Microalbuminuria and Risk of Venous Thromboembolism

Bakhtawar K. Mahmoodi; Ron T. Gansevoort; Nic J. G. M. Veeger; et al.


http://jama.ama-assn.org/cgi/content/full/301/17/1790

Contact me if this article is corrected.

This article has been cited 2 times.

Venous Thromboembolism; Cardiovascular System

Contact me when new articles are published in these topic areas.

Subscribe
http://jama.com/subscribe

Email Alerts
http://jamaarchives.com/alerts

Permissions
permissions@ama-assn.org
http://pubs.ama-assn.org/misc/permissions.dtl

Reprints/E-prints
reprints@ama-assn.org
Microalbuminuria and Risk of Venous Thromboembolism

Bakhtawar K. Mahmoodi, BSc
Ron T. Gansevoort, MD, PhD
Nie J. G. M. Veeger, MSc
Abigail G. Matthews, PhD
Gerjan Navis, MD, PhD
Hans L. Hillege, MD, PhD
Jan van der Meer, MD, PhD†
for the Prevention of Renal and Vascular End-stage Disease (PREVEND) Study Group

The overall incidence of venous thromboembolism (VTE) in developed countries is about 0.15% per year, varying from less than 0.005% in individuals younger than 15 years to as high as 0.5% at 80 years.1-3 More than a century ago, Virchow postulated 3 main causes of thrombosis: stasis of the blood, changes in the vessel wall, and changes in the composition of the blood.4 Known risk factors for VTE fall in the first (stasis) and the third groups (blood composition).5 However, in as many as 50% of VTE cases, none of the known risk factors are present.1

Arterial thromboembolism has historically been viewed as a different pathophysiological entity with distinct risk factors. However, this dichotomy between VTE and arterial thromboembolism has recently been questioned since an increased risk of arterial thromboembolism and atherosclerosis had been reported in patients with prior VTE.6,7 Moreover, an increasing amount of data indicate that classic atherosclerosis risk factors (ie, hypertension, hyperlipidemia, diabetes, obesity, and smoking) may also predispose individuals to VTE.8 This emerging concept may indicate the involvement of vessel wall changes in the pathogenesis of VTE.9

Classic atherosclerosis risk factors are also strongly correlated with microalbuminuria (albuminuria of 30-300 mg/d), which is itself an established risk marker for arterial thromboembolism.10,11 Microalbuminuria is assumed to be a sensitive marker for generalized endothelial dysfunction that is, among others, associated with arteriosclerosis.12,13 Microalbuminuria is independently associated with an increased risk for VTE.

Context Microalbuminuria (albuminuria 30-300 mg per 24-hour urine collection) is a well-known risk marker for arterial thromboembolism. It is assumed that microalbuminuria reflects generalized endothelial dysfunction. Hence, microalbuminuria may also predispose for venous thromboembolism (VTE).

Objective To assess whether microalbuminuria is associated with VTE.

Design, Setting, and Participants Prevention of Renal and Vascular End-stage Disease (PREVEND) study, an ongoing community-based prospective cohort study initiated in 1997. All inhabitants of Groningen, the Netherlands, aged 28 through 75 years (n=85421) were sent a postal questionnaire and a vial to collect a first morning urine sample for measurement of urinary albumin concentration. Of those who responded (40856), a cohort (8592 participants) including more participants with higher levels of urinary albumin concentration completed screening at an outpatient clinic. Screening data were collected on urinary albumin excretion (UAE) and risk factors for cardiovascular and renal disease.

Main Outcome Measure Symptomatic and objectively verified VTE (ie, deep vein thrombosis, pulmonary embolism, or both) between study initiation and June 1, 2007.

Results Of 8574 evaluable participants (mean [SD] age, 49 [13] years; 50% men), 129 experienced VTE during a mean (SD) follow-up period of 8.6 (1.8) years, corresponding to overall annual incidence of 0.14% (95% confidence interval [CI], 0.11%-0.19%). Annual incidences were 0.12%, 0.20%, 0.40%, and 0.56% in participants with UAE of less than 15 (n=6013), 15-29 (n=1283), 30-300 (n=1144), and greater than 300 (n=134) mg per 24-hour urine collection, respectively (P for trend <.001). When adjusted for age, cancer, use of oral contraceptives, and atherosclerosis risk factors, hazard ratios associated with UAE levels of 15-29, 30-300, and greater than 300 mg/24 h were 1.40 (95% CI, 0.86-2.35), 2.20 (95% CI, 1.44-3.36), and 2.82 (95% CI, 1.21-6.61), respectively, compared with participants with UAE of less than 15 mg/24 h (global P=.001). Adjusted hazard ratio for microalbuminuria vs normoalbuminuria (UAE <30 mg/24 h) was 2.00 (95% CI, 1.34-2.98; P <.001). Microalbuminuria-related number needed to harm was 388 per year.

