Relationship Between Plasma Fibrinogen and Coronary Heart Disease in Women

Margita Eriksson, Nils Egberg, Sarah Wamala, Kristina Orth-Gomér, Murray A. Mittleman, Karin Schenck-Gustafsson

Abstract—Plasma fibrinogen is an independent risk factor for coronary heart disease (CHD) in men; however, its role in women is less clear. We examined the ability of plasma fibrinogen to predict CHD in a community-based, case-control study of women aged 65 years or younger living in the greater Stockholm area. Cases were all patients hospitalized for an acute coronary event between February 1991 and February 1994. Controls were randomly selected from the city census and were matched to cases by age and catchment area. Plasma fibrinogen was measured 3 to 6 months after hospitalization by using a fibrinogen assay based on fibrinogen polymerization time measurement. Of the 292 consecutive cases, 110 (37%) were hospitalized for an acute myocardial infarction and 182 (63%) for angina pectoris. The mean age ± SD in both patients and controls was 56 ± 7 years. Mean levels of plasma fibrinogen in patients and controls were 3.66 ± 0.81 and 3.25 ± 0.64 g/L (P < 0.0001), respectively. The age-adjusted odds ratio (OR) for CHD in the highest versus the lowest quartile of plasma fibrinogen was 6.0 (95% confidence interval [CI], 3.5 to 10.4). After adjustment for age, cigarette smoking, body mass index, systolic blood pressure, total cholesterol, high density lipoprotein cholesterol, triglycerides, and educational level, the OR was 3.0 (95% CI, 1.6 to 5.5). Further adjustment for C-reactive protein yielded the same result. In both premenopausal and postmenopausal women, the multivariate-adjusted ORs were 7.0 (95% CI, 1.8 to 28.3) and 2.1 (95% CI, 1.0 to 4.4), respectively. These results provide evidence that plasma fibrinogen is associated with an excess risk of CHD in women. (Arterioscler Thromb Vasc Biol. 1999;19:67-72.)

Key Words: fibrinogen ■ coronary heart disease ■ women

In recent years the role of plasma fibrinogen as an independent cardiovascular risk factor has been increasingly recognized. It is well demonstrated that occlusive thrombi are found in most cases of acute myocardial infarction (MI), sudden cardiac ischemic death, and unstable angina pectoris. Thrombosis is recognized as the central mechanism of these atherosclerotic complications.¹ There may also be a thrombotic component in the process of atherosclerosis.² Several large, prospective, epidemiological studies of healthy, middle-aged persons, mostly men, revealed a significant association between plasma fibrinogen level at entry and subsequent cardiovascular events.³⁻⁴ Plasma fibrinogen has also been associated with morbidity and mortality in coronary heart disease (CHD) patients⁵⁻¹¹ and to the extent of coronary atherosclerosis.¹²

The possible relation between plasma fibrinogen and cardiovascular risk in women has been less investigated. Hemostatic and endothelial function in relation to thrombogenesis and CHD may be of particular importance in women,¹³ because women with MI and anginal chest pain are more often free of angiographically visualized coronary atherosclerosis than are men.¹⁴ The purpose of this study was to evaluate the role of plasma fibrinogen as a determinant for CHD in women in a large, community-based, case-control study in the greater Stockholm area.

Methods

Study Groups

All female residents in the greater Stockholm area, aged 65 years or younger, who were hospitalized for an acute coronary event between February 1991 and February 1994 were asked to participate. Patients were included in the study if they had a diagnosis of: (1) either definite or suspected MI based on World Health Organization criteria of typical chest pain, typical enzyme patterns, and diagnostic ECG changes (ECG changes were classified using the Minnesota code); (2) unstable angina pectoris, defined as angina pectoris of recent onset, angina with deterioration during the previous 4 weeks before admission with respect to pain intensity and duration, or anginal pain at rest or during very low physical exertion; or (3) spasm angina, defined as angina pectoris at rest with pathological ST-segment changes on ECG and with normal coronary arteries on coronary angiography. In the 2 latter cases, coronary angiograms were sometimes performed on an emergency basis.

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Arterioscler Thromb Vasc Biol. is available at http://www.atvbaha.org
In all, 335 women were identified who fulfilled these criteria. Forty-three patients (13%) were not eligible for the study: 5 of them died between hospitalization and examination, 13 were too sick to visit the research center, 2 could not participate because of transportation difficulties, and 2 declined because they were recruited for other studies. Another 21 patients declined to participate for other reasons. Based on the hospital administrative diagnosis registry, the proportion of patients missed in our study group was 12%.

