Fibrinogen Catabolism in Patients with Type II and Type IV Hyperlipidemia

Effect of Dietary and Clofibrate Treatment on Laboratory Findings

Anthony Fletcher, Norma Alkjaersig, Gustav Schonfeld, and Joseph Witztum

Fibrinogen catabolism was studied by plasma fibrinogen chromatography and other methods in 99 subjects with hyperlipoproteinemia Types IIa, IIb, and IV, and in 24 control subjects with normal blood lipid values. Subjects with either a history of thromboembolic vascular disease or clinical evidence of atherosclerosis were excluded. Type II subjects (i.e., the combined group of Type IIa and IIb subjects) showed an elevation of plasma high molecular weight fibrinogen complexes, which is indicative of enhanced fibrin formation. They also showed an elevation of fibrinogen-first-derivative, which is indicative of fibrinogenolysis and increased plasma euglobulin activity. Subjects with Type IV hyperlipoproteinemia showed similar findings to those of Type II except that high molecular weight fibrinogen complex concentration was normal. Subsequently, 36 patients received a fat-controlled, low cholesterol diet and were studied in a blind, random, crossover study of dietary vs clofibrate treatment. Although total cholesterol and triglyceride levels fell significantly during the treatment periods, chromatographic findings of abnormal plasma fibrinogen remained unchanged. (Arteriosclerosis 1981; 1:202–209)

The role of local fibrin deposition in atherosclerosis in humans remains uncertain. Histological evidence supports the view that local fibrin and platelet deposition is an integral pathological feature of progressive atherosclerosis. Elevation of plasma fibrinogen has also been shown to be as significantly associated with the development of ischemic heart disease as elevation of cholesterol. Yet studies to demonstrate enhanced fibrin formation in patients with atherosclerosis have seldom been attempted. Whether abnormal fibrinogen catabolism occurs in patients with hyperlipidemia Types II and IV (namely, patients at risk of developing age-accelerated atherosclerosis), is unknown. Although studies with isotopically labeled fibrinogen have failed to show a shortened half-life survival time in the atherosclerotic subject, fibrin formation under physiological conditions accounts for only 2% to 3% of overall fibrinogen catabolism. Consequently, fibrinogen $T_\alpha$ is an insensitive measure of fibrin formation and deposition, and failure to demonstrate alteration in fibrinogen $T_\alpha$ survival does not exclude substantial change in fibrin formation rates.

Plasma fibrinogen chromatography has provided a new approach to the study of fibrinogen catabolism. This procedure quantifies in plasma the percentage and concentration of high molecular weight fibrinogen complexes (HMWFC), native fibrinogen, and derivatives of fibrinogen smaller than the native molecule, collectively termed "fibrinogen-first-derivative" and mostly composed of fibrinogen fragments X and Y.
Biochemical and clinical evidence suggests that the percentage and concentration of HMWFC reflects the rate of fibrin formation in vivo and that the concentration of fibrinogen derivatives smaller than the native molecule reflects the rate of fibrinogenolysis. Plasma fibrinogen chromatographic studies show that plasma HMWFC is significantly increased in patients with stroke risk factors, documented coronary artery disease, and those followed long after acute myocardial infarction—all conditions in which atherosclerotic disease is considered of primary etiological importance.

In this study we examined subjects with Type II and IV hyperlipoproteinemia for evidence of altered fibrinogen catabolism. These subjects had no history of thromboembolic vascular disease nor any clinical evidence of atherosclerosis; however, they showed laboratory evidence of disturbed fibrinogen catabolism and enhanced fibrin formation during the baseline observation period. In a blind, random study, we tested the effects of dietary and clofibrate therapies on laboratory findings.

Methods

Patient Population

Patients referred to the Lipid Research Center had a medical history taken, were examined and screened for lipid abnormalities using standard methods. Patients with normal lipid screen values served as a control group. Patients with abnormal screening tests underwent full lipid profile studies including estimations of total plasma cholesterol, triglycerides, and the triglyceride and cholesterol contents of high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL). In assigning patients to diagnostic groups, we used the cut-off points for LDL cholesterol established by the Lipid Research Clinic prevalence studies. We chose triglyceride levels arbitrarily as follows: Type IIa = LDL-cholesterol (C) > 200 mg/dl, triglyceride (TG) < 200 mg/dl; Type IIb = LDL-C > 200 mg/dl, TG > 250 mg/dl; Type IV = LDL-C < 200 mg/dl, TG > 250 mg/dl.

