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Atrial fibrillation and venous thromboembolism: evidence of bidirectionality in the Atherosclerosis Risk in Communities Study

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Summary

Background—Atrial fibrillation (AF) and venous thromboembolism (VTE) frequently co-occur. These conditions have shared risk factors and are accompanied by coagulation abnormalities. Furthermore, mechanistic pathways may directly link the disorders.

Objectives—To test the hypothesis that individuals with incident AF are at greater risk of developing VTE, and those with VTE are at elevated risk of AF. We also tested whether associations were stronger in the first 6 months after the initial diagnosis, and explored race differences.

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Addendum
P. L. Lutsey, A. Alonso, and A. R. Folsom were responsible for the concept and design.
P. L. Lutsey, F. L. Norby, A. Alonso, M. Cushman, L. Y. Chen, E. D. Michos, and A. R. Folsom were responsible for acquisition, analysis, or interpretation of data.
P. L. Lutsey drafted the manuscript.
P. L. Lutsey, F. L. Norby, A. Alonso, M. Cushman, L. Y. Chen, E. D. Michos, and A. R. Folsom critically revised the manuscript for important intellectual content.
F. L. Norby performed the statistical analysis.
A. R. Folsom obtained funding.

Disclosure of Conflict of Interests
E. D. Michos reports an honorarium from Siemens Diagnostics, unrelated to the submitted work. The other authors state that they have no conflict of interest.
Patients/Methods—15,129 ARIC study participants (45-64 years, 55% female, 26% black) were followed from 1987-2011 for incident AF and VTE (median follow-up 19.8 years). Multivariable-adjusted Cox regression was used, with AF and VTE modeled as time-dependent exposures.

Results—Incident AF was associated with greater risk of subsequent incident VTE [HR (95%CI): 1.71 (1.32-2.22)]; the association was stronger in blacks [2.30 (1.48-3.58)] and during the first 6 months after AF diagnosis [5.08 (3.08-8.38)]. Similarly, incident VTE was associated with increased risk of incident AF [1.73 (1.34-2.24)], especially in blacks [2.40 (1.55-3.74)] and in the first 6 months after VTE diagnosis [4.50 (2.61-7.77)].

Conclusions—The occurrence of AF was associated with increased risk of incident VTE, and occurrence of VTE was associated with greater risk of incident AF. Associations were particularly strong among blacks, and during the first 6 months after the initial diagnosis, though they remained elevated even after 6 months. These findings highlight patient populations that may be at increased risk of AF and VTE, and perhaps should be targeted with preventive strategies.

Keywords
atrial fibrillation; epidemiology; venous thromboembolism; racial disparities; Atherosclerosis Risk in Communities (ARIC) Study

Introduction
Atrial fibrillation (AF) and venous thromboembolism (VTE) are common conditions, particularly among the elderly [1]. The lifetime risk for AF is 1 in 4 [2], while the lifetime risk for VTE is 1 in 8 [3]. Both AF and VTE have substantial morbidity and mortality [1], thus necessitating further investigation of predisposing factors. As recently reviewed [4], AF and VTE frequently co-exist, and it has been suggested that each disorder is a risk factor for the other. This hypothesis warrants further study.

Conventionally, deep vein thrombosis (DVT) and pulmonary embolism (PE) are viewed as different clinical manifestations of the same disease. Thrombi typically originate in the deep veins (usually of the legs) and can embolize to the pulmonary arteries, transiting through the right heart. However, about one-half of patients with PE have no evidence of DVT by compression ultrasonography [5-7] or magnetic resonance imaging [8], suggesting that some PE events may arise in situ or from sites other than the deep veins of the legs. It is well-established that AF can promote thrombus formation in the left atrium, which can lead to ischemic stroke [1] and possibly myocardial infarction [9]. Case reports have shown that thrombus formation can occur in the right atrium of AF patients [4], but less is known about how frequently this occurs and whether it leads to PE. VTE risk may be particularly elevated in the time-period shortly after AF diagnosis as it may take time for patients to return to sinus rhythm and for anticoagulant control to stabilize.

