Fibrinogen Concentration and Risk of Ischemic Stroke and Acute Coronary Events in 5113 Patients With Transient Ischemic Attack and Minor Ischemic Stroke

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Background and Purpose—Fibrinogen is an independent risk factor for coronary events in population-based studies and in patients with coronary heart disease, but there is uncertainty about prediction of stroke, particularly in secondary prevention.

Methods—We studied unpublished data from 3 prospective studies of patients with recent transient ischemic attack (TIA) or minor ischemic stroke: the United Kingdom TIA Aspirin (UK-TIA) trial (n = 1860); the Dutch TIA trial (n = 2960); and the Oxford TIA Study (n = 293). By separate and pooled analysis, we used Cox models to determine the relationship between fibrinogen and risk of ischemic stroke and other vascular events during 23 272 patient-years of follow-up and adjusted for other risk factors.

Results—There was no significant heterogeneity in fibrinogen risk associations between studies. Fibrinogen predicted subsequent ischemic stroke, with a pooled hazard ratio (HR) for values above the median of 1.34 (95% CI, 1.13 to 1.60; P = 0.001). The association tended to be stronger in patients with nonlacunar (HR = 1.42; 95% CI, 1.13 to 1.78; P = 0.002) than lacunar syndromes (HR = 1.09; 95% CI, 0.80 to 1.49; P = 0.58), but was not significantly so (P = 0.18). There was no association with hemorrhagic stroke (adjusted HR = 1.09; 95% CI, 0.55 to 2.17; P = 0.81). Fibrinogen predicted acute coronary events (adjusted HR = 1.42; 95% CI, 1.18 to 1.70; P < 0.001) and all ischemic vascular events (adjusted HR = 1.31; 95% CI, 1.15 to 1.49; P < 0.001), but not nonvascular death (adjusted HR = 1.24; 95% CI, 0.90 to 1.70; P = 0.19).

Conclusions—In patients with a previous TIA or ischemic stroke, risks of recurrent ischemic stroke and acute coronary events increase linearly with fibrinogen levels, but the relationships are weaker than in some previous population-based studies. (Stroke. 2004;35:2300-2305.)

Key Words: epidemiology • fibrinogen • risk factors • stroke prevention • thrombosis

Fibrinogen is involved in primary hemostasis, platelet aggregation, and leukocyte-endothelial cell interactions and is the major determinant of whole blood and plasma viscosity. Elevated levels are associated with atherosclerosis and have been reported in patients with coronary heart disease, peripheral vascular disease, and carotid stenosis. Fibrinogen levels also predict vascular events in population-based studies and in patients with coronary or peripheral vascular disease, but there is uncertainty about prediction of stroke. Several reviews have shown that subjects with fibrinogen in the highest tertile are at twice the risk of cardiovascular events as subjects in the lowest tertile, but only a few studies have looked at stroke as a distinct outcome event and none made any distinction in relation to type or severity of stroke. Four small cohort studies in patients with transient ischemic attack (TIA) or ischemic stroke have been reported, but all confined analysis to the risk of all cardiovascular events combined. A report from the Dutch TIA trial found a trend toward an increased risk of stroke at fibrinogen levels > 3 g/L, but this trial did not have sufficient power to assess reliably the relationship between fibrinogen and ischemic stroke. Consequently, there is uncertainty about whether fibrinogen is a useful predictor of stroke in patients with a previous TIA or ischemic stroke.

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By pooled analysis of detailed individual patient data from 3 studies of patients with a previous TIA or minor ischemic stroke, we determined the relationships between baseline fibrinogen concentration and the risks of ischemic stroke, hemorrhagic stroke, acute coronary events, and other vascular events.23–25

Methods

Individual patient data were obtained from 3 studies of patients with a previous TIA or minor ischemic stroke: the United Kingdom TIA Aspirin (UK-TIA) trial,23 the Dutch TIA trial,24 and a cohort study from Oxford, UK.25 The UK-TIA trial was a multicenter randomized control trial of long-term treatment with aspirin (600 mg twice daily, 300 mg once daily or placebo) in 2435 patients. The Dutch TIA trial was a multicenter 2×2 factorial randomized control trial of 3150 patients (3131 randomized to aspirin, 30 mg versus 283 mg and 1473 to atenolol, 50 mg versus placebo). In both trials, patients were followed-up by a neurologist every 4 months. The Oxford TIA cohort was a prospective study of 293 patients who had remained stroke-free for at least 3 months (median=3.8 years, interquartile range [IQR]: 2.2 to 5.8) after a TIA. Follow-up was performed through their family physicians.

