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# Hematocrit and incidence of venous thromboembolism

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## Abstract

**Background:** Patients with polycythemia vera with high hematocrit have increased risk of venous thromboembolism (VTE).

**Objective:** To determine whether high hematocrit in the general population is also associated with elevated VTE risk.

**Methods:** The prospective Atherosclerosis Risk in Communities Study performed a complete blood count in 13 891 adults aged 45 to 64 in 1987 to 1989. We identified incident hospitalized VTEs through 2015 and performed proportional hazards regression analyses using race-sex–specific categorization of hematocrit percentiles (ie, <5th, 5th to <25th, 25th to <75th, 75th to <95th, and 95th-100th percentiles, with the 25th to <75th percentile serving as the reference).

**Results:** Over a median follow-up of 26 years, 800 participants had an incident venous thrombosis of the leg and/or a pulmonary embolism. There was a nonlinear association of hematocrit with VTE incidence, with risk elevated 72% for participants above the 95th percentile of hematocrit compared with the reference. Specifically, hazard ratios (95% confidence intervals) of incident VTE were 1.27 (0.91-1.76), 1.06 (0.87-1.28), 1 (reference), 1.17 (0.98-1.40) and 1.72 (1.30-2.27) across the 5 hematocrit percentiles, adjusted for age, race, sex, body mass index, smoking status and pack-years, and other confounding variables. The association of high hematocrit with VTE was limited to provoked VTE, with little evidence for unprovoked VTE. Hemoglobin above the 95th percentile also was associated with an increased risk of VTE. In contrast, there were no significant associations of platelet, leukocyte, neutrophil, or lymphocyte counts with VTE incidence.

**Conclusion:** High hematocrit and hemoglobin in a general middle-aged population sample were associated with increased long-term risk of VTE, particularly provoked VTE.

KEYWORDS

hematocrit, hemoglobin, prospective studies, pulmonary embolism, venous thrombosis

**Essentials**

- We examined whether high hematocrit is associated with elevated venous thromboembolism (VTE) risk.
- We followed a middle-aged population cohort for 26 years, identifying 800 incident VTEs.
- The adjusted VTE hazard ratio was 1.72 (95% confidence interval, 1.30-2.27) for hematocrit ≥95th versus 25th to <75th percentiles.
- High hematocrit in the general population is associated with increased long-term risk of VTE.

## 1 | INTRODUCTION

Patients with markedly elevated hematocrit due to polycythemia vera are at increased risk of arterial thrombosis and venous thromboembolism (VTE). This risk has been attributed in part to increased blood viscosity created by elevated hematocrit.[1] Reduction of hematocrit to <45% reduces thrombotic risk in polycythemia vera.[2] In contrast, raising hematocrit in anemic patients with renal disease or cancer using erythrocyte-stimulating agents increases thrombosis risk.[3,4] Whether modestly elevated hematocrit may increase VTE risk in the general population is uncertain.[5] A large Norwegian population-based epidemiological cohort study suggested that a higher hematocrit may increase incidence of VTE,[6] and a large clinical study reported that elevated hematocrit was associated with increased recurrence of VTE in women but not in men.[7] A large Danish population-based cohort found a U-shaped association between hematocrit and VTE, but it was overall not statistically significant.[8] A small case-control study also found no independent association of hematocrit with VTE[9] but was potentially underpowered. We reported no significant association of hematocrit with VTE incidence in early follow-up of the population-based Longitudinal Investigation of Thromboembolism Etiology (LITE).[10]

With longer follow-up of the Atherosclerosis Risk in Communities (ARIC) study component of LITE and far more events than in our previous analysis, we reexamined the association of hematocrit with VTE incidence. Because a few research studies have associated VTE risk with other aspects of the complete blood count,[8,11–14] and diseases manifest as altered levels of these often increase VTE risk, we also tested in a supplemental analysis whether higher leukocyte or platelet counts in ARIC also may be associated with elevated risk of VTE.

