The Relationship of Fibrinogen and Factors VII and VIII to Incident Cardiovascular Disease and Death in the Elderly

Results From the Cardiovascular Health Study

Russell P. Tracy, Alice M. Arnold, Walter Ettinger, Linda Fried, Elaine Meilahn, Peter Savage

Abstract—Little is known about the prospective associations of fibrinogen, factor VII, or factor VIII with cardiovascular disease (CVD) and mortality in the elderly. At baseline in the Cardiovascular Health Study (5888 white and African American men and women; aged ≥65 years), we measured fibrinogen, factor VIII, and factor VII. We used sex-stratified stepwise Cox survival analysis to determine relative risks (RRs) for CVD events and all-cause mortality (up to 5 years of follow-up), both unadjusted and adjusted for CVD risk factors and subclinical CVD. After adjustment, comparing the fifth quintile to the first, fibrinogen was significantly associated in men with coronary heart disease events (RR=2.1) and stroke or transient ischemic attack (RR=1.3), and also with mortality within 2.5 years of follow-up (RR=5.8) and later (RR=1.7). Factor VIII was significantly associated in men with coronary heart disease events (RR=1.5) and mortality (RR=1.8), and in women with stroke/transient ischemic attack (RR=1.4). For both factors, values were higher in those who died, whether causes were CVD-related or non–CVD-related, but highest in CVD death. Factor VII exhibited associations with incident angina (RR=1.44) in men and with death in women (RR, middle quintile compared with first=0.66). However, in general, factor VII was not consistently associated with CVD events in this population. We conclude that, if confirmed in other studies, the measurement of fibrinogen and/or factor VIII may help identify older individuals at higher risk for CVD events and mortality. (Arterioscler Thromb Vasc Biol. 1999;19:1776-1783.)

Key Words: atherosclerosis ■ cardiovascular diseases ■ fibrinogen ■ risk factors ■ thrombosis

Over the last 10 years, the concept of thrombosis risk factors has been accepted, with much research focused on fibrinogen1 and factor VII.2–3 Fibrinogen has been observed to be an independent risk factor for incident cardiovascular disease (CVD) events in a wide variety of studies.4–8 The results regarding factor VII have been less consistent in longitudinal studies,4,9–11 despite extensive support from cross-sectional research.12–18 Fewer longitudinal studies have been done assessing other components such as factor VIII,10,19 tissue-type plasminogen activator (t-PA)20 and plasminogen activator inhibitor-1 (PAI-1).21,22

Relatively little is known from large cohort studies about the epidemiology of thrombosis risk factors in the elderly. The Northwick Park Heart Study (NPHS) has reported that the association of fibrinogen with incident CVD in men diminished with age, but had no individuals older than 64 years at baseline.23 The Framingham group reported a different result, finding significant associations in older men and women (65 to 69 years at baseline).24 Little is known about any other thrombosis risk factors in the elderly.

The Cardiovascular Health Study (CHS) was designed to promote such analyses, having measured fibrinogen, factor VII, and factor VIII at baseline, along with estimates of subclinical CVD such as carotid ultrasonography, electrocardiography, echocardiography, and ankle–arm blood pressure. We have used these measures to determine the relations of these thrombosis risk factors to incident CVD events in this large cohort of healthy elderly individuals, both before and after adjusting for traditional risk factors and underlying CVD.

Methods

The Cardiovascular Health Study

The CHS design has been published.25 The 4 field centers (Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and, Pittsburgh, Pennsylvania) recruited 5201 participants in year 2 of the study, and a second cohort (the African American Health Study) recruited a second cohort of 4385 participants in year 4 of the study. From these, 5888 white and African American men and women aged ≥65 years were included in the analyses. The CHS design has been published.25

Received May 14, 1998; revision accepted November 20, 1998.

