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The association between red cell distribution width and venous thromboembolism is not explained by myocardial infarction, stroke, or cancer

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Abstract

Background: Red cell distribution width (RDW) is a risk marker of venous thromboembolism (VTE), myocardial infarction (MI), stroke, and cancer. Due to interrelations between these diseases, the association between RDW and VTE may be explained by MI, stroke, or cancer.

Objective: To investigate whether the effect of RDW on VTE could be explained by intermediate development of MI, stroke, or cancer.

Methods: RDW was measured in 24 363 participants of the Tromsø Study in 1994-1995. Incident VTE, MI, stroke, and cancer were registered until December 31, 2010. Conventional and cause-specific Cox-regression models were used to estimate hazard ratios (HR) for VTE with 95% confidence intervals (CI) across categories of RDW.

Results: There were 502 first VTEs during a median follow-up of 16 years. In conventional Cox regression analysis, RDW in the highest quartile was associated with a 71% (HR 1.71, 95% CI 1.09-2.67) and 27% (HR 1.27, 95% CI 0.88-1.85) higher risk of VTE in men and women, respectively, compared to subjects in the lowest quartiles. The risk of VTE among subjects with RDW in the highest quartile was similar for men and women of postmenopausal age. In cause-specific analysis, where each individual contributed with person-time until the first occurring event only, the risk estimates were similar to those of the conventional Cox-regression analysis.

Conclusion: Our findings suggest that the association between RDW and future risk of VTE is not explained by intermediate development of MI, stroke, or cancer.

KEYWORDS
cardiovascular diseases, erythrocyte indices, neoplasms, risk factors, venous thrombosis

Essentials

- Red cell distribution width (RDW) is associated with future risk of venous thromboembolism (VTE).
- Strong interrelations between RDW and other VTE-related diseases may explain this relationship.
- Cause-specific analyses were performed to asses risk estimates of VTE by RDW.
- The association between RDW and VTE was not explained by myocardial infarction, stroke, or cancer.

1 | INTRODUCTION

Red cell distribution width (RDW) is an easy accessible and inexpensive measure of the variation in volume of circulating erythrocytes calculated by most automated blood cell counters as part of the routine blood cell count analysis.[1] RDW and mean corpuscular volume (MCV) have traditionally been used in a classification system for anemia.[2] High RDW is seen in microcytic and macrocytic anemia, but can also result from conditions that modify the red blood cells due to premature release of immature cells into the bloodstream such as hemoglobinopathies, hemolysis or hemolytic anemia.[3] Growing evidence suggest that RDW may have clinical applications for many disorders.[4] Recent meta-analyses have reported associations between high RDW and future risk of cardiovascular disease, heart failure, and all-cause mortality.[5–7]

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is a severe and potentially lethal disease, with serious short and long-term complications. Previously, we[8] and others[9,10] have reported an association between RDW and future risk of VTE. As RDW is a numerical concept, it is likely to assume that the observed associations between RDW and various diseases are explained by underlying pathological mechanisms. However, the underlying explanation for the association between RDW and VTE remains unsettled. A relation between arterial thromboembolic diseases and risk of VTE has been reported in several studies.[11-14] Moreover, cancer is associated with a four- to sevenfold increased risk of VTE, and 15% of cancer patients develop a symptomatic VTE during the course of their disease.[15–18] We have recently found associations between high RDW and carotid atherosclerosis progression,[19] as well as future risks of myocardial infarction (MI),[20] ischemic stroke,[21] and cancer[22] using data from the Tromsø Study. Given the interrelation between these diseases and VTE, we hypothesized that the observed association between RDW and VTE could be explained by intermediate development of cancer or arterial thromboembolic disorders. In cause-specific analysis, failure time is calculated to the first occurring disease, thereby eliminating the possibility that one disease alters the risk of another. In order to explore whether the apparent association between RDW and VTE could be explained by intermediate development of MI, stroke, or cancer, we conducted cause-specific analysis of the relationship between RDW and VTE in a general adult population cohort with follow-up information on all four disease outcomes.

