Fibrin D-Dimer, Tissue-Type Plasminogen Activator, von Willebrand Factor, and Risk of Incident Stroke in Older Men

S. Goya Wannamethee, PhD; Peter H. Whincup, PhD; Lucy Lennon, MSc; Ann Rumley, PhD; Gordon D. Lowe, DSc

Background and Purposes—Abnormalities in blood coagulation and the fibrinolytic system have been associated with increased risk of stroke, but few prospective studies have studied the associations in older adults. We have examined the associations between fibrin D-dimer, tissue-type plasminogen activator, and von Willebrand factor (vWF) and risk of stroke in older men and examined their predictive roles separately in normotensive and hypertensive men.

Methods—Prospective study of 3358 men aged 60 to 79 years with no previous diagnosis of myocardial infarction or stroke and without atrial fibrillation followed-up for an average of 9 years, during which there were 187 incident stroke events.

Results—Increased levels of D-dimer and vWF were associated with significantly increased risk of major stroke events after adjustment for potential confounders, including systolic blood pressure (adjusted hazard ratios and 95% confidence interval per standard deviation increase in D-dimer and vWF were 1.24 [95% confidence interval, 1.08–1.44] and 1.25 [95% confidence interval, 1.09–1.45], respectively). No associations were seen with tPA after adjustment. The positive associations between D-dimer and vWF and incident stroke remained after additional adjustment for markers of inflammation (C-reactive protein, IL-6). D-dimer was associated with stroke in both normotensive and hypertensive men; vWF showed stronger associations in normotensive than in hypertensive men (test for interaction: *P*=0.52 for D-dimer; *P*<0.01 for vWF).

Conclusions—Fibrin D-dimer and vWF are associated with increased risk of stroke in older men. These associations were not explained by their associations with inflammation. D-dimer may be a useful marker to identify those at high risk for stroke among hypertensive men. (Stroke. 2012;43:1206-1211.)

Key Words: cerebrovascular disease ■ epidemiology ■ etiology ■ risk factors

Abnormalities in the coagulation and fibrinolytic system have been associated with increased risk of coronary heart disease in observational studies and in meta-analyses of these, but the roles of hypercoagulability and fibrinolysis in stroke have been less studied. Thrombus formation is a key mechanistic event in ischemic stroke and various markers of coagulation and fibrinolytic factors have been suggested as possible predictors of stroke. The von Willebrand factor (vWF) is synthesized primarily by vascular endothelial cells and promotes platelet adhesion and aggregation, leading to thrombus formation. Increased levels of vWF in stroke patients have been reported in several case-control studies, but prospective studies have been inconsistent, with some showing a positive relationship and others showing no relationship between vWF and stroke risk. Fibrin D-dimer is the primary degradation product of cross-linked fibrin and is a marker of activated coagulation and fibrinolysis. Tissue-type plasminogen activator (tPA), produced and released mainly by endothelial cells, acts on plasminogen to form plasmin, and tPA antigen may be indicative of impaired fibrinolytic function. Circulating levels of D-dimer and tPA are increased in acute stroke and have been shown to be positively associated with incident stroke. The vWF, D-dimer, and tPA levels increase markedly with age, but few studies have examined the associations between coagulation markers, fibrinolytic function, and incident stroke in the elderly population, in whom incident stroke rates are particularly high. D-dimer and tPA are also implicated in the inflammatory response. However, the extent to which associations between D-dimer and tPA and stroke risk can be explained by associations with inflammation, which has been implicated in the pathogenesis of stroke, has not been well-studied. We therefore have examined the independent associations between fibrin D-dimer, tPA, and vWF levels.
and risk of incident stroke in a prospective cohort of older men followed-up for a mean period of 9 years. We also examined the prognostic role of these factors separately in hypertensive individuals, who are at particularly high risk for development of stroke.

