

Activation of Hemostasis and Decline in Cognitive Function in Older People

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Objective—To determine whether activation of hemostatic function (thrombosis and fibrinolysis) is associated with cognitive decline in older people.

Methods and Results—We studied 5804 people (age, 70–82 years) in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). Mean follow-up was 3.2 years, including annual measurement of speed of information processing (letter, digit coding, and Stroop), verbal memory (picture–word naming), and basic and instrumental activities of daily living. Raised levels of markers of thrombin generation (D-dimer and prothrombin fragment 1+2) were associated independently with increased rate of cognitive decline (eg, Stroop increased by 4.44 s [SEM, 0.68] in bottom tertile of D-dimer compared to 5.46 [SEM, 0.71] in highest tertile; $P < 0.05$) and deterioration in activities of daily living. This increased rate of decline was attenuated but not removed when subjects with incident nonfatal stroke were omitted from the analysis. It also persisted when adjustments were made for inflammation (C-reactive protein and IL-6).

Conclusion—Older patients with increased markers of thrombin generation (D-dimer and prothrombin fragment 1+2) are at increased risk for cognitive decline and deterioration in ability to perform activities of daily living. This is likely attributable to increased risk of cerebral ischemic damage (including covert disease) associated with prothrombotic states. (*Arterioscler Thromb Vasc Biol.* 2010;30:605-611.)

Key Words: aging ■ cognition ■ fibrinolysis ■ stroke ■ thrombosis

Vascular disease is an important and potentially preventable contributor to cognitive decline and dementia in older people.¹ Postmortem studies have shown that Alzheimer pathology is important; however, on its own it is often not sufficient to cause major cognitive impairment. However the combination of Alzheimer pathology and ischemic cerebrovascular disease (particularly small-vessel ischemia) has particular risk for dementia.² Longitudinal population studies have shown that traditional vascular risk factors, particularly hypertension, diabetes mellitus, and cigarette smoking, are associated with increased risk of dementia.^{3,4}

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Activation of thrombosis and fibrinolysis is associated with increased risk of ischemic vascular disease, and so these alterations in hemostasis also might be expected to be linked with cognitive decline and dementia.⁵ Dementia is associated with increased levels of thrombin–antithrombin complexes, D-dimer, and tissue plasminogen activator.⁶ Hemostatic activation, including elevated D-dimer, may also be associated with increased risk of disability.⁷ However, further research,

including prospective longitudinal data, is required to clarify the strength of association of markers of hemostatic function with functional and cognitive decline in older age. We aimed to determine associations of markers of hemostatic function with changes in cognition and activities of daily living (ADL) in older people, building on the existing longitudinal clinical dataset from the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) by extending the laboratory analyses on stored baseline blood samples in the biobank.

Subjects and Methods

The PROSPER study was a randomized placebo-controlled trial of Pravastatin in 5804 subjects (2520 in Scotland, 2184 Ireland, and 1100 the Netherlands), aged 70 to 82 years, with vascular risk factors or known vascular disease.⁸ The follow-up from the randomized controlled phase of the trial was completed by May 2002. The trial showed that 3.2 years of lipid-lowering treatment with pravastatin 40 mg reduced the risk of myocardial infarction in elderly subjects.⁹

The following laboratory analyses were performed on baseline blood samples (stored at -80°C unless stated): fibrin D-dimer and tissue plasminogen activator antigen (enzyme-linked immunosorbent assay; Biopool AB), prothrombin fragment 1+2, and thrombin–antithrombin complexes (enzyme-linked immunosorbent assay; Dade Behring), von

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Willebrand factor antigen levels (enzyme-linked immunosorbent assay; rabbit antihuman polyclonal antibodies; Dako), and fibrinogen (Clauss method; MDA180 coagulometer; Trinity Biotech; calibrant 9th British standard National Institute for Biological Standards and Control) were all measured in citrated plasma. Plasma viscosity was measured at high shear rates (>300/s) in a capillary viscometer (Coulter) at 37°C; analyses were performed on fresh K₂EDTA samples in real-time in the Scottish cohort, and the results for plasma viscosity for Ireland and the Netherlands were adjusted for analysis of frozen stored samples.¹⁰ IL-6 (enzyme-linked immunosorbent assay; R& D Systems) and high-sensitivity C-reactive protein (automated particle-enhanced immunoturbidimetric assay; Roche UK) were measured on stored K₂EDTA samples. All laboratory analyses were conducted by technicians blind to the identity of samples.