## 2 | METHODS

### 2.1 | Study sample and design

Previous publications described the overall ARIC study design, methods, and VTE incidence rates in detail.[15,16] Briefly, using population-based sampling methods, 15 792 predominantly black or white men and women aged 45 to 64 years from 4 US communities (Forsyth County, NC; suburban Minneapolis, MN; Washington County, MD; Jackson, MS) enrolled and underwent a baseline (Visit 1) examination in 1987 to 1989. The estimated response rate of eligible individuals was 60%. The institutional review committees at each study center approved the ARIC protocol, and ARIC staff obtained informed participant consent. ARIC maintained contact with the participants via annual or semiannual telephone calls and periodic reexaminations of the cohort.

### 2.2 | Baseline (1987-1989) measurements

Each of the 4 ARIC centers drew blood after a requested overnight fast (3% did not fast) and stored whole blood temporarily at 4°C. Within 24 hours, local hospital laboratories at each center performed a complete blood count (hemoglobin, hematocrit, platelet, and leukocyte counts but not red blood cell indices) using standard automated cell counters. Three of the 4 centers (not Washington County) obtained leukocyte differentials, and neutrophil and lymphocyte counts were estimated as the product of the percentages of these cell types times the total white blood cell count. ARIC reported the blood count values as a service to participants and their physicians, with abnormal values identified.

We measured other potential VTE risk factors at baseline; participants reported their race category, histories of venous thrombosis and cancer, smoking status, and amount smoked. We calculated pack-years of smoking. Technicians recorded current medication use via review of medication bottles, including antihypertensive and diabetes agents, and measured sitting blood pressure 3 times via a random-zero sphygmomanometer after a 5-minute rest; we averaged the final 2 measurements. The technicians measured height and weight to derive body mass index (BMI). We defined diabetes as a fasting serum glucose of ≥126 mg/dL, nonfasting serum glucose of ≥200 mg/dL, a self-reported physician diagnosis of diabetes, or use of antidiabetic medication in the past 2 weeks. ARIC estimated glomerular filtration rate (eGFR) from creatinine using the Chronic Kidney Disease Epidemiology Collaboration algorithm,[17] and we defined CKD as eGFR <60 mL/min/1.73 $m^2$. Research laboratories measured plasma factor VIII and von Willebrand factor as previously described.[18]

### 2.3 | Identification of incident VTE

After the Visit 1 baseline examination, ARIC staff telephoned participants annually or semiannually and asked about all hospitalizations in the previous year. Staff then obtained and recorded in-hospital International Classification of Diseases, Ninth Revision, Clinical Modification codes for all discharge diagnoses and copied

selected hospital record material for VTE validation through 2015. To validate VTE events, 2 physicians reviewed the records using standardized criteria,[16] requiring positive imaging tests for diagnosis of clinically recognized deep vein thrombosis (DVT) and pulmonary embolism (PE). The physicians subclassified VTEs based on the medical record as provoked (associated with cancer within 1 year or major trauma, surgery, or marked immobility within 90 days) or unprovoked (none of these triggers). For this report, we restricted DVTs to those in the lower extremity or vena cava, because upper extremity DVTs were relatively few and almost always the result of indwelling venous catheters.