The 102 consecutive patients fulfilling the criteria for Types IIa, IIb, and IV hyperlipidemia were examined twice at 1-month intervals, to confirm the diagnosis. Three patients were withdrawn from the hyperlipidemia series because their lipid levels returned to normal during this observation period. The series included 99 patients with hyperlipidemia and 24 age- and sex-matched controls. Thirty patients had Type IIa, 25 had Type IIb, and 44 had Type IV hyperlipidemia. The average patient age was 46.3 ± 7.6 (so) years; 83 were men. Twenty-four patients were 20% heavier than their ideal body weights.

All tests for age and sex differences among the control and individual patient groups were negative.

At the end of the 2-month baseline observation period, 48 patients gave informed consent to be studied in a blind, random, medication test. The patients were prescribed a fat-controlled lower cholesterol “prudent diet” throughout the study. After an initial 2-month dietary period, the patients were studied in a double-blind crossover test using placebo or clofibrate (2 g/day). Each treatment period was 3 months long. Thirty-six patients completed the entire study; only data from these patients have been analyzed.

Using previously described precautions, we drew blood samples and examined them by plasma fibrinogen chromatography. Plasma fibrinogen chromatographic values for the control patients (table 1) were essentially similar to values published previously. Fibrinogen, antithrombin III, α2 macroglobulin, α1 antitrypsin, and plasminogen were assayed by radial immunodiffusion. Radial immunoassays are expressed as corrected mm2; antigen concentration was proportional to this area. Coagulation factor XIII concentration was assayed by the methods of Lorand et al., and Ittyerah et al., and the dextran sulphate-precipitated euglobulin lysis activity was assayed by the fibrin plate method.

Statistical Analysis

Multiple blood samples were withdrawn at monthly intervals during baseline and treatment periods, and the sample values for each patient during each treatment period (2 or 3 months) were averaged before data processing. Thus, values for n given in the text or tables refers to the number of averaged patient values during a single treatment period, rather than to the actual number of determinations. Deviations from the mean have been expressed throughout as the standard error. Since the study plan was designed before the research was performed, all data flowing directly from the plan have been analyzed as a priori (planned) data. For this reason, we have not corrected significance values for the number of comparisons made. For analysis of data flowing indirectly from the experimental design, (i.e., correlation coefficients, etc.) we have taken into account the number of comparisons performed.

Since some statisticians advocate that all multiple comparison data tests should be corrected for the number of comparisons made, we have also calculated Dunn's correction for the data shown in tables 1 and 2. The Dunn correction reduces the significance of differences established by conventional t testing. For example, its
application to the table 1 data requires that, to establish a significant difference at the 5% level, a p value of 0.017 be established by conventional t testing. For the table 2 data, a p value of 0.0125 is needed to claim significance at the 5% value. Application of the Dunn correction to the table 1 data means that all values followed by a single asterisk (i.e., significant at the 5% level by conventional t testing) do not show statistical significance, whereas those values followed by a double asterisk are significant at the 5% level. In table 2, values marked with a single asterisk or dagger (significant at the 5% level by conventional t testing) are not significant when the Dunn correction is applied, but values with a double asterisk or double dagger are significant at p < 0.05 after applying the Dunn corrections. Other higher claimed significance values are reduced in corresponding fashion.

Results

Baseline Studies

Laboratory findings of blood coagulation and fibrinolysis for the three hyperlipidemic groups, Types IIa, IIb, and IV, during the baseline period are compared with those of the normal control group (table 1). Since statistically significant differences were not detected between Types IIa and IIb laboratory data, findings for the combined Type II patients are also shown.

Total fibrinogen (mg/dl) did not differ among the hyperlipidemic groups or among these groups and the normal controls, but differences were found among the subject groups and the controls with respect to the percentage and concentration of native fibrinogen and its catabolic derivatives — HMWFC and fibrinogen-first-derivative.

