

# Association of Fibrinogen With Cardiovascular Risk Factors and Cardiovascular Disease in the Framingham Offspring Population

James J. Stec, BS; Halit Silbershatz, PhD; Geoffrey H. Tofler, MD; Travis H. Matheny, MLA; Patrice Sutherland, BS; Izabela Lipinska, PhD; Joseph M. Massaro, PhD, Peter F.W. Wilson, MD; James E. Muller, MD; Ralph B. D'Agostino Sr, PhD

**Background**—Fibrinogen has been identified as an independent risk factor for cardiovascular disease and associated with traditional cardiovascular risk factors. Also, the role of elevated fibrinogen in thrombosis suggests that it may be on the causal pathway for certain risk factors to exert their effect. These associations remain incompletely characterized. Moreover, the optimal fibrinogen assay for risk stratification is uncertain.

**Methods and Results**—In 2632 subjects from cycle 5 of the Framingham Offspring Population, fibrinogen levels were determined with a newly developed immunoprecipitation test (American Biogenetic Sciences) and the functional Clauss method. With the immunoprecipitation method, there were significant linear trends across fibrinogen tertiles ( $P < 0.001$ ) for age, body mass index, smoking, diabetes mellitus, total cholesterol, HDL cholesterol, and triglycerides in men and women. The Clauss method had significant results ( $P < 0.030$ ), except for triglycerides in men. Fibrinogen levels were higher for those with compared with those without cardiovascular disease. After covariate adjustment, fibrinogen remained significantly higher in those with cardiovascular disease with the use of the immunoprecipitation test ( $P = 0.035$  and  $P = 0.018$  for men and women, respectively) but not with the Clauss method.

**Conclusions**—Fibrinogen was associated with traditional cardiovascular risk factors. Elevation of fibrinogen may provide a mechanism for risk factors to exert their effect. Also, fibrinogen levels were higher among subjects with cardiovascular disease compared with those without disease. The immunoprecipitation test showed a stronger association with cardiovascular disease than the Clauss method, suggesting that it may be a useful screening tool to identify individuals at increased thrombotic risk. (*Circulation*. 2000;102:1634-1638.)

**Key Words:** fibrinogen ■ cardiovascular disease ■ Framingham Offspring Study

Fibrinogen has been identified as a major independent risk factor for cardiovascular disease.<sup>1,2</sup> Fibrinogen has also been associated with traditional cardiovascular risk factors,<sup>3-6</sup> suggesting that elevation of fibrinogen may be a pathway by which these risk factors exert their effect. There are several mechanisms by which fibrinogen may increase cardiovascular risk. First, it binds specifically to activated platelets via glycoprotein IIb/IIIa, contributing to platelet aggregation. Second, increased fibrinogen levels promote fibrin formation. Third, it is a major contributor to plasma viscosity. Finally, it is an acute-phase reactant that is increased in inflammatory states.

The objectives of this study were first to evaluate the association between fibrinogen and several traditional risk factors, including age, body mass index, cigarette smoking, diabetes mellitus, total cholesterol, HDL cholesterol, and triglycerides, and second to determine the association of

fibrinogen with prevalent cardiovascular disease. Because the optimal fibrinogen assay for use in risk stratification remains uncertain, we compared a newly developed immunoprecipitation test (functional intact fibrinogen, FiF; American Biogenetic Sciences) with the Clauss method.

## Methods

### Study Population

The study subjects were members of the Framingham Offspring Study, a long-term evaluation of risk factors for cardiovascular disease. The design and methodology of the Framingham Offspring Study have been previously reported.<sup>7</sup> The participants are either natural or adopted children of the original Framingham Study Cohort or spouses of participating children with a mean age of  $55 \pm 10$  years. During the fifth offspring examination cycle administered between January 1991 and January 1995, 3799 subjects visited the Framingham Heart Study. Of these, only 2632 subjects had both fibrinogen measurements taken.

Received March 6, 2000; revision received May 3, 2000; accepted May 8, 2000.

