Hyperfibrinogenemia and Functional Outcome From Acute Ischemic Stroke

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Background and Purpose—Epidemiological studies have found strong correlations between elevated plasma fibrinogen levels and both ischemic stroke incidence and stroke mortality. Little is known about the influence of fibrinogen levels on functional stroke outcome.

Methods—Placebo data from the Stroke Treatment with Ancrod Trial (STAT) and European Stroke Treatment with Ancrod Trial (ESTAT) were analyzed. Fibrinogen levels were determined within 3 hours (STAT) or 6 hours (ESTAT) of stroke onset and at preset intervals throughout 5 days of intravenous infusions. Barthel Index scores at 90 days quantified functional outcomes. The association between initial fibrinogen levels and functional outcomes was evaluated using a multiple logistic regression analysis.

Results—Fibrinogen levels increased gradually over the first 24 hours from a pretreatment median value of 340 mg/dL to a 24-hour median value of 376 mg/dL. In a univariate analysis, the proportion of patients with good functional outcome decreased with increasing quartiles of initial fibrinogen levels in both STAT (36.0% to 26.2%) and ESTAT (53.8% to 24.8%). In a multifactorial analysis, the same trend was observed. Patients with initial fibrinogen levels <450 mg/dL had better outcomes in both studies; the difference (42.0% versus 21.6%) was significant in ESTAT (P=0.0006), even when corrected for age and initial stroke severity.

Conclusion—The independent association of higher initial fibrinogen levels with poor outcome needs to be verified using a larger acute stroke dataset. Even in the present small populations, the apparent association of these 2 variables suggests that treatments designed to reduce fibrinogen levels could potentially be important in treating acute ischemic stroke. (Stroke. 2009;40:1687-1691.)

Key Words: fibrinogen ■ functional outcome ■ defibrinogenation ■ acute ischemic stroke

Epidemiological studies have established that in individuals, with or without a history of ischemic events, elevated fibrinogen levels are strongly and independently correlated with the risk of coronary heart disease, stroke, and peripheral arterial disease.1-8 For example, a meta-analysis of 6 prospective observational studies incorporating 92 147 person-years2 concluded that fibrinogen levels were a powerful, independent predictor for myocardial infarction and stroke. Disparities in population and inclusion criteria among these studies only served to buttress the clarity of the trend: risk of myocardial infarction and stroke increased in a uniform and continuous manner from the lowest to highest tertile of plasma fibrinogen levels.

An association between fibrinogen levels and the risk of stroke was also supported by a large meta-analysis of individual records for 154,211 participants with 1.38 million person-years of follow-up in 31 studies. Participants were excluded if they had preexisting coronary heart disease or stroke. Although elevated fibrinogen was also associated with other risk factors like age, smoking, blood pressure, and cholesterol, the relationship to stroke persisted even with correction for these confounds.8

The influence of plasma fibrinogen levels at stroke onset on outcome from stroke is not as well studied. Accordingly, we evaluated fibrinogen levels in the placebo arms of 2 acute, interventional studies of the defibrinogenating agent ancrod to determine whether there was an association between initial fibrinogen levels and functional outcome at 90 days.9,10 The initial (pretreatment) fibrinogen levels in the placebo groups in the Stroke Treatment with Ancrod Trial (STAT; blood...
drawn within 3 hours of stroke onset) and the European Stroke Treatment with Ancrod Trial (ESTAT; blood drawn within 6 hours of stroke onset) form the basis of this report.

Methods

Study Design
The study designs for STAT and ESTAT have been detailed elsewhere, key demographics are presented in the Table. Patients were enrolled between 1992 and 1998 (STAT) and between 1996 and 2000 (ESTAT) if they presented within 3 hours (STAT) or 6 hours (ESTAT) of the onset of acute ischemic stroke and had no intracranial, extravascular blood on the initial CT scan. Blood was drawn for fibrinogen determinations in all patients before beginning study drug. Fibrinogen levels were monitored at preset intervals throughout the 5 days of continuous (0 to 72 hours) and intermittent (72 to 120 hours) intravenous infusions, and functional outcome was determined at 90 days using the Barthel Index. The study drug was infused initially at one of 3 different rates based on pretreatment fibrinogen levels: <350 mg/dL (slowest), 350 to 449 mg/dL, or ≥450 mg/dL. After correction for pretreatment stroke severity and age, the proportion of these patients who had good functional outcomes at 90 days was 19.2%. The proportion of 212 patients with lower initial fibrinogen levels who had good functional outcomes was higher, 32.1%, although the difference was not statistically significant. Based on quartiles of initial fibrinogen levels ranked from lowest to highest (Figure 3), the proportion of patients achieving good functional outcomes generally fell as the fibrinogen rose. In a multifactorial analysis, however, the initial fibrinogen level