2 | MATERIAL AND METHODS

2.1 | Study population

Study participants were recruited from the fourth (1994-1995) survey of the Tromsø Study, where the entire population aged ≥25 years living in the municipality of Tromsø, Norway, were invited to participate. The population is predominantly Caucasians of Norwegian origin, with no known sickle cell disease or thalassemia. A detailed description of the study design and population has been published elsewhere.[23] The regional committee of medical and health research ethics approved the study, and all subjects gave their written consent to participate. A total of 27 158 persons aged 25-97 years participated in the study. Persons who did not give their written consent to medical research (n = 202), those not officially registered as inhabitants of the municipality of Tromsø at date of study enrolment (n = 41), persons with missing RDW measurement (n = 632), persons with known VTE (n = 57), MI (n = 728), stroke (n = 302), or cancer (n = 682) before baseline were excluded. Furthermore, we excluded persons diagnosed with cancer within one year after baseline (n = 110) to avoid that the RDW measurement could be influenced by an occult cancer. Accordingly, 24 363 participants were included in the study. Incident events of VTE, MI, stroke, and cancer were recorded from the date of enrolment through the end of follow-up, December 31, 2010.

2.2 | Baseline measurements

Baseline information was collected by self-administered questionnaires, blood samples, and a physical examination in 1994-1995. For measurement of blood cell variables (including RDW), 5 mL of blood was drawn from an antecubital vein into a vacutainer tube containing EDTA as an anticoagulant and analyzed within 12 hours in an automated blood cell counter (Coulter Counter, Coulter Electronics, Luton, UK). RDW was calculated by dividing the standard deviation of MCV by MCV and multiplying by 100 to express the result as a percentage.[24] Height and weight were measured wearing light clothes and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Information on smoking habits was obtained from standard, self-administered questionnaires.

2.3 | Outcome ascertainment

The University Hospital of North Norway is the only hospital in the region, and all diagnostic radiology and hospital care is provided exclusively by this hospital. The hospital discharge diagnosis registry covers both hospitalizations and outpatient clinic visits. Moreover, the unique Norwegian national 11-digit identification number allowed linkage to national and local diagnosis registries. The National Causes of Death Registry covers all subjects registered as inhabitants of Norway at the time of their death, without regard to whether the death took place in Norway or abroad.

All VTE events during follow-up were identified by searching the hospital discharge diagnosis registry, the autopsy registry and the radiology procedure registry at the University Hospital of North Norway. Trained personnel reviewed the medical record for each potential case of VTE. A VTE event was considered verified and recorded when presence of clinical signs and symptoms of DVT or PE were combined with objective confirmation tests (by compression ultrasonography, venography, spiral computed tomography, perfusion-ventilation scan, pulmonary angiography, autopsy), and resulted in a VTE diagnosis that required treatment, as previously described in detail.[25] VTE cases from the autopsy registry were recorded when the death certificate indicated VTE as cause of death or a significant condition associated with death.

All first-time events of MI were identified by linkage to the diagnosis registries at the University Hospital of North Norway and the National Causes of Death Registry at Statistics Norway. Cases of possible incident nonfatal and fatal MI were identified by a broad search for relevant International Classification of Diseases (ICD), 9th and 10th revision codes. An independent end-point committee validated all possible events of MI based on a combination of signs and symptoms, information from electrocardiograms, cardiac biomarkers and autopsy reports, as previously described in detail.[20]

Stroke was defined according to the World Health Organization definition as rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, and with no apparent cause other than vascular origin. First-ever non-fatal and fatal strokes were identified by a search for relevant ICD codes. An independent endpoint committee validated all possible hospitalized and non-hospitalized stroke events, as previously described.[21]

All cancer diagnoses in the Norwegian population are registered in the Cancer Registry of Norway and information about cancer in the cohort was obtained by linkage to the cancer registry using the unique 11-digit personal identification number. In a recent evaluation of the data quality, the Cancer Registry of Norway had a completeness of 98.8% with 94% of the cases being histologically verified.[26] The cancer registry provided information on the date of diagnosis, location of disease, and cancer stage, as previously described.[22]

2.4 | Statistical analyses

Statistical analyses were performed with STATA version 13.0 (Stata Corporation, College Station, TX, USA). Participants were categorized into quartiles based on the distribution of baseline RDW. An additional cut-off point was established at the 95th percentile of RDW. Age-adjusted baseline characteristics according to quartiles of RDW were assessed by analyses of variance (ANOVA).