From the Departments of Pathology and Biochemistry and the Laboratory for Clinical Biochemistry Research (R.P.T.), University of Vermont College of Medicine, Burlington, Vermont; the Department of Biostatistics (A.M.A.), University of Washington, Seattle; the Departments of Internal Medicine and Public Health Sciences (W.E.), Bowman Gray School of Medicine, Winston-Salem, NC; the Departments of Medicine and Epidemiology (L.F.), Johns Hopkins University, Baltimore, Maryland; the Department of Epidemiology and Population Sciences (E.M.), London School of Hygiene and Tropical Medicine, London, UK; and the Division of Epidemiology and Clinical Applications (P.S.), National Heart, Lung, and Blood Institute, NIH, Bethesda, Maryland, for the Cardiovascular Health Study Investigators (see Acknowledgments for a full listing).

Correspondence to Russell P. Tracy, PhD, Laboratory for Clinical Biochemistry Research, University of Vermont, 55A South Park Drive, Colchester, VT 05446. E-mail rtracy@sahs.uvm.edu

Reprint requests to CHS Coordinating Center, Century Square, Suite 2025, 1501 Fourth Avenue, Seattle, WA 98101.

© 1999 American Heart Association, Inc.

Arterioscler Thromb Vasc Biol. is available at http://www.atvbaha.org

1776
American Cohort) consisting of primarily African Americans in year 5. All participants gave informed consent, and all relevant institutional committees on human research approved the study. All participants were 65 years of age or older. Major exclusion criteria included illness requiring institutionalization, being wheelchair bound, being treated currently for cancer, and planned movement from the area within 3 years.25

We assessed medical history, quality of life, social support, personal health habits, and diet through the use of standardized questionnaires. We also collected information on medication use.27 The baseline clinical examination included measures of anthropometry, blood pressure,28,29 electrocardiogram (ECG),30 carotid ultrasonography,31 echocardiogram,32 and blood chemistries33 including an oral glucose tolerance test.

Definitions
Blood pressure was used in analyses either as the average seated systolic blood pressure or a history of “high blood pressure”; diabetes was defined by the new American Diabetes Association (ADA) guidelines,34 ie, fasting glucose $\geq$126 mg/dL or taking insulin or oral hypoglycemics; impaired fasting glucose was defined as a fasting glucose value in the range 110 to 125 mg/dL; smoking was defined as “ever smoker” by self-report or by pack-years of smoking; obesity was estimated by using body mass index (BMI; units of kg/m²). Clinical and subclinical CVD were defined based on the resting ECG, echocardiogram, carotid artery duplex scanning, ankle-brachial blood pressure, history of CVD, Rose questionnaire,35 previous cardiovascular surgery, and use of medications consistent with the diagnosis of angina or congestive heart failure, as previously described.36 Subclinical CVD was considered present with any of the following: seated ankle–arm blood pressure index <0.9,37 internal carotid wall thickness, as judged from carotid ultrasonography,38,39 >80th percentile, common carotid wall thickness >80th percentile, carotid stenosis >25%, major ECG abnormalities,40,41 abnormal ejection fraction on echocardiogram,42,43 abnormal wall motion on echocardiogram, Rose questionnaire claudication positive, and Rose questionnaire angina positive.

Particular care was given to incident CVD and mortality data collection in CHS.43,44 Incident CVD events, including angina pectoris, myocardial infarction (MI), stroke, transient ischemic attack (TIA), and death, were identified by 6-month telephone calls and annual clinic visits. Further verification was done by the CHS Events Subcommittee, using Medicare Part A hospital discharge lists.45 For MI and angina, International Classification of Diseases codes 410 through 414, 427.4, 427.5, and 428 were reviewed. Silent MI was defined as the development of new Q waves (major codes 410 through 414, 427.4, 427.5, and 428 were reviewed. Silent MI was defined as the development of new Q waves). We also performed analyses stratified by cohort only, adjusting for age, sex, clinic site, and race (original cohort only), using ANOVA. We performed some analyses by separating CVD-related mortality from non–CVD-related mortality. P<0.05 was used as evidence of significance.