PE can also lead to AF through increasing pulmonary vascular resistance and right ventricular afterload by obstructing the pulmonary arteries, and via the release of vasoconstrictive mediators and inflammatory cytokines [4, 10, 11]. Resultant increased right atrial pressure and strain may trigger AF. Patients presenting with massive or submassive PE
have elevated right ventricular systolic pressure [12]. While it is established that PE can cause AF acutely and risk of AF may be highest shortly after diagnosis with PE, there is evidence to support the notion that adverse effects of PE on cardiac function may be long-term [13].

In sum, a bidirectional relationship may be present between AF and VTE. Yet, the associations may not be causal in many cases, but rather due to the coincidence of two chronic conditions in patients with poor health. PE and AF have several shared risk factors, such as older age, obesity, heart failure and inflammatory states [4], and both conditions are associated with a procoagulant state [14, 15]. Using longitudinal data from the Atherosclerosis Risk in Communities (ARIC) study, we tested the hypotheses that a) individuals with incident AF are at elevated risk of developing VTE, and particularly for VTE presenting as PE without DVT, and b) individuals with incident VTE are at greater risk of developing AF, especially when the VTE presents with PE (regardless of DVT status). For both hypotheses we speculated that associations would be stronger in the first 6 months after an AF or VTE diagnosis, respectively. If a bidirectional relationship does exist between AF and VTE, findings from this research may help to identify patients who should be targeted for preventive strategies, given their elevated risk.

Methods

The ARIC study is a longitudinal cohort which began in 1987-1989 when 15,792 individuals, aged 45-64 years and predominantly black or white, were recruited from 4 U.S. communities: suburbs of Minneapolis, Minnesota; Forsyth County, North Carolina; Jackson, Mississippi; Washington County, Maryland [16]. Participants have been followed continuously for hospitalizations and deaths, and have taken part in numerous follow-up clinical visits. Relevant to this analysis, visit 2 took place in 1990-1992, visit 3 in 1993-1995, and visit 4 in 1996-1998. For the present analysis follow-up ended December 31, 2011, since this is the last date for which validated VTE events are available. The ARIC study protocol has had continuous approval from local institutional review boards, and all participants gave written informed consent.

For the present analysis we excluded individuals who were not black or white and blacks from the Minnesota and Maryland centers due to small numbers (n = 103), as well as those who at baseline had a missing or unreadable electrocardiogram (n = 242), prevalent AF by ARIC administered electrocardiograms (n = 37), prevalent VTE (n = 76), or were missing key covariates (n = 205). For both hypotheses, the final analytic sample size was 15,129.

Incident AF and VTE ascertainment

Participants were followed for hospitalizations and deaths through 1) annual telephone calls to participants or proxies (>90% participation), 2) active surveillance of local hospital discharge indexes, 3) searches of state death records and 4) linkage to the National Death Index. Trained abstractors collect information from all hospitalizations, including International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for discharge diagnoses and procedures associated with each hospitalization.
Potential VTE cases were identified from hospital records with ICD-9-CM codes indicating possible VTE (415.1×, 451, 451.1×, 451.2, 451.8×, 451.9, 453.0, 453.1, 453.2, 453.8, 453.9, 996.7×, 997.2, and 999.2, and procedure code 38.7). Records of potential cases were then extracted, and independently reviewed by two physicians (ARF and MC) [17]. DVT was defined on the basis of duplex ultrasound or venogram or, in rare cases, by impedance plethysmography, computed tomography, or autopsy. Definite PE required ventilation/perfusion scanning showing multiple segmental or subsegmental mismatched perfusion defects, or a positive pulmonary angiogram, computed tomography, or autopsy [17]. Incident VTE was defined as the first occurrence of validated DVT or PE from baseline through the end of follow-up.

Incident AF was identified through electrocardiograms performed at study visits, and through diagnostic codes from hospitalization discharge summaries [18]. At each visit a standard supine 12-lead resting electrocardiogram was recorded after a 12-hour fast, and at least one hour after smoking tobacco or ingestion of caffeine. All electrocardiogram recordings were done with MAC PC Personal Cardiographs (Marquette Electronics, Inc., Milwaukee, WI), and were transmitted by telephone to the ARIC Central Electrocardiogram Reading Center for coding, interpretation and storage. Electrocardiogram recordings automatically coded as AF were visually re-checked by a trained cardiologist to confirm the diagnosis [19]. AF was also considered present if the ICD-9-CM codes 427.31 or 427.32 were listed in any hospitalization. AF events associated with open cardiac surgery were not included. In a validation study conducted within ARIC, the positive predictive value of this case definition was very good at ≈90% and the sensitivity was >80% [18]. The AF incidence date was defined as the earliest date in which an AF diagnosis was made during follow-up.