Control subjects were selected from the census registry of greater Stockholm. For each case, a healthy woman born on the same day or another day as close as possible and living in the same hospital catchment area as the case patient was invited to the research center. “Former smoker” was defined as one who had ceased smoking at least 1 year before examination. Women with a history of previous MI (MI group, 5%; angina group, 7%; Table 1) were recruited for other studies. Another 21 patients declined to participate, mostly due to administrative reasons, eg, difficulty to take time from work. In these instances another woman was selected from the census registry.

Data Collection
All patients were examined as outpatients between 3 and 6 months after hospitalization. At that time the patients were considered to be in a stable clinical and metabolic state and not in an acute phase for plasma fibrinogen.15 Matched controls were examined during a corresponding time period. In both cases and controls blood sampling was evenly distributed over the year to avoid influence of seasonal variation. Patients were kept on their usual medications.

Blood samples were drawn between 8 and 10 AM while the subject was in a supine position and after 5 minutes of supine rest and an overnight fast. Weight was measured in kilograms and height in centimeters. Body mass index (BMI) was calculated as weight/height2 . Systolic and diastolic blood pressures were measured in a supine position after a 5-minute rest. Hypertension was defined as blood pressure >150/90 mm Hg or having received treatment for hypertension. Diabetes mellitus was defined as either insulin-dependent or non–insulin-dependent diabetes mellitus. Smoking habits were assessed by questionnaire and categorized as never smoked, former smoker, or current smoker. A “former smoker” was defined as one who had ceased smoking at least a year before examination.

Menopausal status was assessed during a gynecological interview. “Postmenopausal” was defined as having had no menstrual periods for at least 6 months, if bilateral oophorectomy had occurred (surgical menopause), or if the woman had started hormone replacement therapy (HRT) before menopause and was older than 50 years at the time of her inclusion into the study. Full details of the study design have been described elsewhere.16

Laboratory Methods
Venous blood was drawn by antecubital, direct venipuncture without stasis into vacuum tubes containing 0.13 mol/L trisodium citrate (9:1 blood/citrate, vol/vol). The blood samples were immediately mixed and centrifuged at 2000g for 15 minutes at room temperature. The supernatant plasma was snap-frozen and stored at −70°C. All samples were taken by the same nurse. Plasma fibrinogen determination was performed with a polymerization rate method.17 The reference interval was 2.1 to 4.2 g/L. Inter-assay and intra-assay coefficients of variation were 2.4% and 3.3%, respectively, with a mean level of 2.2 g/L. With a mean level of 1.0 g/L, inter-assay and intra-assay coefficients of variation were 3.3% and 3.0%, respectively.

Total cholesterol was determined with CHOD-PAP and triglycerides with GPD-PAP enzymatic methods with reagents from Boehringer Mannheim. HDL was determined after isolation of the LDL and VLDL from serum by precipitation. The cholesterol content of the supernatant, ie, HDL cholesterol, was measured enzymatically. Lipoprotein(a) (Lp[a]) was analyzed using an immunoturbidimetric method from INCSTAR Corp. C-reactive protein (CRP) was measured by immunonephelometric assay.

Statistical Methods
Tests of normality were performed to verify the distribution of study variables. Both the Shapiro-Wilk W test and the skewness and kurtosis tests showed that plasma fibrinogen and several covariates were not normally distributed in the study group (P<0.0001). Therefore, the Wilcoxon signed-rank test was used to evaluate differences in continuous variables between cases and controls. The χ2 test was performed for discrete variables. Odds ratios (ORs), as measures of relative risk, were estimated using logistic regression analyses, and 95% confidence intervals (CIs) were computed. Trend tests were performed to test the linear effect of fibrinogen on the presence of CHD.13 Conditional logistic regression and age-adjusted unconditional logistic regression analyses were performed but did not differ largely. By using unconditional logistic analyses, power problems in subgroup analyses were avoided. Multivariable logistic regression models were performed to control for confounding factors. All continuous covariates were categorized in quartiles based on the distributions in the control group. We observed multiple control subjects whose fibrinogen levels were exactly equal to the cutoff points of 2.8 g/L (n=17), 3.1 g/L (n=22), and 3.6 g/L (n=16) for fibrinogen, resulting in a loss of symmetry in the number of controls in each quartile. All tests were 2-tailed. Statistical analysis was performed on an Apple Macintosh computer by using Statsoft statistical program software.19 A value of P<0.05 was considered statistically significant.