Conclusion Microalbuminuria is independently associated with an increased risk for VTE.

JAMA. 2009;301(17):1790-1797.
changes in the levels of several coagulation proteins. The effect of coagulation disorders is more evident in the pathogenesis of VTE than in the pathogenesis of arterial thromboembolism. Hence, in theory, a link between microalbuminuria and VTE is likely; however, research addressing this issue has yet to be conducted. We performed a study to assess whether microalbuminuria is associated with VTE in a population-based cohort study.

METHODS

Study Population and Design

This study was conducted on participants in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study. The PREVEND study was designed to investigate prospectively the natural course of albuminuria and its relation to renal and cardiovascular disease in a large cohort drawn from the general population. Details of the study protocol have been published elsewhere and can be found at http://www.prevend.org. In brief, during 1997-1998, all 85,421 inhabitants of the city of Groningen, the Netherlands, between the ages of 28 and 75 years old were sent a 1-page postal questionnaire regarding demographics, cardiovascular morbidity, use of medication, and pregnancy, and a vial to collect a first morning void urine sample. A total of 40,856 (47.8%) individuals responded (FIGURE 1). Since the link between cardiovascular or renal disease and microalbuminuria in individuals with insulin-dependent diabetes mellitus was well established, and pregnant females may present with temporary microalbuminuria, these individuals were excluded from the PREVEND study. After the additional exclusion of individuals who were unable or unwilling to participate in the study, a total of 6000 individuals with a urinary albumin concentration of 10 mg/L or greater and a random control sample of individuals with a urinary albumin concentration of less than 10 mg/L (n=2592) completed the screening protocol and formed the baseline PREVEND cohort (n=8592). These participants twice visited an outpatient department where demographic, anthropometric, and cardiovascular risk factors were assessed. For the current analysis, 18 participants were excluded because of missing data on 24-hour urinary albumin excretion (UAE), leaving a total of 8574 participants. The PREVEND study has been approved by the local medical ethics committee and is conducted in accordance with the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Laboratory Measurements and Definitions

Fasting blood samples were obtained during the morning in all participants. Serum creatinine, total cholesterol, and plasma glucose were measured by dry chemistry (Eastman Kodak, Rochester, New York). High-density lipoprotein cholesterol was measured with a homogeneous method (direct HDL, Aeroset TM System, Abbott Laboratories, Abbott Park, Illinois). Triglycerides were measured enzymatically. High-sensitivity C-reactive protein was determined by nephelometry (BN II, Dade Behring, Marburg, Germany). Plasma antigen levels of tissue plasminogen activator and plasminogen activator inhibitor type-1 were measured using an ELISA kit from Technoclone Gmbh (Vienna, Austria). Participants collected two 24-hour urine samples, in which urinary albumin concentration was determined by nephelometry with a threshold of 2.3 mg/L and intra- and inter-assay coefficients of variation of less...
than 2.2% and less than 2.6%, respectively (Dade Behring Diagnostic, Marburg, Germany).

Hypertension was defined as systolic blood pressure of 140 mm Hg or greater or diastolic blood pressure of 90 mm Hg or greater, or the use of antihypertensive drugs. Diabetes was defined as a fasting glucose level of 126 mg/dL or greater (≥7.0 mmol/L), nonfasting plasma glucose level of 200 mg/dL or greater (≥11.1 mmol/L), or the use of oral antidiabetic drugs. Hypercholesterolemia was defined as a total serum cholesterol concentration of 250 mg/dL or greater (≥6.5 mmol/L), or in the case of a previous myocardial infarction (MI) or stroke a concentration of 193 mg/dL or greater (≥5.0 mmol/L), or the use of lipid-lowering drugs. The metabolic syndrome was defined according to the Adult Treatment Panel III of the National Cholesterol Education Program. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Estimated glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease study equation, taking into account sex, age, race, and serum creatinine level. Low-density lipoprotein cholesterol was estimated using the Friedewald formula. The UAE was measured as the mean of two 24-hour urine collections and was classified according to clinical classes: low-normal (<15 mg/24-hour urine collection), high-normal (15-29 mg/24-hour urine collection), microalbuminuria (30-300 mg/24-hour urine collection), and macroalbuminuria (>300 mg/24-hour urine collection).