**Other variables of interest**

The ARIC study protocol was similar (typically identical) across study visits. Participants self-reported age, sex, race, cigarette smoking status, physical activity (modified Baecke questionnaire) [20] and prevalent coronary heart disease (CHD) and heart failure. As has been done previously in ARIC, [21] prevalent HF at baseline was defined as the following: 1) an affirmative response to “Were any of the medications you took during the last 2 weeks for heart failure?” or 2) stage 3 or “manifest heart failure” by Gothenburg criteria. Prevalent coronary heart disease (CHD) was defined by self-reported previous physician diagnosis of MI or coronary revascularization, or prevalent MI by 12-lead electrocardiogram.

Trained staff measured height, waist circumference, and blood pressure using standardized protocols. Fasting (12-hour) blood samples were drawn, and plasma and serum were frozen at −70°C until analyzed, as previously described in detail [16]. Participants were also asked to bring their current medications to the clinic visits; medication names and dosages were recorded. Prevalent diabetes was defined as fasting glucose ≥26 mg/dL, nonfasting glucose ≥200 mg/dL, self-reported physician diagnosis of diabetes, or being on diabetes medication. Estimated glomerular filtration rate (eGFR) was calculated using the 2012 CKD EPI equation, which incorporates both cystatin C and creatinine [22].

During annual follow-up phone calls participants reported information about all medications currently being taken (including oral anticoagulants). At the time the study was conducted,
warfarin was the only anticoagulant with widespread usage in the United States. Other antithrombotic drugs like aspirin and clopidogrel were not considered anticoagulants in the present analysis. Incident stroke was identified in a manner similar to incident AF and VTE; records of all possible strokes were adjudicated.

**Statistical analysis**

Characteristics of the final analytic sample at visit 1 are reported, for the overall sample and according to whether the participant developed incident AF or VTE during follow-up.

To test hypothesis #1, which evaluated whether individuals with incident AF were at elevated risk of developing VTE, Cox proportional hazards regression was used, with person-time accruing from the visit 1 date until the date of the incident VTE event, death, loss-to-follow-up, or December 31, 2011 (end of study). Incident AF status was included in the models as a time-dependent exposure; participants contributed person-time to the “no AF” category until the time of incident AF, when they began contributing person-time toward the “AF” category.

Nested models were used; in general, covariate information came from the clinic visit preceding development of AF. Model 1 adjusted for age, sex and race-site (5-level variable). Model 2 further adjusted for income, education, physical activity, smoking, waist circumference, height, systolic blood pressure, anti-hypertensive medication, diabetes, prevalent CHD, prevalent heart failure, eGFR and anticoagulant use. Model 3 additionally adjusted for anticoagulant use as time-varying covariate using information from annual follow-up phone calls. In addition to VTE overall as the outcome, we also analyzed separately PE events without DVT, and events that included evidence of DVT (participants were censored at first VTE event). Further, we conducted analyses modeling incident AF status as a 3-level time-dependent exposure (i.e. no AF, <6 months since AF diagnosis, ≥6 months since AF diagnosis). Using this modeling, it is possible for a person with AF to contribute person-time to all 3 categories. Kaplan-Meier curves were also constructed to examine the cumulative incidence of VTE longitudinally by AF status.

Analyses for hypothesis #2, which tested whether individuals with incident VTE are at elevated risk of developing AF, followed a similar pattern to the hypothesis #1 analyses. Differences were that a) person-time accrued from baseline until the date of the incident AF event, death, loss-to-follow-up, or December 31, 2011 (end of study), b) covariate information came from the clinic visit preceding development of VTE, c) incident VTE status was included as a time-dependent exposure, and d) in secondary analyses we evaluated as exposures events with evidence of PE, and those that only presented with DVT.

