Received: 28 November 2019 | Revised: 26 March 2020 | Accepted: 1 April 2020

DOI: 10.1002/rth2.12351

ORIGINAL ARTICLE

rpth research & practice in thrombosis & haemostasis

Atrial fibrillation, venous thromboembolism, ischemic stroke, and all-cause mortality: The Tromsø study

Erin Mathiesen Hald MD, PhD[1,2] | Maja-Lisa Løchen MD, PhD[3] | Ellisiv B. Mathiesen MD, PhD[1,4] | Tom Wilsgaard PhD[3] | Inger Njølstad MD, PhD[1,3] | Sigrid K. Brækkan PhD[1,2] | John-Bjarne Hansen MD, PhD[1,2]

[1]K. G. Jebsen - Thrombosis Research and Expertise Center (TREC), Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway

[2]Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway

[3]Epidemiology of Chronic Diseases Research Group, Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway

[4]Brain and Circulation Research Group, Department of Clinical Medicine, UiT, The Arctic University of Norway, Tromsø, Norway

Correspondence
Erin Mathiesen Hald, K.G. Jebsen TREC, Faculty of Health Sciences, UiT The Arctic University of Norway, 9037 Tromsø, Norway.
Email: erin.mathiesen.hald@uit.no

Funding information
Stiftelsen Kristian Gerhard Jebsen; Northern Norway Regional Health Authority

Handling Editor: Dr Suzanne Cannegieter

Abstract

Background: Atrial fibrillation (AF) is associated with increased risk of ischemic stroke and all-cause mortality. Patients with AF are also at increased risk of venous thromboembolism (VTE), but information on how AF impacts VTE-related mortality is scarce.

Objectives: To investigate the impact of AF on all-cause mortality in subjects with and without a thromboembolic event (VTE or ischemic stroke).

Methods: We followed 29 833 participants from the Tromsø study (1994-2008) through 2013 and recorded all deaths during follow-up. Incident AF, VTE, and ischemic stroke were registered as time-dependent exposures. We calculated mortality rates (MRs) by exposure during follow-up and obtained hazard ratios (HRs) for death with 95% confidence intervals (CIs).

Results: A total of 2087 AF cases, 756 VTEs, and 1279 ischemic strokes were registered during a median follow-up of 18.7 years, and 4797 people (16.1%) died. The age-adjusted MR for participants without any event was 1.19 per 100 person-years (PY; 95% CI, 1.15-1.23). Compared to these participants, subjects with the joint AF + VTE exposure had a 3.7-fold increased risk of death (HR, 3.67; 95% CI, 2.77-4.66) in age- and sex-adjusted analyses, similar to the risk observed for VTE alone (HR, 3.76; 95% CI, 3.28-4.30). Participants with stroke had a 2.9-fold increased risk of death (HR, 2.85; 95% CI, 2.56-3.18), and the risk was further increased in participants with both AF and stroke (HR, 4.38; 95% CI, 3.85-4.98).

Conclusions: AF was significantly associated with increased risk of death in participants with incident stroke. In contrast, concomitant AF was not associated with excess mortality risk in VTE patients.

KEYWORDS

atrial fibrillation, cohort studies, mortality, stroke, venous thromboembolism

Essentials

- The impact of atrial fibrillation (AF) on venous thromboembolism (VTE) mortality is unclear.
- In total, 29 833 participants from the general population were included.
- The joint exposure of AF and VTE was associated with a death risk similar to that for VTE only.
- AF was associated with increased risk of death subjects with stroke, but not in those with VTE.

1 | INTRODUCTION

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia of clinical significance, and a major contributor to the public health burden.[1,2] AF independently predicts excess morbidity and increases all-cause mortality rates 2-fold in the general population.[1,3] The most detrimental complication of AF is ischemic stroke, and the risk of stroke is up to 5-fold increased in patients with AF.[1,4] Furthermore, stroke patients with AF have increased short- and long-term case-fatality rates.[5,6] Epidemiologic studies have reported 2-fold higher mortality rates in stroke patients with AF compared to those without.[7,8]

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third-leading cause of cardiovascular death after myocardial infarction (MI) and ischemic stroke and affects 1 to 3 per 1000 persons annually in Western populations.[9,10] While the impact of AF on the risk of ischemic stroke have been known for decades, recent epidemiologic studies have demonstrated that AF also increases the risk of VTE.[11-13] A population-based Taiwanese study reported a 3-fold increased risk of VTE in subjects with AF.[11] Similarly, Sundbøll et al[12] found a 2.4-fold higher incidence rate for PE in the first year following AF diagnosis. In a previous publication from the Tromsø study, the risk of VTE, and PE in particular, was significantly higher in subjects with incident AF than in those without.[13] Further cause-specific analyses demonstrated that the excessive PE risk conveyed by AF could not be explained by the intermediate development of ischemic stroke.[4]

Despite diagnostic and therapeutic advances during the past decades, the all-cause mortality rates after VTE, especially after PE, remain substantial.[14] Whether AF is a prognosticator in VTE has not been extensively studied, even though the 2 conditions frequently coexist.[15-17] AF upon hospital admittance was associated with reduced survival after VTE in some studies,[18,19] while others report no impact on mortality regardless of AF onset.[16,20] A recently published meta-analysis found AF at admission to be predictive of in-hospital death in patients with PE in unadjusted analyses.[21]

To what extent AF impacts VTE mortality in the general population is unclear. In the present study, we therefore aimed to investigate the joint effect of AF and VTE on the risk of all-cause mortality. For comparison, we simultaneously assessed the joint effect of AF and ischemic stroke on the risk of mortality within the same population.