We believed it was important to combine the 2 cohorts for relative risk (RR) estimates, to increase power and generalizability. To do this, we accounted for differences in means and variances across the 2 cohorts and sexes by calculating standardized blood factor variables. For each of the blood factors, the mean for the sex/cohort subgroup was subtracted from each individual’s value with the result divided by the standard deviation for the variable in that sex/cohort subgroup. This operation had the effect of standardizing each of the 4 cohort/sex subgroups to a mean value of 0 and an SD of 1, minimizing differences that might have occurred as a result of the 3 years separating the measurements.

Multivariate analyses were done with the Cox proportional hazards analysis. This is essentially a survival analysis that explores the dependence of the event rate on the variables of interest. Proportional hazards models assume that the hazard ratio describing the increased risk associated with a 1-unit increase in a covariate remains constant over time. This assumption was assessed in all cases and found to be lacking for fibrinogen and death in men, so separate models were established for mortality in men occurring <2.5 years and $\geq$2.5 years after the baseline examination. For all Cox models, we entered the standardized form of the blood factor of interest as a continuous linear variable, and then checked for any nonlinear (quadratic) effects, ie, a quadratic association between increasing blood factor levels and risk. If we found no evidence for a quadratic effect, we report a standardized RR, ie, the risk associated with an increase equal to 1 SD of the blood factor. When a quadratic effect was identified, we report an overall P value for the model, because a standardized RR could not be calculated. We also established models in terms of quintiles of each blood factor and determined the RR of each quintile compared with the first. Quintiles were established based on all CHS participants in each of the 4 sex/cohort subgroups.

Because there were relatively few associations with angina in the analyses of means, we concentrated on CHD, stroke/TIA, and mortality as the events of primary interest. However, we also analyzed factor VII with respect to angina. Models were stratified by sex. For each blood factor and outcome variable, we generated 2 models, 1 with the blood factor as the only predictor (unadjusted) and 1 adjusted for other known, major risk factors of CVD. Risk factors were selected for entry by a stepwise procedure (using P<0.05 for entry) from the following list: age, black race, clinic site, ever smoker, pack-years smoked, diabetes, history of hypertension, HDL cholesterol, LDL cholesterol, BMI, and presence of any subclinical CVD. If the hemostasis factor being studied remained in the model after all steps were performed, we interpreted that to mean that the association of that factor with the outcome was independent of other major CVD risk factors, including the presence of subclinical disease.
Results

The total number of CHS participants was 5888, 5201 from the main cohort and 687 from the African American cohort. Fibrinogen results were available on 5788 participants. Of these, 1 was excluded as outside of a predetermined physiological range (>800 mg/dL). Factor VII results were available on 5779 participants. We excluded 23 of the values for being outside of a predetermined range of 40% to 300%. Factor VIII values were available on 5121 participants (factor VIII was not done on the African American cohort); 10 values were excluded as outside the range 40% to 300%.

Analyses of Mean Values

Although not always statistically significant, in all cases (ie, men and women, main cohort and African American cohort) for fibrinogen, and in most cases for factor VIII, unadjusted baseline values were higher in those with subsequent events than in those without (Table). Unadjusted factor VII values were generally similar, comparing those with and without events, but were significantly higher in men with subsequent angina and CHD.

Analyzing men and women together in the main cohort, and adjusting for age, sex, race, and clinic site, significant differences persisted for fibrinogen and subsequent CHD (P≤0.001), angina (P≤0.05), and death from any cause (P≤0.001); for factor VIII and CHD (P≤0.05), subsequent stroke/TIA (P≤0.01), and death from any cause (P≤0.001); and for factor VII and subsequent angina (P≤0.01). Although fibrinogen was higher in those who died of both non-CVD and CVD causes, compared with those still alive, the values were higher in those who died of CVD causes than in those who died of other causes. Similar findings were true for factor VIII, but not factor VII (Figure 1).