Ethical Considerations
This study was approved by the Ethics Committee at Karolinska Institute. All patients and controls gave informed consent.

Results
A total of 292 patients and 292 controls were included. Their mean age (±SD) was 56±7 years (range, 30 to 65). Seventy-seven percent of the patients were hospitalized for acute MI and 63% for angina pectoris. In all, 21% of the 292 patients had a history of previous MI (MI group, 5%; angina group, 16%; Table 1).

The baseline characteristics of the 292 patients and 292 controls are summarized in Table 1. Obesity (as assessed by BMI), hypertension, diabetes, smoking, and low socioeconomic status were significantly more prevalent among patients. The patients had significantly higher levels of total cholesterol, LDL, Lp(a), and triglycerides and lower levels of HDL. The mean value for plasma fibrinogen was significantly higher in patients than in controls and tended to be higher in diabetics than in nondiabetics, 3.93±0.97 and 3.62±0.79 g/L, respectively (P=0.12 [NS]). The age-adjusted mean value for plasma fibrinogen was significantly higher in postmenopausal women not using HRT, 3.74±0.87 g/L, and in premenopausal women, 3.64±0.95 g/L, compared with postmenopausal women using HRT, 3.30±0.80 g/L (P=0.008). Results in the previous-MI group (21%) did not differ from those in the whole group regarding smoking, diabetes mellitus, plasma fibrinogen, and CRP.

The ORs for being a patient in each of the fibrinogen quartiles are shown in Table 2, with the lowest quartile as the reference category. The age-adjusted OR for CHD in the highest versus the lowest quartile of fibrinogen was 6.0 (95% CI, 3.5 to 10.4) and the multivariate-adjusted OR was 3.0 (95% CI, 1.6 to 5.5).

When all logistic models were repeated without data for the diabetic patients, the age-adjusted OR for CHD in the highest versus the lowest quartile of fibrinogen was 5.5 (95% CI, 3.2 to 9.7), and the corresponding multivariate-adjusted OR was 2.9.
Among women who had never smoked (32% of cases, 46% of controls), the age-adjusted OR for CHD in the highest versus the lowest quartile of fibrinogen was 5.1 (95% CI, 2.2 to 11.9) (P for trend, 0.0001). After adjustment for age, BMI, systolic blood pressure, total cholesterol, HDL, triglycerides, and educational level, the corresponding OR was 4.4 (95% CI, 1.7 to 11.5) (P for trend, 0.002).

Although CRP was strongly associated with plasma fibrinogen levels (P<0.0001), controlling for CRP did not alter the results. After adjustment for age and CRP, the OR for CHD associated with the highest quartile of fibrinogen was 6.1 (95% CI, 3.5 to 10.7). After further adjustment for smoking, BMI, systolic blood pressure, total cholesterol, HDL, triglycerides, and educational level, the OR was 3.2 (95% CI, 1.7 to 6.0).

TABLE 2. ORs for CHD According to Plasma Fibrinogen Quartiles

<table>
<thead>
<tr>
<th>Quartiles</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen, g/L</td>
<td>≤2.8</td>
<td>&gt;2.8, ≤3.1</td>
<td>&gt;3.1, ≤3.6</td>
<td>&gt;3.6</td>
<td></td>
</tr>
<tr>
<td>Patients, n</td>
<td>27</td>
<td>57</td>
<td>91</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>Controls, n</td>
<td>81</td>
<td>67</td>
<td>80</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted (95% CI)</td>
<td>2.68 (1.52–4.71)</td>
<td>3.63 (2.13–6.20)</td>
<td>6.01 (3.48–10.39)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted (95% CI)*</td>
<td>1.70 (0.91–3.16)</td>
<td>2.19 (1.21–3.96)</td>
<td>2.98 (1.60–5.52)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

N=584.