Mean plasma HMWFC were higher in Type IIa (9.5%), Type IIb (8.3%), and in the combined Type II group than in the controls (7%); these differences did not reach conventional statistical significance, although in the Type IIa and combined Type II groups, p was < 0.1. Similarly, mean HMWFC concentration was higher in Type Ila (29.9 mg/dl), in Type IIb (26.8 mg/dl), and in combined Type II (28.5 mg/dl) than in the controls (20.7 mg/dl), but only the differences between the combined Type II and control

<table>
<thead>
<tr>
<th>Laboratory data</th>
<th>Type Ila (n=30)</th>
<th>Type IIb (n=25)</th>
<th>Type Ila &amp; b (n=55)</th>
<th>Type IV (n=44)</th>
<th>Normal control (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMWFC</td>
<td>9.5 ±1.2</td>
<td>8.3 ±0.96</td>
<td>9.0 ±1.4</td>
<td>7.3 ±0.72</td>
<td>7.0 ±0.92</td>
</tr>
<tr>
<td>(% total fibrinogen)</td>
<td>±1.2</td>
<td>±0.96</td>
<td>±1.4</td>
<td>±0.72</td>
<td>±0.92</td>
</tr>
<tr>
<td>Native fibrinogen</td>
<td>58.2**</td>
<td>58.6***</td>
<td>58.4***</td>
<td>56.9***</td>
<td>65.5</td>
</tr>
<tr>
<td>(% total fibrinogen)</td>
<td>±2.1</td>
<td>±5.0</td>
<td>±1.4</td>
<td>±1.5</td>
<td>±1.6</td>
</tr>
<tr>
<td>Fibrinogen 1st derivative</td>
<td>32.1*</td>
<td>33.1*</td>
<td>32.5*</td>
<td>35.9****</td>
<td>27.5</td>
</tr>
<tr>
<td>(% total fibrinogen)</td>
<td>±1.4</td>
<td>±1.9</td>
<td>±1.1</td>
<td>±1.3</td>
<td>±1.7</td>
</tr>
<tr>
<td>Total fibrinogen (mg/dl)</td>
<td>312.0</td>
<td>318.0</td>
<td>315.0</td>
<td>315.0</td>
<td>308.0</td>
</tr>
<tr>
<td>HMWFC (mg/dl)</td>
<td>29.9 ±3.8</td>
<td>28.6 ±3.5</td>
<td>28.5*</td>
<td>21.5 ±2.6</td>
<td>20.7 ±2.9</td>
</tr>
<tr>
<td>Native fibrinogen (mg/dl)</td>
<td>180.4</td>
<td>186.3</td>
<td>183.1</td>
<td>180.7</td>
<td>203.2</td>
</tr>
<tr>
<td>Fibrinogen 1st derivative (mg/dl)</td>
<td>101.1</td>
<td>105.1*</td>
<td>102.9*</td>
<td>112.7***</td>
<td>84.6</td>
</tr>
<tr>
<td>α2 macroglobulin (mm2)</td>
<td>25.1 ±0.66</td>
<td>25.0 ±0.56</td>
<td>25.1*</td>
<td>23.8*</td>
<td>27.6</td>
</tr>
<tr>
<td>α1 antitrypsin (mm2)</td>
<td>26.2*</td>
<td>25.9*</td>
<td>26.1***</td>
<td>24.3</td>
<td>22.8</td>
</tr>
<tr>
<td>Plasma factor XIII (U/ml)</td>
<td>28.8 ±0.99</td>
<td>28.9*</td>
<td>28.9**</td>
<td>30.1***</td>
<td>25.8</td>
</tr>
<tr>
<td>Euglobulin lysis 176.0 ±14.2</td>
<td>186.0****</td>
<td>181.0******</td>
<td>203.0****</td>
<td>114.0</td>
<td></td>
</tr>
<tr>
<td>fibrinogen plate</td>
<td>±11.0 ±14.2</td>
<td>±8.8</td>
<td>±14.3</td>
<td>±19.2</td>
<td></td>
</tr>
</tbody>
</table>

Student's t test values (normal group vs Types Ila, IIb, Ila & b, or IV groups) = *p < 0.05; **p < 0.02; ***p < 0.01; ****p < 0.001.