Identification and Validation of Venous Thromboembolic Events

We used the regional anticoagulation clinic database to identify participants of the PREVEND study who developed VTE between January 1, 1997, and June 1, 2007. This clinic monitors the anticoagulant therapy of all patients in the city of Groningen and in a well-defined geographical area proximal to the city. For fatal VTE cases, we searched the national registry of death certificates (Central Bureau of Statistics, The Hague/Heerlen, the Netherlands) and, as an additional check of the anticoagulant clinic database, we searched the database of the national registry of hospital discharge diagnoses (Prismant, Utrecht, the Netherlands). Patients’ medical records were reviewed for all participants of the PREVEND study who had VTE according to any of the aforementioned databases. The investigators (B.K.M. and N.J.G.M.V.) who collected these clinical data were blinded for the UAE status of these participants.

Only objectively verified symptomatic thromboembolic events were considered. Deep vein thrombosis was confirmed by compression ultrasound; and pulmonary embolism, by ventilation/perfusion lung scanning, spiral computed tomography, or at autopsy. VTE was considered provoked if it had occurred at or within 3 months after having acquired risk factors including major surgery, trauma, immobilization for more than 7 days, oral contraceptives, hormone therapy, pregnancy, malignant disease, or miscellaneous (ie, long-distance travel for longer than 4 hours, active infectious disease, paresis/paralysis of the leg, or heart failure). In the absence of these acquired risk factors, VTE was considered unprovoked.

Statistical Analysis

We assessed adjusted annual incidences of VTE for the enrichment of our cohort with participants with higher UAE, using survey probability weights. The observation time for each patient was defined as the period from the testing of albuminuria (1997-1998) until the first episode of VTE or a censoring event (withdrawal from the study, moving out of the city, death, or end of the study). The 95% confidence intervals (CIs) were computed by a Jackknife approach assuming a Poisson distribution, and the P value for the test of trend was calculated via the Mantel-Haenszel method.

To evaluate the effects of baseline characteristics on VTE-free survival, we used univariate and sex- and age-adjusted Cox proportional hazards models. A multivariate model was developed that considered known VTE risk factors (ie, age, malignancies, BMI, and use of oral contraceptives) as well as cardiovascular risk factors that yielded a P <.15 from the univariate model. Results were expressed as hazard ratios (HRs) with 95% CIs and P values.

Continuous variables are presented as mean (SD) or as medians with the interquartile range (IQR) for skewed data. Categorical data are presented as counts and frequencies. For continuous data, differences were evaluated by Kruskal-Wallis test or 1-way analysis of variance, depending on the normality of the data. Categorical variables were compared with χ² test of association. Statistical significance was considered as a 2-tailed P <.05. All statistical analyses were performed using STATA software version 10.0 (StataCorp LP, College Station, Texas).

RESULTS

Study Population

Individuals who responded (40 856) were more often women (54.4% vs 45.4%) and older (mean age 51.9 vs 46.4 years) than those who did not (Figure 1). The randomly selected group of 2592 participants with urinary albumin concentration of less than 10 mg/L was representative of the 30 890 eligible responding individuals with urinary albumin concentration of less than 10 mg/L, as previously reported.

The table represents baseline clinical characteristics of the analyzed study cohort of 8574 participants stratified into subgroups of UAE. Of the overall cohort, 70% (6013), 15% (1283), 13% (1144), and 1.6% (134) of participants had UAE of less than 15, 15-29, 30-300, and greater than 300 mg per 24 hour urine collection, respectively. The prevalence of male sex, hypertension, hyperlipidemia, current smoking status, diabetes, metabolic syndrome, history of myocardial infarction, stroke, malignancy, and use of oral contraceptives were all higher in participants with increased levels of UAE (P < .05). Similarly, age, BMI, total cholesterol, low-density lipoprotein cho-
Urinary Albumin Excretion and Venous Thromboembolism

