Plasma d-Dimer and Incident Ischemic Stroke and Coronary Heart Disease
The Atherosclerosis Risk in Communities Study

Aaron R. Folsom, MD; Rebecca F. Gottesman, MD, PhD; Duke Appiah, PhD; Eyal Shahar, MD; Thomas H. Mosley, PhD

Background and Purpose—Epidemiological studies have documented that plasma d-dimer, a fibrin degradation product, is a risk marker for coronary heart disease, but there is limited prospective evidence for stroke. Given that thrombosis is a key mechanism for many strokes, we studied whether d-dimer is a risk marker for ischemic stroke incidence in the Atherosclerosis Risk in Communities (ARIC) Study.

Methods—We measured d-dimer in 11,415 ARIC participants free of stroke and coronary heart disease in 1992 to 1995. We followed them for stroke, stroke subtype, and coronary heart disease events through 2012.

Results—Over a median of 18 years of follow-up, 719 participants had incident strokes (628 ischemic and 91 hemorrhagic). d-dimer was associated positively with risk of total, ischemic, and cardioembolic strokes, with risk elevated primarily for the highest quintile of d-dimer. After adjustment for other cardiovascular risk factors, the hazard ratio for the highest versus lowest quintile of d-dimer was 1.30 (95% confidence interval, 1.02–1.67) for total stroke, 1.33 (95% confidence interval, 1.02–1.73) for ischemic stroke, and 1.79 (95% confidence interval, 1.08–2.95) for cardioembolic stroke. There was no association with hemorrhagic, lacunar, or nonlacunar stroke categories. d-dimer was positively but weakly associated with coronary heart disease incidence.

Conclusions—A higher basal plasma d-dimer concentration in the general population is a risk marker for ischemic stroke, especially cardioembolic stroke. (Stroke. 2016;47:18-23. DOI: 10.1161/STROKEAHA.115.011035.)

Key Words: coronary disease ■ epidemiological studies ■ fibrin fragment D ■ prospective studies ■ stroke
Lesions stated in imaging reports as being lacunar still needed to meet ARIC criteria, to be classified as lacunar.

### Ascertainment of CHD

Using published criteria, we defined CHD incidence as (1) a definite or probable myocardial infarction, (2) a definite CHD death, or (3) a coronary revascularization.

### Statistical Analysis

Of the 12887 ARIC participants who attended visit 3, we excluded those without d-dimer measurement (n=340), those with CHD or stroke before d-dimer assessment (n=1080), and those who were either not white or not black in Jackson or Forsyth County (n=72).

This left a maximum of 11415 participants for analyses of incident stroke and subtypes. We computed time at risk from the date of d-dimer blood draw to the date for the earliest of the following: incident stroke, death, last contact, or end of follow-up. We treated the occurrence of a hemorrhagic stroke before an ischemic stroke as a censoring event and vice versa.

Using version 9.3 of SAS (SAS Institute, Cary, NC), we described participants’ characteristics by d-dimer quintile. We plotted Kaplan–Meier curves and used Poisson regression to compute incidence rates for quintiles of d-dimer. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals of incident ischemic stroke, with a test for trend in stroke using the quintile median d-dimer values to represent each quintile. We also computed hazard ratios in relation to continuous d-dimer and produced restricted cubic spline graphs with knots at the 5th, 35th, 65th, and 95th percentiles. We verified that the proportional hazards assumption held (P>0.05) for all outcomes by testing a log time by d-dimer interaction term. Because there was no evidence of multiplicative d-dimer by race or d-dimer by sex interactions (P>0.05), we pooled these subgroups. Model 1 for d-dimer and stroke adjusted for age, sex, race, and ARIC field center; model 2 additionally for systolic blood pressure, antihypertensive medication use (yes or no), diabetes mellitus status (yes or no), total and high-density lipoprotein cholesterol, body mass index, smoking status (never, former, current), alcohol intake, sports score, and education level (≤high school, high school, >high school). Model 3 additionally adjusted for prevalent atrial fibrillation, heart failure, left ventricular hypertrophy by ECG, and peripheral artery disease (all yes or no).

### Results

Among the 11415 participants free of stroke and CHD at ARIC visit 3, plasma d-dimer was higher in women than in men, in blacks than in whites, and was associated positively with most stroke risk factors, other than lipids, and other prevalent cardiovascular conditions (Table 1). Over a median of 18 years of follow-up (maximum=20 years), 719 participants had incident definite plus probable stroke events (628 ischemic and 91 hemorrhagic).

