagulability and of plasma fibrinogen, the central protein of the coagulation system, in this complex scenario has been suspected for many years, and has recently been documented by experimental and clinical evidence: human gelatinous and fibrous plaques are rich in fibrinogen and its degradation products; thrombin, fibrinogen, and fibronectin are involved in cell proliferation; fibrinogen is involved in mechanisms (platelet aggregation, endothelial cell injury, and plasma viscosity) that play a central role in the formation of thrombi; and thrombosis is a major determinant of myocardial ischemia. Early epidemiological evidence has associated high levels of plasma fibrinogen with cardiovascular disease (CVD). Moreover, drugs that lower the progression of coronary heart disease also reduce plasma fibrinogen levels in young postinfarction males. Recommendations for the management of CVD in the general population as well as for people with previous cardiovascular events were recently formulated jointly by various medical associations. These recommendations focus on preventive interventions based on the summation of risks rather than addressing the individual who is a carrier of an isolated high-risk factor (the philosophy being that individuals with a combination of borderline risks may actually be at considerably greater risk than subjects with a single very high risk factor). Thus, these recommendations for the primary prevention of coronary heart disease in clinical practice focus only on cholesterol, hypertension, and smoking habits. Because patients at risk for the development of fibrinogen-related ischemic complications of atherosclerosis can be easily identified and treatment strategies have been developed to protect against these complications, clinically oriented prevention recommendations should consider the role of fibrinogen in CVD. In an effort to strengthen the clinical
TABLE 1. Fibrinogen and CVD: Prospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Recruited Population</th>
<th>No. of Subjects</th>
<th>Follow-up (years)</th>
<th>Age</th>
<th>Smokers</th>
<th>No. Events</th>
<th>Fibrinogen Mean (SD)*</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gothenburg20</td>
<td>Sweden</td>
<td>Men (random sample)</td>
<td>792</td>
<td>13.5</td>
<td>50</td>
<td>24.8</td>
<td>129</td>
<td>330 (NA) vs 360 (NA)</td>
<td>Fibrinogen is significant cardiovascular risk factor.</td>
</tr>
<tr>
<td>NPHS21</td>
<td>England</td>
<td>Men without CVD</td>
<td>1494</td>
<td>10.0</td>
<td>40–64</td>
<td>44.4</td>
<td>106</td>
<td>290 (±59) vs 315 (±71)</td>
<td>Stronger association between CHD and high fibrinogen level within first 5 years of follow-up as compared with its total duration.</td>
</tr>
<tr>
<td>Framingham22</td>
<td>USA</td>
<td>Men without CVD</td>
<td>554</td>
<td>12.0</td>
<td>47–79</td>
<td>39.7</td>
<td>Men 164</td>
<td>291.4 (±56)§</td>
<td>Fibrinogen is independent CV risk factor.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women without CVD</td>
<td>761</td>
<td>12.0</td>
<td>47–79</td>
<td>36</td>
<td>Women 147</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROCAM23</td>