Overall, 129 participants developed at least 1 VTE during a mean (SD) observation period of 8.6 (1.8) years, corresponding to survey design–adjusted annual incidence of 0.14% (95% CI, 0.11%-0.19%), ranging from 0.12% (95% CI, 0.09%-0.17%) in participants with UAE of less than 15 mg/24 h to 0.56% (95% CI, 0.26%-1.47%) in participants with UAE of greater than 300 mg/24 h (Table 2). These annual incidences were 0.40% (95% CI, 0.26%-0.65%) in microalbuminuric vs 0.12% (0.10%-0.17%) in normoalbuminuric participants (UAE <30 mg/24 hour urine collection). The drop-out rate due to study withdrawal and migration out of the city was 16% (1388) and was comparable between subgroups of UAE (P = .17). For these individuals, the available mean (SD) observation period was 6.5 (1.8) years.

The most commonly encountered first VTE was deep vein thrombosis (73, 57%), followed by pulmonary embolism (44, 34%), and combined deep vein thrombosis and pulmonary embolism (12, 9%). Types of VTE (pulmonary embolism vs deep vein thrombosis) did not differ among subgroups of UAE (P = .23). Of pulmonary embolism cases, 4 out of 56 (7%) were fatal. Of participants with VTE during follow-up, 24 (19%) had prior VTE and that rate was similar among different subgroups of UAE (P = .47). At onset of VTE, 63 participants (49%) were exposed to an acquired risk factor for VTE: 20 (32%) had a malignancy, 14 (22%) had surgery or trauma, 8 (13%) had a combined malignancy and surgery, 8 (13%) used oral contraceptives, 4 (6%) were immobilized, and 9 (14%) had other acquired risk factors.

Figure 3 shows the association of various variables at baseline with the unadjusted and sex- and age-adjusted risk of VTE. In the univariate analyses, multiple variables were associated with VTE. After adjustment for sex and age, only UAE, BMI, premenopausal use of oral contraceptives, and plasminogen activator inhibitor type-1 levels were significantly related to VTE. The multivariate Cox model included the following variables: UAE, established risk factors, and was comparable between subgroups of UAE (P = .17).

### Table. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall</th>
<th>&lt;15</th>
<th>15-29</th>
<th>30-300</th>
<th>&gt;300</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, No.</td>
<td>8574</td>
<td>6013</td>
<td>1283</td>
<td>1144</td>
<td>134</td>
<td>.001</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>4282 (50)</td>
<td>2737 (46)</td>
<td>727 (56)</td>
<td>732 (64)</td>
<td>89 (66)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>49 (13)</td>
<td>47 (12)</td>
<td>52 (13)</td>
<td>56 (12)</td>
<td>58 (13)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>26.1 (4.2)</td>
<td>25.6 (4.0)</td>
<td>26.8 (4.3)</td>
<td>27.8 (4.8)</td>
<td>28.9 (4.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Medical history, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2916 (34)</td>
<td>1481 (25)</td>
<td>607 (48)</td>
<td>725 (64)</td>
<td>103 (77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2316 (32)</td>
<td>1416 (28)</td>
<td>392 (35)</td>
<td>441 (43)</td>
<td>67 (58)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>375 (4.4)</td>
<td>140 (2.4)</td>
<td>87 (6.9)</td>
<td>122 (10.8)</td>
<td>26 (19.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>3243 (38)</td>
<td>2227 (37)</td>
<td>516 (40)</td>
<td>457 (40)</td>
<td>43 (33)</td>
<td>.04</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>1633 (21)</td>
<td>812 (15)</td>
<td>354 (30)</td>
<td>408 (39)</td>
<td>59 (48)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>270 (3.2)</td>
<td>100 (1.7)</td>
<td>61 (8.6)</td>
<td>93 (8.1)</td>
<td>16 (11.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>80 (1.0)</td>
<td>39 (0.7)</td>
<td>13 (1.0)</td>
<td>24 (2.2)</td>
<td>4 (3.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Malignancy</td>
<td>134 (1.6)</td>
<td>79 (1.3)</td>
<td>28 (2.2)</td>
<td>24 (2.1)</td>
<td>3 (2.3)</td>
<td>.048</td>
</tr>
<tr>
<td>Use of oral contraceptives, No. (%)</td>
<td>889 (34)</td>
<td>695 (33)</td>
<td>104 (35)</td>
<td>84 (46)</td>
<td>6 (38)</td>
<td>.003</td>
</tr>
<tr>
<td>Laboratory measurements, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>81 (15)</td>
<td>82 (14)</td>
<td>82 (16)</td>
<td>77 (16)</td>
<td>68 (20)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>218 (44)</td>
<td>215 (43)</td>
<td>222 (42)</td>
<td>227 (44)</td>
<td>237 (50)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>51 (15)</td>
<td>55 (15)</td>
<td>48 (15)</td>
<td>47 (15)</td>
<td>44 (12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>142 (41)</td>
<td>140 (41)</td>
<td>146 (38)</td>
<td>150 (41)</td>
<td>156 (43)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Laboratory measurements, median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>103 (75-149)</td>
<td>97 (72-139)</td>
<td>112 (79-167)</td>
<td>126 (88-190)</td>
<td>134 (96-199)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>1.28 (0.56-2.98)</td>
<td>1.08 (0.48-5.20)</td>
<td>1.48 (0.67-3.30)</td>
<td>2.23 (1.03-4.66)</td>
<td>2.64 (1.27-5.50)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>tPA, µg/L</td>
<td>3.13 (2.31-4.65)</td>
<td>3.03 (2.26-4.49)</td>
<td>3.29 (2.39-4.82)</td>
<td>3.51 (2.52-5.42)</td>
<td>4.02 (2.86-6.32)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PAI-1, µg/L</td>
<td>72.2 (41.6-124.3)</td>
<td>66.4 (38.3-113.6)</td>
<td>85.9 (48.0-149.0)</td>
<td>92.8 (53.8-155.5)</td>
<td>96.6 (57.7-169.4)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate by the MDRD formula; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; PAI-1, plasminogen activator inhibitor-1; tPA, tissue plasminogen activator.