From the Institute for Prevention of Cardiovascular Disease, Cardiovascular Division, Beth Israel Deaconess Medical Center, Harvard Medical School (J.J.S., G.H.T., I.L., J.E.M.); Boston University, Mathematics and Statistics Department (H.S., R.B.D'A.); and Boston University School of Public Health, Department of Epidemiology and Biostatistics (J.M.M.), Boston, Mass; and the National Heart, Lung and Blood Institutes, Framingham Heart Study and National Institutes of Health (T.H.M., P.S., P.F.W.W.), Framingham, Mass.

Correspondence to Ralph B. D'Agostino, PhD, Boston University, Mathematics and Statistics Department, 111 Cummington St, Boston, MA 02215. E-mail ralph@bu.edu

© 2000 American Heart Association, Inc.

*Circulation* is available at <http://www.circulationaha.org>

**TABLE 1. Association of Fibrinogen With Traditional Cardiovascular Risk Factors**

	FiF (A) Fibrinogen Tertiles			Clauss (A) Fibrinogen Tertiles		
	Low (n=418)	Mid (n=418)	High (n=420)	Low (n=422)	Mid (n=421)	High (n=413)
<b>Men*</b>						
Age	52.3 (±0.50)	56.7 (±0.49)	58.6 (±0.46)	51.7 (±0.49)	56.2 (±0.48)	59.8 (±0.46)
Body mass index	27.2 (±0.18)	28.6 (±0.22)	29.0 (±0.22)	27.5 (±0.18)	28.6 (±0.21)	28.8 (±0.23)
Smoking	13.4%	18.2%	24.8%	11.8%	19.2%	25.5%
Diabetes mellitus	3.1%	9.3%	14.0%	4.5%	10.0%	12.1%
Total cholesterol	193.7 (±1.60)	201.9 (±1.55)	204.5 (±1.70)	196.6 (±1.64)	201.7 (±1.52)	201.8 (±1.73)
HDL cholesterol	46.5 (±0.56)	43.8 (±0.56)	38.3 (±0.48)	45.0 (±0.60)	42.9 (±0.53)	40.7 (±0.52)
Triglycerides	116.3 (±3.53)	152.6 (±3.96)	213.2 (±7.10)	155.2 (±5.54)	161.0 (±5.88)	166.3 (±4.98)
	Low (n=459)	Mid (n=459)	High (n=458)	Low (n=449)	Mid (n=461)	High (n=466)
<b>Women†</b>						
Age	51.4 (±0.45)	55.6 (±0.46)	58.3 (±0.43)	51.7 (±0.45)	55.4 (±0.45)	58.1 (±0.45)
Body mass index	24.5 (±0.19)	26.5 (±0.22)	29.5 (±0.30)	24.5 (±0.18)	26.7 (±0.22)	29.2 (±0.31)
Smoking	13.1%	20.9%	22.9%	12.2%	20.4%	24.0%
Diabetes mellitus	0.9%	3.3%	9.6%	3.1%	3.7%	6.9%
Total cholesterol	198.4 (±1.65)	207.7 (±1.75)	220.0 (±1.79)	201.9 (±1.77)	209.5 (±1.83)	214.3 (±1.69)
HDL cholesterol	61.4 (±0.68)	56.2 (±0.70)	50.3 (±0.72)	59.8 (±0.72)	56.0 (±0.73)	52.2 (±0.71)
Triglycerides	101.0 (±2.35)	130.0 (±2.96)	188.2 (±7.61)	125.2 (±4.43)	144.0 (±6.53)	149.3 (±4.19)

Values given are mean (±SE) for continuous parameters, and percent prevalence for dichotomous parameters.

\*For every risk factor, the linear trend across the FiF tertiles is significant ( $P<0.001$ ). For every risk factor except triglycerides, the linear trend across the Clauss tertiles is significant ( $P<0.030$ ). Lower FiF tertile=109.6 to 286.4; mid FiF tertile=286.5 to 351.7; upper FiF tertile=352.0 to 652.5. Lower Clauss tertile=172.0 to 276.0; mid Clauss tertile=277.0 to 326.0; upper Clauss tertile=327.0 to 815.0.