<td>Germany</td>
<td>Men without CVD</td>
<td>2044</td>
<td>6.0</td>
<td>40–65</td>
<td>28.7</td>
<td>82</td>
<td>263 (±63) vs 288 (±68)</td>
<td>Fibrinogen is a powerful independent cardiovascular risk factor.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women without CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRIPS24</td>
<td>Germany</td>
<td>Men without CVD</td>
<td>5231</td>
<td>5.0</td>
<td>40–60</td>
<td>36.7</td>
<td>107</td>
<td>364 (±84) vs 424 (±97)</td>
<td>Fibrinogen is a risk factor for myocardial infarction.</td>
</tr>
<tr>
<td>SHHS 125</td>
<td>Scotland</td>
<td>Men without CVD</td>
<td>3930</td>
<td>8.0</td>
<td>40–59</td>
<td>38.6</td>
<td>Men 191</td>
<td>276 (NA) vs 287 (NA)</td>
<td>Fibrinogen is an important CV risk factor.</td>
</tr>
<tr>
<td>CSCHDS26</td>
<td>England</td>
<td>Men without CVD</td>
<td>4641</td>
<td>10/9.33†</td>
<td>45–59</td>
<td>50.9</td>
<td>571</td>
<td>364 (±81) vs 398 (±89)</td>
<td>Fibrinogen is an independent CV risk factor.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women without CVD</td>
<td>3760</td>
<td>8.0</td>
<td>40–59</td>
<td>37.8</td>
<td>Women 67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIC27</td>
<td>USA</td>
<td>Men without CVD</td>
<td>6297</td>
<td>5.2</td>
<td>45–64</td>
<td></td>
<td>Men (w) 178</td>
<td>295 (±65) vs 320 (±65)</td>
<td>Fibrinogen could mediate some of the effect of other risk factors. Fibrinogen proved to be a CHD risk factor.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women without CVD</td>
<td>8180</td>
<td>5.5</td>
<td>45–64</td>
<td></td>
<td>Women (w) 65</td>
<td>306 (±65) vs 346 (±65)</td>
<td></td>
</tr>
<tr>
<td>Fowkes28</td>
<td>Scotland</td>
<td>Intermittent claudication</td>
<td>617</td>
<td>1.0</td>
<td>65</td>
<td>44</td>
<td>36</td>
<td>NA</td>
<td>Fibrinogen is an independent predictor of coronary death in patients with claudication.</td>
</tr>
<tr>
<td>ECAT29-30</td>
<td>Europe</td>
<td>AP</td>
<td>2700</td>
<td>2.0</td>
<td>&gt;45</td>
<td>19.8</td>
<td>106</td>
<td>300 (±71) vs 328 (±74)</td>
<td>Strong association between fibrinogen and coronary event in patients with CHD.</td>
</tr>
<tr>
<td>SHHS 235</td>
<td>Scotland</td>
<td>Men with CHD</td>
<td>1163</td>
<td>8.0</td>
<td>40–59</td>
<td></td>
<td>Men 197</td>
<td>290 (NA) vs 311 (NA)</td>
<td>Fibrinogen is a risk factor in patients with CHD.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women with CHD</td>
<td>1102</td>
<td>8.0</td>
<td>40–59</td>
<td></td>
<td>Women 81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIP31</td>
<td>Israel</td>
<td>Men with CHD</td>
<td>3092</td>
<td>3.1</td>
<td>59</td>
<td>11</td>
<td>114</td>
<td>345§</td>
<td>High plasma fibrinogen characterizes CVD patients who are more likely to die from CHD.</td>
</tr>
<tr>
<td>Toss32</td>
<td>Sweden</td>
<td>Men and women</td>
<td>965</td>
<td>0.5</td>
<td>70</td>
<td>19</td>
<td>137</td>
<td>356§</td>
<td>The increased risk associated with elevated fibrinogen levels is independent of, and additive to, the prognostic influence of myocardial damage.</td>
</tr>
</tbody>
</table>