Baseline characteristics and blood pressure were recorded at entry in each study. Cholesterol was not measured in the Dutch TIA trial. Data on baseline computed tomography (CT) brain imaging were collected routinely in the Dutch-TIA trial, but not in the UK-TIA trial. We therefore defined presentation with a lacunar TIA or stroke on the basis of clinical assessment alone in the UK TIA trial, but on the additional presence of an appropriate lacunar lesion on CT brain scan in the Dutch TIA trial. These data were not available for the Oxford TIA cohort.

In the UK-TIA trial, a fasting sample of venous blood was taken shortly after randomization and plasma was transported to a central laboratory in Oxford and frozen at –20°C. Fibrinogen levels were determined by allowing diluted plasma to clot to completion in 300 microliter wells and then measuring the opacity of the clot, which is linearly related to the fibrinogen content.26 A modification to the published method involved measuring opacity at 405 nm rather than 300 nm. Samples were tested in triplicate and the mean value recorded. A previous validation study27 showed that the results were highly correlated with results by the Clauss method.28 The same assay was used in the same laboratory for samples taken from the Oxford TIA cohort. In both studies, all assays were performed blinded to outcome. In the Dutch TIA trial, venous blood was sampled at baseline and fibrinogen was measured in each center by the method of Clauss.28 Each center used local “normal blood pools,” based on the blood of 40 healthy volunteers.

All strokes, nonfatal myocardial infarctions, and deaths were recorded during follow-up. According to brain imaging or postmortem data, strokes were subdivided into ischemic stroke or primary intracerebral hemorrhage. In a few cases, where no imaging or postmortem data were available, strokes were classified as ischemic. The following outcomes were used for analysis of the predictive value of baseline fibrinogen: ischemic stroke; intracerebral hemorrhage; acute coronary event (acute myocardial infarction or sudden death with coronary thrombosis at autopsy, or sudden death presumed to be the result of coronary thrombosis); other vascular death (eg, ruptured aortic aneurysm, systemic embolism); all ischemic vascular events (a composite of the above); and nonvascular death.

Analysis

To control for possible differences in measurement between the centers in the Dutch TIA trial, baseline values of fibrinogen were standardized within each center by subtracting the center mean and dividing by the center standard deviation. Medians and quintiles of these standardized values were then calculated. For the UK-TIA trial and the Oxford-based TIA cohort, absolute fibrinogen values were used.

Within each study, the associations between fibrinogen and baseline clinical characteristics and risk factors were determined across quintiles of fibrinogen. Heterogeneity between (P Trend) and trends across (P Trend) quintiles were calculated with χ² tests and ANOVA as appropriate (Table). Within each study, Cox proportional hazards models, stratified by center, were used to obtain hazard ratios (HRs; 95% CI) for fibrinogen values above versus below the median. HRs were also adjusted for all measured potentially confounding vascular risk factors (Table). In the pooled analysis, greater statistical power allowed analysis by quintiles of fibrinogen. Cox proportional hazards models, stratified by study, were used to obtain crude and adjusted HRs for each quintile compared with the first quintile. The method of floating absolute risk was used to estimate confidence intervals.29

There is considerable intra-individual variation in fibrinogen measurements, so correction of risk relations for the effects of regression dilution is necessary.30 In 70 consecutive patients from the Oxford TIA cohort, repeat blood samples were therefore taken at the end of the first year of follow-up. All analyses were performed with SPSS (version 10.0; SPSS).

Results

Fibrinogen was available in 1860 (76%) patients from the UK-TIA trial, 2960 (95%) patients from the Dutch TIA trial, and 293 (100%) patients from the Oxford-based TIA cohort, and was distributed normally in each study. However, the median value (IQR) was lower in the Dutch TIA trial (3.21g/L, IQR=2.70 to 3.60) than in the UK-TIA trial (3.89g/L, 3.16 to 4.56) and Oxford-based cohort (3.95g/L, 3.41 to 4.54). This difference remained after controlling for differences in patient characteristics. In contrast to the UK-TIA trial, there was significant variation in the nonstandardized fibrinogen values between centers in the Dutch TIA trial (P<0.001).

In the UK-TIA trial, there were 210 ischemic strokes and 225 acute coronary events during a mean follow-up of 7.25 years. The respective numbers in the Dutch TIA trial and the Oxford-based TIA cohort were 257 and 187 in 2.6 years, and 45 and 65 during 10 years. The pooled analyses included 512 ischemic strokes, 51 hemorrhagic strokes, 477 acute coronary events, and 1005 acute ischemic vascular events during 23 272 patient-years of follow-up.