Subjects and Methods
The British Regional Heart Study is a prospective study of cardiovascular disease involving 7735 men aged 40 to 59 years from 1 general practice in each of 24 British towns who were screened between 1978 and 1980.21 The population studied was socioeconomically representative of British men but consisted almost entirely of white Europeans (99%). In 1998 to 2000, all surviving men, now aged 60 to 79 years (mean age, 68.7 years), were invited for a 20-year follow-up examination. The men completed a questionnaire that included questions regarding their medical history and lifestyle behavior. They were requested to fast for a minimum of 6 hours, during which time they were instructed to drink only water and to attend for measurement at a prespecified time between 0800 and 1800 hours. All men were asked to provide a blood sample, collected using the Sarstedt Monovette system. The samples were frozen and stored at -20°C on the day of collection and transferred in batches for storage at 70°C until analysis, performed after no more than 1 freeze–thaw cycle. Twelve-lead electrocardiograms were recorded using a Siemens Sicard 460 instrument and were analyzed and coded in accordance with Minnesota coding definitions at the University of Glasgow ECG core laboratory based at Glasgow Royal Infirmary.22 Atrial fibrillation was defined according to Minnesota codes 8.3.1 and 8.3.3. The men were asked whether a doctor had ever told them that they had angina or myocardial infarction (heart attack, coronary thrombosis) or stroke, and they were asked to bring their medication to the examination session; 4252 men (77% of survivors) attended for examination and 4084 men had at least 1 of the 3 markers (vWF, tPA, or D-dimer) measured. We excluded men with a recall of a diagnosis of myocardial infarction or stroke (n = 613) and men with atrial fibrillation (n = 113) because D-dimer is known to be elevated in patients with atrial fibrillation who are at high risk for thromboembolic events,23 leaving 3358 men for analysis.

Cardiovascular Risk Factors
Anthropometric measurements including body weight, height, and waist circumference were performed. Details of measurements and classification methods for smoking status, physical activity, body mass index, waist circumference, social class, blood pressure, blood lipids, glucose, and forced expiratory volume in 1 second have been described.24–26 Men with a doctor’s diagnosis of diabetes or those with a fasting glucose of ≥7 mmol/L (World Health Organization

### Table 1. Baseline Characteristics (1998–2000) in 3358 Men Without Pre-Existing Myocardial Infarction or Stroke and Without Atrial Fibrillation According to Incident Stroke Status

<table>
<thead>
<tr>
<th></th>
<th>No Stroke (N=3171)</th>
<th>Development of Stroke (N=187)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>68.2 (5.37)</td>
<td>71.0 (5.40)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.84 (3.64)</td>
<td>26.74 (3.44)</td>
<td>0.73</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>96.95 (10.24)</td>
<td>97.22 (9.83)</td>
<td>0.71</td>
</tr>
<tr>
<td>Inactive (%)</td>
<td>32.3</td>
<td>37.4</td>
<td>0.15</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>13.0</td>
<td>13.9</td>
<td>0.73</td>
</tr>
<tr>
<td>Manual workers (%)</td>
<td>53.4</td>
<td>56.7</td>
<td>0.38</td>
</tr>
<tr>
<td>Moderate/heavy drinkers (%)</td>
<td>18.4</td>
<td>20.4</td>
<td>0.44</td>
</tr>
<tr>
<td>Using blood pressure lowering treatment (%)</td>
<td>19.5</td>
<td>26.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Angina (%)</td>
<td>8.4</td>
<td>9.6</td>
<td>0.57</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>10.4</td>
<td>11.8</td>
<td>0.57</td>
</tr>
<tr>
<td>ABO blood group O (%)</td>
<td>47.8</td>
<td>43.9</td>
<td>0.29</td>
</tr>
<tr>
<td>ABO blood group A (%)</td>
<td>29.3</td>
<td>29.6</td>
<td>0.92</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>149.50 (23.65)</td>
<td>157.47 (25.24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>85.39 (10.93)</td>
<td>87.35 (11.96)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>6.05 (1.05)</td>
<td>6.11 (1.14)</td>
<td>0.50</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.33 (0.34)</td>
<td>1.32 (0.36)</td>
<td>0.65</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>2.64 (0.66)</td>
<td>2.46 (0.49)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Glucose* (mmol/L)</td>
<td>5.81 (5.25–6.08)</td>
<td>5.92 (5.23–6.19)</td>
<td>0.23</td>
</tr>
<tr>
<td>CRP (mg/L)*</td>
<td>1.63 (0.78–3.21)</td>
<td>2.11 (1.05–3.90)</td>
<td>0.002</td>
</tr>
<tr>
<td>IL-6 (pg/mL)*</td>
<td>2.34 (1.51, 3.30)</td>
<td>2.89 (1.73, 4.24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>3.23 (0.72)</td>
<td>3.37 (0.79)</td>
<td>0.01</td>
</tr>
<tr>
<td>D-dimer (ng/mL)*</td>
<td>79.0 (47.0–77.48)</td>
<td>103.5 (60.95, 160.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>tPA (ng/mL)</td>
<td>10.78 (4.30)</td>
<td>11.39 (4.39)</td>
<td>0.05</td>
</tr>
<tr>
<td>vWF (IU/dL)</td>
<td>136.54 (50.68)</td>
<td>150.04 (45.04)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Mean (SD) unless specified.
BMI indicates body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; FEV1, forced expiratory volume in 1 second; HDL, high-density lipoprotein; IL, interleukin; IU, international units; SBP, systolic blood pressure; SD, standard deviation; tPA, tissue-type plasminogen activator; vWF, von Willebrand factor; WC, waist circumference.