As shown in Table 2 and Figure, d-dimer was associated positively with incidence rates of total stroke, total ischemic stroke, and its cardioembolic stroke subtype. In contrast, d-dimer was not associated significantly with hemorrhagic stroke or the lacunar and nonlacunar subtypes of ischemic stroke after adjustment for demographic factors (Table 2). Even though the tests for continuous d-dimer associations were statistically significant and cubic spline analyses (Figure IA–IC in the online-only Data Supplement) confirmed that the...
associations were approximately linear, the incidence rates were elevated mainly for the highest versus lowest quintiles of \( \text{d-dimer} \) for total stroke (Model 1: HR=1.43), ischemic stroke (HR=1.47), and especially cardioembolic stroke (HR=2.06). \( \text{d-dimer} \) was associated significantly with both definite and probable total stroke (Model 1: HRs=1.33 and 1.86, respectively, for highest versus lowest quintile; Table I in the online-only data Supplement).

Adjustment for other stroke risk factors somewhat attenuated the associations of \( \text{d-dimer} \) with stroke (Table 2). Yet, model 2 hazard ratios for the highest versus the lowest quintile of \( \text{d-dimer} \) remained statistically significant for total stroke (HR=1.30), total ischemic stroke (HR=1.33), and cardioembolic stroke (HR=1.79). Adjustment of these 3 associations for prevalent cardiovascular conditions (Model 3) had little impact. Additional adjustment for NT-proBNP, TnT, and C-reactive protein (Model 4) slightly strengthened these associations.

To assess whether \( \text{d-dimer} \) may add to total stroke prediction, we computed the area under the receiver operating characteristic curve (AUC) for Model 2, with and without log \( \text{d-dimer} \). The AUC was 0.797 without \( \text{d-dimer} \) and rose to only 0.798 with \( \text{d-dimer} \).

For comparison with the associations for stroke, Table 3 shows that \( \text{d-dimer} \) was positively but more weakly associated with CHD incidence.

### Discussion
This large prospective epidemiological investigation found that a higher plasma level of \( \text{d-dimer} \) in the general population, particularly being in the highest \( \text{d-dimer} \) quintile, was a moderately strong, independent risk factor for ischemic stroke, especially the cardioembolic stroke subtype. In contrast, \( \text{d-dimer} \) was not a risk factor for hemorrhagic stroke or the lacunar and noncardioembolic subtypes of ischemic stroke. We also corroborated a weak positive association of \( \text{d-dimer} \) with CHD, which has been well-documented. Despite the association of \( \text{d-dimer} \) with stroke incidence, suggesting a possible pathogenic role of elevated \( \text{d-dimer} \), \( \text{d-dimer} \) did not improve the prediction of future stroke, when added to other stroke risk factors.

\( \text{d-dimer} \) is a fibrinogen degradation product that reflects thrombus formation and breakdown. Prior studies have also documented that \( \text{d-dimer} \) levels vary in the general population and tend to correlate positively with other cardiovascular risk factors. Thus, some individuals seem to have an increased prothrombotic tendency, which may be in part because of elevated risk factors, but which may independently increase their risk of future atherothrombotic and venous thromboembolic events. All 4 previous prospective epidemiological studies of \( \text{d-dimer} \) and stroke also found a positive association for total or ischemic stroke. One reported a positive association with hemorrhagic stroke, in contrast with our findings. No
previous study examined ischemic stroke subtypes to evaluate particular risk for cardioembolic stroke. In addition, no previous study included a large group of nonwhite participants, and none adjusted for so many potential confounders as we did. It is striking that a small elevation in d-dimer measured in middle-aged ARIC participants was associated with increased ischemic stroke incidence >20 years of follow-up, in addition to greater prevalences of subclinical brain infarction and carotid atherosclerosis.8

We anticipated and confirmed that d-dimer is associated most strongly with cardioembolic stroke, as it is the subtype most closely linked to fibrin thrombi. Adjustment for
prevalent medical conditions associated with d-dimer, which might predispose to thrombi (ie, atrial fibrillation, left ventricular hypertrophy by ECG, heart failure, and peripheral artery disease) did not affect the d-dimer association with cardioembolic stroke. However, certainly some participants would have developed these during the 20 years of follow-up, and the inability to control for this confounding might have exaggerated the hazard ratios for d-dimer. Adjustment for NT-proBNP and TnT, which we previously showed were strong risk markers for cardioembolic stroke,13 had no impact on the d-dimer associations. A limitation to this adjustment was that these biomarkers were not available at the time of d-dimer assessment, but only 3 years later.