Multivariate Analyses

The covariates that were significant for each of the final sex-stratified models were essentially the same for a given outcome, for all 3 hemostasis variables. In women, the covariates that entered the final models for CHD were age, diabetes status, hypertension, and the presence of any subclinical disease; for stroke/TIA in women, they were age, clinic site, diabetes status, hypertension, LDL cholesterol,
and any subclinical disease; and for death in women, they were age, diabetes status, pack-years of cigarettes, BMI, and any subclinical disease; for later deaths, they were age, diabetes status, hypertension, pack-years of cigarettes, BMI, LDL cholesterol, and any subclinical disease.

After adjustment, fibrinogen (Figure 2A) was not significantly associated with any events in women. In men, fibrinogen was significantly associated with CHD, stroke/TIA, and, in a particularly strong manner, mortality. For early death, the RR (95% confidence interval, CI) of the highest quintile was substantial, 5.8 (3.1 to 11.0). For later death the RRs were lower.

After adjustment, factor VII was weakly, but significantly, associated with stroke/TIA in women when a quadratic term was included in the model. The quadratic term reflected relatively increased risk in the first quintile of the factor VII distribution compared with the middle (Figure 2B). A similar pattern was observed for mortality in women, which, however, was not statistically significant after adjustment. Factor VII was also weakly associated with incident angina in men after adjustment, with a standardized RR and CI of 1.19 (1.00 to 1.27).

After adjustment, factor VIII was associated with incident CHD and death in men and stroke/TIA in women (Figure 2C). The association with CHD in men was primarily because of an increased risk in the fifth quintile. There were moderately strong associations of factor VIII with CHD and death in women in unadjusted models that were eliminated by adjustment.

Discussion

Fibrinogen

The covariates that entered the Cox models were essentially the same for fibrinogen as for the other 2 hemostatic factors. Although there were some differences, these were essentially the expected predictors of CVD events such as lipids, diabetes status, and blood pressure. The major finding of this study is that, as in middle-aged men, fibrinogen is an independent risk factor for CHD, stroke/TIA, and mortality in elderly men. This was true even when the analyses were extensively adjusted for other CVD risk factors and the presence of subclinical cardiovascular disease. The adjusted upper quintile RR for death occurring <2.5 years after baseline was substantial, ≈5.8. However, this RR value must be viewed with caution, because after stratification, the number of deaths in the reference group was small (n = 18). The other adjusted upper quintile RRs were moderate in strength, ≈2.1 for CHD, 1.3 for stroke/TIA, and 1.7 for deaths occurring after 2.5 years. We found little evidence to support fibrinogen as a risk factor in elderly women, after adjusting for other known risk factors and subclinical disease. This finding is in agreement with the results of the Framingham group. However, we did note that the adjusted upper quintile RR of CHD in women was 1.5, with a standardized RR of 1.13 (0.99 to 1.29), a value that might achieve significance as the number of CHD events in women increases with time.

The nature of the association of fibrinogen with CVD events and death is unclear. Because fibrinogen levels are sensitive to inflammation, fibrinogen might reflect underlying...
atherosclerotic disease. In contrast, higher values may contribute to an increased risk of thrombotic events. We have speculated that both of these mechanisms may be at play. The findings of (1) a stronger association of fibrinogen with early death compared with later death and (2) elevated levels in non–CVD-related as well as CVD-related death are consistent with accelerating inflammation being associated with rapidly progressing illness. We have suggested this mechanism to explain the association observed between declining cholesterol values and mortality in the elderly. However, our data do not rule out a possible role of higher fibrinogen contributing to a hypercoagulable state, especially because (1) those with CVD-related death had higher values than those with non–CVD-related death, (2) coagulation activity markers increase in the elderly, and (3) markers of fibrin formation predict CVD events in this same cohort. Genetic studies of fibrinogen might ultimately clarify this issue, because a prospective genetic study cannot be confounded by underlying subclinical disease. To date, however, the few prospective studies that have been done have not been consistent.