†For every risk factor, the linear trend across the FiF tertiles and across the Clauss tertiles is significant ( $P<0.010$ ). Lower FiF tertile=104.8 to 280.2; mid FiF tertile=280.3 to 344.9; upper FiF tertile=345.0 to 742.0. Lower Clauss tertile=138.0 to 284.0; mid Clauss tertile=285.0 to 335.0; upper Clauss tertile=336.0 to 598.0.

They were 1256 men, 175 of whom had known cardiovascular disease, and 1376 women, 92 of whom had cardiovascular disease. For the present analysis, cardiovascular disease included history or evidence of coronary artery disease, myocardial infarction, stable and unstable angina, stroke, intermittent claudication, and congestive heart failure. Criteria of events have been reported elsewhere.<sup>8</sup> Diabetes was defined as either taking insulin or an oral hypoglycemic agent or having a fasting blood sugar level of  $\geq 140$  mg/dL on or before cycle 5. Smoking was defined as currently smoking.

### Blood Sample and Analysis

Blood samples were collected from an antecubital vein between 8 and 9 AM after an overnight fast. For determination of fibrinogen, blood samples were anticoagulated with 3.8% trisodium citrate (9:1 vol/vol) and kept on ice until centrifugation at 2500g for 30 minutes at 4°C. Plasma samples were quickly frozen and stored at  $-70^{\circ}\text{C}$  for subsequent analysis. Fibrinogen levels were determined with the immunoprecipitation test (Functional Intact Fibrinogen, FiF) and Clauss<sup>9</sup> method. FiF uses a monoclonal antibody (45J) specific for the  $\alpha$ -appendage on the intact fibrinogen molecule.<sup>10</sup> The calibration curve is created with serial dilutions of standard lyophilized plasma of 273 mg/dL (Baxter Laboratories) from 600 to 75 mg/dL. Both positive (lyophilized plasma at a concentration of 235 mg/dL, Baxter Laboratories) and negative (fibrinogen deficient) controls are run with each assay along with test plasma to determine whether the assay is within the acceptable range. The turbidity of the solution is read at a wavelength of 340 nm with a Molecular Devices UV Max kinetic microplate reader first after 4 minutes of incubation. Then, 0.2 mg/mL of the 45J antibody is added, and the absorbance is read again after 15 minutes of incubation. The fibrinogen concentration is determined from a standard calibration

curve, and the change in absorbance at 340 nm is determined after the addition of the 45J antibody.

### Statistical Analysis

The analysis described below was performed for each sex and fibrinogen assay.

The association between fibrinogen and traditional risk factors for cardiovascular disease was determined by first grouping subjects into sex-specific fibrinogen tertiles. Then, for age, body mass index, total cholesterol, HDL cholesterol, and triglycerides, a test for linear trend across the tertiles (based on a 1-way ANOVA) was performed for each risk factor. For diabetes and smoking, a test for linear trend across the tertiles (based on logistic regression) was performed for each risk factor.

Mean fibrinogen levels within the 2 assays were calculated (unadjusted and least square means) for both prevalent cardiovascular disease and no cardiovascular disease. The relationship of fibrinogen to prevalent cardiovascular disease was determined with a logistic regression model; both univariate and multivariate models were used. Multivariate models adjusted for age, body mass index, cigarette smoking, diabetes mellitus, total cholesterol, and triglycerides.