*Conversion factors: To convert values for cholesterol, HDL, or LDL to mmol/L, multiply by 0.0259; to convert values for triglycerides to mmol/L, multiply by 0.0113; to convert CRP to mg/L, multiply by 9.52; to convert PAI-1 to µg/L, multiply by 19.231.

*P* values are based on χ² test for categorical data and on Kruskal-Wallis test or 1-way analysis of variance for continuous data, depending on the normality of the data.®BMI is calculated as weight in kilograms divided by height in meters squared.

*The percentages are the proportion of premenopausal women using oral contraceptives in the given groups of urinary albumin excretion.*

©2009 American Medical Association. All rights reserved.
ALBUMINURIA AND VENOUS THROMBOEMBOLISM

Figure 2. Adjusted Annual Incidences of Venous Thromboembolism in Relation to Urinary Albumin Excretion by Clinical Class

The annual incidences are adjusted for the enrichment of the cohort with participants with higher urinary albumin excretion using the survey probability weights.

VTE risk factors (ie, age, malignancies, BMI, and use of oral contraceptives), hypertension, current smoking, history of myocardial infarction, eGFR, C-reactive protein, and plasminogen activator inhibitor-1. In this model, UAE of 15-29, 30-300 and greater than 300 mg per 24-hour urine collection had HRs of 1.40 (95% CI, 0.86-2.35; \( P = .14 \)), 2.20 (95% CI, 1.44-3.36; \( P < .001 \)) and 2.82 (95% CI, 1.21-6.61; \( P = .02 \)), respectively, as compared with participants with UAE of less than 15 mg per 24 hour urine collection (global \( P = .001 \)). When UAE was entered as a dichotomous variable, that is, microalbuminuria vs normoalbuminuria (<30 mg/24 hour urine collection) in the multivariate Cox model, microalbuminuria conferred an HR of 2.00 (95% CI, 1.34-2.98; \( P < .001 \)). This adjusted HR conferred by microalbuminuria was 1.93 (95% CI, 1.24-3.03; \( P = .004 \)) if participants with prior VTE were excluded from the analysis. Of the mentioned variables in the multivariate model, age and eGFR were entered as continuous variables. Since metabolic syndrome is a cluster of other cardiovascular risk factors\(^{31} \) and tissue plasminogen activator complexes with plasminogen activator inhibitor type-1, these 2 variables were not included in the multivariate model so as to minimize collinearity.

