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Associations of Inflammatory and Hemostatic Variables With the Risk of Recurrent Stroke

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Background and Purpose—Several prospective studies have shown significant associations between plasma fibrinogen, viscosity, C-reactive protein (CRP), fibrin D-dimer, or tissue plasminogen activator (tPA) antigen and the risk of primary cardiovascular events. Little has been published on the associations of these variables with recurrent stroke. We studied such associations in a nested case-control study derived from the Perindopril Protection Against Recurrent Stroke Study (PROGRESS).

Methods—Nested case-control study of ischemic (n=472) and hemorrhagic (n=83) strokes occurring during a randomized, placebo-controlled multicenter trial of perindopril-based therapy in 6105 patients with a history of stroke or transient ischemic attack. Controls were matched for age, treatment group, sex, region, and most recent qualifying event at entry to the parent trial.

Results—Fibrinogen and CRP were associated with an increased risk of recurrent ischemic stroke after accounting for the matching variables and adjusting for systolic blood pressure, smoking, peripheral vascular disease, and statin and antiplatelet therapy. The odds ratio for the last compared with the first third of fibrinogen was 1.34 (95% CI, 1.01 to 1.78) and for CRP was 1.39 (95% CI, 1.05 to 1.85). After additional adjustment for each other, these 2 odds ratios stayed virtually unchanged. Plasma viscosity, tPA, and D-dimer showed no relationship with recurrent ischemic stroke, although tPA was significant for lacunar and large artery subtypes. Although each of these variables showed a negative relationship with recurrent hemorrhagic stroke, none of these relationships achieved statistical significance.

Conclusions—Fibrinogen and CRP are risk predictors for ischemic but not hemorrhagic stroke, independent of potential confounders. (*Stroke*. 2005;36:2143-2147.)

Key Words: hemostasis ■ inflammation ■ stroke

There is increasing evidence that hemostatic and inflammatory variables are associated with cardiovascular events in prospective studies, including coronary heart disease (CHD) and stroke.¹ Most data are available for fibrinogen, which may play a causal role in atherothrombotic events through effects on atherogenesis, thrombogenesis, or ischemia distal to atherothrombotic stenoses or occlusions.¹⁻⁴ Several prospective studies have reported that fibrinogen is associated with risk of stroke,⁵⁻⁹ although not the Caerphilly and Speedwell studies.¹⁰ Plasma fibrinogen is an important determinant of plasma and blood viscosity, which have also been reported to be associated with the risk of CHD,¹¹⁻¹⁵ although reports for stroke have been conflicting.^{10,13} In part, the possible association between viscosity and stroke may be mediated by an association between viscosity and elevated carotid

intima-media thickness, at least in men.¹⁶ Ernst et al¹⁷ observed that fibrinogen, plasma viscosity, blood viscosity, and cholesterol were associated with risk of recurrence over 2 years in 523 survivors of first stroke. Similar findings have been reported for recurrent myocardial infarction.¹⁸

There are fewer published data on the association of other hemostatic or inflammatory variables with risk of CHD and stroke.¹ Recent meta-analyses have shown that C-reactive protein (CRP),^{3,19} von Willebrand factor (vWF),^{19,20} fibrin D-dimer,²¹ and tissue plasminogen activator (tPA) antigen,²² but not plasminogen activator inhibitor type 1,²² are associated with risk of CHD events in samples of general populations. There are limited published data for the associations of CRP,^{23,24} vWF (or its complexed coagulation factor, factor VIII),^{8,9,23,24}

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D-dimer^{7-9,25} or tPA antigen^{8,9,25-27} with risk of stroke in prospective studies.

In PROGRESS,^{28,29} baseline plasma samples were centrally stored for analysis, in nested case-control studies, of emerging potential risk factors for recurrent stroke, including hemostatic and inflammatory variables.²⁸ Here, we report the associations of plasma fibrinogen, viscosity, CRP, D-dimer, and tPA antigen with recurrent strokes (ischemic and hemorrhagic).