For conventional analysis of the association between RDW and VTE, person-time of follow-up was calculated from the date of enrolment (1994/1995) to the date of an incident VTE diagnosis, to the date when the participant died or moved from the municipality of Tromsø, or to the end of the study period (December 31, 2010), whichever came first. For the cause-specific analysis, person time was

calculated from the date of enrolment to the date of the first occurring diagnosis of VTE, MI, stroke, or cancer, to the date when the participant died or moved from Tromsø, or to the end of the study period, whichever came first. Crude incidence rates (IR) with 95% confidence intervals (CI) were calculated and expressed as number of events per 1000 person-years at risk. Cox proportional hazard regression models were used to obtain crude and multivariable adjusted hazard ratios (HR) with 95% CI for VTE according to RDW quartiles. The lowest RDW quartile was used as reference category in the Cox models, and age was used as timescale. The multivariable model included BMI, smoking, white blood cell count and hemoglobin. The proportional hazards assumption was tested by Schoenfeld residuals, and no violation was found.

Premenopausal women are prone to iron deficiency anemia, which might cause elevated RDW without other underlying causes.[24,27] Therefore, we divided the female cohort into two age groups using the age of 55 years as cut-off.[28] This cut-off age was chosen because most women have completed the menopausal transition by the age of 55.[28] Cox regression analysis were used to calculate conventional and cause-specific HRs of VTE for those with RDW levels in the upper population-based quartile compared with those with RDW in the three lower quartiles. The lower quartiles were combined in order to maintain statistical power despite a significant reduction of VTE events in the subgroup analysis. Finally, conventional and cause-specific HRs were calculated after stratification on anemia (defined as hemoglobin levels <12.0 g/dL in women and <13.0 g/dL in men).

3 | RESULTS

Mean RDW levels were 12.8% in men and 12.9% in women. The mean age of participants increased across increasing quartiles of RDW. Age-adjusted characteristics across quartiles of RDW, as well as above the 95th percentile, are shown in Table 1. The mean white blood cell count and proportion of smokers and subjects with anemia increased with higher categories of RDW, whereas the mean hemoglobin concentration decreased. The proportion of subjects with anemia was higher in women than in men in all RDW categories while the proportion of smokers showed a more pronounced increase across RDW quartiles in men than in women.

In total, there were 502 incident VTEs (IR 1.5 per 1000 person-years), 1612 MIs (IR 4.8 per 1000 person-years), 956 strokes (IR 2.9 per 1000 person-years), and 2144 cancers (IR 6.6 per 1000 person-years) during a median follow-up time of 16.0 years (total follow-up time: 328 732 person-years). IRs and hazard ratios of VTE according to quartiles of RDW are shown in Table 2. As expected, the number of events and IRs was lower in the cause-specific analyses compared to the conventional analyses. Moreover, the total follow-up time decreased to 311 467 person-years. The IRs increased across increasing quartiles of RDW in men and women. Similar to previous findings,[8,10] subjects with RDW in the highest quartile had increased risk of VTE compared to those in the lowest quartile (HR 1.43, 95% CI 1.08-1.91). The risk increased further for study participants with

TABLE 1 Age-adjusted baseline characteristics of the study population (n = 24 363) by quartiles (Q) and above the 95th percentile (pct) of red cell distribution width (RDW) stratified by gender. Values are given as percentages with absolute numbers in brackets or as means ± one standard deviation

RDW	Q 1	Q 2	Q 3	Q 4	Above 95th pct
Men					
N	2 933	3 120	3 015	2 334	368
RDW range (%)	11.0-12.3	12.4-12.7	12.8-13.2	13.3-30.5	14.3-30.5
Age (years)	39 ± 11	43 ± 12	46 ± 13	53 ± 14	60 ± 14
BMI (kg/m$^{2)}$)	25.5 ± 3.5	25.6 ± 3.7	25.5 ± 3.9	25.5 ± 4.2	25.2 ± 4.4
Smoking (%)	26.1 (836)	33.9 (1095)	40.7 (1212)	55.1 (1188)	57.7 (183)
Hemoglobin (g/dL)	14.9 ± 1.1	14.9 ± 1.1	14.8 ± 1.1	14.6 ± 1.4	14.1 ± 1.7
WBC (10^9/L)	6.7 ± 1.8	7.0 ± 2.1	7.1 ± 2.0	7.6 ± 2.1	7.8 ± 2.1
Anemia (%)[a]	1.5 (24)	1.4 (31)	1.6 (53)	5.4 (155)	18.1 (76)
Women					
N	3 392	3 264	3 136	3 169	855
RDW range (%)	10.7-12.3	12.4-12.7	12.8-13.2	13.3-24.5	14.3-24.5
Age (years)	41 ± 13	45 ± 14	48 ± 15	50 ± 16	47 ± 15
BMI (kg/m$^{2)}$)	24.4 ± 3.5	24.7 ± 3.7	24.8 ± 3.9	25.0 ± 4.2	25.1 ± 4.4
Smoking (%)	31.0 (1 124)	34.3 (1 136)	41.7 (1 276)	42.5 (1 277)	37.0 (314)
Hemoglobin (g/dL)	13.5 ± 1.1	13.4 ± 1.1	13.4 ± 1.1	12.9 ± 1.4	12.2 ± 1.7
WBC (10^9/L)	7.0 ± 1.8	7.1 ± 2.1	7.3 ± 2.0	7.3 ± 2.1	7.0 ± 2.1
Anemia (%)[a]	2.5 (118)	3.6 (120)	5.6 (158)	17.1 (524)	38.5 (332)