*Healthy vs subjects with CHD; †Caerphilly-Speedwell follow-up; §mean of all samples.

impact of measuring plasma fibrinogen, we performed a meta-analysis to answer the following questions: (1) Is epidemiological evidence still supporting plasma fibrinogen as an independent risk factor for cardiovascular disease? (2) Is plasma fibrinogen measurement improving prediction of future ischemic events by established risk factors? (3) What areas of uncertainty remain with respect to the association between fibrinogen and CVD?

Methods

Twenty-two studies20–41 (MEDLINE search from 1984 to September 1998) (Tables 1 and 2), in which the association of plasma fibrinogen concentrations with the risk of CVD had been evaluated, were scrutinized. Other relevant studies were identified by resuming recent reviews.10,14,15,42 Studies not providing enough information as to the criteria adopted for the present meta-analysis (ie, odds ratios [ORs], confidence intervals [CIs], and/or the possibility of recalculating crude ORs) were not used.

Statistical Analysis

Data from different studies were combined using the general variance-based method.43–53 This method requires only information on the OR estimate and 95% CI of each study.44 95% CIs were used to assess the variance of each study effect. When provided by the authors, adjusted ORs and their CIs were preferred. Crude ORs and their 95% CIs were used when an adjusted estimate was not provided. These estimates were used to carry out the overview for all studies as well as for the subgroups.

To examine the strength of the association between total cardiovascular events and the different subgroups, we fitted a multivariate inverse variance–weighted linear regression of the logarithmic...
TABLE 2. A. Fibrinogen and CVD: Cross-Sectional Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Recruited Population</th>
<th>No. of Subjects</th>
<th>Age</th>
<th>Smokers %</th>
<th>Fibrinogen Mean*</th>
<th>No. Events</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHHS</td>
<td>Scotland</td>
<td>GP</td>
<td>Men 3615</td>
<td>40 to 59</td>
<td>50.9</td>
<td>227 vs 251</td>
<td>Men 248</td>
<td>Plasma fibrinogen is a risk factor for CHD and stroke.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Women 3168</td>
<td></td>
<td></td>
<td>234 vs 263</td>
<td>Women 72</td>
<td></td>
</tr>
<tr>
<td>Finnrisk</td>
<td>Finland</td>
<td>GP (random sample)</td>
<td>2365</td>
<td></td>
<td>23</td>
<td>341 vs 384</td>
<td>Men 88</td>
<td>Fibrinogen is associated with prevalent CHD but causality cannot be proved.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Women 54 vs 59*</td>
<td></td>
<td></td>
<td>341 vs 381</td>
<td>Women 44</td>
<td></td>
</tr>
<tr>
<td>PVC METRA</td>
<td>France</td>
<td>Workers with 1 CV risk factor</td>
<td>652</td>
<td>47.6 vs 49*</td>
<td>42.7</td>
<td>315 vs 338</td>
<td>426</td>
<td>Plasma fibrinogen remains a statistical independent predictor after allowing correction for multiple CV risk factors.</td>
</tr>
<tr>
<td>SHARP</td>
<td>USA and Japan</td>
<td>GP</td>
<td>3571</td>
<td>78</td>
<td>6</td>
<td>231 vs 403†</td>
<td>1051</td>
<td>It is not possible to distinguish whether this association is casual or a marker for progressive disease.</td>
</tr>
<tr>
<td>MONICA</td>
<td>Scotland</td>
<td>GP (random sample)</td>
<td>Men 658</td>
<td>25 to 75</td>
<td>...</td>
<td>...</td>
<td>Men 176</td>
<td>Fibrinogen is a CV risk factor.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Women 720</td>
<td></td>
<td>...</td>
<td>Women 242</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B. Fibrinogen and CVD: Case-Control Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Cases Character</th>
<th>No. Cases</th>
<th>No. Controls</th>
<th>Age†</th>
<th>Smokers %†</th>
<th>Fibrinogen Mean†</th>
<th>No. Events</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qizilbash</td>
<td>England</td>
<td>TIA/Minor stroke</td>
<td>105</td>
<td>232</td>
<td>67.7 vs 67.6</td>
<td>75 vs 68</td>
<td>408 vs 365</td>
<td>115</td>
<td>Fibrinogen is an important risk factor for stroke.</td>
</tr>
<tr>
<td>Resch</td>
<td>Germany</td>
<td>Second stroke</td>
<td>60</td>
<td>60</td>
<td>62.5 vs 64.6</td>
<td>66 vs 56</td>
<td>396 vs 344</td>
<td>154</td>
<td>Hyperfibrinogemia is an independent risk factor for cardiovascular events in stroke survivors.</td>
</tr>
<tr>
<td>ARIC</td>
<td>USA</td>
<td>Carotid artery wall thickening</td>
<td>385</td>
<td>385</td>
<td>55.5 vs 56.8</td>
<td>...</td>
<td>316 vs 287</td>
<td>215</td>
<td>Significant association between plasma fibrinogen and early atherosclerosis of carotid arteries.</td>
</tr>
<tr>
<td>LETS</td>
<td>the Netherlands</td>
<td>Deep vein thrombosis</td>
<td>199</td>
<td>199</td>
<td>44§</td>
<td>37 vs 36</td>
<td>340 vs 330</td>
<td>216</td>
<td>Positive association between plasma fibrinogen level and thrombotic risk.</td>
</tr>
</tbody>
</table>