## Results

### Assay Characteristics

The coefficient of variance for the FiF and Clauss assays, as determined by analysis of a single pooled plasma sample 10 times consecutively, was 6.2% for FiF and 2.6% for Clauss. The regression analysis for 10 plasma samples that were run on 2

**TABLE 2. Association Between Prevalent Cardiovascular Disease and Fibrinogen**

	Unadjusted			Adjusted		
	CVD	No CVD	<i>P</i>	CVD	No CVD	<i>P</i>
<b>Men</b>						
FiF, mg/dL	354±5.46	319±2.32	<0.001	333±5.16	322±2.00	0.0348
Clauss, mg/dL	328±4.00	303±1.73	<0.001	313±3.98	305±1.54	0.1002
<b>Women</b>						
FiF, mg/dL	370±9.04	316±2.28	<0.001	336±7.25	319±1.89	0.0177
Clauss, mg/dL	338±6.62	313±1.63	<0.001	320±5.60	314±1.46	0.2529

CVD indicates cardiovascular disease. Values are mean±SE. Unadjusted probability value assesses difference between CVD status with logistic regression with no covariates. Adjusted probability value assesses difference between CVD status with logistic regression adjusting for age, body mass index, smoking, diabetes mellitus, total cholesterol, and triglycerides.

consecutive days using FiF was 0.99. The linear regression relationship (*R*) between the FiF and Clauss assays was 0.64.

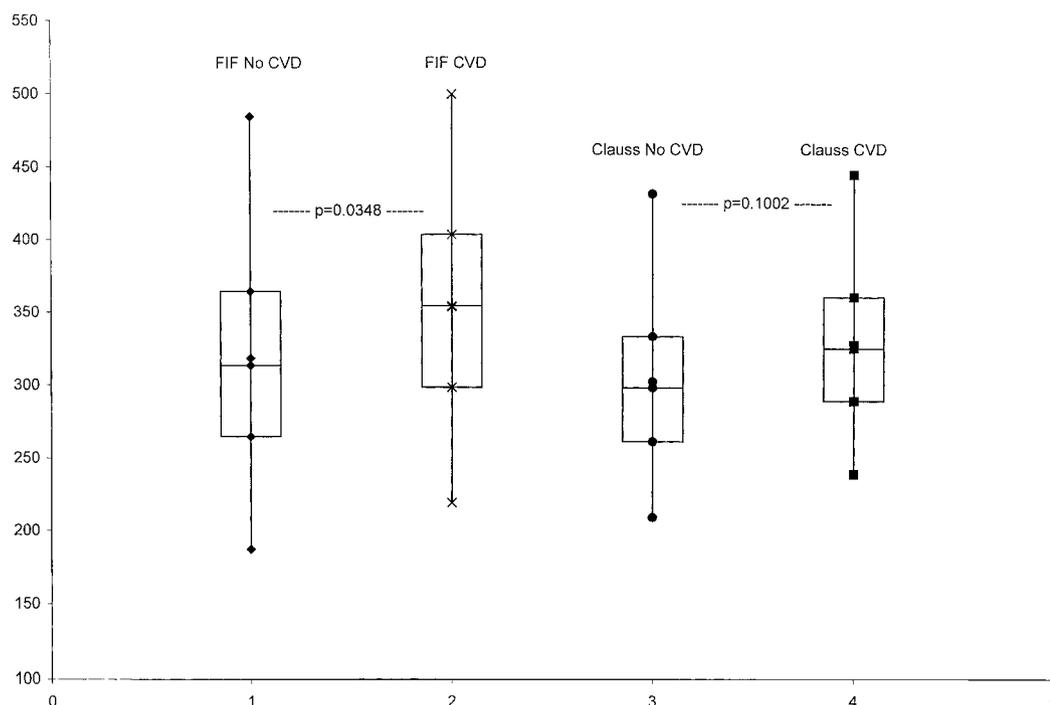
### Association With Traditional Risk Factors

Traditional risk factors for cardiovascular disease were analyzed in relation to fibrinogen values obtained with both methods (Table 1). With the FiF assay, for both men and women, there was a significant linear trend across fibrinogen tertiles ( $P<0.001$ ) for the traditional cardiovascular risk factors of age, body mass index, smoking, diabetes mellitus, total cholesterol, HDL cholesterol, and triglycerides. For all risk factors except HDL cholesterol, the risk factor increased as FiF increased. For HDL cholesterol, the risk factor decreased with increasing FiF. For women, risk factor relationships across Clauss fibrinogen tertiles were similar to