For both hypotheses, in the 48 instances when VTE and AF occurred during the same hospitalization, we censored the participant at this time so that neither the VTE nor the AF event was counted in the analysis. Interactions by age, race and sex were evaluated by including cross-product terms in the models. In sensitivity analyses we also censored upon cancer diagnosis and additionally adjusted for number of hospitalizations as a time-varying covariate, and additionally adjusted for incident stroke.
Results
At baseline, the 15,129 individuals in our analytic sample were 55.0% female, 25.8% black and on average (± SD) 54.2 ± 5.8 years old. Descriptive characteristics of the participants at baseline, overall and stratified according to whether they developed AF or VTE during follow-up, are presented in Table 1. The overall study sample was followed for a mean of 19.8 ± 6.0 years (median 22.5 years) with a maximum follow-up of 25.1 years. The number of incident AF and VTE events by calendar year are presented in Supplemental Figure 1.

Association of AF with incident VTE
A total of 2,048 participants developed AF (prior to or without VTE) during follow-up. The average age at the time of developing AF was 74.1 ± 7.7 years old. After developing AF, these individuals contributed 10,759 years of person-time to the analysis. After an AF diagnosis there were 68 VTE events, yielding a VTE incidence rate of 6.3 per 1000 person-years. By contrast, in the absence of AF there were 613 VTE events, for a VTE incidence rate of 2.4 per 1000 person-years. In multivariable-adjusted models, having AF (versus no AF) was associated with greater risk of incident VTE; the HR (95% CI) was 2.02 (1.56-2.61) after adjustment for demographics (model 1), 1.71 (1.32-2.22) accounting for risk factors (model 2), and 1.88 (1.44-2.45) after further adjusting for anticoagulant use information from annual follow-up phone calls (model 3). In a sensitivity analysis additionally adjusting for stroke as a time-dependent covariate, the HR was 1.73 (1.32-2.25).

When subgroups were evaluated, the association was stronger in blacks [2.30 (1.48-3.58)] than in whites [1.56 (1.14-2.15)], p-interaction 0.02 (model 2 results shown). This interaction is depicted visually using Kaplan Meyer curves (Figure 1). There was no evidence of interaction by sex. In sensitivity analyses where we censored upon cancer diagnosis and additionally adjusted for number of hospitalizations the results were similar [HR: 1.98 (1.44-2.73)].

Of the 68 VTE events that occurred after AF, 17 were classified as PE only, and 51 had evidence of DVT (with or without PE). Hazard ratios (model 2 adjustments) associated with having AF (versus no AF) were 1.41 (0.85-2.36) for events presenting as PE without evidence of DVT, and 1.86 (1.37-2.51) for VTE events with evidence of DVT. Results when the outcomes were DVT only and DVT plus PE are shown in Supplemental Table 1.

When AF status was modeled as a time-dependent 3-level exposure (Table 3), the HR (model 2) for incident VTE during the 1st 6 months after an AF diagnosis was 5.08 (3.08-8.38), whereas for ≥6 months since the AF diagnosis the HR was 1.42 (1.06-1.90), as compared to in the absence of AF. The HR’s were similar with additional adjustment for time-dependent anticoagulation (model 3).

Association of VTE with incident AF
A total of 613 individuals developed incident VTE prior to or without AF. The average age at VTE was 69.9 ± 7.9 years old, and after their VTE event they contributed 2,990 person-years to the analysis and experienced 62 AF events, with an incidence rate of 20.7 per 1,000
person-years (Table 4). In those without incident VTE there were 2,048 AF events, for an incidence rate of 7.3 per 1,000 person years. Incident VTE was associated with elevated risk of AF after adjusting for demographics [model 1: 1.94 (1.50-2.50)] and cardiovascular risk factors [model 2: 1.73 (1.34-2.24)]. However, the association was attenuated with additional adjustment for time-dependent anticoagulant use [model 3: 1.20 (0.91-1.57)]. In a sensitivity analysis additionally adjusting for stroke as a time-dependent covariate, the HR was 1.16 (0.89-1.53).

When subgroups were evaluated, the association of incident VTE with AF was stronger in blacks [2.40 (1.55-3.74)] than whites [1.46 (1.07-2.01)] (p interaction = 0.04); see also Figure 2. There was no interaction by sex. In sensitivity analyses where we censored upon cancer diagnosis and additionally adjusted for number of hospitalizations the HR was 2.14 (1.57-2.91).