HMWFC = high molecular weight fibrinogen complexes.
Table 2. Cholesterol and Triglyceride Values for Individual Groups During Each Treatment Period (Mean ± se)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Type Ila</th>
<th>Type Iib</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total cholesterol</td>
<td>Total triglycerides</td>
<td>Total cholesterol</td>
</tr>
<tr>
<td>Base</td>
<td>301*** ± 13</td>
<td>133</td>
<td>312*** ± 13</td>
</tr>
<tr>
<td>Diet</td>
<td>286*** ± 12</td>
<td>135</td>
<td>289*** ± 13</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td>278*** ± 14</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>*<em>249</em> ± 13</td>
<td></td>
<td><strong>271</strong> ± 16</td>
</tr>
<tr>
<td>Control</td>
<td>229 ± 13</td>
<td>120</td>
<td>248</td>
</tr>
</tbody>
</table>

Student’s t test values (daggers indicate previous treatment period, asterisks, the control group), \( t = p < 0.05 = * \) vs control group; \( tt = p < 0.01 = ** \) vs control group; \( ttt = p < 0.001 = * \) vs control.

Dietary Placebo and Clofibrate Treatment Periods

Of the 48 hyperlipidemic subjects in the treatment group, 36 patients (12 Type Ila, nine Type Iib, and 15 Type IV) completed all phases of the study. Data from the 12 patients who dropped out of the study have been excluded from the tabulated data, since the time of subject dropout was highly variable. However, before exclusion of these data, the combined data from the subjects who completed the study and those who did not were analyzed, with essentially similar results. Table 2 shows total cholesterol and triglyceride values for all patients completing the base study and the dietary placebo and clofibrate treatment periods. The statistical significance of group treatment differences in table 2 was tested after log transformation of lipid values, a procedure undertaken to normalize the data.

During the dietary and placebo treatment periods, cholesterol values fell an average of 9% to 12% in all subjects (NS). There was also a significant fall in total triglycerides in Type Iib (\( p < 0.05 \)) and Type IV (\( p < 0.001 \)). During the clofibrate treatment period, there was a significant fall in cholesterol values in Type Ila (\( p < 0.01 \)) but essentially no change in Types Iib and IV. Clofibrate treatment resulted in highly significant falls in total triglycerides in all patient groups (\( p < 0.01 \) to 0.001).

During the clofibrate treatment period, when the lipid values showed the greatest depression,
cholesterol values remained significantly higher than normal in Types IIa and IIb, but not in Type IV, while total triglyceride values remained significantly higher than normal in Types IIa and IIb. Thus, combined clofibrate and dietary treatment, while reducing cholesterol levels 13% to 20% in the patient groups, produced a relatively much greater fall in triglyceride values, which ranged from 34% to 72%. Because the order of placebo and clofibrate treatment was randomized, the data were analyzed to test whether treatment sequence affected the lipid values, but it did not.

Table 3 shows plasma fibrinogen chromatographic and related findings for combined Type II and Type IV patients during the base period, diet plus placebo, and diet plus clofibrate periods. Overall, the values in this table are similar to those in table 1; no statistically significant differences between individual groups receiving the various therapies were observed.

When the base placebo and clofibrate data were examined by analysis of variance, however, statistically significant differences were detected during the treatment periods. For the total population, both plasma fibrinogen (mg/dl) and native fibrinogen (mg/dl) fell ($p < 0.001$ in both cases) during the clofibrate treatment period, and fibrinogen-first-derivative (mg/dl) was reduced during both dietary and clofibrate treatments. HMWFC (mg/dl) was elevated ($p = 0.041$) in Type IV patients during both dietary and clofibrate treatment periods. It is not likely that this change in HMWFC concentration is due to analytical error, since all analyses were performed blind and because of the long patient recruitment period; plasma samples from all study phases were analyzed randomly, not sequentially, during treatment phases.

Other analyses of variance in both total and individual treatment groups were not statistically significant, although they did show percentage changes in fibrinogen fractions in line with the concentration figures above.

Lipid fraction data from the three types of hyperlipidemic subjects at baseline and during treatment periods were tested for correlation with the fibrinogen and blood coagulation data. Although a number of statistically significant correlations were observed among specific lipid fractions and Factor XIII, total fibrinogen, euglobulin lysis activity, HMWFC concentration, and fibrinogen-first-derivative concentration, the correlation patterns were inconsistent, and the number of "significant" correlations observed did not greatly exceed those expected to occur on a chance basis.