In neither of the trials was there an association between fibrinogen and treatment allocation, but increasing age, female sex, smoking, and increasing systolic blood pressure were consistently associated with higher levels (Table). A significant association with cholesterol was observed in the UK-TIA trial. There was no difference between the mean (SD) fibrinogen level (g/L) in patients presenting with a lacunar syndrome versus a nonlacunar syndrome in the UK-TIA trial (3.90[1.10] versus 3.89[1.12], P=0.89) or in the proportion of patients with fibrinogen above the median value in the Dutch TIA trial in relation to the presence of lacunar infarct on CT brain scan (50.9% versus 48.9%, P=0.36).

In the UK-TIA trial, mean (SD) fibrinogen was higher in patients with vascular events during follow-up: ischemic stroke (n=210) –4.10 (1.02) versus 3.87 (1.12), P=0.005; coronary event (n=225) –4.17 (1.10) versus 3.86 (1.11), P<0.001; all ischemic vascular events (n=451) –4.12 (1.11) versus 3.82 (1.11), P<0.001. Similar differences were seen in the Oxford cohort: ischemic stroke (n=42) –4.18 (1.14) versus 3.98 (0.98), P=0.22 (ANOVA); coronary event (n=65) –4.10 (1.10) versus 3.98 (0.98), P=0.43; and all ischemic vascular events (n=114) –4.18 (1.13) versus 3.90 (0.92), P=0.02. We did not analyze absolute values of fibrinogen in the Dutch TIA trial.
Figure 1 shows the HRs for outcome events for fibrinogen values above the median in the 3 studies separately and pooled. In each study, there was a trend toward increased risk with higher fibrinogen levels, and there was no heterogeneity between the studies for any of the outcomes. After adjustment for other vascular risk factors and treatment allocation, the pooled HR for acute ischemic stroke was weak (1.21; 95% CI, 1.01 to 1.44; $P = 0.04$), but the associations remained highly significant for acute coronary events (1.42; 95% CI, 1.18 to 1.70; $P < 0.001$) and all acute ischemic vascular events (1.31; 95% CI, 1.15 to 1.49; $P < 0.001$).

The association between fibrinogen and risk of ischemic stroke was stronger in patients with nonlacunar syndromes than lacunar syndromes (pooled HR=1.42; 95% CI, 1.13 to 1.78; $P = 0.002$ versus 1.09; 95% CI, 0.80 to 1.49; $P = 0.58$). This trend was present in both the UK-TIA trial and the Dutch TIA trial but was not statistically significant (interaction: $P = 0.18$). The pooled HRs for risk of hemorrhagic stroke were 1.11 (95% CI, 0.56 to 2.20; $P = 0.76$) without adjustment and 1.09 (95% CI, 0.55 to 2.17; $P = 0.81$) after adjustment.

Figure 2 shows the pooled HR from the Cox model stratified by study for each quintile. For all 3 of the main outcomes, the unadjusted relationships showed highly statistically significant linear trends toward increasing risk with increasing fibrinogen (all $P < 0.001$). After adjustment for other risk factors, the associations remained significant for risk of ischemic stroke.
(P = 0.01), acute coronary events (P < 0.001), and all acute ischemic vascular events (P < 0.001).

The reliability coefficient for repeated fibrinogen measurement after 1 year of follow-up in the Oxford TIA cohort was 0.64 (95% CI, 0.47 to 0.77).

**Discussion**

By pooling data from 3 studies, we had sufficient power to study the relationship between fibrinogen and the risks of ischemic stroke and coronary vascular events as separate outcomes. Despite differences between the studies and the methods of measurement of fibrinogen, the findings were consistent. The relationship between fibrinogen and risk of ischemic stroke was weaker than in previous studies of patients with coronary heart disease, which have reported HRs for ischemic stroke for the top versus bottom tertile of up to nearly 3.4,5,10,12,14 The weaker association might be because we studied patients with preexisting cerebrovascular disease, in whom risk factors that are predictive of the development of cerebrovascular disease in population-based studies or coronary heart disease cohorts might be less predictive. In support of this explanation, the fibrinogen risk relation for acute coronary events in our populations was more in keeping with that reported in previous studies.

Fibrinogen was a stronger predictor of acute coronary events than ischemic stroke in each study and in the pooled analysis. However, the relationship with nonstroke outcomes was not statistically significantly different from that with ischemic stroke (Figure 2). There was a trend toward a stronger association between fibrinogen and risk of acute ischemic stroke in patients with nonlacunar syndromes than in patients with lacunar syndromes, but the difference, although interesting and plausible, was not statistically significant.