BMI, body mass index; WBC, white blood cell count.

[a]Anemia defined as hemoglobin levels <12.0 g/dL in females and <13.0 g/dL in men.

RDW above the 95th percentile (RDW > 14.3%) (Table 2). The association between RDW and risk of VTE was stronger in men than in women. In the cause-specific analysis, subjects with RDW in the highest quartile had a 54% (HR 1.54, 95% CI 1.09-2.18) higher risk of VTE compared to subjects with RDW in the lowest quartile. As in the conventional analysis, the risk increased further in subjects with RDW above the 95th percentile (Table 2). In sex-stratified analyses, the cause-specific risk estimates were essentially identical to those in the conventional analysis, as the HR for men in the highest RDW quartile versus men in the lowest quartile was 1.74 and 1.71, respectively (Table 2).

In subgroup analysis, women of postmenopausal age (≥55 years) had similar risk of VTE as men (Table 3), as those with RDW in the highest quartile had a 37% higher risk of VTE (HR 1.37, 95% CI 1.01-1.86) compared to those with RDW in the three lower quartiles. In contrast, women younger than 55 years had no increased risk of VTE (HR upper quartile vs. quartile 1-3: 1.07, 95% CI 0.65-1.74) by RDW. The results in the cause-specific analysis did not differ from those in the conventional analysis. Subjects with anemia and high RDW had no increased risk of VTE (HR quartile 4 vs. quartile 1-3: 0.68, 85% CI 0.21-2.20) (Table S1), whereas subjects without anemia had similar risk of VTE as the entire cohort (HR quartile 4 vs. quartile 1-3: 1.36, 95% CI 1.12-1.65). Similar results were found in the cause-specific analysis of subjects with and without anemia (Table S1). However, the latter results must be interpreted with caution since there were only 13 cases of VTE among subjects with anemia.

4 | DISCUSSION

In this large, population-based cohort study, we found no evidence that the association between RDW and VTE is explained by intermediate development of MI, stroke, or cancer. In the cause-specific analysis, where each individual contributed with person-time until the first occurring event of arterial thrombosis, cancer, or VTE, the risk estimates for VTE were essentially similar to the results from the conventional Cox-analysis. Moreover, subgroup analysis of women of pre- and postmenopausal age, as well as subjects without and with anemia, showed no difference in risk of VTE between conventional and cause-specific analysis. These findings suggest that RDW was associated with VTE regardless of intermediate development of MI, stroke, or cancer. The association between RDW and VTE was similar in men and women of postmenopausal age, whereas no association was found between RDW and VTE in women of premenopausal age or in subjects with anemia.

RDW is calculated from the mean corpuscular volume and is a numerical concept. Hence, the increased variation in red blood size is likely due to some underlying condition(s).

