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Red Cell Distribution Width and Risk of Atrial Fibrillation and Subsequent Thromboembolism: The Tromsø Study

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Abstract

Introduction Red cell distribution width (RDW) is associated with cardiovascular diseases, including atrial fibrillation (AF) and venous thromboembolism (VTE). Whether RDW is a risk marker for thromboembolic events in AF patients is scarcely known. We aimed to assess the association between RDW and the risk of AF, and AF-related VTE and ischemic stroke, in a population-based cohort.

Methods We measured RDW in 26,111 participants from the Tromsø Study (1994–-1995), and registered incident AF cases through December 31, 2013. Among participants with AF, first-ever VTEs and ischemic strokes were registered from the date of AF diagnosis through the end of follow-up. We calculated hazard ratios (HRs) with 95% confidence intervals (CIs) for AF by quartiles of RDW. Furthermore, we calculated cause-specific HRs for VTE and ischemic stroke by tertiles of RDW for participants with AF.

Results There were 2,081 incident AF cases during a median of 18.8 years of follow-up. Subjects with RDW in the highest quartile (RDW $\geq$ 13.3%) had 30% higher risk of AF than those in the lowest quartile (RDW $\leq$ 12.3%). Among those with AF, subjects with RDW in the upper tertile had a doubled risk of ischemic stroke (HR 2.07, 95% CI 1.20–3.57). In contrast, RDW was not associated with incident VTE in subjects with AF.

Conclusion RDW was significantly associated with incident AF in a general population. Among subjects with AF, high RDW was associated with ischemic stroke, but not VTE.

Keywords
- venous thrombosis
- arterial thrombosis
- epidemiological studies
- red cell distribution width

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Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia of clinical importance, and contributes extensively to morbidity and mortality in the population.[1–3] Ischemic stroke is generally considered the most detrimental complication of AF,[4] but recent studies have also established AF as a risk factor for venous thromboembolism (VTE).[5,6]

Red cell distribution width (RDW) is an inexpensive and easily available measure of variation in erythrocyte size. Traditionally, RDW has been used in the differentiation of anemias, but RDW has recently also emerged as a risk marker for cardiovascular morbidity and mortality,[7–9] including myocardial infarction (MI),[9] heart failure,[10] ischemic stroke,[11,12] and VTE.[13,14] A few studies have also implicated RDW as a risk marker for AF.[15–18] In a case–control study including 117 patients with AF and 60 controls, RDW was found to be associated with AF in multivariable logistic regression analysis,[16] and in another case–control study by Liu et al, RDW was significantly higher in the AF group than in controls (12.7% vs. 12.4%; $p < 0.05$).[17] A recent meta-analysis examining the impact of hematological parameters on AF occurrence found higher RDW in participants with new-onset AF compared with those with sinus rhythm.[19] Furthermore, RDW was significantly increased in patients with AF recurrence.[19]

To what extent RDW is associated with thromboembolic outcomes in patients with AF has not been extensively studied. A dose–response relationship between increasing RDW and risk of stroke in AF patients was found in a large registry-based study,[20] while small case–control studies have reported diverging results.[21,22] Interestingly, increasing CHA2DS2-VASC score, an established prediction score for thromboembolism in AF patients,[23,24] was positively correlated with RDW levels in subjects with AF in several studies.[17,20,25] Whether RDW contributes to the excess VTE risk in patients with AF is not known.

In the present study, we aimed to assess (1) the association between RDW and incident AF in a general population cohort, and (2) whether RDW was associated with incident thromboembolism (VTE and ischemic stroke) in subjects with AF.