ORs for total events as dependent variable against the variables. The weights that were obtained with the variance-based method were adopted for the regression analysis. χ² was used to assess the magnitude of heterogeneity among studies, ie, the within-group heterogeneity (Het-w). The χ² with degrees of freedom 1 less than the number of groups was used to assess the magnitude of the heterogeneity of the ORs between the subgroups of studies, ie, the between-group heterogeneity (Het-b).

Subgroup Analysis

Duration of follow-up, mean plasma fibrinogen values at baseline, percentage of current smokers, mean age of the study population, and study design (prospective, cross-sectional, and case-control) were taken into consideration to stratify for potential confounders (subgroup analyses). Continuous variables were dichotomized according to their approximate median values. The criteria used for subgroup analysis according to different study designs (prospective, cross-sectional, and case-control) are given below.

Prospective Studies

Cardiovascular events were presented according to tertiles of fibrinogen in the majority of the studies. The relationship between fibrinogen levels and cardiovascular events was determined by comparing higher and lower tertiles of fibrinogen. The results of 3 prospective studies (Gothenburg and Scottish Heart Health Study, Caerphilly-Speedwell) published as quintiles were recalcualted into tertiles using a conservative approach that assumes a linear increase in events within quintiles. This method tends to underestimate the risk associated to fibrinogen tertiles.

Cross-Sectional Studies

The effect of fibrinogen level in cross-sectional studies was evaluated by comparing upper and lower quartiles. Three studies presented their results as quartiles of fibrinogen. In the Prevention Cardiovasculaire en Medecine du Travail study, tertiles of fibrinogen were used because the results were presented only as unadjusted estimates of the OR of the higher tertile of plasma fibrinogen level compared with the lower one. Sharp et al presented their results as quintiles of fibrinogen. These were recalculated.

Case-Control Studies

OR and 95% CI values were computed by comparing higher quartiles of fibrinogen to lower ones. In 1 case, it was not possible to recalculate risk estimates into quartiles; thus the unadjusted estimate according to the median value, as presented by the authors, was used.

Results

Is the Epidemiological Evidence Still Supporting Plasma Fibrinogen as an Independent Risk Factor for Cardiovascular Disease?