Materials and Methods

The design²⁸ and principal results²⁹ of PROGRESS have been published previously. Briefly, 6105 patients with a history of stroke or transient ischemic attack (TIA) were recruited and each patient randomly assigned active treatment (n=3051) or placebo (n=3054). For those deemed suitable by the responsible physician, dual therapy was allocated: perindopril with indapamide or double placebo. Others received monotherapy: perindopril or single placebo. Patients were followed for a mean of 3.9 years, during which time stroke (fatal or nonfatal) occurred in 307 (10%) in the active treatment group and 420 (14%) in the placebo group (relative risk reduction, 28%; 95% CI, 17 to 38; $P<0.0001$).²⁹

At baseline, venous blood samples collected from 5918 (97%) of patients were anticoagulated with K₂ EDTA and centrifuged at 2000g for 10 min at 4°C. Aliquots (1.5 mL) of plasma were stored at -80°C for an average of 6 years. Plasma fibrinogen was assayed by immunonephelometry (Dade-Behring).³⁰ Plasma viscosity was measured in a semiautomated capillary viscometer (Coulter) and expressed at 37°C with a correction for storage of frozen samples.³¹ Fibrin D-dimer and tPA antigens were measured by ELISAs (Biopool) as described previously.^{21,22} CRP was measured by high-sensitivity nephelometry (Dade Behring). Laboratory personnel were "blinded" to the case-control status of samples. The interassay coefficients of variation for control samples were: fibrinogen 5.3%; viscosity 0.9%; tPA 6.5%; D-dimer 5.3%; and CRP 3.9%.

The base population for this study was all those who had plasma frozen and stored within 48 hours of venipuncture and whose most recent qualifying event (stroke or TIA) at baseline in the clinical trial occurred >1 month ago. These restrictions give protection against deterioration of the blood samples and confounding attributable to acute-phase reactant increases in blood variables as a result of the incident stroke or its acute complications.

Stroke cases comprised anyone with a stroke recorded during follow-up. Using standard methodology for nested case-control studies,³² each case was randomly matched to between 1 and 3 controls selected from all those free of recurrent stroke at the time of recurrent stroke for that case. Under this sampling scheme, any case may be selected as a control for other cases for whom recurrent stroke predates their own, whereas cases may have common controls. The overall sample size was restricted so that the total number of people selected who had no stroke during follow-up outnumbered the cases in the ratio of 1 to 2. Matching variables were age (within 5 years), sex, treatment allocated (active/placebo), therapy (mono/dual), region (Australia or New Zealand/China/Japan/France or Belgium/Italy/Sweden/UK or Ireland) and most recent qualifying event (ischemic stroke or TIA/hemorrhagic stroke/stroke of unknown type) at the trial baseline. Prespecified ischemic and hemorrhagic stroke substudies isolated those cases and their matched controls, who had ischemic or hemorrhagic strokes as their first recorded stroke event.

Odds ratios were calculated according to equal thirds of the distribution of each risk factor in the total sample (cases and controls together) using conditional logistic regression models.³² As well as unadjusted analyses (allowing only for the confounding effects of the matched variables, by design), additional adjustments through the regression model were made for systolic blood pressure, smoking (current/non), peripheral artery disease, statin therapy, and antiplatelet therapy. Because fibrinogen and CRP are acute-phase proteins, each was additionally adjusted for the other.

Results

The nested case-control study included 1773 patients: 591 were cases (83 hemorrhagic strokes, 472 ischemic strokes, and 36 of unknown type), and 1182 were controls who did not subsequently become cases. Controls satisfying all matching criteria were found for 572 of these cases; 19 were incompletely matched. After the addition of cases who acted as matched controls for other cases and taking account of controls who acted for >1 case, there were 33 cases with 1, 213 with 2, and 345 with 3 matched controls. Altogether, 89 cases served as controls for ≥ 1 other case.

Table 1 shows, according to type of stroke, summaries of the demographic randomization group and risk factor data according to whether the subject became a case or not during PROGRESS. In this presentation, unique cases and controls are shown, that is, after removing duplicates consequent to the unbiased nested design. In the ischemic stroke study, fibrinogen and CRP were significantly ($P<0.05$) higher in cases than controls, as was systolic blood pressure and the prevalence of diabetes, smoking, peripheral artery disease, atrial fibrillation, and left ventricular hypertrophy. In the hemorrhagic stroke study, there were no significant differences, although this could be explained by the lack of power.