These findings for fibrinogen are in contrast to the results from the NPHS group. In the NPHS, the association of fibrinogen with CVD risk in men diminished to insignificance by the age of 64 years at baseline. Our data are more consistent with the report of the Framingham group, which indicated that the association of fibrinogen with risk included men who were 70 years old at baseline. Both of these previous studies, however, had limited power to address this issue in the elderly.

**Factor VII**

After adjustment, the only significant associations for factor VII were with angina in men (weakly) and with stroke/TIA in women. The latter association was characterized by diminished risk in the upper 4 quintiles compared with the first. The
reason for any possible increased risk of stroke associated with low factor VIIc levels is currently unknown.

In contrast to the results from the NPHS, where factor VII was strongly, positively, and independently associated with ischemic events in middle-aged men, our results do not support an important role for factor VII levels in assessing CVD risk in older men. Other recent longitudinal studies of middle-aged men have had mixed results, generally failing to find strong independent associations of factor VII with CVD. Factor VIIc assays are known to differ considerably from laboratory to laboratory, and the NPHS investigators have suggested that such a methodological difference might explain the differences observed in the various studies. Another difference between the NPHS and other studies is that the samples in the NPHS were not collected from fasting individuals, and their results may have reflected, at least in part, the postprandial activation state of factor VII. Also, factor VII may reflect more severe underlying disease. In the original NPHS report, factor VII was related to events within 5 years of blood drawing but not to later events. In the PROCAM study, the relation of factor VII to CVD events was stronger in fatal events than in nonfatal events (although not independently significant in either).9

**Factor VIII**

To our knowledge, this is the first report to identify factor VIII as a significant CVD risk factor in a longitudinal study of otherwise healthy elderly individuals. Higher factor VIII concentrations were independently associated with incident stroke/TIA in elderly women and incident CHD and death in elderly men. Moderately strong associations with CHD and death in women were attenuated by adjustment for other CVD risk factors. In studies of the middle-aged, the NPHS measured factor VIII and observed a nonsignificant trend of increasing events with increasing factor VIII levels, and a report from the Atherosclerosis Risk in Communities (ARIC) investigators indicated an independent association of factor VIII with mortality, but not CHD, in both men and women of middle age.10

There are several reasons to believe that these associations may be at least partly causal in nature. First, factor VIII, along with factor V, is a key procoagulant cofactor and is capable of dramatically increasing the rate of the factor IXa–catalyzed activation of factor Xa in a dose-dependent manner; second, the concentration of factor VIII, ≈0.5 nmol/L, is much lower than factor V (≈20 nmol/L), suggesting that small changes in factor VIII level may be critical; third, there is abundant evidence from studies of hemophilia A that low factor VIII levels are associated with bleeding; and fourth, several cross-sectional studies have demonstrated increased factor VIII levels in individuals considered at high risk for future events. However, as for fibrinogen, caution must be used in interpreting our results as evidence for causality, because factor VIII levels are increased in an inflammation-sensitive manner.

**Implications**

Our results have several implications. First, because lipid levels have limited usefulness in estimating CVD risk in older people, measurement of fibrinogen and factor VIII may help identify a high-risk group of older individuals that would benefit the most from multifactor counseling.

Second, recent research has suggested that interventions as simple as a small dose of aspirin may be effective in primary prevention in middle-aged men and that the mechanism of action may be through an antiinflammatory effect. We speculate that, if true, part of this effect may be mediated by the inflammation-sensitive thrombosis risk factors fibrinogen and factor VIII.

Third, it seems likely that plasma levels of fibrinogen and factor VIII in part reflect the degree of underlying disease and in part indicate an increased potential for thrombosis given a provocation. This suggests possible efficacy for targeted intervention of these factors in the elderly with elevated values, should specific therapeutic agents become available. Several lipid-lowering drugs are known to affect fibrinogen levels, and may provide initial agents for testing this hypothesis, at least with regard to fibrinogen.