Table. Summary of STAT and ESTAT Placebo Populations

<table>
<thead>
<tr>
<th>Study</th>
<th>STAT</th>
<th>ESTAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>252</td>
<td>618</td>
</tr>
<tr>
<td>Age, years; mean±SD</td>
<td>73.1±11.6</td>
<td>67.7±12.6</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>53.2</td>
<td>60.0</td>
</tr>
<tr>
<td>Initial stroke severity (SSS score excluding gait, median, low scores represent more severe deficits)</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>70.2</td>
<td>56.5</td>
</tr>
<tr>
<td>Initial blood pressure</td>
<td>151/79</td>
<td>158/86</td>
</tr>
<tr>
<td>History of diabetes mellitus, %</td>
<td>20.6</td>
<td>22.8</td>
</tr>
<tr>
<td>History of atrial fibrillation, %</td>
<td>27.4</td>
<td>22.8</td>
</tr>
<tr>
<td>Current tobacco use, %</td>
<td>21.0</td>
<td>24.8</td>
</tr>
</tbody>
</table>

SSS indicates Scandinavian Stroke Scale.

Fibrinogen Measurements
Fibrinogen levels were measured using the Clauss method with instruments using photo-optical determinations of the end point.

Good Functional Outcome
Good functional outcome required that patients survive 90 days and have a Barthel Index total score of 95 to 100 or, for patients with prestroke disability, a score at least as high as the prestroke Barthel Index.

Statistical Analysis
The relationship of initial fibrinogen level to good functional outcome was evaluated using a multiple logistic regression model, which allows for the modeling of multiple predictor variables simultaneously. The initial fibrinogen level was used as a predictor variable both continuously and categorically based on cut points of quartiles after first ranking the fibrinogen level from lowest to highest. Additionally, categorical analyses were based on the cut points used to determine dosing in these ancrod studies, specifically whether the initial fibrinogen level was <450 mg/dL or ≥450 mg/dL. For all analyses, results were adjusted for the covariates of age and initial stroke severity using the Scandinavian Stroke Scale score. The LSmeans and 95% CIs from PROC GENMOD in SAS are presented. Statistical significance required P<0.05 (2-tailed test).
was not significantly associated with outcome, whereas age and initial stroke severity were.

A similar result was found in the ESTAT population (Figure 4). Ninety-two placebo-treated patients had fibrinogen levels ≥450 mg/dL. The proportion of patients with good functional outcome at 90 days corrected for pretreatment stroke severity and age was 21.6% for this group. The proportion of 523 patients with lower initial fibrinogen levels who had good functional outcomes was higher, 42.0%, and this difference was statistically significant (P=0.0006). Based on quartiles of initial fibrinogen levels (Figure 5), the proportion of patients achieving good functional outcomes was highest in the lowest quartile and lowest in the highest quartile. In a multifactorial analysis, the initial fibrinogen level, however, was not significantly associated with outcome, whereas age and initial stroke severity were.

**Discussion**

Because fibrinogen is an acute phase reactant, elevated fibrinogen levels may be associated with severity of the ischemic event. The study designs of STAT and ESTAT required measurement of fibrinogen levels at regular intervals after stroke onset. Samples taken at 3-hour intervals during the initial 12 hours, and every 12 hours thereafter through day 5 showed that fibrinogen levels in the placebo arm increased slowly over the first 24 hours and continued to rise over the first 5 days. Thus, high initial levels probably did not reflect an acute response to the stroke. One might still question whether the fibrinogen levels in Figure 1 were lowered either by hemodilution or by procoagulant-induced fibrinogen consumption as has been reported with substantial hemodilution in settings of surgery and trauma. Significant hemodilution from normal saline is unlikely because placebo subjects would have received no more than the approximately 1 L of normal saline given with ancrd to patients in the active arm over the 5-day study period. Furthermore, the slow rate of our saline infusion (the maximum initial infusion rate of 0.6 mL/kg per hour or <1% of blood volume over 1 hour) is well below the 30% replacement with saline associated with a procoagulant effect by Ng et al and the 10% replacement not associated with a procoagulant effect.