2 | METHODS

2.1 | Study population

Participants were recruited from the fourth (1994-1995), fifth (2001-2002) and sixth (2007-2008) surveys of the Tromsø study, an ongoing population-based cohort study of inhabitants of Tromsø, Norway. All inhabitants of Tromsø (Tromsø 4) or parts of the population (Tromsø 5 and 6) aged ≥ 25 years were invited to participate, and 30 586 persons between 25 and 97 years of age attended ≥1 of the surveys. A detailed description of the Tromsø study cohort has been published previously.[22] We excluded all participants who withdrew their consent to medical research after the Tromsø study inclusion date (n = 181); participants not officially registered as residents of Tromsø (n = 23); and those with VTE (n = 87), ischemic stroke (n = 215), or AF (n = 247) prior to study enrollment. A total of 29 833 participants were included in the study, and followed from the inclusion date to December 31, 2013. Incident cases of AF, VTE, and ischemic stroke, as well as deaths among all study participants were registered throughout follow-up. The study was approved by the Regional Committee for Medical and Health Research Ethics, and all participants gave their informed, written consent.

2.2 | Baseline measurements

Information on body mass index (BMI), hypertension, self-reported diabetes, smoking, and total cholesterol was obtained on the date the participant attended the Tromsø study. Blood pressure measurements were carried out using an automatic device (Dinamap Vital Signs Monitor, 1846; Critikon Inc). After 2 minutes of seated rest, 3 recordings were taken on the upper right arm at 1-minute intervals, and the mean of the last 2 values was used in the analyses. Those with systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or currently using antihypertensive drugs were classified as having hypertension. Nonfasting blood samples were obtained from all study participants, and serum total cholesterol was measured as previously detailed.[23] Height and weight were measured with the participant in light clothing and no shoes. BMI was calculated as weight in kilograms divided by the height in meters squared (kg/m^2). History of diabetes and current smoking was obtained from self-administered questionnaires, and information on prior MI was obtained from the cardiovascular

end point registry of the Tromsø study. Information regarding cancer diagnosis, either prior to study inclusion or during follow-up, was obtained by linkage to the Cancer Registry of Norway. Participants with a diagnosis of nonmelanoma skin cancer were classified as cancer free.

2.3 | Ascertainment of AF

Incident AF was identified by searching the discharge diagnosis registry at the University Hospital of North Norway and the Norwegian Cause of Death Registry at the Norwegian Institute of Public Health, using the International Classification of Diseases, Ninth Revision (ICD-9) codes 427.0-427.99 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. An electrocardiogram documenting AF was a prerequisite for AF diagnosis, and all events were adjudicated by an independent end point committee. Episodes of transient AF documented only in relation to cardiac surgery or an acute MI were not classified as AF events.

2.4 | Ascertainment of VTE

Incident VTE cases were identified 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.[24] All hospital care and relevant diagnostic radiology in the Tromsø municipality are provided solely by this hospital. Trained personnel reviewed the medical record of each potential patient with VTE for case validation. A VTE episode was verified and recorded as a validated outcome when clinical signs and symptoms of VTE were combined with objective confirmation tests (compression ultrasonography, venography, spiral computed tomography, perfusion–ventilation scan, pulmonary angiography, or autopsy) and resulted in treatment initiation. For cases retrieved from autopsy records, a VTE event was recorded when the death certificate designated VTE as the cause of death or a significant condition contributing to death. Participants diagnosed with concurrent PE and DVT were registered as having PE. The VTE events were further classified as unprovoked (no provoking factors) or provoked (≥1 provoking factor[s]) based on the presence of provoking factors at the time of diagnosis. Immobilization (bed rest ≥ 3 days, wheelchair, long-haul travel ≥ 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 (eg, intravascular catheter) were considered provoking factors.

2.5 | Ascertainment of ischemic stroke

Information on first-ever ischemic strokes was obtained by linkage to the diagnostic registries of the University Hospital of North Norway and the Norwegian Cause of Death Registry at The Norwegian Institute of Public Health, using the ICD, Eighth Revision (ICD-8) and ICD-9 codes 430-438, and ICD-10 codes I60-I69 (cerebrovascular diseases). Systematic text searches were also performed in the medical records for patients with ICD-8 and ICD-9 diagnosis codes 410-414 and 798-799, and ICD-10 codes I20-I25 and R96, R98 and R99, to ensure case completeness. The World Health Organization 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 leading to death with no apparent cause other than vascular origin.[25] Moreover, imaging tests (computed tomography or magnetic resonance imaging) or autopsy were required in order to exclude intracerebral or subarachnoid hemorrhage. An independent end point committee followed a detailed protocol according to established diagnostic criteria for case validation.

2.6 | Outcome

Information on deaths was retrieved from the Norwegian Population Registry by use of the unique national person identification number.