During 8 years of follow-up, 3% of microalbuminuric participants and 1% of normoalbuminuric participants developed VTE (Figure 4). As compared with participants with normoalbuminuria, the microalbuminuria-related number needed to harm was 388 per year.

When we confined our analysis to participants with unprovoked VTE, UAE of 15-29, 30-300 and >300 mg per 24-hour urine collection conferred HRs (adjusted for age, malignancies, BMI, and use of oral contraceptives) of 1.07 (95% CI, 0.48-2.35), 3.03 (1.71-5.38), and 4.97 (1.87-13.18), respectively, as compared with participants with UAE of less than 15 mg per 24-hour urine collection (global \( P < .001 \)). Hazard ratios were 1.74 (95% CI, 0.94-3.24), 1.50 (0.77-2.92), and 0.98 (0.13-7.22), respectively, for provoked VTE (global \( P = .31 \)).

When UAE measured in 24-hour urine collection was substituted by urinary albumin concentration measured in a spot urine sample, the adjusted HR for microalbuminuria (ie, urinary albumin concentration 20-200 mg/L) was the same, that is, 1.95 (95% CI, 1.34-2.83; \( P < .001 \)) as compared with normoalbuminuria (ie, urinary albumin concentration <20 mg/L). When the multivariate Cox model was also adjusted for the enrichment of the study cohort with participants with higher UAE, using survey probability weights,\(^{37} \) the corresponding HR for microalbuminuria measured in 24-hour urine collection was 2.33 (95% CI, 1.34-4.05; \( P = .003 \)), as compared with normoalbuminuria.

As previously reported for UAE and arterial thromboembolism,\(^{11,28} \) we found a gradual relationship between UAE and VTE in the normal range of UAE (<30 mg/24 h): adjusted HRs of UAE 10-19 and 20-29 mg per 24-hour urine collection were 1.31 (95% CI, 0.81-2.11) and 1.86 (95% CI, 1.00-3.43), as compared with UAE of less than 10 mg per 24-hour urine collection. Finally, there was no interaction between UAE and eGFR (\( P = .67 \)).

**COMMENT**

This study explored the relationship between microalbuminuria and VTE. A clear gradual relationship was found between levels of UAE and the incidence of VTE, even in the normal range of UAE. Besides UAE, multiple classic atherosclerosis risk factors were related to VTE in univariate analyses. However, after adjustment for sex and age, only UAE, BMI, premenopausal use of oral contraceptives, and plasminogen activator inhibitor type-1 levels were related to VTE. In a multivariate model, UAE remained an independent predictor of VTE. About half of the VTE cases were unprovoked. Moreover, higher levels of UAE were particularly associated with unprovoked VTE.

Several studies addressed the link between atherosclerosis risk factors and VTE.\(^{8,29-33} \) Our results on atherosclerosis risk factors are consistent with a comparable community-based prospective cohort study\(^{33} \) in which only BMI and diabetes were related to VTE; after adjustment for age, sex, and race.
In our study, diabetes was not related to VTE; however, our results could not be generalized to all diabetics since individuals with insulin-dependent diabetes were excluded. In a recent meta-analysis, obesity, hypertension, diabetes, and higher triglyceride levels were positively associated with VTE, whereas higher high-density cholesterol levels were inversely related to VTE, and smoking and total cholesterol were not significantly related to increased risk of VTE. However, there was a significant heterogeneity among studies evaluated in this meta-analysis. Moreover, most of the analyzed studies were not primarily conducted to assess the link between atherosclerosis risk factors and VTE, some were limited to only 1 sex, and the results from cohort studies were not adjusted for age. In our study, metabolic syndrome, a cluster of cardiovascular risk factors, was not related to elevated risk of VTE after sex and age adjustment. In several studies, meta-

©2009 American Medical Association. All rights reserved.