The trial protocol included annual measurement of cognitive function and ADL; we have published a detailed description of the cognitive tests used in the PROSPER study.¹¹ All study nurses were trained in test administration by a neuropsychologist and 2 experienced testers for ≥ 2 days before performing the study assessments. Yearly training sessions occurred at all centers. Administration of the tests was conducted using explicit guidelines for test administration. Baseline cognitive performance was taken as the mean of 2 measures taken 2 weeks apart to improve reliability of the assessment of baseline status. The Mini-Mental State Examination is used widely to screen for cognitive impairment and dementia.¹² A cut-off score of ≥ 24 points was used as an inclusion criterion to eliminate those with poor cognitive function at baseline. Attention and processing were assessed using the Stroop-Color Word test¹³ and the Letter-Digit Replacement test.¹⁴ The former, in the key part III of the test, presents color names printed in incongruously colored ink (eg, the word green printed in blue ink). Performance, timed in seconds to complete the test, measures the ability to discard the irrelevant name (green) in favor of the color of the ink (blue). The latter asks the subject to fill in digits next to letters according to a key. Outcome is the number of correct entries in 60 seconds. Memory was tested using the Picture-Word Recall test based on the Groningen-Fifteen Words test.¹⁵ This measures recall, both immediate and after 20 minutes, of 15 pictures (rather than words to overcome any language problem). The outcome variable is the mean number of correctly recalled pictures over 3 immediate trials and number recalled after the delay.

Data were gathered on change in extended and basic ADL. We used a 7-point instrumental ADL (IADL) scale (maximum score, 14)¹⁶ and the 20-point Barthel index.¹⁷ Administration of these scales was through interview of patients by trained nurses and use of explicit guidelines for scoring.

Statistical Analysis

The results of hemostatic markers were grouped in tertiles. Baseline cognitive function and change in cognition were calculated for each tertile of each measure of hemostatic function to allow for simplified presentation of the data; however, analyses were performed for continuous data to maximize statistical power. All probability values calculated for the association of hemostatic measures with cognition/ADL are for continuous data. The association between hemostatic markers and baseline cognitive status was examined using general linear models adjusting for baseline covariates (age, gender, country, education, history of vascular disease, history of diabetes, smoking, alcohol intake, blood pressure, and, when applicable, test version); deterioration in cognition was examined using general linear models adjusting for these covariates plus treatment allocation (pravastatin/placebo) and baseline cognition or ADL, as appropriate. The following variables had a positively skewed distribution and were log-transformed to give a near-normal distribution for analyses: D-dimer, prothrombin fragment 1+2, and thrombin-antithrombin complexes. We examined whether any associations might be attributable to inflammation by including highly sensitive C-reactive protein and IL-6 in multivariate analyses. Analyses of change in cognitive function were also performed for the subgroup of patients with no incident nonfatal stroke to determine whether any association of hemostatic function with cognitive decline was independent of clinical stroke. Analyses of change in instrumental and basic ADL were performed for the subgroup of patients with no incident nonfatal stroke or myocardial infarction to determine whether any association of hemostatic function with decline in ADL was independent of these clinical events.

Table 1. Clinical Characteristics and Results of Laboratory Analyses of Baseline Hemostatic Variables From Subjects in the PROSPER Study Who Were Not Using Warfarin (n=5699)

	Results	N With Valid Laboratory Result
Age, y	75.3 (3.4)	...
Gender, male/female ratio	2728/2971	...
Systolic blood pressure	154.6 (21.8)	...
Diastolic blood pressure	83.8 (11.4)	...
Body mass index	26.8 (4.2)	...
Current smoker	1537 (27%)	...
Diabetes mellitus	611 (11%)	...
Hypertension	3539 (62%)	...
Vascular disease	2474 (43%)	...
D-dimer* (ng/mL)	274 (1.7)	5618
Prothrombin fragment 1+2,* nmol/L	288 (1.4)	4473
Thrombin-antithrombin complexes,* μ g/L	3.7 (1.7)	4473
Plasma viscosity, mPa.s	1.312 (0.079)	5436
Fibrinogen, g/L	3.59 (0.74)	5531
Tissue plasminogen activator, ng/mL	11.02 (4.04)	5527
von Willebrand factor, IU/dL	141 (46)	5509