Table 2 shows the odds ratios for hemorrhagic, ischemic, and total stroke associated with thirds of the hemostatic and inflammatory variables. Also included is a test for trend across the thirds. None of the variables showed any significant relationship with hemorrhagic stroke. Only fibrinogen and CRP showed significant associations with ischemic stroke: the odds ratio (95% CI) comparing the last to the first third was 1.43 (1.08 to 1.89) for fibrinogen and 1.52 (1.15 to 2.00) for CRP. Adjustment for systolic blood pressure and smoking, in addition to the matching variables adjusted by design, attenuated the odds ratios by 2% to 10%. A noticeable difference between the 2 sets of results is the negative relationships for hemorrhagic stroke and the positive relationships for ischemic stroke for all variables. As a consequence, and because ischemic strokes outnumbered hemorrhagic by almost 6:1, results for total stroke were an attenuated version of those for ischemic stroke. Only fibrinogen had a significant relationship.

To investigate subtypes of ischemic stroke, we analyzed 66 cases of large artery infarct and 114 cases of lacunar infarct, and their matched controls, separately. The only other subtype identified in PROGRESS was cardioembolic, which had too few cases with blood samples (29) to justify analyses. Allowing for the much wider CIs, results were generally similar to those for all ischemic strokes. Thus, the odds ratio (95% CI) for large artery infarct for the adjusted analysis of Table 2, comparing the top to bottom thirds, was 1.34 (0.59 to 3.04) for fibrinogen and 1.48 (0.64 to 3.43) for CRP. Corresponding results for lacunar infarct were 1.82 (0.99 to 3.13) and 1.86 (1.00 to 3.43). Now there was, however, evidence of a positive effect for tPA, in contrast to the overall result. The corresponding results to those above were 1.78 (0.81 to 3.91) and 1.98 (1.10 to 3.60), with P values for trend of 0.07 and 0.02, respectively.

The correlation between fibrinogen and CRP was 0.49 in cases and controls. There was no interaction between them

TABLE 1. Baseline Summary Data for All Subjects in the Nested Case-Control Study Classified by Whether or Not They Developed Either of the Major Subtypes of Stroke During PROGRESS

Variable	Hemorrhagic Stroke Study			Ischemic Stroke Study		
	Cases (n=83)	Controls (n=199)*	P Value	Cases (n=472)	Controls (n=1011)*	P Value
Mean (95% CI)						
SBP, mm Hg	149.7 (145.4–154.0)	145.9 (143.4–148.4)	0.11	149.9 (148.1–151.6)	147.4 (146.3–148.6)	0.02
DBP, mm Hg	88.4 (85.9–91.0)	85.9 (84.5–87.2)	0.08	86.0 (85.1–87.0)	85.0 (84.4–85.7)	0.10
Age, y†	62.5 (60.6–64.5)	62.4 (61.2–63.6)	0.92	66.5 (65.7–67.3)	66.2 (65.7–66.7)	0.48
BMI, kg/m ²	24.9 (24.1–25.7)	25.3 (24.8–25.8)	0.42	25.8 (25.5–26.2)	25.5 (25.3–25.7)	0.13
Fibrinogen, g/L	3.58 (3.40–3.76)	3.76 (3.63–3.89)	0.11	3.87 (3.79–3.96)	3.73 (3.70–3.78)	0.005
Viscosity, mPa.s	1.28 (1.26–1.30)	1.30 (1.29–1.31)	0.06	1.29 (1.28–1.30)	1.29 (1.28–1.29)	0.54
tPA, ng/mL	8.61 (7.53–9.69)	9.08 (8.41–9.76)	0.45	9.44 (8.98–9.89)	9.00 (8.72–9.28)	0.11
D-dimer, ng/mL	118.4 (72.2–164.6)	161.0 (109.1–212.8)	0.23	198.7 (160.1–237.4)	183.0 (157.7–208.3)	0.50
CRP, mg/L‡	1.47 (1.10–1.96)	1.62 (1.35–1.94)	0.57	2.20 (1.98–2.45)	1.91 (1.77–2.05)	0.03
No. (%)						
Malest	63 (76)	154 (77)	0.88	348 (74)	750 (74)	0.85
Diabetes	6 (7)	19 (10)	0.65	85 (18)	113 (11)	0.0004
Smokers	15 (18)	43 (22)	0.63	110 (23)	173 (17)	0.006
Active treatment†	22 (27)	52 (26)	1.00	208 (44)	462 (46)	0.58
Dual therapy†	45 (54)	110 (55)	0.90	265 (56)	569 (56)	1.00
Previous heart disease	11 (13)	39 (20)	0.23	91 (19)	172 (17)	0.31
Peripheral artery disease	1 (1)	7 (4)	0.94	32 (7)	39 (4)	0.02
Treated hypertension	49 (59)	117 (59)	1.00	250 (53)	483 (48)	0.07
Atrial fibrillation	7 (8)	12 (6)	0.45	54 (11)	75 (7)	0.01
Valvular heart disease	2 (2)	1 (1)	0.21	14 (3)	24 (2)	0.49
Left ventricular hypertrophy	13 (16)	17 (9)	0.09	41 (9)	59 (6)	0.05
Statin therapy	5 (6)	13 (7)	1.00	36 (8)	77 (8)	1.00
Antiplatelet therapy	39 (47)	104 (52)	0.44	362 (77)	780 (77)	0.84