After model 2 adjustments, the HR (95% CI) for incident AF associated with any PE (versus no VTE) was 1.29 (0.83-2.01), whereas when the exposure was events presenting as DVT only the HR for incident AF was 2.05 (1.50-2.78). Supplemental Table 2 presents results when the exposures were PE without DVT, and VTE presenting as both PE and DVT.

When VTE was modeled as a 3-level exposure (Table 5), with absence of AF as the reference group, within the first 6 months after incident VTE the HR for incident AF was 4.50 (2.61-7.77), whereas beyond 6 months after an incident VTE event the HR was 1.49 (1.12-1.98) (model 2 adjustments).

**Discussion**

In this community-based longitudinal study of over 15,000 older adults, there was evidence of a bidirectional association between incident AF and incident VTE. Incident AF was associated with a 2-fold increased risk of future VTE. Similarly, occurrence of VTE was associated with an almost 2-fold higher risk of subsequent AF. These associations were only modestly attenuated after accounting for additional cardiovascular risk factors. Emphasizing the strength of the association of these two diseases, risk of developing the subsequent condition was approximately 5-fold higher in the first 6 months after diagnosis with the first condition. Furthermore, there were important differences by race; as compared to whites, blacks were at greater risk of incident VTE subsequent to AF, and of incident AF subsequent to VTE.

Our finding that incident AF is associated with greater risk of incident VTE, and that this association is particularly pronounced in the first 6 months after AF diagnosis, is consistent with findings recently reported by the Tromsø study [23]. AF has also been linked to prior VTE via several other lines of evidence [4], including a longitudinal analysis of the Longitudinal Health Insurance Database 2000 [24], two case-control studies [25, 26], registry studies of PE patients [4], small clinical studies [10, 11], and autopsy studies [27]. In the present paper we conducted analyses by VTE classification (i.e. PE without VTE, DVT (with or without PE)) in order to provide information about whether AF may be an independent risk factor for PE through the pathway of right atrial thrombi formation. If, in
fact, AF leads to VTE through right atrial thrombus formation and subsequent PE, the
association between AF and risk of PE without evidence of DVT should be stronger than
associations between AF and risk of events including DVT. In our analyses, the risk of PE
without DVT was not especially elevated. In contrast, in the Tromsø study the magnitude of
the association for incident PE after AF was stronger than for incident DVT after AF [23].
However, their confidence intervals were wide and overlapping, it is not clear how they
analyzed cases presenting with both DVT and PE, and it is unclear the extent to which
patients presenting with PE also received leg imaging. The latter is also a limitation of the
present ARIC analyses. It is possible AF risk may be elevated in the context of DVT due to
either a procoagulant state or shared risk factors.

VTE was likewise associated with approximately 2-fold higher incidence of AF in the
present analysis. Similar findings were reported in the Tromsø study [28], and in a
longitudinal registry based analysis of hospital admissions data [29]. Numerous registries of
PE patients and small clinical studies, dating back to 1943, have reported AF becoming
apparent shortly after the development of PE [4]. Since the proposed mechanism linking
VTE to greater AF risk acts through elevated right ventricular systolic pressure in the
context of PE, we also evaluated as exposures incident PE and incident DVT, separately.
Contrary to our hypothesis, the association with AF was not stronger when the exposure was
incident PE. Also in our analysis, risk of AF following PE was attenuated when we adjusted
for anticoagulant therapy as a time-varying covariate. Novel research in animal models has
suggested that inhibition of coagulation can prevent the development of atrial fibrosis [30],
and therefore AF. Accordingly, anticoagulation prescribed for PE may also lower risk of
developing AF.

Race differences were present in the risk of VTE subsequent to AF, and of AF subsequent to
VTE, with associations being stronger in blacks than whites. While biological racial
differences may underlie these observations, we speculate that these findings are due to
racial disparities in access to care, likelihood of seeking treatment for more mild disease,
treatment intensity and anticoagulation control [31-33]. Using ARIC study data, it has been
previously reported that, relative to white individuals with AF, black individuals with AF are
at greater risk of stroke, heart failure, coronary heart disease and mortality [34]. The ARIC
findings presented both herein and previously underscore the need to improve management
of chronic health conditions among black patients in order to mitigate health disparities.
Notably, blacks have a lower overall incidence of AF relative to whites [18], but a higher
incidence of VTE [3].