2.7 | Statistical analyses

We performed statistical analyses using STATA version 15.0 (Stata Corporation). Attained age was used as the time scale, defining the participant's age at enrollment as entry time, and the age at the time of a censoring event (ie, death, migration, or study end) as exit time. We calculated crude mortality rates (MRs) and hazard ratios (HRs) for death during follow-up by exposure status during follow-up (no event, AF only, VTE only, ischemic stroke only, or >1 exposure). Poisson regression models were used to obtain age-adjusted MRs. All participants contributed with nonexposed person-time from the baseline inclusion date to the date of a first event, and then with exposed time from that date onward. For participants who developed both AF and VTE, AF and ischemic stroke, or VTE and ischemic stroke, a third observational period was counted from the date of the second diagnosis through the end of follow-up, and for those who experienced all 3 events (AF, VTE, and ischemic stroke), a fourth observational period was counted from the date of the third diagnosis through the end of follow-up (Figure 1). In total, 29 833 subjects contributed with 33 899 observational periods. We further performed stratified analyses by type of VTE (PE or DVT), separate analyses of unprovoked and provoked VTEs, and analyses in which participants with cancer were censored on the date of cancer diagnosis. We tested the assumption of proportional hazards using Schoenfeld residuals and found that the "VTE only" and the "AF + VTE" exposures violated the assumption

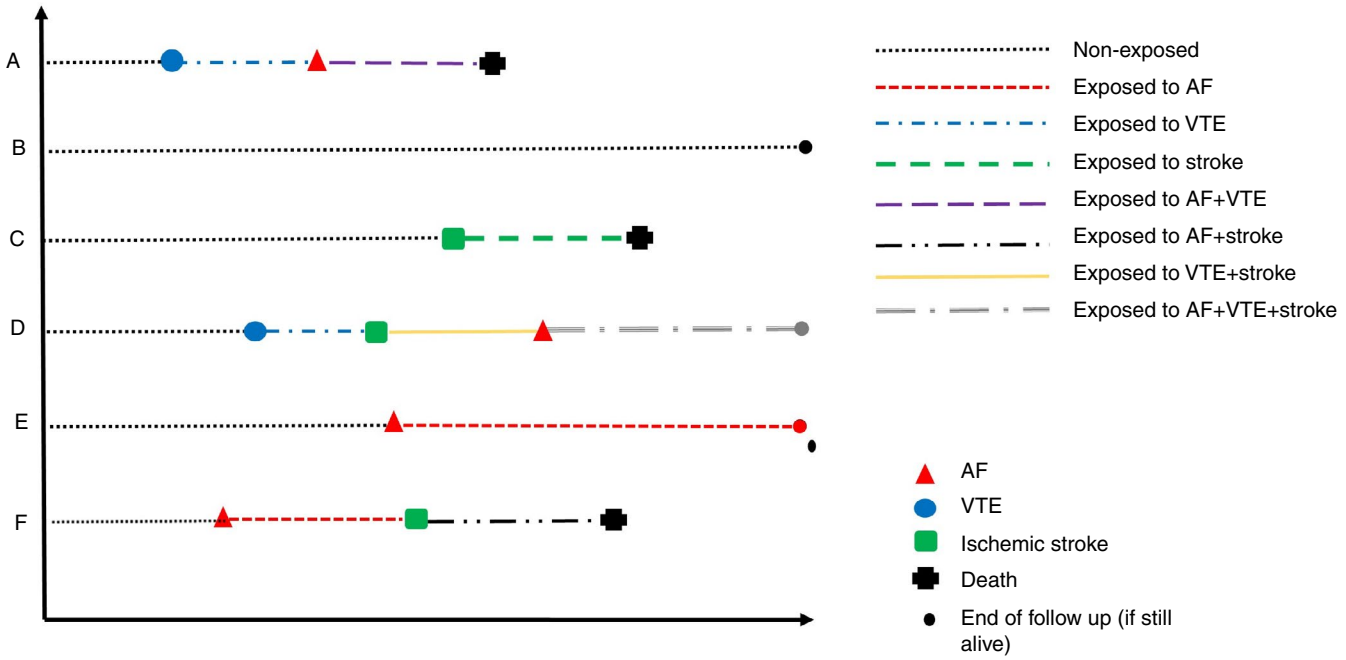

FIGURE 1 Examples of exposure time measured in patients during follow-up. The Tromsø Study 1994-2013. Person A: Contributed with nonexposed person-time from inclusion, then with "exposed to VTE" person-time from the date of VTE until AF diagnosis, then with "exposed to AF + VTE" person-time from that day onward until death. Person B: Nonexposed to any event throughout the study period. Person C: Contributed with nonexposed person-time from inclusion, then with "exposed to stroke" person-time from the date of ischemic stroke until death. Person D: Contributed with nonexposed person-time from inclusion, with "exposed to VTE" person-time from the date of VTE until stroke diagnosis, then with "exposed to VTE + stroke" person-time to AF diagnosis, and then with "exposed to AF + VTE + stroke" person-time until end of follow-up. Person E: Contributed with nonexposed person-time from inclusion until AF diagnosis, then with "exposed to AF" until end of follow-up. Person F: Contributed with nonexposed person-time from inclusion, with "exposed to AF" person-time form the date of AF until stroke diagnosis, and then with "exposed to AF + stroke" person time until death. AF, atrial fibrillation; VTE, venous thromboembolism

of proportional hazards. We consequently calculated HRs in different age groups (younger vs older participants). Statistical interactions between the different exposures and sex were tested by including cross-product terms in the Cox regression models. A borderline significant interaction term was found for sex and AF, and sex and ischemic stroke, and we further performed analyses stratified on sex. The number of participants included in the adjusted regression models varied slightly due to missing data for some covariates (in total 1.1% missing).