Results are of continuous variables are mean (SD) except for measurements,* which are geometric means (with SD calculated from the log-transformed distribution). Categorical variables are numbers (%) except where stated. Numbers of subjects with valid results are given for laboratory analyses.

Results

A small number of patients were using warfarin at study baseline (105 subjects; 1.8% of the population). This subgroup had lower D-dimer (geometric mean, 150 ng/mL; SD, 1.8 ng/mL; prothrombin fragment 1+2, 94 nmol/L; SD, 1.6 nmol/L; thrombin-antithrombin complex levels, 2.3 μ g/L; SD, 1.7 μ g/L; $P < 0.0001$) compared to those not using warfarin (as expected¹⁸), and so they were excluded to prevent any bias associated with using this drug. The summary results for the hemostatic variables are presented in Table 1. Levels of prothrombin fragment 1+2 and thrombin-antithrombin complexes were greatly increased in samples from Leiden compared to Ireland and Scotland. This gross discrepancy was not seen in the other assays. This pattern of findings is artifactual; however, we have been unable to identify the cause. Therefore, the results of prothrombin factor 1+2 and thrombin-antithrombin complexes are reported only for the Scottish and Irish cohorts.

Associations between hemostatic factors and changes in cognition and ADL are presented in Tables 2 through 4. All associations are adjusted for baseline covariates as listed in Subjects and Methods and in the footnotes to the Tables.

Markers of Thrombin Generation

Increased D-dimer was associated both with worse baseline cognitive function (with the exception of immediate Picture-Word Recall; Table 2) and a greater rate of decline in performance (Table 3, Figure). After additional adjustment for markers of inflammation (log C-reactive protein and log IL-6), associations of D-dimer with decline in letter-digit coding ($P = 0.027$) and IADL ($P = 0.002$) persisted; however, the associations with declines in Stroop ($P = 0.12$) and immedi-

Table 2. Baseline Cognition and ADL by Tertiles of Hemostatic Measures

Hemostatic Measure	Tertile	Cognitive Function					
		Stroop Part III		Letter–Digit Coding		Picture–Word Recall (Immediate)	
		Baseline (SE)	<i>P</i>	Baseline (SE)	<i>P</i>	Baseline (SE)	<i>P</i>
D-dimer	I	67.0 (0.75)	0.024	23.3 (0.20)	0.0009	9.39 (0.055)	0.35
	II	67.9 (0.75)		22.7 (0.20)		9.32 (0.054)	
	III	68.3 (0.77)		22.5 (0.21)		9.33 (0.056)	
Prothrombin fragment 1+2	I	72.5 (0.90)	0.81	21.2 (0.23)	0.52	8.91 (0.063)	0.011
	II	72.2 (0.92)		20.9 (0.23)		9.13 (0.064)	
	III	72.2 (0.94)		21.0 (0.24)		9.11 (0.066)	
Plasma viscosity	I	66.9 (0.77)	0.12	23.2 (0.21)	0.0004	9.36 (0.057)	0.030
	II	67.4 (0.75)		22.9 (0.21)		9.38 (0.055)	
	III	68.9 (0.78)		22.5 (0.21)		9.25 (0.057)	
Tissue plasminogen activator	I	67.1 (0.77)	<0.0001	23.0 (0.21)	<0.0001	9.31 (0.056)	0.36
	II	66.6 (0.77)		23.1 (0.21)		9.41 (0.056)	
	III	69.4 (0.76)		22.4 (0.21)		9.32 (0.055)	
von Willebrand factor	I	67.2 (0.78)	0.054	22.9 (0.21)	0.17	9.40 (0.057)	0.056
	II	67.7 (0.76)		22.9 (0.21)		9.36 (0.055)	
	III	68.3 (0.77)		22.7 (0.21)		9.30 (0.056)	