The bidirectional association between the occurrence AF and VTE, particularly in the first 6
months after diagnosis, highlights population groups that may be at particularly elevated risk
for developing the other condition subsequently. According to present guidelines not all AF
patients are recommended anticoagulation [35], and not all VTE patients receive
anticoagulation for secondary prevention [36]. For patients with co-occurring VTE and AF,
but for which neither condition when considered in isolation meets the criterion for requiring
anticoagulation, physicians should carefully weigh the advantages versus the bleeding risks
of oral anticoagulation [4].
This study has several strengths including the longitudinal design, well-enumerated population with excellent retention, careful event surveillance, assessment of potential confounders, and validation of VTE events. There are also limitations of our study. In regards to AF ascertainment, AF events were not validated. Also, asymptomatic [37] AF and AF managed exclusively in an outpatient facility could not be identified, because the large majority of our incident AF cases were ascertained from the hospitalization discharge records. We have found, however, adequate validity of these codes for the identification of AF events.[18] Furthermore, it can be difficult to accurately identify the exact date of AF incidence. Misclassification was also almost certainly present in the categorizations of VTE subtypes, since not everyone with PE undergoes leg imaging, and lung imaging is not always conducted among individuals with DVT but no symptoms of PE. Furthermore, major changes in the diagnosis of AF and VTE have taken place over the course of this study, particularly with small PEs being more likely to be identified later in follow-up. However, the etiologic association should be constant over time, and misclassification in earlier years as a result of less sensitive diagnostic testing would likely bias our results toward the null. Additionally, information about use of oral anticoagulants was collected annually; ideally surveillance for oral anticoagulant use would have been continuous. Other limitations of the present analysis are a) the limited numbers of dual events, b) the inability to ascertain health care context, access, attention, and treatment, c) residual confounding from the multiple morbidities that may predispose to both AF and VTE, and c) for some analyses there were few events and therefore precision was low.

In conclusion, there appears to be a bidirectional association between VTE and AF, whereby individuals with AF are at approximately 2-fold greater risk of being diagnosed with incident VTE, and individuals with VTE are at about 2-fold higher risk of being diagnosed with AF. The risk of subsequent disease was particularly elevated in the initial 6 months after diagnosis with the first condition, and the associations were stronger for blacks than for whites. Clinicians should be cognizant that these conditions are frequently comorbid. Guidelines promoting oral anticoagulation to prevent ischemic stroke in AF patients [35] may have the added benefit of also providing protection against VTE, and anticoagulation to prevent VTE recurrence [36] may additionally protect against AF [4].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References


Essentials

- Atrial fibrillation (AF) may increase risk of venous thromboembolism (VTE), and vice versa.
- Bidirectionality was assessed prospectively via data from 15,129 black and white individuals.
- AF was associated with greater risk of developing VTE, and VTE with greater risk of AF.
- Associations were strongest among blacks and in the first 6 months after initial diagnosis.
Figure 1.
Kaplan-Meier curve* of incident VTE stratified by race (white or black) and AF status: The Atherosclerosis Risk in Communities Study, 1987-2011
*Participants contribute to the strata without AF until the incident AF event. Log-rank test p<0.0001.
Figure 2.
Kaplan-Meier curve* of incident AF stratified by race (white or black) and VTE status: The Atherosclerosis Risk in Communities Study, 1987-2011

*Participants contribute to the strata without VTE until the incident VTE event. Log-rank test p<0.0001.
## Table 1

Characteristics of participants overall, and by incident AF and incident VTE status, respectively: The Atherosclerosis Risk in Communities Study

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<th>All</th>
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<th>Incident VTE</th>
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</tr>
<tr>
<td>Use of oral anticoagulants, %</td>
<td>0.4</td>
<td>0.3</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Follow-Up Characteristics (1987-2011)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulant use, %</td>
<td>5.7</td>
<td>2.9</td>
<td>23.5</td>
</tr>
</tbody>
</table>

*Values correspond to mean ± SD or percentage.