(Reprinted) JAMA, May 6, 2009—Vol 301, No. 17 1795
bolic syndrome was associated with an approximately 2-fold increased risk of VTE.35 However, this link might be due to the association between individual features of the metabolic syndrome and VTE.35

The value of microalbuminuria as an independent predictor of arterial thromboembolism has been demonstrated in individuals with diabetes as well as in those without.10,11,16,17 In our previous publication,10 microalbuminuria was related to an adjusted relative risk of 1.29 (95% CI, 1.04-1.60) and 1.38 (1.10-2.26) for MI and stroke, respectively, as compared with participants with normoalbuminuria. In the HOPE study,11 adjusted HRs for MI, stroke, or cerebrovascular death were 1.75 (95% CI, 1.49-2.05) and 1.42 (1.18-1.71) in the placebo and intervention group, respectively. In comparison, in the current analysis microalbuminuria conferred an adjusted HR of 2.00 (95% CI, 1.34-2.98) for VTE, as compared with normoalbuminuria. Moreover, nephrotic-range proteinuria is a well-known risk factor for VTE and predisposes at least as often to VTE as arterial thromboembolism.38 The high risk of VTE in individuals with nephrotic-range proteinuria is assumed to be secondary to loss of anticoagulant proteins. In individuals with microalbuminuria, this is unlikely to be a direct cause; more likely, the increased risk of VTE is secondary to endothelial injury and/or the related changes in the levels of procoagulant proteins.9,12-19

The fact that microalbuminuria has a high prevalence in the general population (7.2%) suggests that on the population level, microalbuminuria may be an important risk factor for VTE.39 Moreover, in contrast to most of the established VTE risk factors, microalbuminuria could be treated by nonanticoagulant medication (eg, renin-angiotensin system inhibitors). Future studies are needed to evaluate the effect of these drugs on the risk of VTE.

Our study has some potential limitations that should be addressed. The incidence of VTE in our cohort may be underestimated as VTE cases were retrospectively identified. However, as compared with other prospective studies, the annual incidence of 0.14% is rather elevated given the very high incidence of VTE in individuals older than 75 years, whereas our cohort was confined to individuals aged 28 to 75 years. Furthermore, VTE was not adjudicated by an independent committee. Nevertheless, since only symptomatic and objectively verified events were considered, misclassification seems unlikely. Enrichment with participants with higher UAE is unlikely to have influenced our risk estimates (ie, HRs), as these estimates did not significantly change after accounting for the study design. Since we used predefined cut-off values for UAE, spectrum bias is unlikely despite the differences in sex and age between individuals who responded and those who did not. Due to lack of sufficient statistical power, as only 134 participants were known with malignant disease, malignancy was not associated with VTE after age and sex adjustment. Data on the use of oral contraceptives could not be generalized as participants younger than 28 years were not enrolled.

Despite these limitations, this is the first study assessing a link between microalbuminuria and VTE. Moreover, the PREVEND cohort is unique in its large population-based prospective setting in which UAE is assessed in two 24-hour urine samples, which is considered the criterion standard for measuring UAE. Although criterion standard is desirable for the proof of concept, in the clinical setting microalbuminuria is generally assessed in a spot urine sample. When we used the microalbuminuria definition for a spot urine sample (ie, urinary albumin concentration of 20-200 mg/L), results were the same.

In conclusion, microalbuminuria is an independent risk factor for VTE. The relative risk of VTE associated with microalbuminuria is comparable to previously reported risk of MI or stroke in individuals with microalbuminuria.

**Author Contributions:** Mr Mahmoodi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Mahmoodi, Gansevoort, van der Meer.

**Acquisition of data:** Mahmoodi, Veeger.

**Analysis and interpretation of data:** Mahmoodi, Gansevoort, Veeger, Matthews, Navis, Hillege, van der Meer.

**Statistical analysis:** Mahmoodi, Matthews.

**Study supervision:** van der Meer.

**Financial Disclosures:** None reported.

**Funding/Support:** The PREVEND Study has been made possible by grants from the Dutch Kidney Foundation.

**Role of the Sponsor:** The Dutch Kidney Foundation was not involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

**Additional Contributions:** We thank Frits R. Rosendaal, MD, PhD, Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands; and Martin H. Prins, MD, PhD, Department of Clinical Epidemiology and Medical Technology Assessment, Academic Hospital, Maastricht, the Netherlands, for clinical and statistical advice. Neither individual received compensation for the contributions.

Dr van der Meer recently died following a sudden illness. We thank Hanneke C. Kluij-Nelmans, MD, PhD, Department of Hematology, University Medical Center Groningen, Groningen, the Netherlands, for providing help to guide the paper during revision after Dr van der Meer’s death.

### REFERENCES


10. Hillege HL, Jansen WM, Bak AA, et al. PREVEND Study Group. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and


©2009 American Medical Association. All rights reserved.