There are some other drawbacks to this study. First, we had only 1 measure of plasma d-dimer. Insofar as there is random biological or laboratory variability in d-dimer concentrations, the observed associations of d-dimer with stroke incidence would tend to underestimate the true associations. With a single measure, we also could not examine whether change in d-dimer or d-dimer concentration just before stroke occurrence is pathogenically important. Second, although our validation of stroke events was thorough, it was based, as in most epidemiological studies, on medical reviews and not standardized neurological examinations of all potential stroke patients. We likely misclassified some cardioembolic strokes, because even when the stroke records indicated a potential cardiac source of embolus, neither we nor the attending physicians could always verify that embolism truly occurred. We also could not readily separate our nonlacunar ischemic stroke group into large vessel disease versus other ischemic or cryptogenic ischemic strokes. Third, our prior publication demonstrating a positive association of d-dimer with subclinical lacunar infarcts7 is seemingly in conflict with the present results showing no association with clinical lacunar strokes. This may result from limitations in the classification process for clinical lacunar stroke or possibly from differences related to lacune subtypes, as the subtypes might have different probabilities of clinical presentation and contrasting risk factor associations.18

In conclusion, a higher basal plasma d-dimer concentration in the general population is a risk marker for ischemic stroke, especially cardioembolic stroke. Whether the association is causal is uncertain, and it seems unlikely that d-dimer could be clinically useful to identify patients at risk of stroke. However, recent evidence indicates that ideal cardiovascular health is associated with both lower d-dimer19 and lower stroke risk,20 suggesting that cardiovascular health may reduce risk of stroke by antithrombotic mechanisms.

Acknowledgments
We thank the staff and participants of the ARIC Study for their important contributions, and Elaine Cornell for supervising d-dimer measurements.

Table 3. Incidence Rates (95% CI) and HRs (95% CI) of d-Dimer in Relation to Incident Coronary Heart Disease, the ARIC Study, 1993 to 2012

<table>
<thead>
<tr>
<th>d-Dimer Quintiles, µg/mL</th>
<th>Continuous d-Dimer per 1−SD Loge Increment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 (≤0.14)</td>
<td></td>
</tr>
<tr>
<td>Q2 (0.15–0.22)</td>
<td></td>
</tr>
<tr>
<td>Q3 (0.23–0.32)</td>
<td></td>
</tr>
<tr>
<td>Q4 (0.33–0.49)</td>
<td></td>
</tr>
<tr>
<td>Q5 (&gt;0.49)</td>
<td></td>
</tr>
</tbody>
</table>

Model 1: HR with 95% CI from Cox proportional hazards model adjusted for age, sex, and race–field center. Model 2: Model 1 additionally adjusted for education level, smoking status, alcohol intake, body mass index, systolic blood pressure, antihypertensive medication use, diabetes mellitus status, total, and high-density lipoprotein cholesterol. ARIC indicates Atherosclerosis Risk in Communities; CI, confidence interval; and HR, hazard ratio.

*1 Loge SD = 0.97 loge µg/mL.
†Unadjusted incidence rate per 1000 person-years with 95% CI.
Sources of Funding

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Disclosures

None.

References

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### Supplemental Table I. Incidence Rates (95% CI) and Hazard Ratios (95% CI) of Definite and Probable Total Stroke in Relation to D-dimer, the ARIC Study, 1993-2012.

<table>
<thead>
<tr>
<th>D-dimer Quintiles, µg/ml</th>
<th>Q1 (≤ 0.14)</th>
<th>Q2 (0.15-0.22)</th>
<th>Q3 (0.23-0.32)</th>
<th>Q4 (0.33-0.49)</th>
<th>Q5 (&gt; 0.49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Stroke Events, n</td>
<td>114</td>
<td>123</td>
<td>151</td>
<td>127</td>
<td>204</td>
</tr>
<tr>
<td>Incidence rate†</td>
<td>3.0 (2.5-3.6)</td>
<td>3.0 (2.5-3.6)</td>
<td>4.1 (3.5-4.8)</td>
<td>3.9 (3.3-4.7)</td>
<td>6.1 (5.3-6.9)</td>
</tr>
<tr>
<td>Model 1 HR</td>
<td>1 (Referent)</td>
<td>0.92 (0.71-1.18)</td>
<td>1.13 (0.88-1.45)</td>
<td>0.99 (0.76-1.28)</td>
<td>1.43 (1.12-1.82)</td>
</tr>
<tr>
<td>Model 2 HR</td>
<td>1 (Referent)</td>
<td>0.89 (0.69-1.16)</td>
<td>1.04 (0.81-1.33)</td>
<td>0.86 (0.66-1.12)</td>
<td>1.30 (1.02-1.67)</td>
</tr>
<tr>
<td>Model 3 HR</td>
<td>1 (Referent)</td>
<td>0.90 (0.70-1.17)</td>
<td>1.04 (0.81-1.34)</td>
<td>0.85 (0.65-1.11)</td>
<td>1.30 (1.02-1.67)</td>
</tr>
</tbody>
</table>