**Acknowledgments**

This work was supported by NHLBI contracts NO1-HC-87079 through 87086. We would like to thank the technical staff of the Laboratory of Clinical Biochemistry Research at the University of Vermont. We also thank our coinvestigators in the CHS: Forsyth County, NC– Bowman Gray School of Medicine of Wake Forest University: Gregory L. Burke, Alan Elster, Walter H. Ettinger, Curt D. Furberg, Edward Haponik, Gerardo Heiss, Dalane Kitzman, H. Sidney Kolopienstein, Margie Lamb, David S. Lefkowitz, Mary F. Lyles, Maurice B. Mittelman, Cathy Nunn, Ward Riley, Gretthe S. Tell, James F. Toole, Beverly Tucker; Forsyth County, NC– Bowman Gray School of Medicine–EKG Reading Center: Kris Calhoun, Harry Calhoun, Farida Rautaharju, Pentti Rautaharju, Loralee Robertson; Sacramento County, CA– University of California, Davis: William Bommer, Charles Bernick, Andrew Duxbury, Mary Haan, Calvin Hirsch, Paul Kellerman, Lawrence Laslett, Marshall Lee, Virginia Poirier, John Robbins, Marc Schenker, Nemat Borhani; Washington County, MD–The Johns Hopkins University: M. Jan Busby-Whitehead, Joyce Chabot, George W. Comstock, Linda P. Fried, Joel G. Hill, Steven J. Kitten, Shiriki Kumanyika, David Levine, Joao A. Lima, Neil R. Powe, Thomas R. Price, Jeff Williamson, Moyes Sziklo, Melvyn Tookman; MRI Reading Center–Washington County, MD– The Johns Hopkins University: R. Nick Bryan, Carolyn C. Melzter, Douglas Fellows, Melanie Hawkins, Patrice Holtz, Michael Kraut, Grace Lee, Larry Schertz, Earl P. Steinberg, Scott Wells, Linda Wilkins, Nancy C. Yue; Allegheny County, PA–University of Pittsburgh: Diane G. Ives, Charles A. Jungreis, Laurie Knepper, Lewis H. Kuller, Elaine Meilahn, Peg Meyer, Roberta Moyer, Anne Newman, Richard Schulz, Vivienne E. Smith, Sidney K. Wolfson; Echocardiography Reading Center (Baseline)–University of California, Irvine: Hoda Anton-Culver, Julius M. Gardin, Margaret Knoll, Tom Kurosaki, Nathan Wong; Echocardiography Reading Center (Follow-Up)–Georgetown Medical Center: John Gottliener, Eva Hausner, Stephen Kraus, Judy Gay, Sue Livengood, Mary Ann Yohe, Retha Webb; Ultrasound Reading Center–Geisinger Medical Center: Daniel H. O’Leary, Joseph F. Polak, Laurie Funk; Respiratory Sciences–University of Arizona-Tucson: Paul Enright; Coordinating Center–University of Washington, Seattle: Alice Arnold, Annette L. Fitzpatrick, Bonnie K. Lind, Richard A. Kronmal, Bruce M. Psaty, David S. Siscovick, Lynn Shemanski, Lloyd Fisher, Will Longstreth, Patricia W. Wahl, David Yanez, Paula Diehr, Maryann McBurnie; NHLBI Project Office: Diane E. Bild, Teri A. Manolio, Peter J. Savage, Patricia Smith, Rachel Solomon, Robin Boineau.

**References**


The Relationship of Fibrinogen and Factors VII and VIII to Incident Cardiovascular Disease and Death in the Elderly: Results From the Cardiovascular Health Study
Russell P. Tracy, Alice M. Arnold, Walter Ettinger, Linda Fried, Elaine Meilahn and Peter Savage

doi: 10.1161/01.ATV.19.7.1776
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/19/7/1776

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org/subscriptions/