3 | RESULTS

A total of 756 VTE events, 1279 ischemic strokes, and 2087 cases of AF were registered during a median of 18.7 years (range, 6 days to 19.3 years) of follow-up. The baseline characteristics of those who developed incident events (AF, stroke, or VTE) during follow-up are summarized in Table 1. Participants with any event during follow-up were markedly older at inclusion than those without an event. Subjects with the joint AF and VTE exposure were on average 20 years older at inclusion, and those with AF and ischemic stroke 22 years older, than participants without any event during follow-up (Table 1). Furthermore, hypertension, diabetes, and a history of MI was more prevalent in those who later developed AF and ischemic stroke. Participants with all 3 events (AF, VTE, and ischemic stroke) had the highest baseline age, BMI, and cholesterol levels and the largest proportion of hypertension, diabetes, and previous MI (Table 1).

The association between AF, VTE, ischemic stroke, and the joint exposures on risk of death is shown in Table 2. During follow-up, a total of 4797 persons (16.1%) died. The overall crude mortality rates were similar for subjects with AF only (MR, 7.58 per 100 PY; 95% CI, 7.03-8.19) and VTE only (MR 7.74 per 100 PY; 95% CI, 6.81-8.81), while the crude MR was considerably higher in participants with the joint exposure AF + VTE (16.8 per 100 PY; 95% CI, 13.3-21.3) (Table 2). After age adjustment, the differences in MRs were markedly attenuated, with similar MRs observed for VTE only and AF + VTE. The latter exposures conferred an almost 4-fold increased risk of death compared with subjects with no event during follow-up in analysis using age as the time scale and adjusted for sex (Table 2).

Participants with the combined exposure of both AF and ischemic stroke during follow-up had a higher age-adjusted all-cause MR of 8.21 per 100 PY (95% CI, 7.22-9.20), compared to those with either AF only (MR, 4.24 per 100 PY; 95% CI, 3.92-4.56) or ischemic stroke only (MR, 4.93 per 100 PY; 95% CI, 4.43-5.43) (Table 2). In age- and sex-adjusted analyses, participants with either AF or ischemic stroke had a more than doubled risk of death compared to participants without either event, while the HR for death was over 4-fold higher in subjects with both events (HR, 4.38; 95% CI, 3.85-4.98) (Table 2).

TABLE 1 Baseline characteristics of participants (n = 29 833) in persons with and without an exposure status during follow-up

	No event (n = 26 350)	AF only (n = 1527)	VTE only (n = 558)	Stroke only (n = 797)	AF + VTE (n = 119)	AF + stroke (n = 403)	VTE + stroke (n = 41)	AF + VTE + stroke (n = 38)
Age, y	45.0 ± 13.6	62.0 ± 12.1	55.7 ± 13.9	61.4 ± 13.1	65.0 ± 10.9	66.9 ± 10.3	65.8 ± 10.4	68.9 ± 8.4
Sex, male	46.4 (12 220)	57.4 (877)	47.9 (267)	58.3 (465)	45.4 (54)	49.1 (198)	46.3 (19)	52.6 (20)
Body mass index, kg/m^2	25.1 ± 3.9	26.7 ± 4.1	26.6 ± 4.3	26.1 ± 3.7	27.6 ± 4.2	27.2 ± 4.5	26.7 ± 2.8	28.9 ± 3.8
Hypertension	30.0 (7902)	67.8 (1035)	50.0 (279)	68.1 (543)	64.7 (77)	78.7 (317)	63.3 (26)	81.6 (31)
Total cholesterol, mmol/L	5.88 ± 1.28	6.66 ± 1.23	6.47 ± 1.32	6.71 ± 1.29	6.75 ± 1.17	6.71 ± 1.23	6.85 ± 1.35	7.03 ± 1.06
Smoking	36.5 (9589)	28.7 (436)	33.3 (185)	41.1 (327)	29.4 (35)	23.1 (93)	30.0 (12)	26.3 (10)
Diabetes	1.4 (376)	4.2 (64)	2.0 (11)	4.4 (35)	3.4 (4)	7.0 (28)	7.3 (3)	10.5 (4)
History of myocardial infarction	6.3 (1664)	30.0 (458)	11.8 (66)	23.5 (187)	25.2 (30)	37.0 (149)	22.0 (9)	42.1 (16)

Note: Values are given as percentages with absolute numbers in parentheses or as means with standard deviations. The Tromsø Study 1994-2013.
AF, atrial fibrillation; VTE, venous thromboembolism.
*For participants with >1 event, age at the last event is given.