### 2.4 | Statistical analysis

From the 15 792 ARIC participants at Visit 1, we excluded 48 who were not black or white, 276 with a self-reported history of VTE, 852 with a self-reported history of cancer, 69 using anticoagulants, 260 with missing blood counts, and 396 with missing covariate information, leaving 13 891 for analysis. For most analysis, we used SAS (version 9.4; SAS Institute Inc, Cary, NC) and focused primarily on hematocrit and hemoglobin. Because men and whites were overrepresented at high levels of hematocrit, we employed race-sex–specific percentile cut points (<5th, 5th to <25th, 25th to <75th, 75th to <95th, and 95th-100th percentiles; Table 1) to yield pooled hematocrit and hemoglobin groups. We tabulated participant characteristics (means or frequencies) across the 5 categories of hematocrit. We tabulated person-time of follow-up until the occurrence of VTE, loss to follow-up, death, or December 31, 2015. Using Cox proportional hazards models, we estimated the hazard ratios of VTE by categories. We used time on study as the time scale. Cox Model 1 adjusted for age (continuous), race (black, white), and sex. Model 2 additionally adjusted for factors that were in some previous papers associated with VTE in ARIC, namely, BMI, baseline cigarette smoking status (current, former, never), pack-years of smoking, diabetes (yes, no), systolic blood pressure, antihypertensive medication use (yes, no), eGFR, von Willebrand factor, and factor VIII. We also performed a cubic spline analysis, using Stata SE version 15.1 (StataCorp, College Station, TX), to visualize the shape of the association of continuous hematocrit with VTE, adjusting for Model 2 covariates. In addition, we tested multiplicative interactions of hematocrit group by sex ($P$ = .19) and by race ($P$ = .06), and none were statistically significant.

We did supplemental analyses of the other blood count parameters, using the following percentiles of their overall distributions for groupings: <25th, 25th to <50th, 50th to <75th, 75th to <95th, and 95th-100th percentiles. Analyses of neutrophils and lymphocytes excluded participants (n = 3121), mainly from Washington County, with no white count differential measured.

We tested the proportional hazard assumption for each blood parameter in a continuous model, using an interaction term between each blood count parameter and time; the assumption held for all blood count parameters, except for a modest deviation for hemoglobin concentration.

## 3 | RESULTS

The analytic sample included 13 891 participants free of VTE and cancer history at baseline. Those above the sex-race–specific 95th percentile of hematocrit were older, more often obese, current and heavier smokers, diabetic, and hypertensive. Factor VIII and von Willebrand factor were highest in the low-hematocrit group (Table 2).

Over a median follow-up of 26 years (maximum, 29 years), 800 ARIC participants had an incident DVT of the leg and/or a PE. As shown in Figure 1 (using the absolute hematocrit values), there was a nonlinear association between Visit 1 hematocrit and total VTE hazard ratio. Compared with the median hematocrit, the VTE hazard was approximately doubled at the highest levels of hematocrit. Low hematocrit also was associated with an elevated VTE hazard ratio (Figure 1), but the confidence interval (CI) overlapped 1.

Using race-sex–specific cut points for hematocrit (Table 3), the hazard ratio of incident VTE using Model 1 was 1.24 (95% CI, 1.04-1.48) for hematocrit in the 75th to <95th percentile and 1.95-fold (1.49-2.56) higher for a value ≥95th percentile, compared with the 25th to <75th percentile reference. In Model 2, these hazard ratios

**TABLE 1** Race-sex specific cut points for Visit 1 hematocrit and hemoglobin, ARIC, 1987-89

| Percentile | <5th | 5th to <25th | 25th to <75th | 75th to <95th | 95th-100th |
|---|---|---|---|---|---|
| Hematocrit (%) | | | | | |
| White males | ≤39.8 | 39.9-42.6 | 42.7-46.4 | 46.5-49.3 | ≥49.4 |
| White females | ≤35.4 | 35.5-38.1 | 38.2-41.6 | 41.7-44.8 | ≥44.9 |
| Black males | ≤37.2 | 37.3-40.9 | 41.0-45.4 | 45.5-49.3 | ≥49.4 |
| Black females | ≤32.5 | 32.6-36.3 | 36.4-40.4 | 40.5-43.9 | ≥44.0 |
| Hemoglobin (g/dL) | | | | | |
| White males | ≤13.3 | 13.4-14.3 | 14.4-15.6 | 15.7-16.6 | ≥16.7 |
| White females | ≤11.7 | 11.8-12.6 | 12.7-13.8 | 13.9-14.8 | ≥14.9 |
| Black males | ≤12.1 | 12.2-13.4 | 13.5-14.9 | 15.0-16.1 | ≥16.2 |
| Black females | ≤10.4 | 10.5-11.8 | 11.9-13.2 | 13.3-14.4 | ≥14.5 |

Abbreviation: ARIC, Atherosclerosis Risk in Communities.