AF, atrial fibrillation; VTE, venous thromboembolism; eGFR, estimated glomerular filtration rate; CHD, coronary heart disease.
**Table 2**

Hazard ratios (95% CIs) of incident VTE after AF, for overall VTE and by VTE type: The Atherosclerosis Risk in Communities Study, 1987-2011

<table>
<thead>
<tr>
<th></th>
<th>No AF (n=13,081)</th>
<th>AF (n=2048)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VTE (n = 681)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Events</td>
<td>613</td>
<td>68</td>
</tr>
<tr>
<td>Person-years</td>
<td>259,659</td>
<td>10,759</td>
</tr>
<tr>
<td>Incidence Rate (95% CI)†</td>
<td>2.4 (2.2-2.6)</td>
<td>6.3 (4.9-8.0)</td>
</tr>
<tr>
<td><strong>Hazard ratio (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1 (REF)</td>
<td>2.02 (1.56-2.61)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1 (REF)</td>
<td>1.71 (1.32-2.22)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1 (REF)</td>
<td>1.88 (1.44-2.45)</td>
</tr>
<tr>
<td><strong>PE (without DVT) (n = 190)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Events</td>
<td>173</td>
<td>17</td>
</tr>
<tr>
<td>Incidence Rate (95% CI)†</td>
<td>0.7 (0.6-0.8)</td>
<td>1.6 (0.96-2.5)</td>
</tr>
<tr>
<td><strong>Hazard ratio (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1 (REF)</td>
<td>1.59 (0.96-2.64)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1 (REF)</td>
<td>1.41 (0.85-2.36)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1 (REF)</td>
<td>1.47 (0.86-2.52)</td>
</tr>
<tr>
<td><strong>Any DVT† (n = 491)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Events</td>
<td>440</td>
<td>51</td>
</tr>
<tr>
<td>Incidence Rate (95% CI)†</td>
<td>1.7 (1.5-1.9)</td>
<td>4.7 (3.6-6.2)</td>
</tr>
<tr>
<td><strong>Hazard ratio (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1 (REF)</td>
<td>2.23 (1.65-3.00)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1 (REF)</td>
<td>1.86 (1.37-2.51)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1 (REF)</td>
<td>2.07 (1.52-2.81)</td>
</tr>
</tbody>
</table>

* Incidence rate is per 1000 person-years.
† Includes events presenting as DVT alone, and those presenting as both DVT and PE.
CI, confidence interval; VTE, venous thromboembolism; AF, atrial fibrillation; DVT, deep vein thrombosis.

Model 1 is adjusted for age, sex and race-field center.
Model 2: Model 1 + income, education, physical activity, smoking, waist circumference, height, systolic blood pressure, anti-hypertensive medication, diabetes, prevalent coronary heart disease, prevalent heart failure, prevalent anticoagulant use and eGFR.
Model 3: Model 2 + time-dependent anticoagulant use.
### Table 3

Hazard ratios (95% CIs) of incident VTE by time since AF diagnosis: The Atherosclerosis Risk in Communities Study, 1987-2011

<table>
<thead>
<tr>
<th>No AF</th>
<th>Time since AF diagnosis</th>
<th>≤6 months</th>
<th>&gt; 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13,081</td>
<td>429</td>
<td>1619</td>
</tr>
<tr>
<td># VTE Events</td>
<td>613</td>
<td>16</td>
<td>52</td>
</tr>
<tr>
<td>Person-years</td>
<td>259,659</td>
<td>859</td>
<td>9,900</td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI)

<table>
<thead>
<tr>
<th>Model</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (REF)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.23 (3.78-10.26)</td>
<td>1.67 (1.25-2.23)</td>
<td>Model 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.08 (3.08-8.38)</td>
<td>1.42 (1.06-1.90)</td>
<td>Model 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.24 (3.17-8.65)</td>
<td>1.55 (1.15-2.09)</td>
<td>Model 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; VTE, venous thromboembolism; AF, atrial fibrillation.

Model 1 is adjusted for age, sex and race-field center.

Model 2: Model 1 + income, education, physical activity, smoking, waist circumference, height, systolic blood pressure, anti-hypertensive medication, diabetes, prevalent coronary heart disease, prevalent heart failure, prevalent anticoagulant use and eGFR.