TABLE 2 All-cause mortality rates (MRs) and hazard ratios (HRs) for death according to exposure categories during follow-up

Exposure	Person-years	Deaths	Crude MR (95% CI)[a]	Age-adjusted MR (95% CI)[a]	HR (95% CI)[b]
None	417 040	3144	0.75 (0.73-0.78)	1.19 (1.15-1.23)	Ref
AF only	8715	661	7.58 (7.03-8.19)	4.24 (3.92-4.56)	2.36 (2.16-2.57)
VTE only	2996	232	7.74 (6.81-8.81)	6.61 (5.76-7.47)	3.76 (3.28-4.30)
Ischemic stroke only	4641	374	8.06 (7.28-8.92)	4.93 (4.43-5.43)	2.85 (2.56-3.18)
AF + VTE	416	70	16.8 (13.3-21.3)	7.37 (5.64-9.10)	3.67 (2.77-4.66)
AF + ischemic stroke	1365	264	19.3 (17.1-21.8)	8.21 (7.22-9.20)	4.38 (3.85-4.98)
VTE + ischemic stroke	123	25	20.3 (13.7-30.0)	10.1 (6.13-14.0)	6.32 (4.26-9.37)
AF + VTE + ischemic stroke	106	27	25.4 (17.4-37.1)	8.05 (5.01-11.1)	4.50 (3.07-6.58)

Note: The Tromsø Study 1994-2013.
AF, atrial fibrillation; CI, confidence interval; VTE, venous thromboembolism.
[a]Per 100 person-years.
[b]Age as time scale and adjusted for sex.

The highest risk of death was observed for subjects with VTE and ischemic stroke (HR, 6.32; 95% CI, 4.26-9.37) (Table 2).

In analyses in which participants with a cancer diagnosis prior to inclusion (n = 839) were excluded, and those diagnosed with cancer during follow-up (n = 2938) were censored at the time of cancer diagnosis, the risk estimates for death by VTE were markedly attenuated. In these analyses, the age-adjusted MR was half of that observed in the total study population (3.77 per 100 PY; 95% CI, 3.07-4.47), and the HR of death reduced to 2.05 (95% CI, 1.70-2.49). In contrast, risk estimates in cancer-free subjects having incident stroke during follow-up were virtually unchanged (Table 3). In analyses stratifying the VTE events by unprovoked and provoked events, HRs for death were also considerably lower in subjects with unprovoked VTE only than for those with provoked VTE only (HR, 1.58; 95% CI, 1.22-2.04 versus 6.60; 95% CI, 5.65-7.70 [data not shown]). For the joint AF + VTE exposure, HRs for death were 2.12 (95% CI, 1.42-3.18) and 5.31 (95% CI, 3.97-7.14) for unprovoked and provoked VTEs, respectively (data not shown).

When analyzing PE and DVT events separately, both events were associated with higher HRs for death compared to AF alone in age- (as time scale) and sex-adjusted analyses (Table 4). HRs for death were similar in patients with PE (HR, 3.65; 95% CI, 2.51-3.31) and patients with DVT (HR, 3.76; 95% CI, 3.19-4.43) compared to participants without an event. Further co-occurrence of AF hardly increased the risk estimates for either exposure (Table 4). In analyses stratified by sex, all HRs were higher in women than in men, but the CIs overlapped (Table 5). The VTE only and the AF + VTE exposures violated the assumption of proportional hazards, suggesting a time-dependent effect of these exposures (ie, age dependency). Both exposures were associated with lower absolute risks, but higher relative risks of death in younger versus older participants. In persons ≤ 65 years, the age- and sex-adjusted HRs for death were 6.26 (95% CI, 5.16-7.60) for the VTE only exposure, and 8.54 (95% CI, 5.63-12.96) for the AF + VTE exposure, while the comparable HRs in those over 65 years of age were 2.84 (95% CI, 2.47-3.19) and 2.90 (95% CI, 2.17-3.90) (data not shown).

TABLE 3 All-cause mortality rates (MRs) and hazard ratios (HRs) for death by exposure during follow-up; participants are censored upon cancer diagnosis

Exposure	Person-years	Deaths	Crude MR (95% CI)[a]	Age-adjusted MR (95% CI)[a]	HR (95% CI)[b]
None	395 928	3131	0.79 (0.76-0.82)	1.26 (1.21-1.31)	Ref
AF only	7337	516	7.03 (6.45-7.68)	3.75 (3.43-4.08)	2.00 (1.82-2.21)
VTE only	2450	111	4.53 (3.76-5.46)	3.77 (3.07-4.47)	2.05 (1.70-2.49)
Ischemic stroke only	4045	313	7.74 (6.93-8.64)	4.62 (4.11-5.14)	2.54 (2.26-2.87)
AF + VTE	308	43	14.0 (10.4-18.8)	5.10 (3.58-6.63)	2.50 (1.84-3.40)
AF + ischemic stroke	1096	216	19.7 (17.2-22.5)	7.95 (6.89-9.02)	4.01 (3.48-4.62)
VTE + ischemic stroke	89	16	17.9 (11.0-29.2)	8.06 (4.11-12.0)	4.34 (2.65-7.11)
AF + VTE + ischemic stroke	80	23	28.9 (19.2-43.5)	7.53 (4.45-10.6)	4.27 (2.82-6.44)

Note: The Tromsø Study 1994-2013.