**TABLE 2** Participant characteristics at Visit 1 according to categories of hematocrit, ARIC, 1987-1989

| Characteristic | Hematocrit (percentiles based on sex-race–specific cut points)[a] | | | | |
|---|---|---|---|---|---|
| | <5th | 5th to <25th | 25th to <75th | 75th to <95th | 95th-100th |
| n | 668 | 2740 | 6899 | 2874 | 710 |
| Age | 54 (6) | 54 (6) | 54 (6) | 54 (6) | 55 (6) |
| Age, % 45-54 y (vs 55-64) | 54 | 56 | 54 | 51 | 48 |
| Sex, % men | 47 | 45 | 46 | 46 | 47 |
| Race, % white (vs black) | 73 | 73 | 74 | 74 | 73 |
| Body mass index, % | | | | | |
| <25 kg/m$^2$ | 41 | 40 | 32 | 28 | 26 |
| 25 to <30 kg/m$^2$ | 40 | 38 | 41 | 39 | 38 |
| ≥30 kg/m$^2$ | 20 | 23 | 27 | 33 | 37 |
| Smoking status, % | | | | | |
| Current smoker | 16 | 17 | 23 | 35 | 54 |
| Former smoker | 36 | 34 | 33 | 28 | 21 |
| Never smoker | 48 | 49 | 43 | 37 | 25 |
| Pack-years smoking | 1.3 (22) | 0.4 (22) | 4 (26) | 11 (32) | 24 (38) |
| Diabetes, % | 11 | 10 | 10 | 15 | 19 |
| Systolic blood pressure, mm Hg | 122 (22) | 119 (19) | 121 (18) | 123 (19) | 125 (20) |
| Hypertensive medication, % | 24 | 21 | 23 | 29 | 39 |
| Factor VIII, % | 145 (52) | 131 (41) | 130 (37) | 131 (39) | 132 (38) |
| von Willebrand factor, % | 126 (54) | 115 (47) | 116 (46) | 119 (47) | 123 (51) |
| eGFR, mL/min/1.73 m$^2$ | 99 (24) | 104 (16) | 103 (15) | 102 (15) | 101 (16) |

Abbreviations: ARIC, Atherosclerosis Risk in Communities; eGFR, estimated glomerular filtration rate.

[a]The 5 groups represent percentiles of the race-sex–specific hematocrit distributions (see Table 1). Values in the table are prevalence or mean (SD) of the characteristic, except for pack-years, which is the median (interquartile range).