*Geometric mean and interquartile range.
criteria) were considered to have prevalent diabetes. Because a high
proportion of men had systolic blood pressure ≥140 mm Hg (63.6%)
and the majority would be classified as having hypertension on
the basis of systolic blood pressure of ≥160 mm Hg, as used in the
Systolic Hypertension in the Elderly Program.27 Hypertension in this
older cohort was defined as systolic blood pressure ≥160 or diastolic
blood pressure ≥90 or using antihypertensive treatment.

Hemostatic and Inflammatory Biomarkers

After the 20-year examination, plasma levels of tPA antigen and
D-dimer were measured with enzyme-linked immunosorbent assays
(Biopool AB, Umea, Sweden), as was vWF antigen (DAKO, High
Wycombe, UK). C-reactive protein (CRP) was assayed by ultrasensi-
tive nephelometry (Dade Behring, Milton Keynes, UK). IL-6 was
assayed using a high-sensitivity enzyme-linked immunosorbent as-
say (R & D Systems, Oxford, UK).

Follow-Up

All men have been followed up from initial examination (1978–
1980) for cardiovascular morbidity and follow-up has been achieved
for 99% of the cohort.28 In the present analyses, all-cause mortality
and morbidity events are based on follow-up from rescreening in
1998 to 2000 at mean age 60 to 79 years to July 2008, a mean
follow-up period of 9 years (range, 8–10 years). Information on
death was collected through the established “tagging” procedures
provided by the National Health Service registers. Fatal stroke
episodes were those coded on the death certificate to International
Classification of Diseases 430 to 438. Nonfatal stroke events were
those that produced a neurological deficit that was present for >24
hours. Evidence regarding nonfatal stroke was obtained by ongoing
reports from general practitioners, by biennial reviews of the
patients’ practice records (including hospital and clinic correspon-
dence) through to the end of the study period, and from repeated
personal questionnaires to surviving subjects after initial examina-
tion. Supplementary information on CT/MRI scans was only avail-
able for 96 (51%) of the 187 stroke cases. Of these, 59 (61%) were
ischemic stroke, 10 (10%) were hemorrhagic strokes, and 27 (29%)
were indeterminate.

