Impact of Fibrinogen Levels on Angiographic Progression and 12-Year Survival in the Armed Forces Regression Study

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Abstract
We assessed the role of fibrinogen levels on angiographic progression and long-term survival among 111 patients with coronary disease enrolled in the Armed Forces Regression Study (AFREGS). Baseline fibrinogen levels and quantitative coronary angiography were performed initially and at 30 months. Progression or nonregression of coronary disease was more prevalent in patients with high fibrinogen than patients with normal fibrinogen (66.1% vs 45.5%; \( P = .022 \)). Twelve-year cardiovascular (CV) mortality was substantially higher if fibrinogen was elevated (17.9% vs 3.6%, \( P = .016 \)). Among patients with elevated fibrinogen and angiographic progression or nonregression, there were 10 deaths and all were CV. Elevated levels of fibrinogen predict the angiographic progression of existing coronary disease and likelihood of CV death. Among patients with elevated levels of fibrinogen, angiographic progression identifies a significantly increased likelihood of a fatal CV event.

Keywords
fibrinogen, atherosclerosis, angiographic progression

Introduction
Inflammation appears central to the initiation and progression of atheromatous disease. Accordingly, several inflammatory markers have been evaluated as potential predictors of cardiovascular (CV) risk. Among the potential predictors, plasma fibrinogen is a particularly attractive target as it is an acute phase reactant, a determinant of blood viscosity, a participant in thrombogenesis, and a cofactor for platelet aggregation. As such, it has long been hypothesized that elevated plasma fibrinogen may reflect a heightened inflammatory state within the vascular wall that is pathogenic for atherosclerosis. This is further supported by the observation that elevated plasma fibrinogen is an independent risk factor for coronary heart disease (CHD), stroke, and vascular death and is also a strong predictor of myocardial infarction in patients experiencing angina pectoris. In addition to its predictive value in CV disease, fibrinogen independently correlates with atherosclerotic burden. This unique property suggests that fibrinogen is not only a binary predictor of risk but may correlate with the progression of atheromatous disease.

Several potential mechanisms have attempted to explain fibrinogen’s role in atheromatous disease. However, it is unclear whether fibrinogen is a causative or reactive agent in the inflammatory process. It has been suggested that fibrinogen acts as a chemotactic agent that recruits smooth muscle cells from the media into the intima, thereby promoting the development of atheroma. It has also been suggested that during atherogenesis, an inflamed vascular wall induces the production of cytokines, which will in turn upregulate the hepatic production of acute phase reactants such as fibrinogen. Further complicating this issue are epidemiological studies that have shown equivocal results regarding fibrinogen as an independent CV risk factor. Given this disparity in understanding, further clarification of the complex interaction between inflammation, angiographic progression, and mortality is needed.

The Armed Forces Regression Study (AFREGS) was a randomized, double-blind, placebo-controlled trial of aggressive medical therapy targeted to increase high-density lipoprotein (HDL) on a baseline of aggressive dietary and lifestyle intervention. The purpose of this substudy was to examine the ability of baseline plasma fibrinogen to predict (1) angiographic progression of atherosclerosis and (2) long-term survival.

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survival among patients with angiographically evident coronary disease.

**Methods**

Men and women aged <76 years, with suspected stable CHD, were recruited from within a 150-mile radius of Wilford Hall Medical Center in San Antonio, Texas. Each patient was required to have a measurable stenosis between 30% and 80% of the luminal diameter within the coronary tree by quantitative coronary angiography. A measure of global coronary atherosclerosis was obtained by averaging the percentage of stenosis in each diseased segment. This was done at baseline and repeated at 30-months follow-up; the catheterization techniques have been previously described in detail.\(^{16}\) Patients with greater than an 80% stenosis of a single vessel were eligible only if they had a favorable prognosis based on functional testing (ability to exercise for more than 9 minutes on a full-Bruce Protocol exercise treadmill test).

The exclusions have previously been published\(^ {16}\) and included a major vascular event (myocardial infarction, cerebrovascular accident, coronary artery bypass grafting, or other coronary catheter-based intervention) within 6 months, a history of congestive heart failure (other than in the setting of a myocardial infarction), a left ventricular ejection fraction <40% by ventriculography, or diabetes (fasting blood glucose ≥110 mg/dL).