Methods

Study Population

Participants were recruited from the fourth survey of the Tromsø Study, an ongoing, prospective health study of the inhabitants of Tromsø, Norway. The fourth survey was performed in 1994 to 1995, and all inhabitants in the Tromsø municipality aged $\geq$ 25 years were invited to participate. In total, 27,158 persons aged 25 to 97 years attended the study, comprising 77% of the eligible population. We excluded those who withdrew their consent to medical research after the Tromsø Study inclusion date ($n = 166$), participants not officially registered as residents of Tromsø ($n = 22$), participants with AF prior to the inclusion date ($n = 234$), and persons with missing RDW measurements ($n = 625$). A total of 26,111 participants were included in the study and followed from the date of enrolment to December 31, 2013. Incident cases of AF during follow-up were registered. In secondary analyses, persons with VTE ($n = 82$) or ischemic stroke ($n = 200$) prior to AF diagnosis were excluded, and VTE and ischemic stroke events were recorded in all persons with a first lifetime diagnosis of AF ($n = 1{,}812$) from the day of AF diagnosis until the end of follow-up. All participants provided informed, written consent, and the Regional Committee for Medical and Health Research Ethics approved the study.

Baseline Measurements

Nonfasting blood samples, self-administered questionnaires, and a physical examination were used to obtain baseline information on all study participants. For the blood cell parameters measurements, including RDW, 5 mL of blood was drawn from an antecubital vein into a vacutainer containing EDTA as an anticoagulant, and analyzed within 12 hours in an automated blood cell counter (Coulter Counter, Coulter Electronics, Luton, United Kingdom). RDW was calculated by dividing the standard deviation of mean corpuscular volume (MCV) by each person's MCV value and multiplying by 100 to convert to a percentage.[26] The analytic coefficient of variation of the RDW measurements was less than 3%. All blood samples were taken at the inclusion date (in 1994/1995). Serum total cholesterol was measured as previously described.[27] Blood pressure measurements were performed using an automatic device (Dinamap Vital Signs Monitor, 1846; Critikon Inc., Tampa, Florida, United States). After 2 minutes seated rest, three recordings were taken on the upper right arm at intervals of 1 minute, and the mean of the last two values was used in the analyses. Participants with systolic blood pressure $\geq$ 140 mm Hg, diastolic blood pressure $\geq$ 90 mm Hg, or currently using antihypertensive drugs were classified as having hypertension. Height and weight were measured with the participant in light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the height in meters squared (kg/m^2). Self-administered questionnaires were used to obtain information on diabetes mellitus and current smoking status. Information on prior MI was obtained from the cardiovascular outcome registry of the Tromsø Study.

Ascertainment of Atrial Fibrillation

Incident AF was identified by searching the discharge diagnosis registry at the University Hospital of North Norway, the sole provider of hospital care for the entire Tromsø municipality, and the Norwegian Cause of Death Registry provided by the Norwegian Institute of Public Health. The Tromsø Study participants' unique identification numbers were linked to these diagnostic registries using the International Classification of Diseases, Ninth Revision (ICD-9) codes 427.0 to 427.99 and Tenth Revision (ICD-10) codes I47 and I48. For subjects with a diagnosis of cardiovascular or cerebrovascular disease, but without a registered arrhythmia diagnosis, paper versions of hospital records (used until 2001) were manually searched for any mention of AF, and the term "atrial fibrillation" was used for text searches in the electronic records. Trained personnel reviewed each potential AF case's medical record. All definite AF diagnoses required electrocardiogram documentation, and were adjudicated by an

independent endpoint committee. When possible, the AF events were further classified into paroxysmal and persistent versus permanent forms. Participants who had paroxysmal AF initially, but who eventually developed a permanent form, were classified as having permanent AF. Persons with transient AF occurring only in relation to cardiac surgery or an acute MI, and subjects who only had AF in the terminal phase (the last week) of life were not classified as having AF.[28]