Statistical Methods

The distribution of D-dimer was skewed to the right and log
transformation was used. Cox proportional hazards model was used
to assess the multivariable adjusted hazards ratio (relative risk) in a
comparison of tertiles of D-dimer, tPA, and vWF and for a 1 SD
increase in these variables. Models were adjusted for potential
confounding and mediating factors in a stepwise manner. In the
adjustment, we included first age and then conventional risk factors
that have been shown to be associated with stroke. To assess the
contribution of inflammation, we additionally adjusted for inflam-
matory risk markers CRP and IL-6. In multivariable analyses,
smoking (never, long-term ex-smokers [≥15 years], recent ex-
smokers [<15 years], and current smokers), social class (manual
versus nonmanual), physical activity (4 groups), alcohol intake (5
groups), diabetes (yes/no), and angina (yes/no) were fitted as
categorical variables; body mass index, forced expiratory volume in
1 second, CRP, and IL-6 were fitted as continuous variables.
Receiver-operating characteristic curves and areas under the curve
c-statistics) were used to assess the ability of D-dimer and vWF to
predict stroke beyond routine clinical risk factors. We also conducted
a supplementary analysis restricting cases to the 59 confirmed
ischemic stroke cases.

Results

During the mean follow-up period of 9 years, there were 187
incident stroke cases (41 fatal and 146 nonfatal), a rate of 6.8
per 1000 person-years, in the 3358 men with no history of
stroke or myocardial infarction and without atrial fibrillation.
Table 1 shows baseline characteristics in the men who had
development of stroke and in those who remained free of
stroke. Men who had development stroke showed signifi-
cantly higher rates of blood pressure treatment and higher
mean levels of systolic and diastolic blood pressures, fibrin-
ogen, CRP, vWF, D-dimer, and tPA, and lower levels of
forced expiratory volume in 1 second.

The Figure shows the Kaplan-Meier estimates of the
cumulative incidence of stroke by tertiles of D-dimer, vWF,
and tPA. Risk of stroke increased significantly with increasing levels of D-dimer and vWF, even after adjustment for age, smoking, physical activity, social class, systolic blood pressure, prevalent diabetes, angina, use of antihypertensive treatment, and forced expiratory volume in 1 second (Table 2). No significant association was seen with tPA after adjustment. Adjustment for ABO blood group made no difference to the findings. Further adjustment for CRP attenuated the associations between vWF and D-dimer with incident stroke, but the trends remained significant. Adjusting for IL-6 instead of CRP yielded results similar to that seen with adjustment for CRP. The adjusted hazards ratio (HR) and 95% CI for a 1 SD increase in log D-dimer was 1.20 (95% CI, 1.02–1.39;  \( P = 0.02 \)) and the corresponding HR for vWF was 1.20 (95% CI, 1.04–1.42;  \( P = 0.009 \)).

The addition of D-dimer to a multivariate model using routinely measured clinical variables and biomarkers to predict stroke (including age, smoking, alcohol intake, body mass index, systolic blood pressure, use of antihypertensive treatment, prevalent diabetes, and lung function) increased the C-statistic from 0.675 (95% CI, 0.637–0.712) to 0.688 (95% CI, 0.651–0.726;  \( P = 0.006 \)). The further addition of vWF increased the C-statistic to 0.693 (95% CI, 0.655–0.729;  \( P = 0.003 \)) when vWF was added to the routine model.

The vWF and D-dimer were significantly associated with both fatal and nonfatal strokes. The adjusted HR (95% CI) for fatal and nonfatal stroke were 1.36 (95% CI, 1.00–1.82;  \( P = 0.04 \)) and 1.23 (95% CI, 1.04–1.44;  \( P = 0.01 \)) for a 1 SD increase in log D-dimer. The corresponding adjusted HR for vWF were 1.51 (95% CI, 1.15–1.98;  \( P = 0.007 \)) and 1.19 (95% CI, 1.01–1.40;  \( P = 0.04 \)), respectively. The tPA showed no appreciable association with either fatal or nonfatal strokes (adjusted HR, 1.24; 95% CI, 0.92–1.68;  \( P = 0.14 \) and adjusted HR, 1.04; 95% CI, 0.88–1.24;  \( P = 0.62 \)), respectively.