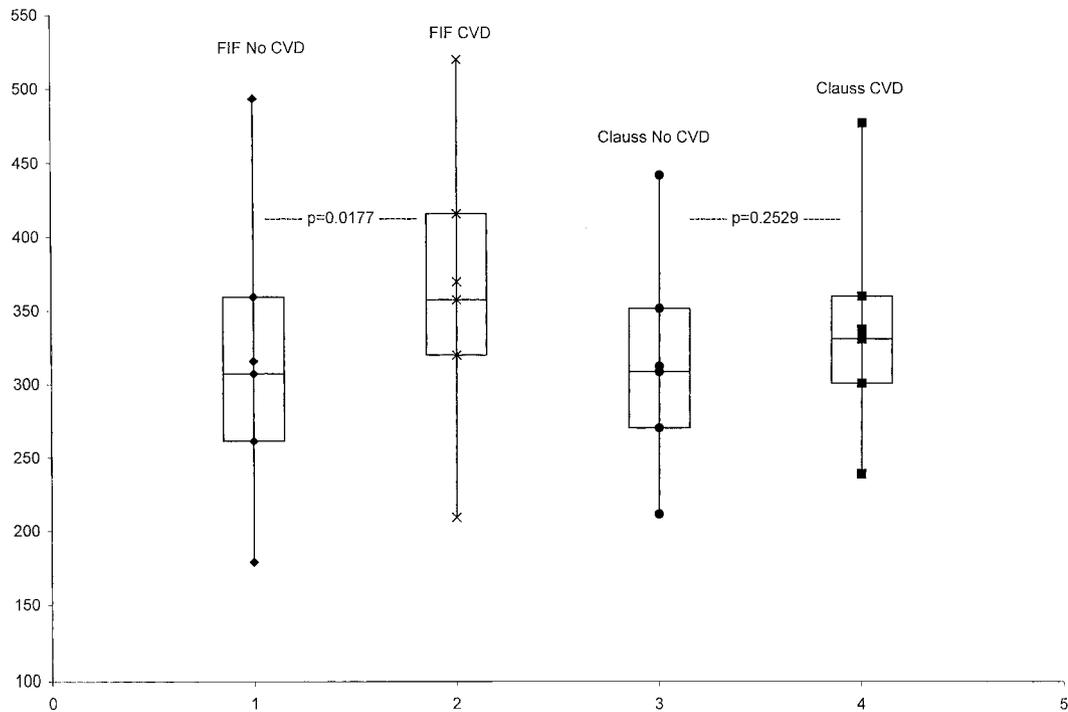
those seen across FiF tertiles ( $P<0.010$ ). For men, relationships across Clauss fibrinogen tertiles were similar to those seen across FiF tertiles for each risk factor ( $P<0.030$ ) except triglycerides. The trend for triglycerides in men, although not significant ( $P=0.150$ ), was still linear.

### Association With Cardiovascular Disease

The two fibrinogen assays were evaluated for their association with cardiovascular disease (Table 2 and Figures 1 and 2). The unadjusted mean fibrinogen concentration for men was higher among those with cardiovascular disease than those without disease with both FiF ( $354\pm 5.46$  versus  $319\pm 2.32$  mg/dL,  $P<0.001$ ) and Clauss ( $328\pm 4.00$  versus  $303\pm 1.73$  mg/dL,  $P<0.001$ ). The unadjusted mean fibrinogen concentrations for women were also higher among those



**Figure 1.** Box-Whisker plots of fibrinogen levels in men with and without prevalent cardiovascular disease (CVD) as assessed by FiF immunoprecipitation and Clauss methods. End points of plots are 2.5% and 97.5% percentiles. Probability values assess difference across cardiovascular disease status with respect to fibrinogen levels after adjustment for covariates. With FiF, fibrinogen levels are significantly higher among men with prevalent cardiovascular disease after adjustment for age, body mass index, smoking, diabetes mellitus, total cholesterol, and triglycerides.