Of the 22 studies contributing to this analysis, 63736 individuals were included and 5712 cardiovascular (CV) events were observed. The end points available for the analysis were fatal and nonfatal coronary heart disease (CHD) for 10 studies, fatal and nonfatal CV events for 4 studies, arterial plaque progression for 2 studies, deep vein thrombosis for 1 study, and myocardial infarction for 4 studies.
Figure 1. Risk of cardiovascular disease for high versus low plasma fibrinogen values. The studies are arranged according to study design (ie, prospective, cross-sectional, and case-control) and year of publication. Separate results are given for individual studies. Each OR and its 95% CI is plotted as a back square and a line. The solid vertical line represents an OR of 1.0 and the broken vertical line indicates the overall OR estimate for all combined studies. The results of the ARIC study are presented separately for white men, black men, white women, and black women. M, data on men; WM, data on white men; BM, data on black men; W, data on women; WW, data on white women; and BW, data on black women. Cutoff values were as follows: Prospective studies–Northwich Park Heart Study (NPHS), 270 and 319 mg/dL; Framingham Study, 265 and 311 mg/dL; Gottingen Risk Incidence and Prevalence Study (GRIPS), 326 and 395 mg/dL; Prospective Cardiovascular Muster Study (PROCAM), 236 and 277 mg/dL; Atherosclerosis Risk in Communities Study (ARIC), 270 and 319 mg/dL; European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study (ECAT), 271 and 331 mg/dL; Bezafibrate Infarction Prevention Study (BIP), 308 and 368 mg/dL; Toss et al,\textsuperscript{32} 338 and 400 mg/dL; Gotthenburg, The Caerphilly and Speedwell Collaborative Heart Disease Studies (CSCS), the Scottish Heart Health Study (SHHS), and the study by Fowkes\textsuperscript{28} et al did not provide cutoff values. Cross-sectional studies–Sharp et al,\textsuperscript{36} 256 and 351 mg/dL; Prevention Cardiovasculaire en Medecine du Travail (PVCMETRA), 288 and 347 mg/dL; The Scottish Heart Health Study (SHHS), the Finrisk Hemostasis Study, and the Monica Study did not provide cutoff values. Case-control studies–Oxfordshire Study, 300 and 430 mg/dL; ARIC, 256 and 337 mg/dL; Resch et al,\textsuperscript{38} median value of fibrinogen was 350 mg/dL; Leiden Thrombophilia Study (LETS), 300 and 500 mg/dL. Results: Prospective studies–All OR, 2.35 (95% CI, 2.14 to 2.57; Het-w, NS); General population OR, 2.46 (95% CI, 2.22 to 2.72; Het-w, NS); Healthy men OR, 2.44 (95% CI, 2.20 to 2.72; Het-w, NS); Healthy women OR, 2.62 (95% CI, 1.92 to 3.58; Het-w, NS); Healthy men OR, 2.46 (95% CI, 1.88 to 3.28; Het-w, NS); Healthy women OR, 2.62 (95% CI, 1.92 to 3.58; Het-w, NS); High risk patients OR, 1.94 (95% CI, 1.58 to 2.38; Het-w, NS); Het-b test, Healthy men versus Healthy women, NS; Cross-sectional studies–OR, 1.52 (95% CI, 1.37 to 1.69; Het-w, NS); Case-control studies–OR, 3.03 (95% CI, 2.14 to 4.29; Het-w, NS). All studies–(prospective, cross-sectional, and case-control) OR, 1.99 (95% CI, 1.85 to 2.13). The Het-w test was statistically significant (P<0.05). When all the prospective studies were considered, a total of 2581 events in 47 323 subjects was observed and the estimate of risk of CVD was more than doubled when comparing the higher tertile to the lower one. Eight prospective studies were conducted in general populations and 1910 CV events were found in 37 684 subjects.\textsuperscript{20–27} The overall estimate of risk of cardiovascular events in subjects in the higher tertile of fibrinogen was more than doubled compared with that of subjects in the lower tertile.

Eight prospective studies were carried out on healthy men and a total of 1587 CV events in 24 983 subjects was observed.\textsuperscript{20–27} Three studies on healthy women reported 404 CV events in 13 803 individuals.\textsuperscript{20,23,26} No difference in the estimate of CV risk was found after separate analyses for men and women (Het-b test, not significant [NS]). Five prospective studies on high-risk subjects recruited 9639 individuals who experienced 671 events.\textsuperscript{26,29,31,32} Subjects in the higher tertile of fibrinogen had a 92% greater risk of CV events. No difference in CV risk was evident between studies in the general population and those in high-risk subjects (Het-b test, NS). No effect modification emerged from studies on subjects with or without previous CVD.

In cross-sectional and case-control studies, the overall estimates of risk in subjects with higher levels of fibrinogen compared with those in the lower tertile were 1.5, and 3 times higher, respectively.

Subgroup Analysis

Duration of follow-up was analyzed only for prospective studies (Figure 2A). Studies with duration of follow-up above and below 5.2 years had comparable ORs (2.5 versus 2.24; Het-b, NS). Similar results were obtained by examining the effect of duration of follow-up in studies that recruited high-risk subjects. In studies in general populations, subjects had an \( \approx \)6.0 year (median) follow-up. Studies with duration of follow up above and below the median value had a similar risk of CV events (OR, 2.40 versus 2.70). Duration of follow up did not influence the results of studies in healthy men as well as in high-risk subjects.