Several reports have evaluated the association between fibrinogen levels at various times and in different populations after stroke onset with mortality and risk of recurrent ischemic events. Turaj et al examined 900 patients with acute ischemic stroke admitted within 24 hours of symptom onset. Case fatality rates at 1 year were higher in patients with fibrinogen levels over 350 mg/dL than in those with lower levels (45.7% versus 31.2%; P<0.001). Di Napoli et al found a significant association between fibrinogen levels obtained within 24 hours of stroke symptom onset and the likelihood of death or new vascular disease within 1 year. Fifty-two percent of patients with first ever acute ischemic stroke whose fibrinogen levels were in the top tertile reached this end point compared with 27.9% of those in the middle tertile and 21.1% of those in the lowest tertile (P=0.0172, for trend). The association, however, was not significant with a multiple logistic regression analysis that included other risk factors, such as age, initial stroke severity, diabetes, and smoking. In an extension of this study that involved more patients and evaluated outcomes over 2 years, the highest versus the lowest tertile of fibrinogen levels was more predictive of fatal or nonfatal vascular events independent of these risk factors on multivariate analysis (hazard ratio 2.13 [95% CI, 1.31 to 3.47]; P=0.0025). Lip et al, however, found no association with either univariate or multivariate analyses between mortality at 1 year and fibrinogen levels obtained within 12 hours of symptom onset in a mixed group
of hospitalized patients with cerebrovascular disease (ischemic stroke, hemorrhagic stroke, and transient ischemic attack [TIA]). Rothwell et al20 demonstrated that, even among patients with a TIA or minor stroke 3 to 4 weeks earlier, fibrinogen levels were associated with long-term outcomes. Among patients enrolled in 3 large trials, the United Kingdom TIA Aspirin trial (n = 1860), the Dutch TIA trial (n = 2960), and the Oxford TIA Study (n = 293), fibrinogen levels predicted the occurrence of a subsequent ischemic stroke with an unadjusted pooled hazard ratio for values above the median fibrinogen level of 134 mg/dL (95% CI, 1.13 to 1.60; P = 0.001); this association was stronger for patients with nonlacunar versus lacunar syndromes. Even adjusted for risk factors including age, smoking, hypertension, and hypercholesterolemia, the association, although weaker, was still significant (P = 0.04). Methodological differences, such as sampling times, fibrinogen quantitation methods, and patient populations, may contribute to the different findings among these studies.

Similar to our observations, fibrinogen levels in the National Institutes of Neurological Disorders and Stroke (NINDS) rt-PA Study remained stable across samples taken at baseline, at 2 hours after initiation of study treatment, and at 24 hours after stroke onset.21 Another study that looked at levels of acute phase reactants at 24-hour intervals after stroke onset found that concentrations of fibrinogen and C-reactive protein peaked at about day 3.22 Lip et al19 reported that the peak occurred between 1 and 2 weeks poststroke. The implications of these findings are that measurement of fibrinogen levels at any time during the first 24 hours do not reflect a reaction to the acute event and would carry similar prognostic value.

In our analysis, higher fibrinogen levels appeared to be related to poorer functional outcome in both the STAT and ESTAT studies. Moreover, in ESTAT, a baseline fibrinogen level ≥450 mg/dL was significantly associated with poor functional outcome at 90 days even taking into account the covariates of age and pretreatment stroke severity. Our results suggesting an association between the initial fibrinogen level and functional outcome from acute ischemic stroke are consistent with the observation by Tanne et al,21 who reported that placebo patients in the NINDS study were more likely to deteriorate, with higher 2-hour fibrinogen levels (P = 0.05), and that higher 24-hour fibrinogen levels were associated with a 40% relative increased 90-day mortality.

Differences in outcomes at higher fibrinogen levels may be related to clot structure. Clots that form in the presence of high fibrinogen concentrations may be made of thinner, more tightly packed fibers that are more resistant to fibrinolysis than clots formed at a lower concentration.23 Therefore, fibrinogen levels in the early poststroke period may have implications for determining the efficacy of thrombolytic treatment. Supporting this hypothesis, González-Conejero et al24 evaluated fibrinogen levels in 200 patients with acute, carotid artery distribution ischemic strokes who were treated with intravenous rt-PA. They found that patients with fibrinogen levels >360 mg/dL had poorer outcomes based on discharge National Institutes of Health Stroke Scale scores (8 [interquartile range 3 to 14] versus 14 [5 to 18]; P = 0.015) and higher 3-month mortality (22.6% versus 9.7%; P = 0.027). They speculated that this might have been related to more stable fibrin clots having been formed in the presence of higher substrate levels of fibrinogen. An additional possible explanation for a relationship between higher fibrinogen levels and poorer outcome could be the higher blood viscosity known to be associated with higher fibrinogen levels2 because increased viscosity could potentially compromise microvascular blood flow in marginally perfused brain areas.

These studies were designed to assess the efficacy and safety of ancrod (a defibrinogenating agent) in acute ischemic stroke rather than the influence of the initial fibrinogen level on outcome; thus, the analyses presented here represent post hoc analyses and should be evaluated in that context. Nonetheless, this emerging association between high initial fibrinogen levels and poor outcome from stroke suggests that defibrinogenation might be a useful therapeutic modality and that fibrinolytics like rt-PA might be more effective if the dose were modestly increased in patients with high admission fibrinogen levels. These therapeutic implications emphasize the importance of determining whether the relationship of fibrinogen to outcome can be confirmed in other databases of acute ischemic stroke and in new prospective studies.

Disclosures
Data and analytic resources used in preparing this manuscript were provided by the current sponsor of ancrod, Neurobiological Technologies, Inc (NTI). Drs Levy and Wasiewski are employees of NTI, Mr Trammel is a contractor of NTI, and the other authors serve on the Steering Committee for the ongoing Ancrod in Stroke Program trials.

References


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