**Figure 2.** Box-Whisker plots of fibrinogen levels in women with and without prevalent cardiovascular disease (CVD) as assessed by FiF immunoprecipitation and Clauss methods. End points of plots are 2.5% and 97.5% percentiles. Probability values assess difference across cardiovascular disease status with respect to fibrinogen levels after adjustment for covariates. With FiF, fibrinogen levels are significantly higher among women with prevalent cardiovascular disease after adjustment for age, body mass index, smoking, diabetes mellitus, total cholesterol, and triglycerides.

with cardiovascular disease with both FiF ( $370 \pm 9.04$  versus  $316 \pm 2.23$  mg/dL,  $P < 0.001$ ) and Clauss ( $338 \pm 6.62$  versus  $313 \pm 1.63$  mg/dL,  $P < 0.001$ ). In both men and women, after adjustment for age, body mass index, smoking, diabetes mellitus, total cholesterol, and triglycerides, FiF ( $333 \pm 5.16$  versus  $322 \pm 2.00$  mg/dL in men,  $336 \pm 7.25$  versus  $319 \pm 1.89$  mg/dL in women) and Clauss ( $313 \pm 3.98$  versus  $305 \pm 1.54$  mg/dL in men,  $320 \pm 5.60$  versus  $314 \pm 1.46$  mg/dL in women) remained higher in those with prevalent cardiovascular disease. In addition, FiF remained significantly associated with prevalent cardiovascular disease after adjustment for all the covariates listed above for both men ( $P = 0.035$ ) and women ( $P = 0.018$ ); however, Clauss assay did not ( $P \geq 0.100$ ).

## Discussion

The results from the present study show strong linear relationships between fibrinogen and traditional risk factors for cardiovascular disease with the immunoprecipitation (FiF) and functional (Clauss) methods. The significant relationships suggest a link between fibrinogen and traditional cardiovascular risk factors. Fibrinogen levels were also higher among men and women with prevalent cardiovascular disease. The results obtained from this study are consistent with and extend those of other studies linking fibrinogen to prevalent cardiovascular disease<sup>11,12</sup> and to traditional cardiovascular risk factors.<sup>13,14</sup>

Although the 2 assays are significantly correlated ( $R = 0.64$ ), a considerable variation between the assays is present, which may be due to the characteristics of fibrinogen

evaluated by each assay. FiF is a monoclonal antibody–based assay that measures the amount of fibrinogen antigen present, whereas Clauss is a clotting time–based method that measures the ability of fibrinogen to be enzymatically converted to a fibrin clot. After adjustment for covariates, FiF remained significantly correlated to prevalent cardiovascular disease in men and women, whereas Clauss did not, suggesting that FiF may be a better overall predictor of risk. Further planned prospective analysis will help to elucidate which assay is better at prospectively identifying people at increased risk.

The Caerphilly<sup>14</sup> and Speedwell<sup>15</sup> studies measured fibrinogen levels with both the nephelometric<sup>16</sup> and Clauss clotting time methods. In the Caerphilly study, fibrinogen was found to be associated with ischemic heart disease with both methods. However, in the Speedwell study, fibrinogen levels were higher in subjects with ischemic heart disease with the nephelometric but not the Clauss method. With Clauss, fibrinogen levels were higher among the Speedwell study subjects without ischemic heart disease. The different results found in the Speedwell study show the need to determine the optimal fibrinogen assay. Although further prospective studies are needed to determine which assay is the best predictor of future events, FiF may be favored as a screening tool because multiple samples may be run concurrently, whereas samples must be run individually with the Clauss method. In contrast to the Clauss method, FiF levels are unaffected by anticoagulants or fibrin degradation products.