The mechanisms underlying the observed association between RDW and VTE remain unsettled, but increased RDW is associated with several biological and metabolic imbalances related to various diseases.[4] Inflammation and oxidative stress might alter iron metabolism, decrease the life span of red cells, and modulate the bone

TABLE 2 Incidence rates (Irs) and hazard ratios (HRs) with 95% confidence intervals (Cis) for venous thromboembolism (VTE) by quartiles and above the 95th percentile (pct) of red cell distribution with (RDW) in all subjects and after gender stratification. In conventional analysis, person-time of follow-up was calculated from the date of enrolment (1994/1995) to the date of an incident VTE diagnosis, to the date when the participant died or moved from the municipality of Tromsø, or to the end of the study period (December 31, 2010), whichever came first. For the cause-specific analysis, person time was calculated from the date of enrolment to the date of the first occurring diagnosis of VTE, MI, stroke, or cancer, to the date when the participant died or moved from Tromsø, or to the end of the study period, whichever came first

RDW	Conventional analysis			Cause-specific analysis		
	Events	IR[a] (95% CI)	HR[b] (95% CI)	Events	IR[a] (95% CI)	HR[b] (95% CI)
All subjects						
Quartile 1	74	0.9 (0.7-1.1)	Reference	52	0.6 (0.5-0.8)	Reference
Quartile 2	114	1.3 (1.1-1.6)	1.11 (0.83-1.49)	82	1.0 (0.8-1.2)	1.20 (0.85-1.71)
Quartile 3	134	1.6 (1.4-1.9)	1.11 (0.83-1.48)	88	1.1 (0.9-1.4)	1.14 (0.80-1.62)
Quartile 4	180	2.5 (2.2-2.9)	1.43 (1.08-1.91)	118	1.8 (1.5-2.1)	1.54 (1.09-2.18)
>95th pct	43	2.8 (2.1-3.8)	1.92 (1.28-2.87)	26	1.8 (1.3-2.7)	1.96 (1.19-3.25)
Men						
Quartile 1	30	0.8 (0.5-1.1)	Reference	22	0.6 (0.4-0.9)	Reference
Quartile 2	48	1.1 (0.8-1.5)	1.16 (0.73-1.84)	32	0.8 (0.6-1.1)	1.13 (0.65-1.95)
Quartile 3	65	1.6 (1.2-2.0)	1.34 (0.86-2.09)	49	1.3 (1.0-1.7)	1.54 (0.92-2.57)
Quartile 4	81	2.8 (2.2-3.5)	1.71 (1.09-2.67)	48	1.9 (1.4-2.5)	1.74 (1.01-3.00)
>95th pct	18	4.7 (2.9-7.4)	2.30 (1.21-4.37)	9	2.8 (1.4-5.3)	2.15 (0.92-5.04)
Women						
Quartile 1	44	1.0 (0.7-1.3)	Reference	30	0.7 (0.5-1.0)	Reference
Quartile 2	66	1.5 (1.2-1.9)	1.07 (0.73-1.57)	50	1.2 (0.9-1.5)	1.24 (0.79-1.96)
Quartile 3	69	1.6 (1.3-2.0)	0.95 (0.64-1.39)	39	1.0 (0.7-1.3)	0.85 (0.52-1.38)
Quartile 4	99	2.3 (1.9-2.9)	1.27 (0.88-1.85)	70	1.8 (1.4-2.2)	1.41 (0.90-2.22)
>95th pct	25	2.2 (1.5-3.2)	1.74 (1.03-2.93)	17	1.6 (1.0-2.5)	1.88 (1.00-3.56)

[a]Incidence rates are per 1000 person-years.
[b]Multivariable model: Sex, body mass index, smoking status, white blood cell count, and hemoglobin levels at baseline. Age is time-scale.

TABLE 3 Number of VTE events and multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for venous thromboembolism (VTE), by quartiles (Q) of red cell distribution width (RDW). Stratified on gender and age 55 (women only). In conventional analysis, person-time of follow-up was calculated from the date of enrolment (1994/95) to the date of an incident VTE diagnosis, to the date when the participant died or moved from the municipality of Tromsø, or to the end of the study period (December 31, 2010), whichever came first. For the cause-specific analysis, person time was calculated from the date of enrolment to the date of the first occurring diagnosis of VTE, myocardial infarction (MI), stroke or cancer, to the date when the participant died or moved from Tromsø, or to the end of the study period, whichever came first

RDW	VTE events	Conventional analysis HR (95%CI)	Cause-specific analysis HR (95%CI)
Men			
Q 1–3	143	Reference	Reference
Q 4	81	1.41 (1.04-1.89)	1.36 (0.94-1.97)
Women			
Age < 55			
Q 1–3	68	Reference	Reference
Q 4	23	1.07 (0.65-1.74)	1.04 (0.58-1.88)
Age > 55			
Q 1–3	111	Reference	Reference
Q 4	76	1.37 (1.01-1.86)	1.56 (1.07-2.25)