Table 3. Treatment Findings (Mean ± se)

<table>
<thead>
<tr>
<th>Laboratory data</th>
<th>Type II a &amp; b</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base</td>
<td>Diet + placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMWFC (mg/dl)</td>
<td>29.7 ± 2.7</td>
<td>31.0 ± 2.6</td>
</tr>
<tr>
<td>Native fibrinogen (mg/dl)</td>
<td>188.0 ± 18.0</td>
<td>174.0 ± 7.8</td>
</tr>
<tr>
<td>Fibrinogen 1st derivative (mg/dl)</td>
<td>102.2 ± 8.1</td>
<td>78.0 ± 3.2</td>
</tr>
<tr>
<td>Total fibrinogen (mg/dl)</td>
<td>310.0 ± 8.0</td>
<td>281.0 ± 3.2</td>
</tr>
<tr>
<td>Antithrombin III (mm²)</td>
<td>25.3 ± 0.48</td>
<td>26.4 ± 0.63</td>
</tr>
<tr>
<td>$\alpha_2$ macroglobulin (mm²)</td>
<td>24.7 ± 0.71</td>
<td>26.8 ± 0.81</td>
</tr>
<tr>
<td>$\alpha_2$ antitrypsin (mm²)</td>
<td>25.4 ± 0.57</td>
<td>26.6 ± 0.73</td>
</tr>
<tr>
<td>Plasminogen CTA (U/ml)</td>
<td>2.1 ± 2.04</td>
<td>2.28 ± 0.05</td>
</tr>
<tr>
<td>Plasma factor XIII (U/ml)</td>
<td>30.0 ± 1.2</td>
<td>28.0 ± 0.83</td>
</tr>
<tr>
<td>Euglobulin lysis (mm²)</td>
<td>112.0 ± 9.5</td>
<td>173.0 ± 11.0</td>
</tr>
</tbody>
</table>

HMWFC = high molecular weight fibrinogen complexes.
Discussion

In all acute thromboembolic clinical disorders in which increased fibrin formation could be documented or reliably inferred, plasma HMWFC has been shown to be substantially elevated. These studies have included the detection of clinically silent, deep vein thrombosis in postoperative patients and the demonstration of local fibrin deposition in renal disease and myocardial and cerebral infarction. In these acute situations, plasma fibrinogen chromatographic findings have returned to normal after disease resolution. Plasma HMWFC has also been shown to be significantly higher in patients with stroke risk factors, patients with coronary artery disease but a negative history of myocardial infarction, and in those who had experienced myocardial infarction at least 6 months earlier — all conditions in which atherosclerotic disease is considered of primary etiological importance.

While plasma HMWFC in the hyperlipidemic patients was persistently elevated over that of the control group during both baseline and treatment periods, only values for the combined Type II group at baseline reached statistical significance ($p < 0.05$). However, the average figures for HMWFC concentration in the Type II subgroups were similar to those of combined Type II during the treatment phases of the study. It may be concluded that the average HMWFC concentration of 30 mg/dl for the Type II subgroups (as contrasted with 21 mg/dl for the controls) represents an approximate 50% increase in plasma HMWFC over control values. Plasma HMWFC in Type IV patients was normal during the baseline period, but during the 8-month treatment phase of the study, it averaged 31 mg/dl (NS), even though during this period only 15 patients were followed. Müller-Berghaus et al. have shown that the plasma clearance of HMWFC in humans is approximately exponential. Nossel et al. estimate from plasma fibrinopeptide A data that, under physiological conditions, fibrin formation in humans averages 25 to 50 mg/day. Consequently, our findings suggest that the hyperlipidemic patient forms 12 to 25 mg fibrin/day more than the controls. This increment is approximately 1% of the total fibrinogen catabolism and would not be detected using an isotopically labeled fibrinogen survival technique, since the standard deviation of this technique is 16%.