Fibrinogen may increase cardiovascular risk in several ways. It plays an important role in platelet aggregation, plasma viscosity, and fibrin formation. Fibrinogen is an

acute-phase reactant that is increased in inflammatory states. Elevations of fibrinogen and C-reactive protein have been identified in patients with unstable angina, supporting the hypothesis that inflammation may play an important role in plaque rupture and thrombosis.<sup>17</sup> C-reactive protein has also been shown to be predictive of future myocardial infarction.<sup>18</sup>

### Traditional Risk Factors

The association of fibrinogen with traditional cardiovascular risk factors shown in this and other studies<sup>3-5,12</sup> suggests that it may be a mechanism through which the risk factors exert their effect. For example, the increased risk of cardiovascular disease<sup>19</sup> and stroke associated with smoking may be mediated in part through fibrinogen. Fogari et al<sup>20</sup> found that fibrinogen levels increased with the number of cigarettes smoked. Fibrinogen levels also quickly fall after smoking cessation, suggesting that this rapid fall in level may be a mechanism for the reduction in cardiovascular risk after smoking cessation.

Elevation in fibrinogen level may also be a mechanism by which obesity increases the risk of cardiovascular disease. A reduction in body mass index after a low-calorie diet for 6 months has been accompanied by a fall in fibrinogen level.<sup>21</sup>

The strong relationship between fibrinogen and LDL cholesterol level suggests that the increased risk of cardiovascular disease associated with elevated LDL levels may be mediated in part through fibrinogen. The Prospective Cardiovascular Munster (PROCAM)<sup>6</sup> study found that individuals who had LDL and fibrinogen levels in the highest tertile had a 6.1-fold increase in coronary risk compared with those in the lowest tertile. The event rate was significantly lower when fibrinogen levels were in the lowest tertile even though LDL remained in the highest tertile.

Thompson and colleagues<sup>22</sup> found fibrinogen to be a strong predictor of coronary events in patients with angina pectoris. In those subjects with high total cholesterol, a high fibrinogen level conferred added risk compared with those with low fibrinogen. Patients in the highest fibrinogen quintile had 3 times the risk of a coronary event than those in the lowest quintile.

Subjects with diabetes mellitus have been found to have hyperreactive platelets. This platelet hyperreactivity may result in part from increased fibrinogen levels associated with diabetes because fibrinogen acts as a cross bridge between platelets. Poor diabetic control has also been particularly associated with higher levels of fibrinogen<sup>23</sup> and other hemostatic variables.<sup>24</sup>

### Conclusions

These data from the Framingham Heart Study support and further characterize the association between fibrinogen and cardiovascular disease. First, elevation of fibrinogen may be a mechanism by which certain traditional risk factors exert their effect on risk. Second, fibrinogen levels are higher among subjects with prevalent cardiovascular disease. These findings, together with prospective studies identifying fibrinogen as an independent risk factor, add strength to the proposal that fibrinogen should be used in population screening to identify individuals at increased thrombotic risk. In the present study, the immunoprecipitation test (FiF) showed a stronger association with prevalent cardiovascular disease than did the Clauss method.

### Acknowledgments

This work was supported by grants from the National Institutes of Health (RO1-HL-48157, contract N01HC-38038) and American Biogenetic Sciences.