Ascertainment of Venous Thromboembolism

We identified all incident VTE events by searching the hospital discharge diagnosis registry, the autopsy registry, and the radiology procedure registry at the University Hospital of North Norway as previously described in detail.[29] Trained personnel reviewed the medical records of each potential VTE event for case validation. A VTE episode was recorded as a validated outcome only when clinical VTE symptoms were present and combined with confirmatory tests (compression ultrasonography, venography, spiral computed tomography, perfusion–ventilation scan, pulmonary angiography, or autopsy), resulting in a VTE diagnosis that required treatment. For the VTE events retrieved from autopsy records, a validated event was recorded when the death certificate designated VTE as the cause of death or a significant condition contributing to death. The VTE event was further classified as unprovoked (no provoking factors) or provoked ($\geq$ one provoking factor[s]) based on the presence of provoking factors at the time of diagnosis. Immobilization (bed rest $\geq$ 3 days, wheelchair, long haul travel $\geq$ 4 hours within 14 days prior to the event), major surgery, trauma, or an acute medical condition (acute MI, ischemic stroke, or major infectious disease) within 8 weeks prior to the event, active cancer, or other potential provoking factors described by a physician in the medical record (e.g., intravascular catheter) were regarded as provoking factors.

Ascertainment of Ischemic Stroke

Information on incident ischemic stroke was obtained by linkage to the diagnosis registries at the University Hospital of North Norway and the Norwegian Cause of Death Registry, using an expansive search for the ICD-8 and -9 codes 430–438, and ICD-10 codes I60–I69 (cerebrovascular diseases). Systematic text searches in the medical records for patients with ICD-8 and -9 diagnosis codes 410–414 and 798–799, and ICD-10 codes I20–I25 and R96, R98, and R99 were additionally performed to ensure case completeness. The WHO definition was used to define ischemic stroke: Rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin.[30] Furthermore, imaging tests (computed tomography or magnetic resonance imaging) or an autopsy were required to exclude intracerebral or subarachnoid hemorrhage. An independent endpoint committee followed a detailed protocol according to established diagnostic criteria for case validation.

Statistical Analyses

We performed statistical analyses using STATA, version 15 (Stata Corporation, College Station, Texas, United States). For analysis of the association between RDW and AF, crude incidence rates (IRs) with 95% confidence intervals (CIs) were calculated as the total number of events divided by total person-time at risk, and expressed as events per 1,000 person-years. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% CI for AF by increasing levels of RDW. To assess for nonlinearity or a potential threshold effect, participants were categorized into quartiles based on the distribution of baseline RDW, and the lowest quartile was used as reference. Additionally, a cutoff was fixed at the 95th percentile. Model 1 included age, sex, and BMI, model 2 included the variables of model 1, as well as hemoglobin, white blood cells, and platelet count, and model 3 included the variables of model 2, as well as smoking, hypertension, diabetes, previous MI, and total cholesterol. We used chronological age as the time scale in the regression models, defining the participants' age at study enrollment as entry time, and the age at the time of AF diagnosis or censoring event (i.e., migration, death, or study end) as exit time.

In analyses regarding the risk of VTE and ischemic stroke by RDW levels in the AF population, tertiles based on the baseline RDW distribution were chosen for the categorical analyses due to the smaller population size. Cause-specific Cox proportional hazards models were used to estimate HRs with 95% CIs for VTE and ischemic stroke. In the cause-specific models, the AF patients were followed to the first occurrence of VTE or stroke (e.g., in the analyses of stroke risk, a participant who developed VTE before a stroke would be censored at the date of VTE). Age at AF diagnosis was used as entry time, and the age at the time of a censoring event (i.e., VTE, ischemic stroke, migration, death, or study end) as exit time. The number of participants included in the adjusted regression models varied slightly due to missing data for some covariates (in total 1.5% missing). We tested the assumption of proportional hazards assumption using Schoenfeld residuals and found no violation. Statistical interactions between RDW and sex were tested by including cross-product terms of sex and RDW into the models, and no interactions were found.