Hemostatic Measure	Tertile	Instrumental and Basic ADL			
		Instrumental ADL		Barthel Index	
		Baseline (SE)	<i>P</i>	Baseline (SE)	<i>P</i>
D-dimer	I	13.57 (0.030)	<0.0001	19.74 (0.022)	<0.0001
	II	13.50 (0.030)		19.71 (0.022)	
	III	13.43 (0.031)		19.65 (0.023)	
Prothrombin fragment 1+2	I	13.60 (0.035)	0.86	19.74 (0.025)	0.4989
	II	13.57 (0.036)		19.75 (0.025)	
	III	13.62 (0.036)		19.76 (0.025)	
Plasma viscosity	I	13.55 (0.031)	<0.0001	19.71 (0.023)	0.0057
	II	13.54 (0.031)		19.74 (0.023)	
	III	13.40 (0.032)		19.66 (0.023)	
Tissue plasminogen activator	I	13.54 (0.031)	0.0001	19.73 (0.023)	0.0007
	II	13.53 (0.031)		19.72 (0.023)	
	III	13.43 (0.031)		19.65 (0.022)	
von Willebrand factor	I	13.51 (0.031)	0.0071	19.69 (0.023)	0.2678
	II	13.53 (0.031)		19.72 (0.022)	
	III	13.45 (0.031)		19.68 (0.022)	

Results are least-square mean (SE) for baseline result adjusted for age, gender, country, education, history of vascular disease, history of diabetes, smoking, alcohol intake at randomization, blood pressure, and test version (when applicable). *P* for continuous measures of hemostatic variables.

Baseline D-dimer, I≤217, II>217–333, III>333 ng/mL; n=5618; prothrombin fragment 1+2 (I≤248, II>248–329, III>329 nmol/L; n=4,473; plasma viscosity, I≤1.27, II>1.27–1.34, III>1.34 mPa/s; n=5436; tissue plasminogen activator, I≤9.05, II>9.05–12.27, III>12.27 ng/mL; n=5527; and von Willebrand factor, I≤118, II>118–155, III>155 IU/dL; n=5509. PROSPER study cohort, with subjects not using warfarin.

ate Picture–Word Recall (*P*=0.053) were attenuated. Higher prothrombin fragment 1+2 was also associated with greater rate of decline in cognitive function (Table 3, Figure); adjusting for inflammation had minimal effect, although the decline in Stroop was attenuated and became nonsignificant (*P*=0.083).

When subjects with relevant incident nonfatal vascular events were excluded, there was some attenuation of the associations of increased D-dimer and prothrombin fragment 1+2 with cognitive decline; however, links persisted, particularly for verbal memory and for IADL (Table 4).

Higher thrombin–antithrombin complexes were associated with greater rate of decline only with the Stroop test (*P*=0.012; data not presented). This association persisted when further corrected for markers of inflammation (*P*=0.020) and was only slightly attenuated when subjects with incident nonfatal stroke were excluded (*P*=0.042).

Plasma Viscosity and Fibrinogen

Increased plasma viscosity was associated with worse baseline performance in all aspects of cognition and ADL (Table

Table 3. Change in Cognition and ADL With Mean Follow-Up of 3.2 Years by Tertiles of Hemostatic Measures