Our subpopulation of 111 AFREGS patients was defined in the following manner: of the 143 patients in the original AFREGS analysis, 128 completed their 30-month follow-up catheterization. Of these 128, only 111 patients had baseline fasting fibrinogen levels (measured by the Clauss clotting assay).\(^ {17}\) Patients were thoroughly informed of the details of the study and voluntarily enrolled between January of 1993 and March of 1994. The initial cohort was followed until September of 1996 when the database was locked. Because of funding issues, full analysis of the study data as well as the subsequent long-term follow-up did not occur until 2004, when the amended institutional review board (IRB) application was approved and the initial results were published. Patient follow-up for this substudy occurred for a total of 12.0 ± 0.2 years and patients were monitored for all-cause death and CV death. No patients were lost to follow-up and cause of death was confirmed by hospital record or death certificate if available. Each patient initially signed an “Informed Consent Statement” that was reviewed and approved by the Institutional Review Board at Wilford Hall Air Force Medical Center in San Antonio, Texas. Patient selection has been previously described in detail.\(^ {16}\)

We compiled and analyzed data by using JMP 8.0 software (SAS Institute, Inc, Cary, North Carolina). We dichotomized the patients into “high” and “normal” fibrinogen based on the median baseline fibrinogen of 286 mg/dL, with the high fibrinogen group having a baseline fibrinogen of ≥286 mg/dL. Dichotomized outcomes were compared by using the chi-square test or Fischer exact test where appropriate. Continuous variables were compared using a 2-tailed \(t\) test. Multivariate modeling was performed using forward and backward stepwise nominal logistic regression with a parameter estimate inclusion cutoff of \(P = .2\) to determine a subset of baseline parameters to be used in the model. The baseline variables included in the first step were age, systolic blood pressure, total cholesterol, LDL, HDL, triglycerides, fibrinogen, body mass index (BMI), and fasting blood sugar. Effect likelihood ratios were used to determine effect significance. Survival curves were compared by the log-rank test. For all tests, a \(P\) value of .05 or less was considered significant.

**Results**

Baseline characteristics of all 111 patients are included in Table 1. The mean fibrinogen for all patients was 293 ± 67 mg/dL, with a median fibrinogen of 286 mg/dL (interquartile range = 243-330). We chose to separate our patients into high and normal fibrinogen groups based on this median, and this resulted in a mean fibrinogen of 242 ± 27 mg/dL in the normal fibrinogen group and 343 ± 56 in the high fibrinogen group. This comparison is similar to the means used to define lower fibrinogen (250 mg/dL) and upper fibrinogen (350 mg/dL) in a previous meta-analysis.\(^ {18}\) Fifty-five patients were included in the normal fibrinogen group, whereas 56 patients were included in the high fibrinogen group. Because these patients are a subset of patients from the AFREGS trial, they were randomly assigned to either the treatment group (gemfibrozil 600 mg twice daily, Niacin starting at 250 mg and titrated up to 3000 mg/day as tolerated, and cholestyramine 16 g/d) or placebo therapy for 30 months. Within the normal fibrinogen group, 31 (56.4%) patients received treatment, whereas 28 (50.5%) of patients in the high fibrinogen group received treatment \((P = .57)\). All patients were subject to aggressive diet and exercise modification as previously described.\(^ {16}\)

Table 2 shows the results of a logistic regression analysis of baseline parameters as predictors of death. The 3 most significant variables were age at enrollment, fibrinogen, and triglycerides. Only baseline fibrinogen and age at enrollment had a significance effect <.05 \((P = .02\) and \(P = .01\), respectively). Table 3 shows angiographic changes, death, and CV death dichotomized by high versus normal fibrinogen. Over the 30-month observation period, 62 (55.9%) patients had progression or no regression of their atherosclerosis. Within the normal fibrinogen group, 25 (45.5%) patients had angiographic progression or no regression, whereas 37 (66.1%) patients in the high fibrinogen group had progression or no regression \((P = .02)\). Over the 12-year observation period, there were 17 overall deaths (15.3%) and 12 CV deaths (10.8%). Among the overall deaths, 4 (7.3%) were in the normal fibrinogen group and 13 (23.2%) in the high fibrinogen group \((P = .02)\). Among the CV deaths, 2 (3.6%) were in the normal fibrinogen group and 10 (17.9%) in the high fibrinogen group \((P = .02)\). In Table 4, all-cause mortality and CV mortality are shown dichotomized by those patients with both elevated fibrinogen and...
angiographic progression or no regression versus patients with elevated fibrinogen and angiographic regression. Among patients with elevated fibrinogen and angiographic progression, there were 10 (27%) all-cause deaths while there were 3 (15.8%) all-cause deaths in patients with high fibrinogen and angiographic regression (P = .28). All 10 of the deaths in the patients with high fibrinogen and angiographic progression or no regression were due to CV causes, whereas none of the 3 deaths in the high fibrinogen and angiographic regression group were due to CV causes (P = .01). These 3 non-CV deaths were comprised of 1 patient who died from complications of pneumonia and 2 patients who died from lung cancer. Figure 1 compares 12-year survival between the high fibrinogen group and the normal fibrinogen group via Kaplan-Meier analysis. Long-term survival was significantly better in the normal fibrinogen group (P = .02). Of the 107 patients that had repeat fibrinogen levels at 30 months, 34 (31.8%) experienced a fibrinogen reduction that was independent of treatment (P = .83). When patients with fibrinogen increase were compared with those with fibrinogen decrease, there was no significant difference in overall death (P = .23), CV death (P = .72), or atherosclerotic progression (P = .67).

