Atrial fibrillation and future risk of venous thromboembolism – the Tromsø study

Kristin F. Enga, MD, PhD[1,2], Ina Rye-Holmboe, MD,[1,2] Erin M. Hald, MD[1,2], Maja-Lisa Løchen, MD, PhD[3], Ellisiv B. Mathiesen, MD, PhD [4], Inger Njølstad, MD, PhD [3], Tom Wilsgaard, PhD[3], Sigrid K. Braekkan, PhD[1,2,5], John-Bjarne Hansen, MD, PhD [1,2,5]

[1]K.G. Jebsen Thrombosis Research and Expertise Center, Department of Clinical Medicine, University of Tromsø, Norway; [2]Hematological Research Group, Department of Clinical Medicine, University of Tromsø, Tromsø, Norway; [3] Department of Community Medicine, University of Tromsø, Tromsø, Norway; [4]Brain and Circulation Research Group, Department of Clinical Medicine, University of Tromsø, Tromsø, Norway; [5] Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway.

Correspondence to: Sigrid K. Brækkan, K.G. Jebsen Thrombosis Research and Expertise Center, Department of Clinical Medicine, University of Tromsø, N-9037 Tromsø, Norway, e-mail: sigrid.brakkan@uit.no, telephone: +47 77625106, Fax: +47 77646838

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SUMMARY

Aims: Whether atrial fibrillation is related to risk of venous thromboembolism (VTE) is not extensively studied. Therefore, we investigated the association between atrial fibrillation and future risk of VTE in a population-based cohort.

Methods: In total, 29 975 subjects were recruited from three surveys of the Tromsø study and followed from enrolment (1994-95, 2001-02 and 2007-08) through 2010. Incident events of atrial fibrillation and VTE during follow-up were recorded. Information on potential confounders was obtained at baseline. Cox-regression models with atrial fibrillation as time-dependent variable were used to calculate hazard ratios (HR) for VTE with 95% confidence intervals (CI).

Results: During 16 years of median follow-up, 1604 subjects were diagnosed with atrial fibrillation and 614 with incident VTE. The risk of VTE was substantially increased during the first 6 months after diagnosis of atrial fibrillation (HR 8.44, 95% CI: 5.61-12.69), and remained increased throughout the study period (HR: 1.43, 95% CI 1.43-1.99) compared to those without atrial fibrillation. Atrial fibrillation displayed higher risk estimates for pulmonary embolism (HR: 11.84, 6.80-20.63) than for deep vein thrombosis (HR: 6.20, 3.37-11.39), during the first 6 months, and was still associated with pulmonary embolism (HR: 1.96, 95% CI: 1.24-3.10) but not with deep vein thrombosis (HR: 1.08, 95% CI: 0.66-1.75) more than 6 months after diagnosis.

Conclusion: Atrial fibrillation was associated with increased risk of VTE, and pulmonary embolism in particular. Our findings support the concept that isolated pulmonary embolism may originate from right atrial thrombi due to atrial fibrillation.

Keywords: atrial fibrillation, cohort studies, deep vein thrombosis, pulmonary embolism, risk factors

INTRODUCTION

Pulmonary embolism is generally thought to occur from silent or overt peripheral deep vein thrombosis (DVT), and the two conditions are commonly viewed as clinical manifestations of the same disease, i.e. venous thromboembolism (VTE). However, DVT is not found by ultrasonography or contrast venography in about half of patients with pulmonary embolism [1-3]. Recently, peripheral DVT was found in only 44% of patients with a first pulmonary embolism by advanced magnetic resonance imaging [4], further supporting the concept that pulmonary emboli additionally may arise from sites other than the deep veins, e.g. thrombi of cardiac origin, or by *de novo* formation of thrombi in the lung arteries.

Atrial fibrillation is associated with thrombus formation in the left atrium with subsequent increased risk of systemic embolism, particularly ischemic stroke [5]. To what extent a similar phenomenon occurs in the right side of the heart (i.e. right-side intracardiac thrombosis) has not been extensively studied. However, spontaneous echocontrast has been noted in the right atrium of patients with right heart abnormalities such as atrial fibrillation [6,7], and autopsy studies have displayed clots in the right atrium of patients with atrial fibrillation during their last illness [8], supporting the concept that isolated pulmonary embolism may arise from intracardiac thrombi.

The prevalence of atrial fibrillation in the general population is reported to be 2-3% [9], whereas the reported prevalence of atrial fibrillation ranges from 15 to 21% in patients with acute pulmonary embolism [10-12]. Despite this relatively frequent co-existence of pulmonary embolism and atrial fibrillation, the relationship between the two conditions has not been extensively investigated in prospective observational studies. In a large registry-based nested case-control study, however, the prevalence of atrial fibrillation during 0-3

months prior to the index date was substantially higher in subjects with VTE than in controls [13].

Abnormal haemostasis, including increased fibrin turnover and platelet activation, is well described in patients with atrial fibrillation [14], and the existence of this procoagulant state may promote development of thrombi in the deep veins. Moreover, right-side intracardiac thrombosis due to intra-atrial stasis can potentially lead to isolated pulmonary embolism. We therefore aimed to investigate whether atrial fibrillation was associated with future risk of VTE in a prospective cohort study with subjects recruited from a general population.