We also conducted an additional analysis restricting incident cases to confirmed ischemic strokes (n=59 cases). D-dimer and vWF were both significantly associated with ischemic stroke after adjustment for factors in model 1. The adjusted HR (95% CI) for a 1 SD increase in log D-dimer was 1.55 (95% CI, 1.24–1.94;  \( P = 0.0002 \)) and the corresponding HR for vWF was 1.31 (95% CI, 1.01–1.73;  \( P = 0.03 \)).
Table 3. D-Dimer, von Willebrand Factor, and Relative Hazard Ratio for Incident Stroke in Men With No Pre-Existing Stroke, Myocardial Infarction, and Without Atrial Fibrillation in Normotensive and Hypertensive Men

<table>
<thead>
<tr>
<th></th>
<th>Normotensive (95% CI)</th>
<th>Hypertensive (95% CI)</th>
<th>Test for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate/1000 per Year</td>
<td>Model A</td>
<td>Rate/1000 per Year</td>
</tr>
<tr>
<td></td>
<td>(Cases/N of Men)</td>
<td></td>
<td>(Cases/N of Men)</td>
</tr>
<tr>
<td>D-dimer (tertiles)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.3 (12/589)</td>
<td>1.00</td>
<td>5.1 (24/537)</td>
</tr>
<tr>
<td>2</td>
<td>5.4 (24/527)</td>
<td>1.99 (0.98–4.07)</td>
<td>7.8 (37/572)</td>
</tr>
<tr>
<td>3</td>
<td>8.10 (33/516)</td>
<td>2.71 (1.36–5.39)</td>
<td>13.0 (57/601)</td>
</tr>
<tr>
<td>Per SD increase</td>
<td>1.20 (0.95–1.49)</td>
<td>0.37</td>
<td>1.30 (1.07–1.55)</td>
</tr>
<tr>
<td>vWF (tertiles)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3.1 (15/564)</td>
<td>1.00</td>
<td>6.2 (29/551)</td>
</tr>
<tr>
<td>2</td>
<td>4.7 (21/525)</td>
<td>1.45 (0.73–2.87)</td>
<td>8.4 (40/585)</td>
</tr>
<tr>
<td>3</td>
<td>7.5 (33/543)</td>
<td>2.07 (1.08–3.97)</td>
<td>11.3 (49/574)</td>
</tr>
<tr>
<td>Per SD increase</td>
<td>1.57 (1.25–1.97)</td>
<td>0.0001</td>
<td>1.10 (0.92–1.31)</td>
</tr>
</tbody>
</table>

Normotensive men and hypertensive men had similar age-adjusted mean levels of vWF (137.2 versus 137.1 IU/dL; \( P = 0.95 \)) and D-dimer (geometric mean, 79.0 versus 80.6 ng/mL; \( P = 0.48 \)). In analyses performed separately in normotensive and hypertensive men (Table 3), D-dimer predicted stroke in both normotensive men and in hypertensive men (test for interaction, \( P = 0.52 \)). By contrast, vWF showed stronger associations in normotensive men than in hypertensive men (test for interaction, \( P = 0.01 \)).

Discussion

In this large population study of British men aged 60 to 79 years, we have confirmed the findings of some previous prospective studies9,10,13,14 that circulating levels of hemostatic markers are associated with increased risk of stroke. We have shown that fibrin D-dimer and vWF, but not tPA antigen, are independently associated with incident stroke in older men and their measurements modestly improved prediction of stroke as assessed by improvement in the C statistics. Our findings extend those of other studies of coagulation and fibrinolysis and risk of stroke by observing that these associations are independent from markers of inflammation (CRP and IL-6), an observation not previously reported, and by examining their prognostic role in hypertensive men who are at particularly high risk for development of stroke.