Model 3: Model 2 + time-dependent anticoagulant use.
### Table 4

Hazard ratios (95% CI) of incident AF after VTE, overall and by type of VTE: The Atherosclerosis Risk in Communities Study, 1987-2011

<table>
<thead>
<tr>
<th></th>
<th>No VTE (n=14,516)</th>
<th>VTE (n=613)</th>
</tr>
</thead>
<tbody>
<tr>
<td># AF Events</td>
<td>2,048</td>
<td>62</td>
</tr>
<tr>
<td>Person-years</td>
<td>279,785</td>
<td>2,990</td>
</tr>
<tr>
<td>Incidence Rate (95% CI) *</td>
<td>7.3 (7.0-7.6)</td>
<td>20.7 (16.0-26.4)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1 (REF)</td>
<td>1.94 (1.50-2.50)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1 (REF)</td>
<td>1.73 (1.34-2.24)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1 (REF)</td>
<td>1.20 (0.91-1.57)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>No VTE (n=14,858)</th>
<th>Any PE † (n=271)</th>
</tr>
</thead>
<tbody>
<tr>
<td># AF Events</td>
<td>2,090</td>
<td>20</td>
</tr>
<tr>
<td>Incidence Rate (95% CI) *</td>
<td>7.4 (7.1-7.7)</td>
<td>16.4 (10.4-24.9)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1 (REF)</td>
<td>1.44 (0.93-2.24)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1 (REF)</td>
<td>1.29 (0.83-2.01)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1 (REF)</td>
<td>0.73 (0.46-1.16)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>No VTE (n=14,787)</th>
<th>DVT only (n=342)</th>
</tr>
</thead>
<tbody>
<tr>
<td># AF Events</td>
<td>2,068</td>
<td>42</td>
</tr>
<tr>
<td>Incidence Rate (95% CI) *</td>
<td>7.4 (7.0-7.7)</td>
<td>23.7 (17.3-31.7)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1 (REF)</td>
<td>2.28 (1.68-3.10)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1 (REF)</td>
<td>2.05 (1.50-2.78)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1 (REF)</td>
<td>1.61 (1.18-2.21)</td>
</tr>
</tbody>
</table>

* Incidence rate is per 1000 person-years.
† Includes events presenting as PE alone, and those presenting as both DVT and PE.

CI, confidence interval; AF, atrial fibrillation; VTE, venous thromboembolism.

Model 1 is adjusted for age, sex and race-field center.

Model 2: Model 1+ income, education, physical activity, smoking, waist circumference, height, systolic blood pressure, anti-hypertensive medication, diabetes, prevalent coronary heart disease, prevalent heart failure, prevalent anticoagulant use and eGFR.

Model 3: Model 2 + time-dependent anticoagulant use.
Table 5

Hazard ratios (95% CIs) of incident AF by time since VTE diagnosis: The Atherosclerosis Risk in Communities Study, 1987-2011

<table>
<thead>
<tr>
<th>No VTE</th>
<th>Time since VTE diagnosis</th>
<th>≤ 6 months</th>
<th>&gt; 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td></td>
<td>14,516</td>
<td>175</td>
</tr>
<tr>
<td># AF Events</td>
<td></td>
<td>2,048</td>
<td>13</td>
</tr>
<tr>
<td>Person-years</td>
<td></td>
<td>279,785</td>
<td>244</td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI)

- **Model 1**: 1 (REF) 5.14 (2.98-8.88) 1.66 (1.25-2.21)
- **Model 2**: 1 (REF) 4.50 (2.61-7.77) 1.49 (1.12-1.98)
- **Model 3**: 1 (REF) 4.15 (2.40-7.17) 0.99 (0.73-1.34)

CI, confidence interval; AF, atrial fibrillation; VTE, venous thromboembolism.

Model 1 is adjusted for age, sex and race-field center.

Model 2: Model 1+ income, education, physical activity, smoking, waist circumference, height, systolic blood pressure, anti-hypertensive medication, diabetes, prevalent coronary heart disease, prevalent heart failure, prevalent anticoagulant use and eGFR.

Model 3: Model 2 + time-dependent anticoagulant use.