*Adjusted for age, smoking, BMI, systolic blood pressure, total cholesterol, HDL, triglycerides, and educational level.
With increasing levels of plasma fibrinogen the ORs for angina pectoris and MI increased. In subgroup analyses the multivariate-adjusted ORs for women in the highest versus the lowest quartile of fibrinogen were 2.7 (95% CI, 1.3 to 5.4) and 3.6 (95% CI, 1.4 to 9.2), respectively, for angina and MI patients (Table 3). Furthermore, for both premenopausal and postmenopausal women the ORs increased with increasing plasma fibrinogen levels in subgroup analyses. The multivariate-adjusted ORs for women in the highest versus the lowest quartile of fibrinogen were 7.0 (95% CI, 1.8 to 28.3) and 2.1 (95% CI, 1.0 to 4.4), respectively, for premenopausal and postmenopausal women. The OR for postmenopausal women persisted when data for women on HRT were excluded (Table 3). After comparing the logistic model with an interaction between menopausal status and plasma fibrinogen levels with another model without such interaction, the likelihood χ² test showed that these 2 models were not statistically different from each other (P=0.15).

**Discussion**

Several prospective and cross-sectional studies have revealed that plasma fibrinogen levels have a strong predictive value for CHD and stroke in men, but the role of plasma fibrinogen in women is less clear. Therefore, we assessed the association between plasma fibrinogen and CHD in women. The risk of being hospitalized for an acute coronary event was 6 times higher for women in the highest quartile of fibrinogen compared with women in the lowest quartile. Although they declined to a 3-fold risk, these results remained statistically significant after adjusting for several possible confounders. The results also persisted when analyzing multivariate-adjusted ORs for angina pectoris and MI separately. These findings extend previous observations of plasma fibrinogen levels in angina pectoris and MI patients.

The association between plasma fibrinogen and cardiovascular risk does not establish a cause-effect relation, because plasma fibrinogen levels are related to several major lifestyle and physical characteristics known to be associated with increased risk of CHD in women. 20 We used a multivariate logistic regression technique to adjust for major confounders to further explore the independent contribution of plasma fibrinogen as a cardiovascular risk factor. Diabetes mellitus is a potential confounder of the relationship between plasma fibrinogen and CHD. Therefore, all logistic regression models were repeated without the diabetic patients’ data, with persistent results. A further important confounder is smoking. To control for a possible residual effect due to smoking we also repeated the logistic regression models in women who had never smoked, with similar results. These findings indicate that the effect of plasma fibrinogen on cardiovascular risk is not simply the result of cigarette smoking or diabetes mellitus. Thus, we provide evidence that plasma fibrinogen is associated with excess risk of female CHD, independent of potentially confounding cardiovascular risk factors. Medications such as fibrates and ticlopidine are known to lower plasma fibrinogen. However, there were no users of these agents among the patients and controls. A total of 217 patients and none of the controls were treated with a low dose of aspirin (75 to 160 mg/d). Aspirin therapy in low doses has provided evidence that plasma fibrinogen is associated with increased risk of CHD mortality in women. 21 In the Atherosclerosis Risk in Communities (ARIC) Study, a large, population-based, prospective study, plasma fibrinogen was found to be an important risk factor for CHD mortality in women. 7 Higher levels of plasma fibrinogen were also related to all-cause mortality in this population. The Scottish Heart Health Study, a random population sample with a follow-up period of ~8 years, recently reported plasma fibrinogen to be a risk factor for CHD mortality and all-cause mortality in women. 8 In a Finnish

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**TABLE 3. ORs According to Fibrinogen Quartiles in Subgroup Analyses**

<table>
<thead>
<tr>
<th>Fibrinogen g/L</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-adjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina patients</td>
<td>1</td>
<td>2.96 (1.55–5.65)</td>
<td>3.58 (1.93–6.65)</td>
<td>4.54 (2.39–8.61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MI patients</td>
<td>1</td>
<td>2.16 (0.88–5.29)</td>
<td>3.85 (1.70–8.67)</td>
<td>9.22 (4.15–20.51)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>1</td>
<td>6.94 (2.32–20.77)</td>
<td>7.90 (2.73–22.84)</td>
<td>12.59 (4.17–38.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>1</td>
<td>1.66 (0.85–3.27)</td>
<td>2.45 (1.30–4.62)</td>
<td>4.19 (2.21–7.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariate-adjusted*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina patients</td>
<td>1</td>
<td>1.88 (0.93–3.81)</td>
<td>2.21 (1.12–4.35)</td>
<td>2.65 (1.31–5.38)</td>
<td>0.009</td>
</tr>
<tr>
<td>MI patients</td>
<td>1</td>
<td>1.16 (0.42–3.24)</td>
<td>2.11 (0.83–5.31)</td>
<td>3.56 (1.38–9.19)</td>
<td>0.003</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>1</td>
<td>4.46 (1.18–16.84)</td>
<td>6.22 (1.74–22.22)</td>
<td>7.05 (1.76–28.27)</td>
<td>0.005</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>1</td>
<td>1.15 (0.54–2.42)</td>
<td>1.48 (0.73–3.01)</td>
<td>2.10 (1.01–4.38)</td>
<td>0.024</td>
</tr>
<tr>
<td>Postmenopausal†</td>
<td>1</td>
<td>1.16 (0.47–2.83)</td>
<td>1.57 (0.69–3.60)</td>
<td>2.51 (1.06–5.92)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate 95% CIs.