Hemostatic Measure	Tertile	Cognitive Function					
		Stroop Part III		Letter-Digit Coding		Picture-Word Recall (Immediate)	
		Change (SE)	<i>P</i>	Change (SE)	<i>P</i>	Change (SE)	<i>P</i>
D-dimer	I	4.44 (0.68)	0.045	-1.31 (0.14)	0.070	-0.19 (0.054)	0.011
	II	4.40 (0.68)		-1.65 (0.14)		-0.21 (0.054)	
	III	5.46 (0.71)		-1.76 (0.14)		-0.37 (0.056)	
Prothrombin fragment 1+2	I	6.10 (0.84)	0.058	-1.46 (0.16)	0.023	-0.31 (0.063)	0.0011
	II	5.04 (0.86)		-1.31 (0.16)		-0.33 (0.065)	
	III	7.47 (0.89)		-1.85 (0.17)		-0.45 (0.067)	
Plasma viscosity	I	4.52 (0.70)	0.47	-1.50 (0.14)	0.49	-0.21 (0.056)	0.82
	II	4.52 (0.68)		-1.67 (0.14)		-0.26 (0.055)	
	III	4.83 (0.72)		-1.46 (0.14)		-0.26 (0.057)	
Tissue plasminogen activator	I	4.64 (0.70)	0.32	-1.55 (0.14)	0.92	-0.24 (0.056)	0.28
	II	3.99 (0.69)		-1.43 (0.14)		-0.24 (0.055)	
	III	5.63 (0.70)		-1.64 (0.14)		-0.29 (0.055)	
von Willebrand factor	I	4.35 (0.71)	0.16	-1.43 (0.14)	0.49	-0.22 (0.056)	0.32
	II	4.16 (0.69)		-1.58 (0.14)		-0.17 (0.055)	
	III	5.73 (0.70)		-1.60 (0.14)		-0.36 (0.056)	

Hemostatic Measure	Tertile	Instrumental and Basic ADL			
		Instrumental ADL		Barthel Index	
		Change (SE)	<i>P</i>	Change (SE)	<i>P</i>
D-dimer	I	-0.76 (0.066)	0.0007	-0.40 (0.055)	0.0019
	II	-0.83 (0.066)		-0.47 (0.055)	
	III	-0.97 (0.069)		-0.54 (0.057)	
Prothrombin fragment 1+2	I	-0.67 (0.077)	0.0022	-0.40 (0.062)	0.1473
	II	-0.72 (0.078)		-0.38 (0.063)	
	III	-0.91 (0.081)		-0.44 (0.065)	
Plasma viscosity	I	-0.79 (0.068)	0.25	-0.38 (0.056)	0.0083
	II	-0.79 (0.067)		-0.44 (0.055)	
	III	-0.93 (0.069)		-0.56 (0.057)	
Tissue plasminogen activator	I	-0.82 (0.068)	0.026	-0.39 (0.056)	0.0035
	II	-0.76 (0.068)		-0.38 (0.056)	
	III	-0.95 (0.067)		-0.58 (0.055)	
von Willebrand factor	I	-0.79 (0.068)	0.026	-0.41 (0.056)	0.0061
	II	-0.83 (0.067)		-0.41 (0.055)	
	III	-0.90 (0.068)		-0.51 (0.055)	

Results are least-square mean (SE) for change in score (last recorded results minus baseline results) adjusted for age, gender, country, education, history of vascular disease, history of diabetes, smoking, alcohol intake at randomization, blood pressure, test version (when applicable), baseline test score, and treatment allocation. *P* for continuous measures of hemostatic variables.

Baseline D-dimer, I≤217, II>217–333, III>333 ng/mL; n=5618; prothrombin fragment 1+2, I≤248, II>248–329, III>329 nmol/L; n=4473; plasma viscosity, I≤1.27, II>1.27–1.34, III>1.34 mPa/s; n=5436; tissue plasminogen activator, I≤9.05, II>9.05–12.27, III>12.27 ng/mL; n=5527; and von Willebrand factor, (I≤118, II>118–155, III>155 IU/dL; n=5509). PROSPER study cohort, with subjects not using warfarin.

2) but generally with no greater rate of decline (Table 3). Adjustment for inflammatory status resulted in all baseline differences becoming attenuated and nonsignificant.

Higher fibrinogen levels were associated with increased rate of decline of IADL (*P*=0.0118) but no increase in rate of decline of other cognitive tests (data not presented). Adjustment for markers of inflammatory status resulted in attenuation of rate of decline in instrumental ADL, although this remained statistically

significant (*P*=0.0397). It became nonsignificant when subjects with incident nonfatal stroke were excluded (*P*=0.1011).

Markers of Endothelial Function

Increased tissue plasminogen activator was associated with worse baseline performance in all measures of cognition and ADL (except for Picture-Word Recall; Table 2), with greater rate of decline in instrumental and basic ADL (Table 3).