Results

A total of 2,082 participants (8.0%) experienced incident AF during a median follow-up time of 18.8 years, yielding a crude IR of 4.7 per 1,000 person-years. The mean age at AF diagnosis was 75.0 years (range 34.3–103.1 years). The mean RDW of the study population was 12.9% with a standard deviation of 0.93. Baseline characteristics of study participants across quartiles of RDW are shown in ►**Table 1**. The mean age at study inclusion was 12.5 years higher for participants in the highest versus the lowest quartile of RDW. White blood cell count, BMI, total cholesterol, and the prevalence of daily smoking, diabetes, prior MI, and hypertension increased across quartiles of RDW (►**Table 1**). Participants who developed AF during follow-up were older, had higher BMI, and total cholesterol levels, and a higher prevalence of diabetes and prior MI

Table 1 Baseline characteristics of study participants by quartiles of red cell distribution width (the Tromsø Study 1994–2013)

RDW	Quartile 1 ($n = 6{,}549$)	Quartile 2 ($n = 6{,}682$)	Quartile 3 ($n = 6{,}613$)	Quartile 4 ($n = 6{,}267$)
RDW range (%)	10.7–12.3	12.4–12.7	12.8–13.2	13.3–30.5
Age (y)	40.7 ± 12.3	44.6 ± 13.8	48.6 ± 14.7	53.2 ± 15.9
Sex (male, %)	46.1 (3,022)	49.0 (3,271)	49.5 (3,274)	44.2 (2,771)
Hemoglobin (g/dL)	14.1 ± 1.1	14.2 ± 1.1	14.1 ± 1.1	13.7 ± 1.4
White blood cells ($\times 10^9$/L)	6.9 ± 1.8	7.0 ± 2.1	7.1 ± 2.0	7.3 ± 2.2
Platelets ($\times 10^9$/L)	251 ± 51	249 ± 52	251 ± 55	260 ± 66
Body mass index (kg/m^2)	24.7 ± 3.5	25.1 ± 3.7	25.3 ± 3.9	25.5 ± 4.2
Total cholesterol (mmol/L)	5.7 ± 1.2	6.0 ± 1.3	6.2 ± 1.3	6.3 ± 1.4
Diabetes (%)	1.4 (88)	1.6 (105)	1.6 (128)	1.9 (121)
History of myocardial infarction (%)	4.4 (290)	7.3 (489)	11.2 (739)	15.9 (994)
Hypertension[a] (%)	26.7 (1,745)	32.6 (2,179)	37.3 (2,469)	45.6 (2,860)

Abbreviation: RDW, red cell distribution width.
Note: Values are given as percentages with numbers in brackets or as means with standard deviations.
[a]Defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or self-reported use of antihypertensive medication.

compared with participants without AF (►**Table 2**). Hemoglobin levels and white blood cell counts were higher in those with AF, while there were more daily smokers among participants without than with AF (►**Table 2**).

Crude IRs and HRs for AF across quartiles of RDW are shown in ►**Table 3**. Participants with RDW in the highest quartile had 32% increased risk of incident AF compared with those in the lowest quartile in analyses adjusted for age, sex, and BMI (HR 1.32, 95% CI 1.14–1.52). The relative risk estimates remained unchanged after further adjustment for hematological parameters (model 2), and barely altered after addition of cardiovascular risk factors to the regression model (model 3) (►**Table 3**). Given the wide range of RDW in the highest quartile (13.3–30.5), we performed sensitivity analyses excluding participants with RDW measurements above the 95th percentile (≥ 14.4%), and found similar risk estimates as for the full cohort (data not shown). Participants with RDW measurements above the 95th percentile (≥ 14.4%) had a similar 1.3-fold increased VTE risk when compared with participants in the lowest quartile (multivariable HR 1.30, 95% CI 1.04–1.63) (►**Table 3**). When modeling RDW as a continuous variable, a 1% increment in RDW was associated with a 7% increased risk of AF (HR 1.07, 95% CI 1.02–1.12) after multivariable adjustment (►**Table 3**). We also performed age-stratified analyses in which the risk of AF was assessed in participants younger than and older than 60 years of age at inclusion. When comparing those in the highest versus the lowest quartile of RDW, the positive association was slightly more pronounced in the youngest age group, but the CIs overlapped (multivariable HR 1.38 [95% CI 1.11–1.74] and 1.27 [95% CI 1.09–1.49] for those ≤ 60 years and those < 60 years, respectively) (data not shown). To investigate whether the association between RDW and AF was modified by anemia, we performed analyses in which women with hemoglobin levels < 12 g/L ($n = 976$) and men with hemoglobin levels < 13 g/L ($n = 338$) were excluded. In analyses adjusted for BMI and sex, the risk estimates for nonanemic participants in the highest RDW quartile did not differ from that observed for the total population (HR 1.33, 95% CI 1.15–1.54) (data not shown).