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

*Controls who did not go on to become cases during PROGRESS; †matching variables; ‡analyzed on the logarithmic scale; estimates shown after back-transformation.

for any of the 3 outcomes ($P>0.14$). Extra adjustment of fibrinogen for CRP, or fibrinogen for CRP, made no difference, to 1 decimal place, to either of the adjusted odds ratios comparing the extreme thirds for ischemic stroke.

Discussion

This is the largest reported single prospective study to date of the associations between plasma fibrinogen, viscosity, CRP, fibrin D-dimer, tPA antigen, and the risk of recurrent stroke.^{3,15,19–22} The main finding is that plasma fibrinogen is a significant, independent risk factor for recurrent stroke. This agrees with a previous study in stroke survivors,¹⁷ which observed a significantly higher baseline fibrinogen level for those with recurrent stroke ($n=67$) compared with those who did not experience recurrence ($n=456$), and also with a meta-analysis of 3 other prospective studies of patients with TIA or minor stroke (total recurrent ischemic strokes $n=512$).³³ Our study also clarifies that the association of fibrinogen with recurrent stroke applies only to ischemic stroke, as also observed in the meta-analysis.³³ Indeed, the odds ratio for hemorrhagic stroke was lowest in the highest third of fibrinogen. The association between fibrinogen and

first stroke is currently being studied in the Fibrinogen Studies Collaboration.³⁴

Potential confounders of the association between fibrinogen and ischemic stroke include blood pressure, smoking habit, and the acute-phase reactant behavior of plasma fibrinogen.^{1–4} However, when we additionally adjusted for CRP (the generally accepted best measure of inflammatory reactions in cardiovascular disease¹⁹), estimates of the effect of fibrinogen were little changed for recurrent ischemic stroke. There are several plausible biological pathways through which increasing plasma fibrinogen levels might increase the risk (and outcome) of stroke, including atherogenesis, thrombogenesis, and (through its rheological effects) promoting cerebral ischemia distal to atherothrombotic stenoses or occlusions.^{1–4,13,16,17,35,36} Our results for CRP are consistent with previous studies that reported associations between CRP and risk of a first stroke.^{23,24}

In contrast to previous studies of first¹³ or recurrent¹⁷ stroke, we did not observe a significant association between plasma viscosity and recurrent stroke in the present study; nor did an analysis of first stroke in the Caerphilly and Speedwell studies.¹⁰ A recent meta-analysis of prospective studies ob-

TABLE 2. Odds Ratios (95% CIs) for Hemorrhagic, Ischemic, and Total Stroke by Thirds of Each Variable