Statistically significant elevation ($p < 0.05$ to 0.001) of plasma fibrinogen-first-derivative percentage and concentration was found in both Type II and IV hyperlipidemic groups, and plasma euglobulin lysis activity was substantially elevated over control values. Our use of a newer modification of the euglobulin lysis time procedure may account for our finding that euglobulin lysis activity was increased in the hyperlipidemic patients, whereas another group found that this activity was within the normal range. Thus, significant fibrinogenolysis and increase in plasma fibrinolytic activity presumably secondary to the presence of enhanced fibrin deposition was observed in both Type II and IV patients. However, elevation of plasma HMWFC in the hyperlipidemic groups was substantially less than that observed in patients with overt atherosclerosis, a finding possibly due to the fact that, although the hyperlipidemic patients selected were free of overt clinical atherosclerotic disease, they may have been developing subclinical disease.

Significant enhancement of Factor XIII concentration was shown in all hyperlipidemic groups. While Factor XIII concentration is consistently depressed during acute episodes of thromboembolic vascular disease, Factor XIII increases to above normal levels after disease resolution. Possibly increased Factor XIII concentration in the hyperlipidemics is secondary to the mild enhancement of fibrin formation/deposition present in these groups. It is also suggested that the statistically significant increase in $\alpha_1$ antitrypsin seen in Type II, but not in Type IV, patients can be explained on the same basis. An inhibitor of plasmin and other serine proteases, $\alpha_2$ macroglobulin, was significantly depressed in both Type II and IV patients, a finding possibly secondary to enhanced fibrinogenolysis detected in these groups.

Our findings differ from those of Carvalho et al. who reported that plasma HMWFC was grossly increased in Type II and IV patients. However, these investigators studied a more severely stricken patient group, many of whom had experienced previous episodes of thromboembolic vascular complications, and the study used different assay methods of plasma HMWFC. Nossel et al. have reported that plasma fibrinopeptide A concentration was not increased in hyperlipidemic patients, and they have interpreted this finding as indicating that “hyperlipidemia is not associated with an increased steady state of thrombin activity in vivo in the human.” Since fibrinopeptide A has a plasma $T_1/2$ of 3 minutes while HMWFC has one of several hours, minor local, intermittent thrombin formation might fail to induce detectable increase of plasma fibrinopeptide A, but could alter plasma fibrinogen chromatographic findings.

There is evidence that platelets play a role in the genesis and progression of atherosclerosis. Joist et al. carried out platelet functional assays in 33 of the 99 patients we studied at baseline and in all the control subjects. Type II and IV hyperlipidemic patients showed significantly shorter template bleeding times than did the controls. Increased platelet-Factor 3 availability in platelet-rich plasma and on exposure to collagen...
was also observed, together with increased collagen-induced release of serotonin. These findings indicated increased platelet activity in vivo and in vitro, possibly related to increased platelet turnover and acquired abnormalities of platelet composition. They are consistent with the data from this study, which shows enhanced fibrin formation in the hyperlipidemic groups.

The failure to demonstrate significant changes in fibrinogen catabolism or related findings with dietary or dietary plus clofibrate treatment could be due to several causes. First, although triglyceride levels were substantially reduced by the treatment, the findings for cholesterol were less impressive, and in both instances lipid levels were still increased over control levels at the end of the treatment period. In addition, the period of partial control of lipid levels was comparatively short, compared to the time taken to develop clinical or pathological evidence of atherosclerosis. Finally, the initial degree of fibrinogen catabolic abnormality was minor, and the patient series was small. Ours was a pilot study; it would seem that a larger number of patients who had a greater degree of hyperlipidemia, combined with longer treatment periods, and more effective therapy to reduce lipid levels, will be needed to test the hypothesis that dietary or medication treatment influences fibrinogen catabolism in the hyperlipidemic groups.

On the other hand, the recent World Health Organization clinical trial data, in which increased mortality was observed in hypercholesterolemic subjects given long-term treatment with clofibrate, suggest either that clofibrate inhibits hitherto undescribed toxicity or that attempted control of atherosclerotic disease by depression of cholesterol levels may be clinically disadvantageous.

Acknowledgments

We thank Sung C. Choi and John Levitt for statistical help and advice.

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Index Terms: fibrinogen • fibrinogen derivatives • fibrinolysis • hyperlipoproteinemia • diet clofibrate
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Arteriosclerosis, Thrombosis, and Vascular Biology
1981;1:202-209
doi: 10.1161/01.ATV.1.3.202

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