Among the 2,082 participants who developed AF during follow-up, 270 persons had an ischemic stroke ($n = 190$) or VTE ($n = 80$) before the AF diagnosis, and were excluded from the cause-specific analyses of RDW as a risk marker for AF-

Table 2 Baseline characteristics by development of atrial fibrillation (the Tromsø Study 1994–2013)

	Without AF ($n = 25{,}029$)	With AF ($n = 2{,}082$)
RDW (%)	12.9 ± 0.9	13.1 ± 0.9
Age (y)	45.3 ± 14.4	62.7 ± 11.8
Sex (male, %)	46.6 (11,205)	54.4 (1,133)
Body mass index (kg/m^2)	25.0 ± 3.8	26.9 ± 4.3
Total cholesterol (mmol/L)	6.0 ± 1.3	6.7 ± 1.2
Hypertension[a] (%)	32.5 (7,804)	69.6 (1,449)
Self-reported diabetes (%)	1.4 (344)	4.7 (98)
Daily smoking (%)	37.8 (9,070)	27.9 (579)
History of myocardial infarction (%)	7.7 (1,861)	31.3 (651)
Hemoglobin (total) (g/dL)	14.0 ± 1.2	14.3 ± 1.1
White blood cells ($\times 10^9$/L)	7.1 ± 2.0	7.0 ± 2.0
Platelets, $\times 10^9$/L	254 ± 56	242 ± 56

Abbreviations: AF, atrial fibrillation; RDW, red cell distribution width.
Note: Values are given as percentages with numbers in brackets or as means with standard deviations.
[a]Defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or self-reported use of antihypertensive medication.

Table 3 Crude incidence rates per 1,000 person-years and adjusted hazard ratios with 95% confidence intervals for atrial fibrillation by quartiles of red cell distribution width (the Tromsø Study 1994–2013)

RDW	Persons	Median RDW, % (range)	Person-years	Events	IR	HR, model 1[a]	HR, model 2[b]	HR, model 3[c]
Quartile 1	6,549	12.0 (10.7–12.3)	118,670	255	2.1 (1.9–2.4)	Ref	Ref	Ref
Quartile 2	6,682	12.6 (12.4–12.7)	117,361	446	3.8 (3.5–4.2)	1.14 (0.97–1.33)	1.13 (0.97–1.32)	1.12 (0.96–1.31)
Quartile 3	6,613	13.0 (12.8–13.2)	111,012	619	5.6 (5.2–6.0)	1.18 (1.02–1.37)	1.18 (1.02–1.37)	1.15 (0.99–1.33)
Quartile 4	6,267	14.1 (13.3–30.5)	95,056	762	8.0 (7.5–8.6)	1.32 (1.14–1.52)	1.32 (1.14–1.53)	1.27 (1.09–1.47)
> 95th percentile	1,317	15.7 (14.4–30.5)	18,771	138	7.4 (6.2–8.7)	1.36 (1.10–1.68)	1.49 (1.16–1.80)	1.30 (1.04–1.63)
HR per 1% increase in RDW						1.08 (1.03–1.12)	1.10 (1.05–1.15)	1.07 (1.02–1.12)