Mean fibrinogen values of the subjects recruited in each study were used as rough estimates of the fibrinogen level of the population of origin (Figure 2B). When all the studies were taken into consideration, the risk of CV events was almost twice as high in studies with mean fibrinogen values above 303 mg/dL. No difference in the estimates of risk were apparent when mean fibrinogen...
values measured in the patients recruited were examined according to study design (ie, cross-sectional and case-control studies).

The percentage of smokers in each study was used as an index of the interplay between smoking habits and fibrinogen levels in determining the level of CV risk (Figure 2C). No difference was apparent between studies according to the prevalence of smokers above and below the median value of 36% when all studies were considered. Similar results were obtained by evaluating all prospective studies or prospective studies on males, on the general population or high risk populations alone.

The prevalence of smoking in cross-sectional studies did not change the estimate of risk attributable to fibrinogen levels. It was not possible to evaluate the role of smoking habits in case-control studies.

Figure 2. (A) Risk of cardiovascular disease related to length of follow-up. Prospective studies were divided into subgroups according to the median length of follow-up. (B) Risk of cardiovascular disease related to mean plasma fibrinogen values of examined populations. Studies were divided into subgroups according to the median of mean fibrinogen values of the studies. (C) Risk of cardiovascular disease related to the percentage of current smokers. Studies were divided into subgroups according to the median percentage of smokers included in each study. (D) Risk of cardiovascular disease related to age. Studies were divided into subgroups according to the median of the means of age observed in each study.
Mean of subjects recruited in each study was used to evaluate the role of fibrinogen levels in younger and older patients (Figure 2D). Comparable results were found in the whole study group, in prospective studies of general populations, in prospective studies of high-risk individuals, in cross-sectional studies, and in case-control studies, all of which showed no effect modification.

**Meta Regression**

To examine the strength of the association between total cardiovascular events and the selected subgroups, an inverse variance-weighed multiple linear regression of the logarithmic ORs for total events were used as dependent variables against study design, percentage of smokers, age, and mean plasma fibrinogen values as explanatory variables (Table 3). Cross-sectional studies behaved differently. Mean fibrinogen values and percentage of smokers at baseline did not influence the risk estimates.

**Limitations of the Present Meta-Analysis**

Publication biases and different study designs may have overestimated the risk related to high plasma fibrinogen levels. The somewhat lower estimates of CV risk in cross-sectional studies is likely to be caused by inherent selection biases. This can be because of specific characteristics of this type of study (ie, selection of subjects with better prognosis). Conversely, because of the type of studies or the use of fibrinogen values measured close to the index event (ie, more representative of the hemostatic state before the event), there might have been emphasis in the role of fibrinogen as a CV risk factor in case-control studies. However, the results of the present meta-analysis are strengthened by those of the Scottish Heart Health studies. However, the results of the present meta-analysis, it is unlikely that the selection characteristics of the studies retrieved (mean age, healthy/high-risk subjects, smoking habits, duration of follow-up, and mean plasma fibrinogen values) may have affected the estimates of the risk associated with quantiles of fibrinogen values.

Because different methods with differences in variability, accuracy, precision, and agreement among different laboratories have been used to measure plasma fibrinogen in the studies retrieved (Table 4). This may have hampered the accuracy of the risk estimates. However, the net results of each study—the association between high plasma fibrinogen and stroke and myocardial infarction—were unequivocal. Each method used different cutoff values (see legend of Figure 1). However, comparisons between higher and lower figures (as in the present analysis) reduce the disadvantages inherent to the differences in the methods used.

**Is Plasma Fibrinogen Measurement Improving Prediction of Future Ischemic Events By Established Risk Factors?**

1. **Fibrinogen Interaction With Other Risk Factors**

In the Prospective Cardiovascular Muster study, fibrinogen plasma levels of 277 mg/dL increased by 2-fold the risk of myocardial infarction in subjects with LDL cholesterol >163 mg/dL. In the Framingham study, fibrinogen levels of 312 mg/dL increased by 6-fold the risk of myocardial infarction in smokers. In the Gotheburg study, fibrinogen levels >500 mg/dL increased by 12-fold the risk of stroke in subjects with systolic blood pressure >180 mm Hg.