The vWF was shown to be predictive of stroke in the Rotterdam and Atherosclerosis Risk in Communities (ARIC) studies,9,10 but others have reported no independent association between vWF and stroke11–14; however, many of these studies were based on smaller participant numbers. Our results, generated in a more homogenous population of predominantly white men, provide additional support for an independent association between vWF and stroke that is not explained by inflammation. This finding was similar using CRP (an acute phase protein associated with stroke risk20) and IL-6 (a proinflammatory cytokine that stimulates release of vWF from vascular endothelium29). This association with stroke independent of inflammation might reflect release of vWF as a marker of endothelial disturbance or a prothrombotic tendency because vWF promotes platelet adhesion and aggregation.

The strongest associations with stroke in the present study were observed for D-dimer. Prospective studies on the association between D-dimer and risk of stroke in persons with sinus rhythm are limited. Our findings are consistent with results of 2 previous prospective studies showing D-dimer to predict incident stroke in the general population.13,14 No significant association was seen in the Three-City French cohort study,11 but the number of stroke cases was relatively small. The associations between D-dimer and stroke persisted even after adjustment for CRP or IL-6, suggesting that they are not attributable to persisting inflammatory reactions as measured by these inflammatory markers. By contrast, we found no association between tPA and risk of stroke that is consistent with other prospective studies.13,14

Hypertensive patients have been shown to have elevated levels of D-dimer and vWF in some, but not all, studies.30 D-dimer or vWF was not elevated in hypertensive men in this general older population, but D-dimer was a significant predictor of stroke in hypertensive men, in contrast to vWF, which showed weak associations in hypertensive men. On the basis of these findings, D-dimer rather than vWF is more likely to help in the assessment of stroke risk, particularly in patients with hypertension. Further large studies in hypertensive individuals are needed to formally evaluate whether inclusion of D-dimer assessment as a part of screening would be clinically useful to reduce stroke risk in this population at high risk (eg, by selective use of aspirin).
Our study has some limitations. It was based on an older and predominantly white male population, so the results cannot be generalized directly to women, younger men, or other ethnic groups. The findings were based on a single measurement at the baseline re-examination rather than on repeated assessments, which may lead to underestimation of the true strength of associations. However, we have published estimated regression dilution ratios for D-dimer and vWF over periods of up to 4 years. Taking account of regression dilution would have only modest effects on the adjusted hazards ratios per SD increase, which would increase from 1.24 to 1.33 for D-dimer and from 1.25 to 1.36 for vWF. Although we did not have information on type of stroke in all men, 85% of stroke cases in Great Britain are attributable to ischemia, and nonfatal strokes are likely to be predominantly ischemic. Moreover, additional analysis of confirmed ischemic stroke cases in this study confirmed a relationship between vWF and D-dimer with ischemic stroke. The number of confirmed hemorrhagic stroke in this study was too small to make any inferences about the relationships with hemorrhagic stroke.

In conclusion, we have shown that vWF and fibrin D-dimer are independent predictors of stroke in older men, which is likely to reflect an association with ischemic stroke, and these associations were independent of inflammation. Whether lowering levels of D-dimer and vWF in susceptible older population groups by lifestyle measure or pharmacological means is beneficial remains to be elucidated.

Sources of Funding
The British Regional Heart Study is supported by a British Heart Foundation (BHF) Programme grant (RG/08/013/25942). Analyses of fibrin D-dimer, von Willebrand factor, and tissue-type plasminogen activator were supported by a British Heart Foundation Project grant.

Disclosures
None.

References
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Abstract

背景および目的：血液凝固および線維素溶解系の異常は、脳卒中のリスク上昇と関連しているが、高齢者においてこれらの関係を検討した前向き試験はほとんど実施されていない。我々は、フィブリンD-ダイマー、組織プラスミノゲン活性化因子(t-PA)およびフォン・ウィルブランド因子(vWF)と高齢男性における脳卒中のリスクとの関係を検討し、正常血圧と高血圧の男性とに分けて、その予測的役割を評価した。

方法：年齢が60～79歳で、過去に心筋梗塞または脳卒中に診断されたことがなく、心房細動が認められない男性3,358例を対象とした前向き試験において平均9年間の追跡調査を実施したところ、追跡期間中に187件の脳卒中イベントが発生した。