| Definite stroke Events, n | 93           | 95            | 122           | 101           | 157          |
| Incidence rate†           | 2.4 (2.0-3.0) | 2.3 (1.9-2.9) | 3.3 (2.8-4.0) | 3.1 (2.6-3.8)| 4.7 (4.0-5.5)|
| Model 1 HR                | 1 (Referent) | 0.86 (0.65-1.15)| 1.10 (0.83-1.45)| 0.95 (0.71-1.26)| 1.33 (1.01-1.74)| 0.004 | 1.09 (0.99-1.18) |
| Model 2 HR                | 1 (Referent) | 0.85 (0.64-1.13)| 1.02 (0.77-1.34)| 0.84 (0.62-1.12)| 1.24 (0.94-1.63)| 0.011 | 1.07 (0.97-1.17) |
| Model 3 HR                | 1 (Referent) | 0.85 (0.64-1.14)| 1.02 (0.77-1.34)| 0.83 (0.62-1.12)| 1.22 (0.93-1.61)| 0.016 | 1.06 (0.97-1.16) |

| Probable stroke Events, n | 21           | 28            | 29            | 26            | 47           |
| Incidence rate†           | 0.5 (0.4-0.8) | 0.7 (0.5-1.0) | 0.8 (0.6-1.1) | 0.8 (0.5-1.2) | 1.4 (1.0-1.9)|
| Model 1 HR                | 1 (Referent) | 1.14 (0.64-2.00)| 1.25 (0.71-2.20)| 1.16 (0.64-2.08)| 1.86 (1.09-3.18)| 0.008 | 1.20 (1.02-1.41) |
| Model 2 HR                | 1 (Referent) | 1.09 (0.62-1.92)| 1.11 (0.62-1.97)| 0.92 (0.50-1.69)| 1.57 (0.91-2.70)| 0.044 | 1.16 (0.97-1.38) |
| Model 3 HR                | 1 (Referent) | 1.11 (0.63-1.97)| 1.13 (0.63-2.00)| 0.92 (0.50-1.69)| 1.63 (0.94-2.81)| 0.033 | 1.17 (0.98-1.39) |

**Model 1:** Hazard ratio (HR) with 95% confidence interval from Cox proportional hazards model adjusted for age, sex and race–field center.

**Model 2:** Model 1 additionally adjusted for education level, smoking status, alcohol intake, body mass index, systolic blood pressure, antihypertensive medication use, diabetes status, total and HDL cholesterol.

**Model 3:** Model 2 additionally adjusted for prevalent left ventricular hypertrophy, atrial fibrillation, peripheral artery disease and heart failure.

* 1 Log, standard deviation (SD) = 0.97 log, µg/ml.

† Unadjusted incidence rate per 1,000 person-years with 95% confidence interval.

ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; HR, hazard ratio; SD, standard deviation.
**Supplemental Figure IA.** Restricted cubic spline depicting relationship between log D-dimer and incident total stroke adjusted for age, sex, race and center. Reference value = -1.347 (median). 95% confidence intervals displayed in broken lines. Knots shown as dots set at 5th, 35th, 65th, and 95th percentiles. (Test for non-linear relation = 0.19.)

![Graph](image1)

**Supplemental Figure IB.** Restricted cubic spline depicting relationship between log D-dimer and incident ischemic stroke adjusted for age, sex, race and center. Reference value = -1.347 (median). 95% confidence intervals displayed in broken lines. Knots shown as dots set at 5th, 35th, 65th, and 95th percentiles. (Test for non-linear relation = 0.42.)

![Graph](image2)
Supplemental Figure IC. Restricted cubic spline depicting relationship between log D-dimer and incident cardioembolic stroke adjusted for age, sex, race and center. Reference value = -1.347 (median). 95% confidence intervals displayed in broken lines. Knots shown as dots set at 5th, 35th, 65th, and 95th percentiles. (Test for non-linear relation = 0.80.)