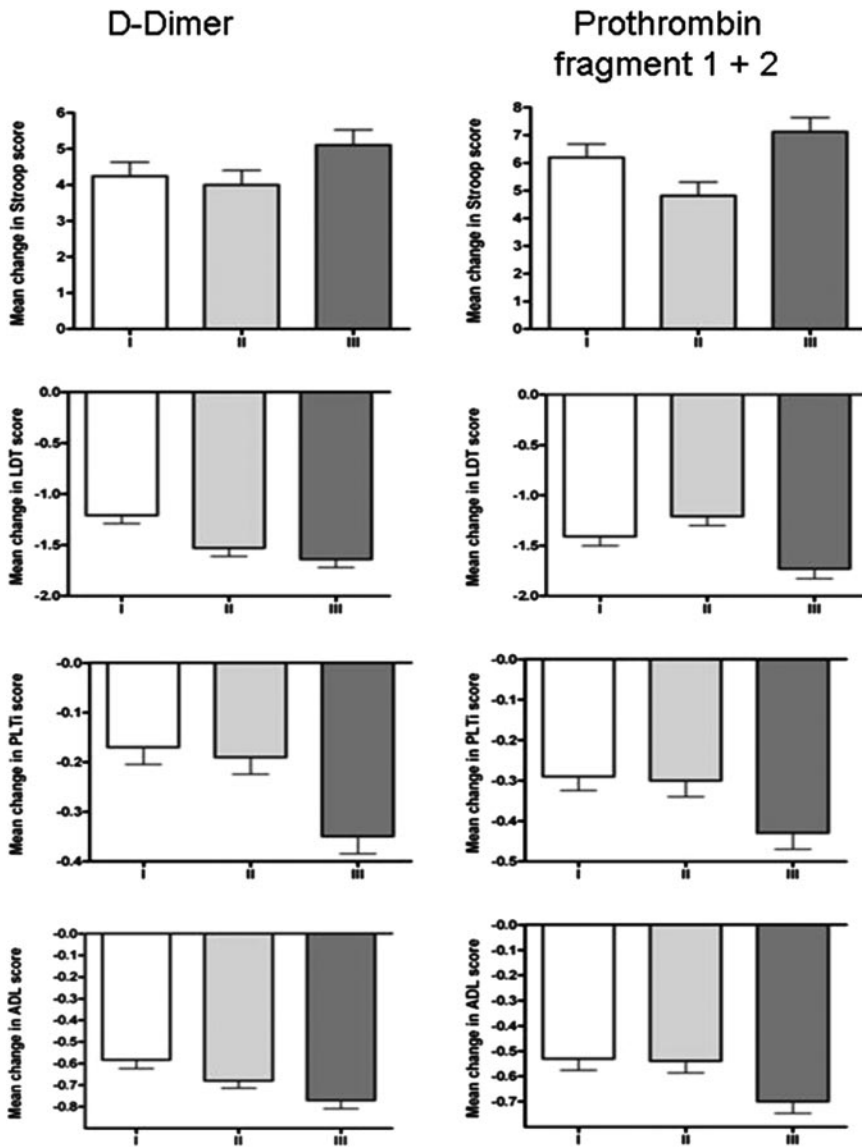


Figure. Change in cognition and instrumental ADL by tertiles of baseline D-dimer ($I \leq 217$ ng/mL; $II > 217-333$ ng/mL; $III > 333$ ng/mL; $n = 5618$) and prothrombin fragment 1+2 ($I \leq 248$ nmol/L; $II > 248-329$ nmol/L; $III > 329$ nmol/L; $n = 4473$). PROSPER study subjects not using warfarin had a mean 3.2 years of follow-up. Results are least-square mean (SE) for change in score (last recorded results minus baseline results) adjusted for baseline test score, treatment allocation, age, gender, country, education, history of vascular disease, history of diabetes, smoking, alcohol intake at randomization, blood pressure, and, when applicable, test version.