### Discussion

In patients with seemingly stable atherosclerosis, plasma fibrinogen levels were strongly predictive of long-term clinical outcome. More interestingly, it appeared to predict both CV and non-CV deaths. Although prior studies have noted the long-term impact of fibrinogen elevation on CV outcome, the development of new CV disease, and on the severity of coronary disease, this is to our knowledge the first study that demonstrates the implication of elevated fibrinogen on the angiographic progression of existing CHD.

As part of the protocol, all patients underwent angiography at a 30-month interval; 45.5% of patients in the normal fibrinogen group had either progression or no regression of coronary disease, whereas 66.1% had progression or no regression of coronary disease in the high fibrinogen group. These angiographic findings are consistent with the intravascular ultrasound findings where fibrinogen levels were positively correlated with annual changes in plaque cross-sectional area. This association between fibrinogen levels and progression of coronary disease, as well as the previous finding that fibrinogen levels reflect atherosclerotic burden, suggests that fibrinogen is more than just a binary predictor of CV mortality and may directly reflect vascular wall inflammation that is part of the process of ongoing atherosclerosis.

In addition to progression of atherosclerosis, elevated fibrinogen predicted both all-cause and CV mortality. During the 12-year observation period, 23.2% of high fibrinogen patients died, whereas only 7.3% of low fibrinogen patients died. Moreover, in the high fibrinogen group, 17.9% of patients suffered a CV death, whereas as 3.6% of the normal fibrinogen group suffered a CV death. This is certainly consistent with the notion that fibrinogen is not only a risk factor for CHD but is also a predictor for the sequelae of CV disease. The predictive

### Table 1. Baseline Demographic Data of Patients

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All Patients; n = 111</th>
<th>Normal Fibrinogen (&lt;Median); n = 55</th>
<th>High Fibrinogen (≥Median); n = 56</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; mean ± SD)</td>
<td>63.4 ± 6.6</td>
<td>61.9 ± 6.6</td>
<td>64.9 ± 6.3</td>
<td>.02</td>
</tr>
<tr>
<td>Female (%)</td>
<td>8.1</td>
<td>5.5</td>
<td>10.7</td>
<td>.49</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>72.9</td>
<td>74.6</td>
<td>71.4</td>
<td>.83</td>
</tr>
<tr>
<td>History of angina (%)</td>
<td>64.8</td>
<td>58.2</td>
<td>71.4</td>
<td>.17</td>
</tr>
<tr>
<td>History of myocardial infarction (%)</td>
<td>43.2</td>
<td>43.6</td>
<td>42.9</td>
<td>1.00</td>
</tr>
<tr>
<td>Previous smoker (%)</td>
<td>86.4</td>
<td>83.6</td>
<td>89.3</td>
<td>.04</td>
</tr>
<tr>
<td>Active smoker (%)</td>
<td>8.1</td>
<td>7.3</td>
<td>8.9</td>
<td>1.00</td>
</tr>
<tr>
<td>Weight (lbs; mean ± SD)</td>
<td>182.5 ± 27.9</td>
<td>182.6 ± 25.7</td>
<td>182.3 ± 30.1</td>
<td>.96</td>
</tr>
<tr>
<td>Body mass index (kg/m²; mean ± SD)</td>
<td>26.5 ± 3.6</td>
<td>26.3 ± 2.9</td>
<td>26.7 ± 4.2</td>
<td>.48</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg; mean ± SD)</td>
<td>138.2 ± 15.4</td>
<td>139.9 ± 13.3</td>
<td>136.6 ± 17.3</td>
<td>.27</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL; mean ± SD)</td>
<td>81 ± 13</td>
<td>81 ± 15</td>
<td>81 ± 11</td>
<td>.79</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL; mean ± SD)</td>
<td>195 ± 32</td>
<td>193 ± 32</td>
<td>197 ± 32</td>
<td>.54</td>
</tr>
<tr>
<td>LDL (mg/dL; mean ± SD)</td>
<td>127 ± 28</td>
<td>127 ± 28</td>
<td>128 ± 27</td>
<td>.90</td>
</tr>
<tr>
<td>HDL (mg/dL; mean ± SD)</td>
<td>34 ± 6</td>
<td>35 ± 6</td>
<td>34 ± 6</td>
<td>.43</td>
</tr>
<tr>
<td>Triglycerides (mg/dL; mean ± SD)</td>
<td>168 ± 82</td>
<td>159 ± 75</td>
<td>177 ± 88</td>
<td>.25</td>
</tr>
<tr>
<td>Treated (total; %)*</td>
<td>59 (53.2)</td>
<td>31 (56.4)</td>
<td>28 (50.5)</td>
<td>.57</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL; mean ± SD)</td>
<td>293 ± 67</td>
<td>242 ± 27</td>
<td>343 ± 56</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL; median)</td>
<td>286</td>
<td></td>
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</tbody>
</table>