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

[a]Per 100 person-years.

[b]Age as time scale and adjusted for sex.

TABLE 4 All-cause mortality rates (MRs) and hazard ratios (HRs) for death according to exposure categories during follow-up

Exposure	Person-years	Deaths	Crude MR (95% CI)[a]	HR (95% CI)[b]
None	417 040	3144	0.75 (0.73-0.78)	Ref
AF only	8715	661	7.58 (7.03-8.19)	2.31 (2.12-2.52)
PE only[c]	1090	80	7.34 (5.90-9.14)	3.65 (2.51-3.31)
Ischemic stroke only	4641	374	8.06 (7.28-8.92)	2.81 (2.51-3.13)
AF + PE[c]	199	35	17.6 (12.7-24.5)	3.68 (2.62-5–15)
AF + ischemic stroke	1365	264	19.3 (17.1-21.8)	4.27 (3.75-4.86)
PE + ischemic stroke[c]	29	8	27.6 (13.8-55.2)	6.03 (3.01-12.1)
AF + PE + ischemic stroke[c]	56	15	26.8 (16.1-44.4)	4.09 (2.46-6.80)
None	417 040	3144	0.75 (0.73-0.78)	Ref
AF only	8715	661	7.58 (7.03-8.19)	2.33 (2.14-2.54)
DVT only[d]	1906	152	7.97 (6.80-9.35)	3.76 (3.19-4.43)
Ischemic stroke only	4641	374	8.06 (7.28-8.92)	2.82 (2.53-3.16)
AF + DVT[d]	217	35	16.1 (11.6-22.4)	3.50 (2.51-4.90)
AF + ischemic stroke	1365	264	19.3 (17.1-21.8)	4.31 (3.79-4.91)
DVT + ischemic stroke[d]	94	17	18.0 (11.2-29.0)	6.37 (3.96-10.3)
AF + DVT + ischemic stroke[d]	50	12	23.9 (13.6-42.1)	4.78 (2.71-8.44)

Note: PE and DVT events are analyzed separately. The Tromsø Study 1994-2013.

AF, atrial fibrillation; CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

[a]Per 100 person-years.

[b]Age as time scale and adjusted for sex.

[c]Participants with DVT only censored at the date of the DVT event.

[d]Participants with PE only censored at the date of the PE event.

4 | DISCUSSION

In this cohort study, we found that incident AF without concurrent VTE or ischemic stroke during follow-up doubled the risk of all-cause mortality. VTE alone was associated with a 4-fold increased risk of death, and was similar to the risk found for AF in combination with ischemic stroke. In patients with VTE, concurrent presence of AF did not further increase the risk estimates for death.

The increase in absolute and relative risks of death by AF observed in our study is in agreement with previous reports.[1,3,26-28] While the excess mortality may be attributable to heart failure, either as a cause or a consequence of AF,[27] others have reported that

TABLE 5 Hazard ratios (HRs) for death in men and women by exposure during follow-up

Women				Men		
Exposure	Person-years	Deaths	HR (95% CI)[a]	Person-years	Deaths	HR (95% CI)[a]
None	223 976	1531	Ref	193 065	1613	Ref
AF only	3657	312	2.51 (2.21-2.85)	5058	349	2.21 (1.96-2.49)
VTE only	1561	127	4.17 (3.47-5.01)	1435	105	3.35 (2.74-4.08)
Ischemic stroke only	1838	169	3.26 (2.78-3.84)	2803	205	2.56 (2.21-2.98)
AF + VTE	219	44	3.88 (2.85-5.27)	196	26	3.47 (2.35-5.13)
AF + ischemic stroke	652	143	5.01 (4.26-6.07)	713	121	3.73 (3.09-4.51)
VTE + ischemic stroke	49	13	8.05 (4.65-13.9)	74	12	5.10 (2.89-9.02)
AF + VTE + ischemic stroke	57	15	4.62 (2.77-7.72)	49	12	4.40 (2.49-7.80)

Note: The Tromsø Study 1994-2013.

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

[a]Age as time scale.

mortality rates remained elevated in patients with AF after adjustment for MI, congestive heart failure, and valvular heart disease.[3] In a large registry-based study with over 270 000 participants, AF was independently associated with all-cause mortality, with higher relative risks for death observed for women across all age groups. Among concomitant diseases, malignancy, chronic renal failure, and chronic obstructive pulmonary disease contributed most to the excess mortality in AF patients.[28]

The role of concurrent AF as a prognosticator in patients with VTE has not been extensively studied. The majority of studies to date have investigated AF in the setting of hospitalization for PE and its impact on short-term case fatality.[15,18,19,29] In a retrospective study involving 270 patients with acute PE, a history of AF was associated with increased intrahospital 1-month and 6-month death rates independent of age.[15] Similarly, Geibel and coworkers found atrial arrhythmias to be associated with increased 30-day mortality in patients admitted with major PE.[18] In the present study, we found that VTE alone was associated with an overall 4-fold increased risk of death, which is similar to the risk reported in the Multiple Environment and Genetic Assessment (MEGA) study.[30] The coexistence of AF did not contribute with additional risk. A plausible explanation for our findings is that patients with VTE in part die as a result of other comorbidities, and that VTE patients with AF are compared to VTE patients with high morbidity risk due to other causes, for instance, cancer. This hypothesis is supported by the observation that the risk estimates for death by VTE were significantly higher in participants with a provoked VTE event than in those with an unprovoked event, and correspondingly attenuated when cancer patients were censored upon cancer diagnosis.