結果：収縮期血圧などの潜在的な交絡因子について補正した後、重症脳卒中イベントのリスクは、D-ダイマーおよびvWF値の増加に伴って有意に上昇した[D-ダイマーおよびvWFが標準偏差分上昇することの補正後のハザード比および95%信頼区間は、それぞれ1.24 (95%信頼区間: 1.08 ~ 1.44)および1.25 (95%信頼区間: 1.09 ~ 1.45)であった。補正後には t-PAとの関係は認められなかった。D-ダイマーおよびvWFと脳卒中発生率との間の相関は、さらに炎症マーカー（C反応性蛋白, IL-6）について補正後も残存した。D-ダイマーは正常血圧および高血圧の両方の男性の脳卒中と関連していた。vWFは高血圧よりも正常血圧の男性において、より強い関連を示した（相互作用に関する検定：D-ダイマーについてp = 0.52、vWFについてp < 0.01）。

結論：フィブリンD-ダイマーおよびvWFは、高齢男性における脳卒中のリスク上昇と関連している。このような関連は炎症との関係からは説明されなかった。D-ダイマーは高血圧男性における脳卒中のリスクを同定するための、有用なマーカーと考えられる。
노년기 남성에서 혈소프리 dime리(D-dimer), 조직플라스미노겐활성제, 본빌브란드인자(von Willebrand factor), 뇌졸중 발생 위험도 연구

Fibrin D-Dimer, Tissue-Type Plasminogen Activator, von Willebrand Factor, and Risk of Incident Stroke in Older Men
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Key Words: cerebrovascular disease ■ epidemiology ■ etiology ■ risk factors

배경과 목적
혈액중고와 혈소프리해의 이상은 뇌졸중 발생 위험도의 증가와 연관된 것으로 알려져 있으며, 노년기 남성에서 그 연관성을 규명한 전향적 연구는 거의 없다. 본 연구에서는 노년기 남성에서 혈소프리 dime리(D-dimer), 조직플라스미노겐활성제, 본빌브란드인자(von Willebrand factor, vWF)와 뇌졸중 발생 위험도의 연관성을 평가하였고, 정상혈압과 고혈압을 가진 환자에서 연관성의 차이를 평가하였다.

방법
심근질환 혹은 뇌졸중의 과거력과 심방세동이 없는 60세에 서 79세 사이의 3,358명 남성들을 대상으로 전향적으로 평균 9년 동안 추적 관찰하였다. 그 기간 동안 187건의 뇌졸중 발생이 있었다.

결과
D-dimer와 vWF 수치의 증가는 수측기 혈압을 포함한 교란변 수 보정 후 주요 뇌졸중 발생 위험도의 증가와 유의한 연관성을 보였다. D-dimer와 vWF의 표준편차계보정 HR와 95% CI는 각각 1.24 (1.08~1.44)와 1.25 (95% CI, 1.09~1.45)였다. 보정 후에도 조직플라스미노겐활성제와의 연관성은 발견되지 않았다. C-반응단백질(C-reactive protein), 인터루킨(interleukin)-6와 같은 염증 표지자들은 보정한 후에도 D-dimer 및 vWF와 뇌졸중 발생 사이의 양의 관계가 존재하였다. D-dimer는 정상 혈압 및 고혈압을 가진 남성 두 군에서 모두 연관성이 있었는데, vWF는 고혈압 남성군보다는 정상 혈압의 남성군에서 더 강한 연관성을 보였다(상관성 검정: D-dimer, P=0.52; vWF, P<0.01).

결론
노년기의 남성에서 D-dimer와 vWF는 뇌졸중 발생 위험의 증가와 연관되어 있다. 이러한 연관성들은 염증 현상과의 관련성으로 설명되지 않았다. D-dimer는 고혈압을 가진 노년의 남성들에서 뇌졸중의 위험도를 예측하는 표지자로 사용할 수 있겠다.