2. **Attributable Risk**

In the Atherosclerosis Risk in Communities study, the role of fibrinogen was marginal, albeit significant, when the data were corrected for major cardiovascular risk factors. However in the Scottish Heart Health Study, which examined various factors, fibrinogen was the second most important factor for predicting causes of death in men and the sixth most important factor for women. Based on the data from >1300 individuals who had experienced recurrence of a coronary event, the Gruppo Italiano per lo Studio della Sopravvivenza Nell’Infarto Miocardico (GISSI) Prevention Group prepared a Coronary Risk Chart for the secondary prevention of CHD. In addition to using fibrinogen levels to determine the overall risk of individual patients, this chart assesses attributable risks for established CV risk factors. Fibrinogen levels higher than median values (371 mg/dL) predicted myocardial reinfarction in younger as much as in older individuals. The prognostic role of fibrinogen for the evaluation of the global risk for CVD was comparable with that of major CV

### Table 3. Analysis of Confounding by Fitting Univariate Inverse Variance-Weighed Multiple Linear Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.8301</td>
<td>0.0843</td>
<td>0.0001</td>
</tr>
<tr>
<td>Case-control studies</td>
<td>0.1292</td>
<td>0.3792</td>
<td>0.7370</td>
</tr>
<tr>
<td>Cross-sectional studies</td>
<td>-0.4887</td>
<td>0.0849</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>0.0079</td>
<td>0.1038</td>
<td>0.9395</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>0.0121</td>
<td>0.0956</td>
<td>0.9002</td>
</tr>
<tr>
<td>Mean plasma fibrinogen value</td>
<td>0.0981</td>
<td>0.0984</td>
<td>0.3308</td>
</tr>
</tbody>
</table>

Prospective studies category is the reference category for Case-control and Cross-sectional studies.

### Table 4. Methods to Measure Plasma Fibrinogen

<table>
<thead>
<tr>
<th>Method</th>
<th>Principle</th>
<th>Interference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravimetry</td>
<td>Fibrin clot weight</td>
<td>Heparin, FDP, DIC, thrombolysis</td>
</tr>
<tr>
<td>Turbidimetry</td>
<td>Fibrinogen → Fibrin conversion</td>
<td>Hemolysis, bilirubin, lipids, FDP, heparin</td>
</tr>
<tr>
<td>Total clottable fibrinogen</td>
<td>Nitrogen content of the clot</td>
<td>Heparin</td>
</tr>
<tr>
<td>Clotting time</td>
<td>Fibrinogen → Fibrin conversion</td>
<td>FDP</td>
</tr>
<tr>
<td>Radial Immunodiffusion</td>
<td>Ag-Ab reaction</td>
<td>Dysfibrinogenemias, liver disease</td>
</tr>
<tr>
<td>Viscometry</td>
<td>Plasma vs serum viscosity</td>
<td>Dysfibrinogenemias, heparin, dysproteinemias</td>
</tr>
<tr>
<td>Nephelometry</td>
<td>Heat-precipitation</td>
<td>Lipids, dysproteinemias</td>
</tr>
</tbody>
</table>
risk factors. Furthermore, prediction of CVD by established factors was improved by 8% when fibrinogen was added to the analysis. Under the same conditions of analysis, cholesterol improved prediction by 5%, hypertension by 5%, and diabetes mellitus by 7% (Figure 3).

What Areas of Uncertainty Remain With Respect to the Association Between Fibrinogen and CVD?

1. Methods to Measure Plasma Fibrinogen
Taking into account accuracy (as evaluated with reference to the gravimetric method), precision (as evaluated by determining the inter- and intra-assay coefficients of variations), and agreement of methods (among different laboratories), the (semiquantitative) Clauss clotting method has been suggested to be a reliable manner of measuring very low and very high plasma fibrinogen levels in short- and long-term studies of repeatability. Recent data support the notion that the nephelometric method may provide a prediction comparable to that of the Clauss method.

Although requiring further confirmation, these observations raise the possibility that commonly recognized reference methods other than the Clauss may be recommended for future epidemiological studies. However, the potential availability of a simpler, easier, and more reproducible method by no means hampers the clinical impact of measuring plasma fibrinogen levels.