In agreement with previous reports,[5,31] we observed an increased all-cause mortality by AF in patients with ischemic stroke. Several mechanisms may explain this finding. Cardiac emboli secondary to AF are typically larger than the platelet rich-thrombi seen in atherosclerotic disease and may occlude larger vessels, resulting in more severe strokes. Furthermore, larger infarction volumes, higher rates of hemorrhagic transformation and cardiac hypoperfusion in patients with AF contributes to increased stroke severity. More severe strokes may in turn result in prolonged immobilization, medical complications, worsened neurological outcome, and increased mortality.[5]

The main strengths of our study include the prospective design, participant recruitment from a general population, and a thorough validation of the exposure events. Information on cancer was available, allowing for an assessment of the impact of a cancer diagnosis on mortality rates. Confirming the established association between AF and ischemic stroke on all-cause mortality in the present study population serves to confirm proper classification of the exposure measures. Nevertheless, our study also has limitations that merit attention. The AF incidence in our study population may be an underestimation, as AF is asymptomatic in many cases. Furthermore, patients with AF treated only by their general practitioners are not included. The omission of patients with AF treated solely in general practice may potentially cause selection bias, as more severe cases of AF are more likely to require hospital treatment. Due to the observational nature of the study design, our study is vulnerable to unmeasured or residual confounding. The higher prevalence of cardiovascular risk factors among people who developed ≥1 exposure events may have resulted in higher heart failure and MI rates among these participants, contributing to excess mortality. Unfortunately, we did not have information on heart failure, stroke sequelae, hospitalizations, or medication use during follow-up. Further knowledge of comorbidities may have added to the etiologic understanding of our findings. Information on antithrombotic medication use was not available. As antithrombotic treatment, either with antiplatelet agents (for ischemic stroke) or with anticoagulants (for all 3 exposures), is the mainstay of therapy for both AF, VTE, and ischemic stroke, it is possible that we underestimate the true risk of death by these exposures in the population. Caution is warranted when interpreting the results

of subgroups in which there are low numbers of the exposure(s) and outcome(s) of interest. In analyses investigating the joint exposures of AF and VTE, or AF and ischemic stroke, we did not take the temporal sequence of events into consideration. However, a bidirectional association exists between AF and VTE,[4,13,32] and although AF is an established risk factor for ischemic stroke, the diagnosis is made after the incident stroke in a significant number of cases.[33] Knowledge of the latter may introduce surveillance bias, as patients with idiopathic ischemic stroke are monitored for potential AF after the incident event. For the scope of the present analysis, we assumed that the temporality of events for the joint outcomes would be of little importance.

In conclusion, the present study confirms the aggravated risk of death by AF in the general population. While concurrent AF is associated with a worse prognosis in subjects with ischemic stroke, the high relative mortality risk in VTE patients is not further increased by the presence of AF.

ACKNOWLEDGMENTS

K. G. Jebsen TREC is supported by an independent grant from the KG Jebsen Foundation. E. M. Hald receives a grant from the Northern Norway Regional Health Authority.

RELATIONSHIP DISCLOSURES

The authors report nothing to disclose.

AUTHOR CONTRIBUTIONS

EMH contributed to data collection, data analysis, and writing of the manuscript. M-LL, EBM, and IN contributed to data collection and revision of the manuscript. TW provided statistical support and contributed to revision of the manuscript. SKB contributed to data collection, data interpretation, statistical support, and revision of the manuscript. J-BHansen contributed to the conception and design of the study, data collection, and interpretation and revision of the manuscript.