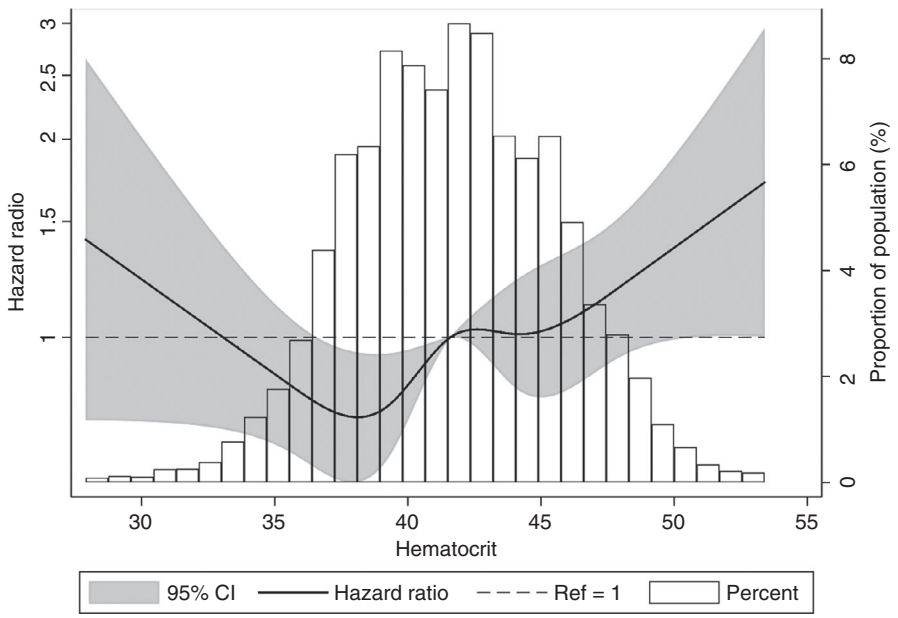


**FIGURE 1** Spline model plotting multivariable-adjusted hazard ratio of venous thromboembolism by continuous hematocrit concentration, ARIC, 1987-89 through 2015. Knots placed at 35.6 (6th percentile), 39.3 (27th percentile), 41.6 (50th percentile), 44.1 (72th percentile), and 48.1 (94th percentile). ARIC, Atherosclerosis Risk in Communities; CI, confidence interval

(95% CIs) were 1.17 (0.98-1.40) and 1.72 (1.30-2.27), respectively. Those in the <5th percentile of hematocrit had a modestly elevated hazard ratio for VTE (Table 3), but the CI overlapped 1. The association of high hematocrit with VTE was present for both PE (with or without DVT) and for isolated DVT (Table 3). The association also was limited almost entirely to provoked VTE (hazard ratio >2), whereas the CI for the hazard ratio for unprovoked VTE overlapped the null.

**TABLE 3** Hazard ratios (95% CIs) of total, provoked, and unprovoked VTE by groups of Visit 1 hematocrit, ARIC, 1987-1989 through 2015

| | Hematocrit (percentiles based on sex-race specific cut points) | | | | |
|---|---|---|---|---|---|
| | <5th | 5th to <25th | 25th to <75th | 75th to <95th | 95th-100th |
| N at risk | 668 | 2740 | 6899 | 2874 | 710 |
| Incident total VTE, n | 40 | 146 | 373 | 180 | 61 |
| Person-years at risk | 13 828 | 61 787 | 155 542 | 62 141 | 13 856 |
| Crude VTE incidence rate (per 1000 person-years) | 2.9 | 2.4 | 2.4 | 2.9 | 4.4 |
| Model 1 hazard ratio (95% CI) | 1.33 (0.96-1.84) | 1.02 (0.84-1.23) | 1 (Reference) | 1.24 (1.04-1.48) | 1.95 (1.49-2.56) |
| Model 2 hazard ratio (95% CI) | 1.27 (0.91-1.76) | 1.06 (0.87-1.28) | 1 (Reference) | 1.17 (0.98-1.40) | 1.72 (1.30-2.27) |
| Incident provoked VTE, n | 22 | 85 | 219 | 114 | 44 |
| Model 1 hazard ratio (95% CI) | 1.24 (0.80-1.92) | 1.01 (0.78-1.30) | 1 (Reference) | 1.34 (1.07-1.68) | 2.41 (1.74-3.33) |
| Model 2 hazard ratio (95% CI) | 1.23 (0.79-1.91) | 1.05 (0.82-1.36) | 1 (Reference) | 1.26 (1.00-1.58) | 2.05 (1.47-2.86) |
| Incident unprovoked VTE, n | 18 | 61 | 154 | 66 | 17 |
| Model 1 hazard ratio (95% CI) | 1.45 (0.89-2.37) | 1.03 (0.77-1.39) | 1 (Reference) | 1.10 (0.83-1.47) | 1.31 (0.80-2.17) |
| Model 2 hazard ratio (95% CI) | 1.31 (0.80-2.14) | 1.06 (0.79-1.43) | 1 (Reference) | 1.05 (0.79-1.40) | 1.21 (0.73-2.02) |
| Incident PE, n | 13 | 71 | 183 | 109 | 31 |
| Model 1 hazard ratio (95% CI) | 0.87 (0.50-1.54) | 0.99 (0.76-1.31) | 1 (Reference) | 1.54 (1.22-1.95) | 2.08 (1.42-3.05) |
| Model 2 hazard ratio (95% CI) | 0.82 (0.47-1.44) | 1.03 (0.78-1.36) | 1 (Reference) | 1.49 (1.17-1.89) | 1.94 (1.32-2.87) |
| Incident DVT, n | 27 | 75 | 190 | 71 | 30 |
| Model 1 hazard ratio (95% CI) | 1.75 (1.17-2.61) | 1.03 (0.79-1.35) | 1 (Reference) | 0.95 (0.73-1.25) | 1.83 (1.25-2.70) |
| Model 2 hazard ratio (95% CI) | 1.69 (1.13-2.55) | 1.07 (0.82-1.40) | 1 (Reference) | 0.88 (0.67-1.16) | 1.53 (1.03-2.27) |