Variable/Third	Hemorrhagic Stroke		Ischemic Stroke		Total Stroke	
	Matched	Further Adjusted*	Matched	Further Adjusted*	Matched	Further Adjusted*
Fibrinogen, g/L						
1 (<3.32)	1	1	1	1	1	1
2 (3.32–4.04)	1.20 (0.65–2.23)	1.17 (0.61–2.22)	1.22 (0.94–1.60)	1.20 (0.92–1.58)	1.19 (0.93–1.51)	1.17 (0.92–1.49)
3 (>4.04)	0.56 (0.29–1.10)	0.57 (0.29–1.14)	1.43 (1.08–1.89)	1.34 (1.01–1.78)	1.28 (1.00–1.64)	1.24 (0.97–1.59)
<i>P</i> (trend)	0.13	0.13	0.009	0.03	0.03	0.06
Viscosity (mPa.s)						
1 (<1.26)	1	1	1	1	1	1
2 (1.26–1.31)	0.70 (0.35–1.42)	0.66 (0.32–1.37)	1.14 (0.87–1.49)	1.09 (0.83–1.42)	1.11 (0.87–1.41)	1.07 (0.84–1.36)
3 (>1.31)	0.72 (0.38–1.36)	0.64 (0.33–1.26)	1.00 (0.76–1.31)	0.95 (0.72–1.24)	0.99 (0.78–1.26)	0.95 (0.75–1.21)
<i>P</i> (trend)	0.35	0.26	0.77	0.91	0.83	0.87
tPA (ng/mL)						
1 (<6.8)	1	1	1	1	1	1
2 (6.8–10.2)	0.75 (0.40–1.40)	0.75 (0.39–1.43)	1.03 (0.79–1.34)	1.05 (0.80–1.37)	0.97 (0.76–1.23)	0.98 (0.77–1.25)
3 (>10.2)	0.67 (0.35–1.26)	0.63 (0.32–1.22)	1.20 (0.92–1.56)	1.17 (0.89–1.53)	1.09 (0.86–1.39)	1.08 (0.85–1.37)
<i>P</i> (trend)	0.39	0.31	0.17	0.23	0.35	0.41
D-dimer (ng/mL)						
1 (<42)	1	1	1	1	1	1
2 (42–11)	0.71 (0.37–1.36)	0.74 (0.38–1.44)	1.06 (0.81–1.38)	1.04 (0.79–1.36)	1.04 (0.82–1.32)	1.04 (0.82–1.32)
3 (>111)	0.72 (0.36–1.41)	0.80 (0.39–1.65)	1.16 (0.88–1.54)	1.13 (0.85–1.50)	1.10 (0.86–1.42)	1.11 (0.85–1.43)
<i>P</i> (trend)	0.40	0.61	0.30	0.40	0.42	0.41
CRP (mg/L)						
1 (<1.14)	1	1	1	1	1	1
2 (1.14–3.34)	0.57 (0.30–1.09)	0.59 (0.31–1.16)	1.37 (1.04–1.80)	1.31 (0.99–1.73)	1.20 (0.94–1.52)	1.16 (0.91–1.49)
3 (>3.34)	0.77 (0.41–1.46)	0.81 (0.42–1.57)	1.52 (1.15–2.00)	1.39 (1.05–1.85)	1.34 (1.05–1.70)	1.26 (0.98–1.61)
<i>P</i> (trend)	0.13	0.22	0.03	0.12	0.14	0.32

Matched indicates matched for age, sex, treatment and therapy allocated, region, and most recent qualifying event; *P* (trend), *P* value for trend across the thirds.

*Further adjusted for systolic blood pressure, smoking, peripheral artery disease prevalence, statin use, and antiplatelet use.

served that circulating levels of tPA antigen were independently associated with risk of CHD.²² There is little published information on the association of tPA antigen with risk of stroke.^{8,9,26,27} In the present study, we observed an association of tPA antigen with risk of lacunar and large artery infarcts, but not ischemic or total stroke. Another meta-analysis observed that circulating levels of fibrin D-dimer (a marker of activation of blood coagulation and fibrinolysis) were also independently associated with risk of CHD.²¹ Again, there is little published information on the association of D-dimer with risk of stroke.^{7–9,25} In the present study, we observed no significant association of D-dimer with risk of recurrent stroke. Two prospective studies^{37,38} have reported significant associations of D-dimer with risk of stroke in patients with atrial fibrillation. Only 11% of patients with ischemic stroke had atrial fibrillation in this study (Table 1).

This study adds to the evidence that plasma fibrinogen and CRP are predictors of risk for (recurrent) ischemic stroke. Meta-analyses are required to determine the additive value of plasma fibrinogen and CRP to classical risk factors in the prediction of first and recurrent stroke and to determine whether or not chronic reduction in fibrinogen or CRP reduces the risk of stroke.

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