Abbreviations: IR, incidence rate; HR, hazard ratio; RDW, red cell distribution width.
[a]Age as time scale, adjusted for sex and body mass index.
[b]Age as time scale, adjusted for sex, body mass index, hemoglobin, white blood cells, and platelets.
[c]Age as time scale, adjusted for sex, body mass index, hemoglobin, white blood cells, platelets, smoking, hypertension, self-reported diabetes, previous myocardial infarction, and total cholesterol.

related thromboembolism. The remaining 1,812 participants with AF were followed for a median of 3.7 years, and there were 264 incident ischemic strokes and 87 VTEs during follow-up. Among the VTE events, 53 (61%) were pulmonary embolisms (PEs) and 34 (39%) were deep vein thromboses (DVTs). Fifty-eight (66.7%) of the VTE events had one or more provoking factor present at the time of diagnosis, and among the provoked events, 50% were attributed to an acute medical condition within 8 weeks prior to the VTE. Seventeen participants experienced both ischemic stroke and VTE during follow-up, and for these participants, follow-up ended when their first thromboembolic event occurred (VTE first = 5, stroke first = 12). The calculated crude IRs and HRs for VTE and ischemic stroke across tertiles of RDW are shown in ►**Table 4**. Crude IRs for ischemic stroke were significantly higher in the highest tertile (IR 4.00 per 100 person-years, 95% CI 3.26–4.90) versus the lowest tertile (IR 2.30 per 100 person-years, 95% CI 1.84–2.89) of RDW. Furthermore, participants with RDW measurements in the highest tertile had a 51% increased risk of ischemic stroke compared with those in the lowest tertile after multivariable adjustment (HR 1.51, 95% CI 1.09–2.10) (►**Table 4**). On the other hand, there was no apparent increased risk of VTE by increasing RDW tertiles in any of the regression models (►**Table 4**). In subgroup analyses, RDW was not associated with either PE or DVT (data not shown).

Discussion

In this population-based cohort study, we confirmed an association between RDW and incident AF and expanded the current knowledge on the impact of RDW on the risk of thromboembolic events in AF patients. The risk of ischemic stroke, but not VTE, was higher with increasing RDW in AF patients.

Our finding of RDW as a risk marker for incident AF is in concurrence with previous reports. In a comparable cohort from the Malmö Diet and Cancer Study,[15] similar HRs for AF by RDW as those obtained in our study were reported. In their study, the highest quartile of RDW was associated with a 1.3-fold increased risk of AF after multivariable analyses, and a 1% increment in RDW was associated with an 8% increase in AF risk.[15] Similarly, Li et al found elevated RDW to be significantly associated with prevalent AF in a recently published Chinese cross-sectional study.[18] In a meta-analysis comprising 2,721 participants with AF, higher baseline RDW was associated with incident AF, but there was significant heterogeneity across the studies.[31]

The biological mechanisms linking increasing RDW to AF are unclear. High levels of RDW may reflect oxidative stress and inflammation, as these factors shorten the life span of red blood cells and hamper bone marrow function, leading to a more heterogeneous erythrocyte population.[32,33] As AF is associated with both systemic inflammation and oxidative stress,[34,35] the association with RDW may partially be mediated through these factors. In the present study, we found that the association between RDW and AF was virtually unchanged after adjustment for white blood cell count, suggesting that other mechanisms than inflammation may be involved in the interplay between RDW and AF. This is in concurrence with a previous report from the Tromsø Study, in which the association between RDW and MI and ischemic stroke was only slightly attenuated after adjustments for C-reactive protein.[36]