Multivariable model: Body mass index, smoking status, white blood cell count, and hemoglobin levels at baseline. Age is time-scale.

marrow's response to erythropoietin.[29,30] RDW is positively correlated with inflammation markers such as high sensitivity C-reactive protein (hs-CRP), interleukin-6 and sTNF-receptor.[31,32] However, studies on the association between inflammation markers and risk of VTE have been inconsistent,[33,34] and in our study, adjustment for white blood cell count did not alter the results. RDW is inversely associated with red blood cell deformability,[35] which may lead to erythrocyte aggregation and altered blood viscosity.[36] In turn, this may promote thrombosis.[37] However, there are no studies on the direct effect of RDW on blood viscosity or the rheological properties of blood.

In the present study, we found no association between RDW and VTE in women of premenopausal age, while women of postmenopausal age had similar risk as men. Previous studies have shown a strong association between RDW and iron deficiency anemia.[24,38] Moreover, iron deficiency has recently been associated with increased risk of VTE recurrence,[39] and anemia might be associated with risk of cerebral venous thrombosis.[40] However, a recent case-control study found no association between anemia and pulmonary embolism.[41] Moreover, the proportion of women with anemia was reported to be considerably higher in those of premenopausal age than in those of postmenopausal age in our cohort.[22] In the present study, we found no association between RDW and risk of VTE in subjects with anemia. These findings indicate that conditions other than anemia that causes high RDW are more likely to explain the link between high RDW and risk of VTE. Future studies are warranted to explore possible underlying mechanisms.

Major strengths of our study include the clear temporal sequence between exposure and outcomes, the large number of participants recruited from a general population, the long-term follow-up and the well-assessed information on RDW and potential confounders. The high attendance rate reduces the risk of selection bias and makes the study population likely to be representative for the general population. Since there is only one hospital providing radiological imaging and hospital care (both in and out-patients) in the region, the chance of missed outcome events in our study is low. Moreover, the Cancer Registry of Norway is considered a complete and valid registry.[26] Some limitations of the study need to be addressed. The RDW was measured at baseline only, and could possibly have changed during the relatively long follow-up. However, this type of non-differential misclassification generally leads to underestimation of true associations. Underlying medical conditions such as lung, heart, kidney and inflammatory diseases may potentially influence RDW. Unfortunately, we did not have information on all these conditions at baseline, and residual confounding can therefore not be completely ruled out.

In conclusion, our findings suggest that the association between RDW and future risk of VTE could not be explained by intermediate development of arterial thromboembolic conditions or cancer. Future studies are warranted to elucidate the underlying pathological mechanisms for the association between RDW and risk of VTE.

AUTHOR CONTRIBUTIONS

TSE analyzed the data and drafted the manuscript. JL, TS, EBM and IN interpreted the results and revised the manuscript. SKB and JBH designed the study, contributed with data collection, and revised the manuscript. All authors read and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Supplementary table 1: Number of events and multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for venous thromboembolism (VTE), by quartiles of red cell distribution width (RDW). Stratified on presence of anemia* at baseline. In conventional analysis, person-time of follow-up was calculated from the date of enrolment (1994/95) to the date of an incident VTE diagnosis, to the date when the participant died or moved from the municipality of Tromsø, or to the end of the study period (December 31, 2010), whichever came first. For the cause-specific analysis, person time was calculated from the date of enrolment to the date of the first occurring diagnosis of VTE, MI, stroke or cancer, to the date when the participant died or moved from Tromsø, or to the end of the study period, whichever came first.

RDW	VTE events	Conventional analysis HR (95% CI)	Cause-specific analysis HR (95% CI)
Non-anemic subjects			
Q 1-3	317	Reference	Reference
Q 4	172	1.36 (1.12-1.65)	1.41 (1.11-1.79)
Anemic subjects			
Q 1-3	5	Reference	Reference
Q 4	8	0.68 (0.21-2.20)	0.60 (0.12-3.08)

Multivariable model: Sex, body mass index, smoking status, white blood cell count, and hemoglobin levels at baseline. Age is time-scale
* Anemia defined as hemoglobin levels <12.0 g/dL in females and <13.0 g/dL in men