We cannot be certain that fibrinogen is a causal risk factor for acute ischemic vascular events. Although we were able to adjust for those other vascular risk factors that have been adjusted for in previous studies, several other potentially confounding factors, including obesity, lack of exercise, alcohol consumption, and social class, were not measured. Moreover, some of the risk factors that we did adjust for were not measured as accurately as would be desired; that is, single measurement of blood pressure (versus multiple measurements), current smoking (versus a more precise measure of smoking), and a diagnosis of diabetes (versus a measurement of glucose intolerance in all patients). All previous studies have these limitations. On the other hand, the analysis with correction for regression-dilution clearly indicates that just a single baseline measurement of fibrinogen will underestimate the true risk association by ~40%.

There are a number of additional methodological issues that merit discussion. First, comparison of absolute fibrino-
gen measurements between the different studies was problematic, as no universally accepted method for measuring fibrinogen exists and different methods were used. Moreover, geographical variations in plasma viscosity have been identified and these may reflect variations in fibrinogen levels. For these reasons, data from the different studies were not simply merged; differences in the absolute baseline values were unresolved after accounting for baseline patient characteristics. The assay used in the Oxford laboratory produced very similar values for patients in the UK-TIA trial and the Oxford TIA cohort, and reproducibility at 1 year was comparable with previous studies, but the fact that measurements were not determined centrally in the Dutch TIA trial led to some uncertainty as to whether values obtained at the different participating centers were comparable. We therefore standardized values within each center to obtain meaningful medians and quintiles. Subsequent analyses of associations of fibrinogen with other risk factors at baseline were consistent across the studies and in keeping with previous studies, and also, there were no significant differences between our 3 cohorts in the prognostic value of fibrinogen, which suggests that the fibrinogen measurements were valid.

Second, fibrinogen is an acute-phase protein and although the acute-phase response is smaller than that of C-reactive protein and other reactants, fibrinogen levels have been shown to correlate with severity of acute stroke. However, although levels of fibrinogen are higher in patients with TIA than controls, they fall only slightly with time after a TIA or minor stroke, suggesting that measurements taken a few weeks or months after the event are a reasonable measure of subsequent values (and probably also prior values). In contrast to 2 previous studies of the prognostic value of fibrinogen following stroke, in which blood was sampled within 24 hours of the event, the delay to recruitment in the UK-TIA trial (34 days, IQR 10 to 51) and the Dutch TIA trial (25 days, IQR 8 to 34) was probably sufficient to avoid any significant bias. Moreover, neither trial recruited patients with major disabling stroke and there was no association between fibrinogen levels and the mean number of days from last TIA or stroke to randomization (Table). The time from presenting TIA to recruitment into the Oxford TIA cohort was well beyond the acute phase (median 3.8 years, IQR 2.2 to 5.8), and only patients who had not experienced a stroke were recruited.

Third, we were unable to adjust the pooled fibrinogen–vascular risk associations for cholesterol level, because it was not measured in the Dutch TIA trial. However, adjustment for cholesterol level in the other 2 cohorts had little effect. Finally, we were unable to determine the effect of fibrinogen on risk of ischemic stroke according to the etiological subtype of the recurrent event. Fibrinogen levels have been reported to be higher in patients with atherothrombotic stroke and lacunar stroke than in patients with cardioembolic stroke, and with evidence of small vessel ischemic changes on brain imaging. We found no significant difference in fibrinogen levels between patients presenting with a lacunar versus nonlacunar syndrome (UK-TIA trial) or between patients with versus without an appropriate lacunar infarct on CT brain scan (Dutch-TIA trial). However, studies with more accurate subtyping of follow-up strokes are required.

Several drugs are known to reduce fibrinogen levels, including bezafibrate, β-blockers, pentoxifylline, and ticlopidine. Moreover, lifestyle modification, including smoking cessation and increased exercise, can reduce fibrinogen levels. The only evidence available so far on the effectiveness of lowering fibrinogen comes from the Bezafibrate Infarction Prevention Study, a randomized trial of bezafibrate in patients with coronary heart disease. In this study, mean fibrinogen concentration was reduced by nearly 20% in the bezafibrate group, but there was no correlation between the degree of reduction in fibrinogen in individuals and the risk of ischemic stroke during follow-up. Ancrod reduces fibrinogen levels.
significantly without also affecting blood pressure or lipids,\textsuperscript{39} but long-term administration is not practical.

In summary, ours is by far the largest published study of the predictive value of fibrinogen in patients with TIA or ischemic stroke and one of only a few studies to determine the predictive value of fibrinogen for ischemic stroke separately. The risk of recurrent ischemic stroke, acute coronary events, and all ischémic vascular events combined increase linearly with fibrinogen levels, but the relationships were weaker than in most population-based studies. Routine measurement of fibrinogen is probably not justified in clinical practice, but it is likely to be of value in stratifying patients according to overall vascular risk in clinical situations where this is required.

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