Increased von Willebrand factor was associated with worse baseline IADL performance ($P = 0.0071$) and greater decline in this domain ($P = 0.0256$) and in basic ADL ($P = 0.0061$). The declines in IADL associated with increased tissue plasminogen activator or von Willebrand factor were diminished when adjusted for markers of inflammation ($P = 0.071$ and $P = 0.0391$, respectively), and were attenuated and became nonsignificant when subjects with incident nonfatal vascular events were excluded ($P = 0.64$ and $P = 0.135$, respectively).

Discussion

We have found that increased levels of D-dimer and prothrombin fragment 1+2 (markers of thrombin generation) are associated with more rapid cognitive decline. The domains affected included speed of information processing, verbal memory, and IADL. The magnitude of effect tended to be ≈ 0.1 to 0.2 points difference in the 14-point IADL scale between the lowest and highest tertiles of these hemostatic factors over ≈ 3.2 years of follow-up. These associations appeared not to be explained by inflammation. In contrast, levels of thrombin-antithrombin complexes did not show

consistent associations with cognitive decline. D-dimer (a fibrin degradation product) is a marker of thrombin generation and cross-linked fibrin turnover, whereas prothrombin fragment 1+2 and thrombin-antithrombin complexes are markers of thrombin generation.¹⁹

Fibrinogen is a large glycoprotein that plays a central role in hemostasis. It increases plasma viscosity and enhances leukocyte adhesion.¹⁹ It is therefore reasonable to consider the results for plasma viscosity and fibrinogen together. Our data showed plasma viscosity was associated more closely with cognitive impairment (at baseline) than fibrinogen, although increased viscosity was not associated with any increase in rate of cognitive decline. The baseline associations of plasma viscosity with cognitive status appeared to be at least partly dependent on increased inflammation.

Endothelial dysfunction is a biologically plausible contributor to vascular cognitive decline in older age. Tissue plasminogen activator acts as a marker of activation of endogenous fibrinolysis. It is a glycoprotein produced mainly by vascular endothelial cells. It activates dissolution of blood

Table 4. Mean Change in Cognitive Function and ADL by Tertiles of D-Dimer and Prothrombin Fragment 1+2 in the PROSPER Study Cohort (Subjects Not Using Warfarin)

Hemostatic Measure	Tertile	Cognitive Function					
		Stroop Part III		Letter-Digit Coding		Picture-Word Recall (Immediate)	
		Change (SE)	P	Change (SE)	P	Change (SE)	P
D-dimer	I	4.24 (0.68)	0.083	-1.21 (0.14)	0.099	-0.17 (0.06)	0.018
	II	4.00 (0.69)		-1.53 (0.14)		-0.19 (0.06)	
	III	5.11 (0.72)		-1.64 (0.14)		-0.35 (0.06)	
Prothrombin fragment 1+2	I	6.20 (0.84)	0.22	-1.41 (0.16)	0.037	-0.29 (0.06)	0.003
	II	4.81 (0.86)		-1.21 (0.16)		-0.30 (0.07)	
	III	7.12 (0.90)		-1.73 (0.17)		-0.43 (0.07)	

Hemostatic Measure	Tertile	Instrumental and Basic ADL			
		Instrumental ADL		Barthel Index	
		Change (SE)	P	Change (SE)	P
D-dimer	I	-0.59 (0.06)	0.003	-0.27 (0.049)	0.0102
	II	-0.68 (0.06)		-0.36 (0.049)	
	III	-0.77 (0.07)		-0.37 (0.051)	
Prothrombin fragment 1+2	I	-0.53 (0.08)	0.033	-0.32 (0.059)	0.8665
	II	-0.54 (0.08)		-0.25 (0.060)	
	III	-0.70 (0.08)		-0.30 (0.061)	

Excludes those who had an incident nonfatal stroke for analyses of cognitive function, and those who had an incident nonfatal stroke or nonfatal myocardial infarction for analyses of instrumental and basic ADL.