A direct effect of erythrocyte dysfunction on the myocardium may contribute to the development of AF. A heterogeneous erythrocyte population may have lower deformability and decreased oxygen-carrier capacity,[37] contributing to reduced myocardial oxygenation and cardiac dysfunction,[38] in turn triggering AF. An association between reduced erythrocyte deformability and cardiac arrhythmias has been demonstrated

Table 4 Crude incidence rates per 100 person-years and hazard ratios for incident venous thromboembolism and ischemic stroke by red cell distribution width in subjects with atrial fibrillation (the Tromsø Study 1994–2013)

	Persons	Median RDW, % (range)	Person-years	Events	IR	HR, model 1[a]	HR, model 2[b]	HR, model 3[c]
Venous thromboembolism								
Tertile 1	627	12.4 (11.3–12.7)	3,256	29	0.89 (0.62–1.28)	Ref	Ref	Ref
Tertile 2	645	13.0 (12.8–13.3)	3,161	23	0.72 (0.48–1.09)	0.75 (0.43–1.31)	0.75 (0.43–1.30)	0.76 (0.43–1.34)
Tertile 3	540	14.1 (13.4–21.6)	2,328	23	0.99 (0.65–1.49)	1.01 (0.58–1.77)	1.00 (0.57–1.76)	0.97 (0.54–1.74)
> 95th percentile	93	15.6 (14.6–21.6)	368	2	0.54 (0.14–2.17)	0.56 (0.13–2.38)	0.57 (0.13–2.45)	0.58 (0.13–2.52)
HR per 1% increase in RDW						1.09 (0.83–1.41)	1.11 (0.84–1.47)	1.11 (0.83–1.48)
Ischemic stroke								
Tertile 1	627	12.4 (11.3–12.7)	3,256	75	2.30 (1.84–2.89)	Ref	Ref	Ref
Tertile 2	645	13.0 (12.8–13.3)	3,161	91	2.88 (2.34–3.54)	1.17 (0.86–1.58)	1.17 (0.86–1.59)	1.20 (0.88–1.64)
Tertile 3	540	14.1 (13.4–21.6)	2,328	93	4.00 (3.26–4.90)	1.50 (1.10–2.04)	1.48 (1.07–2.03)	1.51 (1.09–2.10)
> 95th percentile	93	15.6 (14.6–21.6)	368	20	5.44 (3.51–8.43)	2.11 (1.28–3.46)	2.00 (1.17–3.41)	2.07 (1.20–3.57)
HR per 1% increase in RDW						1.18 (1.03–1.34)	1.17 (1.02–1.35)	1.18 (1.02–1.36)

Abbreviations: IR, incidence rate; HR, hazard ratio; RDW, red cell distribution width.
[a]Age as time scale, adjusted for sex and body mass index.
[b]Age as time scale, adjusted for sex, body mass index, hemoglobin, white blood cells, and platelets.
[c]Age as time scale, adjusted for sex, body mass index, hemoglobin, white blood cells, platelets, smoking, hypertension, self-reported diabetes, previous myocardial infarction, and total cholesterol.

previously.[39] As addressed by a recent review,[40] anemia is associated with both AF development and increased RDW.[40] In the present study, risk estimates for AF were not significantly modified by adjusting for hemoglobin levels in the regression models, nor by excluding anemic participants from the multivariable analyses.

Previous observational studies, including reports from the Tromsø Study, have reported an increased risk of both VTE[13,14] and ischemic stroke[11,12] by RDW in the general population. Several mechanisms underlying these associations have been postulated, including inflammatory conditions, renal dysfunction, malnutrition, and oxidative damage.[41] Increased RDW has also been associated with decreased red blood cell deformability,[37] which increases erythrocyte aggregation,[42] and thus may trigger thrombosis.[43] A few studies have previously explored whether increasing RDW is associated with an excess risk of thromboembolism in AF patients.[20,44–46] In accordance with our results, Saliba et al found RDW to be associated with both absolute and relative risks of stroke in subjects with AF.[20] In their population-based registry study, the stroke risk was 33% higher among AF patients in the highest versus the lowest quartile of RDW.[20] Similarly, in a retrospective study of 5,082 patients with AF, RDW values $\geq$ 13.9% conferred a 1.7-fold increased risk of thromboembolic events (ischemic stroke and peripheral embolism) compared with RDW $<$ 13.9%.[45] Although AF is a risk factor for incident VTE,[6,47,48] RDW measures did not affect VTE risk in the present AF cohort.