*Adjusted for age, smoking, BMI, systolic blood pressure, total cholesterol, HDL, triglycerides, and educational level.
†Postmenopausal women excluding those taking HRT.
population-based, case-control study, women with prevalent CHD had higher plasma fibrinogen concentrations than did women free of CHD.22 In a Swedish case-control study there was a similar, but not statistically significant, association in women.23

The cardioprotective effect of estrogens in women is well established from epidemiological and clinical studies and may explain a substantial proportion of the sex differential in risk of CHD.24 Furthermore, in women hemostatic factors are influenced by menopausal status and use of HRT.25 In the present study postmenopausal women using HRT had significantly lower age-adjusted plasma fibrinogen levels compared with postmenopausal women not using HRT and with premenopausal women. In subgroup multivariate analyses we found premenopausal women in the highest versus the lowest quartile of fibrinogen to have a 7-fold increased risk of CHD compared with postmenopausal women, who had a 2-fold risk of CHD in the highest versus the lowest quartile. The high OR in the premenopausal group is less reliable because of small sample size and wide CI. However, the discrepancy between premenopausal and postmenopausal women may also be a reflection of a more pronounced vessel wall inflammation, as part of the atherosclerosis process, in the premenopausal women. The prognostic value of plasma fibrinogen may also become stronger when the level of other determinants of risk is low.

Plasma fibrinogen is an acute-phase protein. The inflammatory process involved in atherosclerotic vascular disease26 may be part of the explanation for elevated plasma fibrinogen levels in the patient group in the present study. However, after controlling for CRP, another acute-phase protein, the results remained statistically significant. This suggests that plasma fibrinogen is not simply a marker of vessel disease but is directly involved in the pathogenesis of occlusive thrombus formation. There is some evidence that fibrinogen gene polymorphism is related to plasma fibrinogen levels and also possibly to cardiovascular risk.27 Interestingly, there may be a sex-specific effect on the association between genetic variation and plasma fibrinogen levels.28

The physiological importance of elevated plasma fibrinogen levels is not fully understood. The mechanisms by which plasma fibrinogen may be involved in atherothrombosis are rheological alterations, increased platelet aggregability, increased fibrin formation, and stimulation of vascular cell proliferation and migration, with increasing plasma fibrinogen levels.29 Thus, elevated plasma fibrinogen levels, whatever their origin—genetic, as part of the inflammation reaction, or some other reason—may cause a hypercoagulative state that could influence the degree and duration of thrombus formation at the time of coronary injury.

Few studies so far have explored the role of plasma fibrinogen as a cardiovascular risk factor in women, and no previous study has included only females as this study has. Our study has the limitations of a case-control study. However, it is a population sample including nearly all consecutive female patients hospitalized for acute coronary syndromes in the greater Stockholm area between 1991 and 1994. In a future study, prospective data will be analyzed in a follow-up of 3 to 5 years in this population.

In conclusion, the present findings in this unique cohort provide evidence that plasma fibrinogen is associated with excess risk of CHD in women, especially at a younger age. It seems likely that high plasma fibrinogen levels, whatever their origins, contribute substantially to the risk of coronary thrombotic events in women.

Acknowledgments

This work was supported by grant number HL45785 from the National Institutes of Health, Bethesda, Md (to K.O.-G.); grant number B93-19X-1010407 from the Swedish Medical Research Council (to K.S.-G.); a grant from the Swedish Labor Market Insurance Company (to K.O.-G. and K.S.-G.); and a grant from the Swedish Heart and Lung Foundation (to K.S.-G.).

References

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doi: 10.1161/01.ATV.19.1.67
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272
Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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