Results are least-square mean (SE) for change in score (last recorded results minus baseline results) adjusted for age, gender, country, education, history of vascular disease, history of diabetes, smoking, alcohol intake at randomization, blood pressure, test version (when applicable), baseline test score, and treatment allocation. P for continuous measures of hemostatic variables.

clot in the presence of fibrin by converting plasminogen to plasmin, thus cleaving cross-linked fibrin to D-dimer and other fibrin degradation products. Therefore, it can be seen as a marker of endothelial dysfunction. Von Willebrand factor is a large glycoprotein produced by endothelial cells. It mediates platelet adhesion to injured endothelium, a first step in thrombosis. It also acts as a marker of endothelial damage.¹⁹ However, we found no consistent evidence that markers of endothelial dysfunction are associated with more rapid cognitive decline in older people. Increased tissue plasminogen activator was associated with worse baseline cognitive performance in tests of speed of information processing, although it was not associated with increased rate of cognitive decline.

Our data confirm and greatly expand on the results of previous longitudinal studies. The Duke University population studies²⁰ found that D-dimer is predictive of decline in global cognitive function. In a nested case-control study from the Rotterdam cohort, D-dimer, thrombin-antithrombin complexes, and tissue plasminogen activator were all associated with increased risk of dementia.⁶ We have previously published on community-dwelling subjects with atrial fibrillation, in whom elevated D-dimer is associated with development of dementia.²¹ D-dimer is also associated with increased disability in older populations.^{20,22} In the Edinburgh artery study, increased fibrinogen was associated with decline in nonverbal reasoning.²³ In cross-sectional studies, increased plasma viscosity is associated with poorer cognitive function, independent of levels of fibrinogen.²⁴ Therefore, it seems likely that there is a clinically

important association of activation of thrombin generation with increased rate of cognitive decline and dementia in older people, with D-dimer being the marker for which, at present, there is the most evidence. The evidence is less convincing for other hemostatic measures, including plasma viscosity, fibrinogen, and markers of endothelial dysfunction.

Within the PROSPER cohort, known incident vascular events accounted for 44% of the population decline in basic ADL and 36% of the decline in instrumental activities.²⁵ An obvious question is whether the associations of increased hemostatic factors with decline in cognition or ADL are attributable to incident vascular events. We found that recognized incident nonfatal vascular events explained only part of the association of D-dimer and prothrombin fragment 1+2 with decline in cognition and ADL. However, it is possible that patients who have experienced decline have covert ischemic cerebrovascular disease, including progressive small-vessel ischemic cerebrovascular damage. Given the associations of these hemostatic factors with deterioration in verbal memory and ADL, it is also possible that some of these patients have deterioration attributable to Alzheimer pathology. Increasingly, it is recognized that the combination of small-vessel cerebrovascular disease and Alzheimer pathology is extremely common and a potent interactive cause of cognitive decline in older age.¹

Our study does have a number of limitations. The mean follow-up period of 3.2 years is relatively short, and as a result the declines in cognitive function and basic and

instrumental ADL are modest. The availability of only a single baseline measure of markers of hemostatic function is likely to have resulted in underestimation of the strength of the associations with cognitive decline and deterioration in ADL. This is attributable to regression dilution bias.²⁶ The population was selected for a randomized controlled trial and had vascular risk factors or known vascular disease, and so they are not representative of a general elderly population. However, the data set does have a number of strengths. The patients were carefully characterized and followed-up, and so it is possible to explore potential confounding factors in any associations of hemostatic factors with clinical outcomes. We have examined a range of hemostatic factors and measured inflammatory markers, and so we have a much more complete picture of association and potential confounders.

Future research is now warranted on the effects of anti-thrombotics to reduce risk of cognitive decline and dementia. Warfarin is currently the only established oral drug that inhibits thrombin generation; however, this is a rapidly developing field with several highly promising oral agents either in advanced stages of development or about to come to market. For example, the direct thrombin inhibitor, dabigatran, appears to have some advantages over warfarin in the prevention of stroke in patients with atrial fibrillation.²⁷

Conclusion

We found that older patients with increased markers of thrombin generation (D-dimer and prothrombin fragment 1+2) are at increased risk for cognitive decline and deterioration in ability to perform ADL. This is likely to be attributable to development of cerebral ischemic damage (including covert disease) in association with a prothrombotic state. Inflammation appears to play only a modest role in moderating the association of these hemostatic markers with decline in cognition and ADL. We found no consistent evidence that markers of endothelial dysfunction are associated with more rapid cognitive decline in older people.

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Disclosures

None.

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