The mechanisms behind the differential impact of RDW measures on the two thromboembolic outcomes are not known. RDW measures correlate with the CHA2DS2-VASC score,[17,25,46] whose components (Congestive heart failure, Hypertension, Age > 75, Diabetes mellitus, Stroke/TIA/thromboembolism, Vascular disease, Age 65–74, Sex [female]), are associated with stroke risk in AF patients. In contrast, neither hypertension, diabetes mellitus, nor female gender have been associated with VTE risk in prospective studies.[27,49] Thus, it is possible that the excess risk of stroke by RDW in AF patients to some extent reflects a burden of cardiovascular risk factors that have little impact on VTE risk.[50]

The thrombosis potential model proposed by Rosendaal two decades ago emphasizes the multicausal nature of VTE.[51] The model illustrates how a VTE develops once sufficient risk factors have accumulated in a patient, and that VTE risk factors have synergistic effects.[51] We have previously demonstrated that the risk of PE in the first 6 months following AF diagnosis is 11-fold higher when compared with subjects without AF, largely exceeding the comparable risk estimates for ischemic stroke.[48] In the present study, we observed a majority of

provoked VTEs among the AF patients, and one-third of all VTE had suffered an acute medical condition within 8 weeks prior to VTE diagnosis. In concurrence with the thrombosis potential model, it is plausible that the accumulated risk factors in the present population (high age, AF, hospitalizations, and comorbidities) dilute the additional impact of RDW on VTE risk.

Our study has several strengths, including the large number of participants recruited from a general population, and the prospective design with a mean follow-up of almost 19 years. The high attendance rate reduces the risk of selection bias, and the detailed validation of exposures and outcome ensures a clear temporality of events. Several limitations also merit attention. RDW was only measured at inclusion, and may have fluctuated over time. Unfortunately, repeated measurements of RDW are not available for the Tromsø Study population. Nevertheless, nondifferential misclassification of this kind generally leads to an underestimation of true associations. In an earlier report from the Tromsø Study, we found that risk estimates for VTE based on baseline measurements of cardiovascular risk factors (time-fixed analyses) in general corresponded well with risk estimated based on repeated measurements (time-varying analyses).[52] The true incidence of AF in our study may be underestimated, as many episodes of AF are asymptomatic. Furthermore, patients with AF exclusively treated in general practice are not included. We lacked information on heart failure and the use of antithrombotic medication. As the latter effectively reduces thrombosis risk in AF patients, it is possible that we underestimate the true risk of VTE and ischemic stroke by RDW in our AF population. Furthermore, not having information on heart failure makes it difficult to assess the implementation of RDW to existing prediction scores in AF. Among the AF patients, the number of VTE events was small, and our study may be underpowered to detect weak associations.

In conclusion, RDW showed an association with incident AF. In patients with AF, RDW further aggravated the risk of ischemic stroke, but not the risk of VTE.

Authors' Contributions

E.M.H. contributed to data collection, data analysis, and writing of the manuscript. M.-L.L., E.B.M., and I.N. contributed to data collection and revision of the manuscript. J.L. and T.S.E. contributed to revision of the manuscript. T. W. provided statistical support and contributed to revision of the manuscript. S.K.B. contributed to data collection, data interpretation, and revision of the manuscript. J.-B.H. contributed to the conception and design of the study, data collection, and interpretation and revision of the manuscript.

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Conflict of Interest

None declared.

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