2. Pathogenetic Significance
Similar to other acute-phase proteins, expression of fibrinogen (ie, its plasma level) is regulated by interleukin-6 and impaired by transforming growth factor-β. C-reactive protein (CRP) is also an acute-phase reactant; its baseline levels predicted the risk of a first myocardial infarction and stroke independently of other risk factors in apparently healthy men as well as in patients with unstable angina. Fibrinogen correlates with CRP both in men and women. Thus, the question is whether raised plasma fibrinogen is the epiphenomenon of the severity of the vascular damage taking place. Vascular injury, response to vascular injury, and plaque rupture and fissuring are major stages of the development and progression of atherosclerosis. Presently, it is unclear whether plasma fibrinogen is related to 1 or more of these stages. However, although relevant from a therapeutic point of view (ie, measuring plasma fibrinogen to identify subjects in whom interventions on established risk factors affecting specific stages in atherosclerosis have to be greatest), the question is of little relevance from a prognostic point of view.

High fibrinogen levels have been reported to be accounted for by environmental and genetic differences. Some polymorphisms modulate the response of genes to environmental stimuli, ie, the same stimulus may cause different levels of fibrinogen in subjects with different polymorphisms. This is consistent with the possibility that a theoretical level (determined by genes) and a real level (because of the interaction of genes with the environment) of fibrinogen may play a role in the intra- and interpopulation variability of fibrinogen levels and may explain, at least in part, differences in CVD frequency and cardiovascular death between Japan and USA. However, despite its pathophysiological relevance, this information is unlikely to affect the clinical impact of plasma fibrinogen levels.

Areas of Future Research
The gradient of CHD death rate across European countries has been associated with a different distribution of some genotypes affecting plasma levels of factor VII. Some polymorphisms modulate the response of genes to environmental stimuli, ie, the same stimulus may cause different levels of fibrinogen in subjects with different polymorphisms. This is consistent with the possibility that a theoretical level (determined by genes) and a real level (because of the interaction of genes with the environment) of fibrinogen may play a role in the intra- and interpopulation variability of fibrinogen levels and may explain, at least in part, differences in CVD frequency and cardiovascular death between Japan and USA. However, despite its pathophysiological relevance, this information is unlikely to affect the clinical impact of plasma fibrinogen levels.
a similar gradient for fibrinogen is also present also is unclear.

In 2 studies,70,72 molecular variations of plasma fibrinogen have been related to arterial thrombosis regardless of their effect on plasma fibrinogen. Whether the analysis of these markers should be included in the cardiovascular risk factor profile regardless of plasma fibrinogen measurements remains to be clarified. Interleukin-6 gene variants have been reported.90 Their effect on plasma fibrinogen levels and, in turn, CVD, deserves proper investigation.

With 1 exception,16 the lack of clinical trials demonstrating the effectiveness of lowering fibrinogen levels on hard clinical end points is hampering the clinical impact of measuring plasma fibrinogen levels. Plasma levels of fibrinogen are lowered by drugs commonly used in clinical practice (Table 5). Clinical trials with these drugs should be encouraged to implement knowledge on the correlation between fibrinogen and CVD.

Within the area of cerebrovascular disease, it is presently possible to identify groups of subjects who will take advantage of therapies, including antiplatelet agents, antihypertensive therapy (or a combination of both), carotid endarterectomy, and anticoagulation. To improve the impact of plasma fibrinogen and address some of the issues raised above, future prospective observational or interventional studies in vascular medicine should include measurement of fibrinogen (and its genotypes) at the beginning of and at some time during the trials. This would be particularly relevant in large studies, with appropriate statistical power, that include individuals from different geographic areas. We believe that this attitude may refine the overall individual risk, and provide the individual patient with a tailor-made intervention based on a specific mechanism and/or stage of the atherosclerotic vascular disease.

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References

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Giulio Maresca, Anna Di Blasio, Roberto Marchioli and Giovanni Di Minno

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