### References

1. Meade TW, Brozovic M, Chakrabarti RR, et al. Hemostatic function and ischemic heart disease: principal results of the Northwick Park Heart Study. *Lancet*. 1986;6:533-537.
2. Kannel WB, Wolf PA, Castelli WP, et al. Fibrinogen and risk for cardiovascular disease. *JAMA*. 1987;258:1183-1186.
3. Green D, Ruth K, Folsom AR, et al. Hemostatic factors in the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Arterioscler Thromb*. 1994;14:686-693.
4. Barasch E, Benderly M, Graff E, et al, for the principal investigators of the BIP Study Group. Plasma fibrinogen levels and their correlates in 6457 coronary heart disease patients: the Bezafibrate Infarction Prevention (BIP) study. *J Clin Epidemiol*. 1995;48:757-765.
5. Lee AJ, Lowe GDO, Woodward M, et al. Fibrinogen in relation to personal history of prevalent hypertension, diabetes, stroke, intermittent claudication, coronary heart disease, and family history: the Scottish Heart Health Study. *Br Heart J*. 1993;69:338-342.
6. Heinrich J, Balleisen L, Schulte H, et al. Fibrinogen and factor VII in the prediction of coronary risk: results from the PROCAM study in healthy men. *Arterioscler Thromb*. 1994;14:54-59.
7. Kannel WB, Feinleib M, McNamara JR, et al. An investigation of coronary heart disease in families: the Framingham Offspring Study. *Am J Epidemiol*. 1979;110:281-290.
8. Gordon T, Moore FE, Shurtleff D, et al. Some methodologic problems in the long-term study of cardiovascular diseases: observations from the Framingham Heart Study. *J Chronic Dis*. 1959;10:186-206.
9. Von Clauss A. Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens. *Acta Haematol*. 1957;17:237-246.
10. Gargan PE, DaMatta RA, Silverman T, et al. Immunochemical evidence for intramolecular interaction of the carboxyl terminal A (alpha) appendages of plasma fibrinogen. *Coag Fibrinolysis*. 1990;5:465-468.
11. Burr ML, Holliday RM, Fehily AM, et al. Hematological prognostic indices after myocardial infarction: evidence from the Diet and Reinfarction Trial (DART). *Eur Heart J*. 1992;13:166-170.
12. Krobot K, Hense H, Cremer P, et al. Determinants of plasma fibrinogen: relation to body weight, waist-to-hip-ratio, smoking, alcohol, age and sex: results from the second MONICA Augsburg Survey, 1989-1990. *Arterioscler Thromb*. 1992;12:780-788.
13. Balleisen L, Bailey J, Epping PH, et al. Epidemiological study on factor VII, factor VII and fibrinogen in an industrial population: baseline data on the relation to age, gender, body-weight, smoking, alcohol, pill-using and menopause. *Thromb Haemost*. 1985;54:475-470.
14. Yarnell JG, Sweetnam PM, Elwood PC, et al. Hemostatic factors and ischemic heart disease. *Br Heart J*. 1985;52:483-487.
15. Baker IA, Eastham R, Elwood PC, et al. Hemostatic factors associated with ischemic heart disease in men aged 45 to 64 years. *Br Heart J*. 1982;47:490-494.
16. Throp JM, Horsfall GB, Stone MC. A new red-sensitive micro nephelometer. *Med Biol Eng*. 1967;5:51-56.
17. Berk BC, Weintraub WS, Alexander RW. Elevation of C-reactive protein in "active" coronary artery disease. *Am J Cardiol*. 1990;65:168-172.
18. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med*. 1997;336:973-979.
19. Athukorala TM, Ranjini LP. Lipid patterns and fibrinogen levels of smokers and non-smokers. *Ceylon Med J*. 1991;36:98-101.
20. Fogari R, Zoppi A, Marasi G, et al. Association between plasma fibrinogen levels and cardiovascular risk factors in hypertensive men. *J Cardiovasc Risk*. 1994;1:341-345.
21. Ditschuneit HH, Flechtner-Mors M, Adler G. Fibrinogen in obesity before and after weight reduction. *Obesity Res*. 1995;3:43-48.
22. Thompson SG, Keinst J, Pyke SDM, et al. Hemostatic factors and their risk of myocardial infarction or sudden death in patients with angina pectoris (ECAT). *N Engl J Med*. 1995;332:635-641.
23. Vanninen E, Laitinen J, Uusitupa M. Physical activity and fibrinogen concentration in newly diagnosed NIDDM. *Diabetes Care*. 1994;17:1031-1038.
24. el Khawand C, Jamart J, Donkier J, et al. Hemostasis variables in type I diabetic patients without demonstrable vascular complications. *Diabetes Care*. 1993;16:1137-1145.