* Treated patients received a regimen of gemfibrozil, niacin, and cholesteryramine as part of the AFREGS (Armed Forces Regression Study; Citation) Trial.

### Table 2. Nominal Regression for Baseline Parameters as Predictors of Death

<table>
<thead>
<tr>
<th>Baseline Parameter</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment</td>
<td>1.14</td>
<td>1.04-1.13</td>
<td>.01</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>1.01</td>
<td>1.0-1.02</td>
<td>.02</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.01</td>
<td>0.99-1.02</td>
<td>.06</td>
</tr>
</tbody>
</table>

In patients with seemingly stable atherosclerosis, plasma fibrinogen levels were strongly predictive of long-term clinical outcome. More interestingly, it appeared to predict both CV and non-CV deaths. Although prior studies have noted the long-term impact of fibrinogen elevation on CV outcome, the development of new CV disease, and on the severity of coronary disease, this is to our knowledge the first study that demonstrates the implication of elevated fibrinogen on the angiographic progression of existing CHD.
power of fibrinogen was also demonstrated by our multivariate analysis which showed that only fibrinogen levels and age were significant predictors of mortality. Kaplan-Meier analysis also showed improved survival in the normal fibrinogen group compared with the high fibrinogen group.

The combination of elevated fibrinogen and angiographic progression or nonregression was also highly predictive of CV mortality. There were 10 deaths among this cohort, and all 10 of these deaths were due to CV causes. In patients with elevated fibrinogen and angiographic regression, there were 3 deaths and none were due to CV causes. Interestingly, patients who died in the elevated fibrinogen and angiographic regression group died from either cancer or serious infection and, therefore, may have had mechanisms for elevation of acute phase reactants that were separate from CHD. This notion is supported by the finding in a 2005-meta-analysis that fibrinogen is associated with nonvascular causes of death, chiefly comprised of cancer.7 Interestingly, there was no significant difference in fibrinogen change between those patients receiving lipid modifying therapy and those receiving placebo. This may not be surprising given that treatment with at least one of the agents studied, gemfibrozil, has previously been shown not to affect fibrinogen levels.23

In summary, these data support the notion that fibrinogen is an independent risk factor for both all-cause mortality and CV death. This is also, to our knowledge, the first demonstration that elevated baseline fibrinogen predicts angiographic progression of existing CHD. Furthermore, among patients with elevated levels of fibrinogen, concomitant angiographic progression identifies a significantly increased likelihood of a fatal CV event, whereas fibrinogen elevation without angiographic progression appears to predict death from non-CV causation such as cancer or infection.

Conclusions
Elevated levels of fibrinogen predict the angiographic progression of existing CHD in patients with stable disease. Furthermore, elevated fibrinogen predicted the likelihood of all-cause death and CV death in these patients. Among patients with elevated levels of fibrinogen, concomitant angiographic progression identifies a significantly increased likelihood of a fatal CV event, whereas fibrinogen elevation without angiographic progression appears to predict death from non-CV causation such as cancer or infection.

Declaration of Conflicting Interests
The authors declared a potential conflict of interest as follows: Dr Krasuski is on the speaker’s bureau of Pfizer Pharmaceuticals.

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Dr Krasuski is on the speaker’s bureau of Pfizer Pharmaceuticals, Roche Pharmaceuticals, AGA medical, and United Therapeutics, and is both a consultant for and on the speaker’s bureau of Actelion Pharmaceuticals.
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