*Note:* Model 1: Adjusted for Visit 1 age, race, and sex. Model 2: Adjusted for Visit 1 age, race, sex, body mass index, cigarette smoking status, pack-years smoking, diabetes, systolic blood pressure, antihypertensive medications, von Willebrand factor, factor VIII, and eGFR.

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; eGFR, estimated glomerular filtration rate; VTE, venous thromboembolism.

Similar to hematocrit, hemoglobin ≥95th percentile, as expected, also was associated with an increased risk of VTE (Table 4). In contrast, there were no significant associations of Visit 1 platelet, leukocyte, neutrophil, or lymphocyte counts with VTE incidence (Table S1).

## 4 | DISCUSSION

This prospective study found that, compared with a midlevel hematocrit, a single high hematocrit (or hemoglobin) in a general middle-aged population sample was associated with increased long-term risk of VTE over 26 years. The highest category, with hematocrit above the 5th percentile, had a 72% greater risk of VTE compared with the middle category of hematocrit. This was exclusively due to an elevated risk of provoked VTE, with no association for unprovoked VTE. There was no association of VTE with the other blood count parameters studied.

Our findings are partly consistent with apparently the 2 other large general population-based studies on hematocrit and incident VTE. The Copenhagen Study reported a nonsignificant U-shaped association between hematocrit and VTE.[8] Our spline analysis (Figure 1) suggested a U-shaped association that was nonsignificant at the lower end of the hematocrit distribution. The Tromsø Study[6] reported multivariable hazard ratios (95% CIs) of VTE (n = 447) of 1.51 (1.08-2.12) for hematocrit of ≥42% versus <39% in women and 1.54 (1.08-2.21) for ≥46% versus <43% in men. However, the Tromsø Study also found positive associations of hematocrit with unprovoked VTE (hazard ratios, 1.62 [0.98-2.69] in women and 2.37 [1.36-4.15] in men), whereas ARIC found an association only for provoked VTE. It is often inferred that risk factors for unprovoked VTE, or consistently for both unprovoked and provoked VTE, are more likely to be direct causes of VTE than are risk factors limited to provoked VTE. Thus, although we adjusted for smoking, ARIC findings may be most supportive of high hematocrit being related to smoking or smoking-related heart or lung diseases occurring during follow-up, which themselves may lead to provoked more often than unprovoked VTE. For example, a participant with baseline smoking is more likely to develop future cancer then provoked VTE. On the other hand, a Mendelian randomization study showed that a polygenetic risk score for hemoglobin concentration was associated positively with VTE risk in the general population[19]; this suggests a possible causal relationship between hemoglobin or hematocrit and VTE.