REFERENCES

1. KannelWB, Benjamin EJ. Status of the epidemiology of atrial fibrillation. Med Clin North Am. 2008;92:17–40, ix.
2. RahmanF, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. Nat Rev Cardiol. 2014;11:639–54.
3. BenjaminEJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998;98:946–52.
4. HaldEM, Rinde LB, Løchen M-L, Mathiesen EB, Wilsgaard T, Njølstad I, et al. Atrial fibrillation and cause-specific risks of pulmonary embolism and ischemic stroke. J Am Heart Assoc. 2018;7:e006502.
5. AliAN, Abdelhafiz A. Clinical and economic implications of AF related stroke. J Atr Fibrillation. 2016;8:1279.
6. AndersenKK, Andersen ZJ, Olsen TS. Predictors of early and late case-fatality in a nationwide Danish study of 26,818 patients with first-ever ischemic stroke. Stroke. 2011;42:2806–12.
7. MariniC, De Santis F, Sacco S, Russo T, Olivieri L, Totaro R, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke. 2005;36:1115–9.
8. JorgensenHS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. Stroke. 1996;27:1765–9.
9. SilversteinMD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med. 1998;158:585–93.
10. HeitJA. Venous thromboembolism: disease burden, outcomes and risk factors. J Thromb Haemost. 2005;3:1611–7.
11. WangCC, Lin CL, Wang GJ, Chang CT, Sung FC, Kao CH. Atrial fibrillation associated with increased risk of venous thromboembolism. A population-based cohort study. Thromb Haemost. 2015;113:185–92.
12. SundbøllJ, Hováth-Puhó E, Adelborg K, Ording A, Schmidt M, Bøtker HE, et al. Risk of arterial and venous thromboembolism in patients with atrial fibrillation or flutter: a nationwide population-based cohort study. Int J Cardiol. 2017;241:182–7.
13. EngaKF, Rye-Holmboe I, Hald EM, Lochen ML, Mathiesen EB, Njolstad I, et al. Atrial fibrillation and future risk of venous thromboembolism:the Tromso study. J Thromb Haemost. 2015;13:10–6.
14. SogaardKK, Schmidt M, Pedersen L, Horvath-Puho E, Sorensen HT. 30-year mortality after venous thromboembolism: a population-based cohort study. Circulation. 2014;130:829–36.
15. BarraSN, Paiva LV, Providencia R, Fernandes A, Leitao MA. Atrial fibrillation in acute pulmonary embolism: prognostic considerations. Emerg Med J. 2014;31:308–12.
16. KoracevicG, Atanaskovic V. Is atrial fibrillation a prognosticator in acute pulmonary thromboembolism? Med Princ Pract. 2010;19:166.
17. KuklaP, Długopolski R, Krupa E, Furtak R, Szełemej R, Mirek-Bryniarska E, et al. Electrocardiography and prognosis of patients with acute pulmonary embolism. Cardiol J. 2011;18:648–53.
18. GeibelA, Zehender M, Kasper W, Olschewski M, Klima C, Konstantinides SV. Prognostic value of the ECG on admission in patients with acute major pulmonary embolism. Eur Respir J. 2005;25:843–8.
19. KuklaP, McIntyre WF, Koracevic G, Kutlesic-Kurtovic D, Fijorek K, Atanaskovic V, et al. Relation of atrial fibrillation and right-sided cardiac thrombus to outcomes in patients with acute pulmonary embolism. Am J Cardiol. 2015;115:825–30.
20. KellerK, Prochaska JH, Coldewey M, Gobel S, Ullmann A, Jünger C, et al. History of deep vein thrombosis is a discriminator for concomitant atrial fibrillation in pulmonary embolism. Thromb Res. 2015;136:899–906.
21. QaddouraA, Digby GC, Kabali C, Kukla P, Zhan ZQ, Baranchuk AM. The value of electrocardiography in prognosticating clinical deterioration and mortality in acute pulmonary embolism: a systematic review and meta-analysis. Clin Cardiol. 2017;40:814–24.
22. JacobsenBK, Eggen AE, Mathiesen EB, Wilsgaard T, Njolstad I. Cohort profile: the Tromso Study. Int J Epidemiol. 2012;41:961–7.
23. BraekkanSK, Hald EM, Mathiesen EB, Njolstad I, Wilsgaard T, Rosendaal FR, et al. Competing risk of atherosclerotic risk factors for arterial and venous thrombosis in a general population: the Tromso study. Arterioscler Thromb Vasc Biol. 2012;32:487–91.
24. BraekkanSK, Borch KH, Mathiesen EB, Njolstad I, Wilsgaard T, Hansen JB. Body height and risk of venous thromboembolism: the Tromso Study. Am J Epidemiol. 2010;171:1109–15.
25. The World Health. Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. J Clin Epidemiol. 1988;41:105–14.
26. OdutayoA, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ. 2016;354:i4482.
27. MarijonE, Le Heuzey J-Y, Connolly S, Yang S, Pogue J, Brueckmann M, et al. Causes of death and influencing factors in patients with

atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. Circulation. 2013;128:2192–201.
28. AnderssonT, Magnuson A, Bryngelsson I-L, Frøbert O, Henriksson KM, Edvardsson N, et al. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995–2008: a Swedish nationwide long-term case-control study. Eur Heart J. 2013;34:1061–7.
29. BikdeliB, Abou Ziki MD, Lip GYH. Pulmonary embolism and atrial fibrillation: two sides of the same coin? A systematic review. Semin Thromb Hemost. 2017;43:849–63.
30. FlintermanLE, van Hylckama VA, Cannegieter SC, Rosendaal FR. Long-term survival in a large cohort of patients with venous thrombosis: incidence and predictors. PLoS Med. 2012;9:e1001155.
31. ThygesenSK, Frost L, Eagle KA, Johnsen SP. Atrial fibrillation in patients with ischemic stroke: a population-based study. Clin Epidemiol. 2009;1:55–65.
32. HaldEM, Enga KF, Lochen ML, Mathiesen EB, Njolstad I, Wilsgaard T, et al. Venous thromboembolism increases the risk of atrial fibrillation: the Tromso study. J Am Heart Assoc. 2014;3:e000483.
33. SposatoLA, Cipriano LE, Saposnik G, Ruiz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol. 2015;14:377–87.

How to cite this article: Hald EM, Løchen M-L, Mathiesen EB, et al. Atrial fibrillation, venous thromboembolism, ischemic stroke, and all-cause mortality: The Tromsø study. *Res Pract Thromb Haemost*. 2020;4:1004–1012. https://doi.org/10.1002/rth2.12351