Hematocrit well above the normal range, found in polycythemia vera, is clearly associated with increased risk of VTE.[1] The risk of VTE in the Tromsø and ARIC general population studies, however, appears to be increased at hematocrit levels much lower than for polycythemia vera. Mechanistically, high hematocrit increases

**TABLE 4** Hazard ratios (95% CIs) of VTE by groups of Visit 1 hemoglobin, ARIC, 1987-1989 through 2015

| | Hemoglobin (percentiles based on sex-race–specific cut points) | | | | |
|---|---|---|---|---|---|
| | <5th | 5th to <95th | 25th to <75th | 75th to <95th | 95th-100th |
| n | 657 | 2616 | 6876 | 2974 | 768 |
| Incident VTE, n | 40 | 136 | 379 | 188 | 57 |
| Person-years at risk | 13 579 | 58 625 | 155 245 | 64 560 | 15 146 |
| Crude VTE incidence rate (per 1000 person-years) | 2.9 | 2.3 | 2.4 | 2.9 | 3.8 |
| Model 1 hazard ratio (95% CI) | 1.35 (0.97-1.87) | 0.97 (0.80-1.18) | 1 (Reference) | 1.23 (1.03-1.46) | 1.64 (1.24-2.17) |
| Model 2 hazard ratio (95% CI) | 1.32 (0.95-1.83) | 0.98 (0.81-1.20) | 1 (Reference) | 1.16 (0.97-1.38) | 1.47 (1.10-1.95) |

*Note:* Model 1: Adjusted for Visit 1 age, race, and sex. Model 2: Adjusted for Visit 1 age, race, sex, body mass index, cigarette smoking status, pack-years smoking, diabetes, systolic blood pressure, antihypertensive medications, von Willebrand factor, factor VIII, and eGFR.

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; eGFR, estimated glomerular filtration rate; VTE, venous thromboembolism.

platelet margination and adhesiveness.[20–22] However, a more important mechanism by which hematocrit may increase VTE risk is via increased blood viscosity and venous stasis.[1,23]

A previous population-based control study suggested iron deficiency anemia is associated with a 40% increase in VTE,[24] and, although not statistically significant, spline analysis in the Copenhagen Study suggested that VTE may be elevated in those with low hematocrit.[8] We also found a modestly but not statistically significantly increased risk of VTE in ARIC participants with hematocrit or hemoglobin less than the 5th percentile, in the range for anemia. Although ARIC did not characterize the type of anemia, most 45- to 64-year-old anemic adults would have either iron deficiency or anemia of chronic disease. This raises the possibility that hemoglobin and hematocrit may reflect disordered iron metabolism, which may contribute to increased VTE risk. Several studies support this hypothesis; for example, a recent Mendelian randomization study showed that a higher genetically determined iron status may increase risk of VTE.[25] Likewise, analysis from the Tromsø Study recently reported that higher plasma hepcidin was associated with increased VTE incidence.[26] Hepcidin is a key iron-regulatory hormone and an acute phase inflammatory biomarker that is increased in anemia of chronic disease.

Limitations of this study include the observational design and therefore possible residual confounding, meaning we cannot confirm causality. We were unable to capture VTE events treated only in the outpatient setting, yet several pilot studies in ARIC have suggested that the vast majority of initial VTEs during 1987 to 2015, especially as the cohort grew old, were hospitalized. We examined blood counts at only a single time point; blood parameters may have fluctuated during the long follow-up, and such fluctuations would tend to weaken observed associations with VTE. Likewise, confounders likely changed over time, which could have led to over- or underestimation of hazard ratios. Finally, ARIC did not collect data on the causes for elevated hematocrit, nor on red blood cell indices.

In conclusion, a high hematocrit and hemoglobin in a general middle-aged population sample was associated with increased long-term risk of VTE, particularly provoked VTE. Further study could address whether hematocrit or hemoglobin above the 95th percentile might be helpful risk stratification for considering VTE prevention in high-risk settings for provoked VTE.

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## RELATIONSHIP DISCLOSURE

The authors report nothing to disclose.

## AUTHOR CONTRIBUTIONS

ARF designed and performed research and wrote the paper. WW analyzed the data and critically reviewed the paper. RP, PLL, and JDB contributed to and critically reviewed the paper. MC helped design and perform research and critically reviewed the paper.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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