METHODS

STUDY POPULATION

Study participants were recruited from the fourth (1994-95), fifth (2001-02) and sixth survey (2007-08) of the Tromsø Study. To these surveys, the entire population (Tromsø 4) or parts (Tromsø 5 and 6) of the population aged ≥25 years living in the municipality of Tromsø, Norway, were invited to participate. A detailed description of study participation has been published elsewhere [15]. The overall attendance rate was high, ranging from 77% in Tromsø 4 to 66% in Tromsø 6. A total of 30 586 subjects aged 25-97 years participated in at least one of the surveys. The regional committee of medical and health research ethics approved the study, and all subjects gave their written consent to participate. Subjects who did not give their written consent to medical research (n=225), those not officially registered as inhabitants of the municipality of Tromsø at date of study enrolment (n=47), and subjects with VTE (n=76) or atrial fibrillation (n=263) before baseline were excluded. Accordingly, a total of

29 975 subjects were included in the study, and were followed from the date of study inclusion until the end of follow-up, December 31, 2010 (figure 1).

BASELINE MEASUREMENTS

Baseline information about study participants was collected by self-administered questionnaires, blood samples and a physical examination. Questionnaires were used to obtain information on smoking (current smoker yes/no), history of arterial cardiovascular disease (CVD) (angina pectoris, myocardial infarction or stroke) and diabetes. Non-fasting blood samples were collected and serum total cholesterol, triglycerides and high density lipoprotein (HDL) measured as previously described. Systolic and diastolic blood pressure were measured three times with 1 minutes intervals with an automatic device (Dinamap Vital Signs Monitor, 1846, Critikon Inc., Tampa, FL, USA) in a sitting position after 2 minutes of rest, and defined here as the mean of the last two readings. Height and weight were measured with subjects 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).

ATRIAL FIBRILLATION: IDENTIFICATION AND VALIDATION

Incident events of atrial fibrillation occurring during follow-up were identified by the hospital discharge diagnosis registry at the University Hospital of North Norway (included diagnoses from hospitalizations and outpatient clinic) and by the National Causes of Death registry, using the *International Classification of Disease* version 9 (ICD-9) codes 427.0-427.99 and ICD-10 codes I47-I48. In addition, a search through medical records of patients with cardiovascular disease and cerebrovascular events was performed [16]. The diagnosis of atrial

fibrillation had to be documented by an electrocardiogram, and adjudication of the events was performed by an independent endpoint committee. Classification of atrial fibrillation into paroxysmal and persistent versus permanent forms was performed when possible. Subjects having a paroxysmal course of atrial fibrillation initially, but who later developed a permanent form, were classified as having permanent atrial fibrillation. Subjects who could neither be classified as paroxysmal or persistent, and subjects with transient atrial fibrillation occurring only during an acute myocardial infarction or in connection with cardiac surgery, and subjects with atrial fibrillation documented only in the terminal phase (the last week) of life were defined as "other atrial fibrillation".

VENOUS THROMBOEMBOLISM: IDENTIFICATION AND VALIDATION

All incident 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 as previously described [17]. 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 medical record for each potential case of VTE was reviewed by trained personnel, and a VTE event was considered verified and recorded when presence of clinical signs and symptoms of DVT or pulmonary embolism 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 [17]. 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. The VTE events were classified as provoked and unprovoked depending on the presence of provoking factors at the

time of diagnosis. Provoking factors were recent surgery or trauma within the previous 8 weeks, acute medical conditions (acute myocardial infarction, ischemic stroke or major infectious disease), active cancer, immobilization (bed rest >3 days, wheelchair use or long-distance travel exceeding 4 hours within the last 14 days prior to the event) or any other factors described by a physician in the medical record (e.g. intravascular catheter).

STATISTICAL ANALYSES

Subjects who developed atrial fibrillation during the study period contributed with non-exposed person time from the baseline inclusion date to the date of a diagnosis of atrial fibrillation, and then with exposed person time from the date of atrial fibrillation and onwards. Subjects who had incident atrial fibrillation and VTE on the same day (n=7) were excluded from the analyses since the temporal sequence of events could not be determined in these subjects. For each participant, non-exposed and exposed person-years were counted from the date of enrolment (1994-95, 2001-02 or 2007-08) to the date of an incident VTE event, the date the participant died or moved from the municipality of Tromsø, or until the end of the study period, December 31, 2010, whichever came first. Subjects who died (n= 3546) or moved from Tromsø (n=4297) during follow-up were censored at the date of migration or death.

Statistical analyses were performed with STATA version 12.0 (Stata corporation, College Station, TX, USA). Crude incidence rates (IR) of VTE were calculated and expressed as number of events per 1000 person-years at risk. Incidence rate differences were calculated by subtracting the incidence rate among non-exposed from the exposed ($I_{exposed}$-$I_{non\text{-}exposed}$). Cox proportional hazard regression models were used to obtain crude and multivariable adjusted hazard ratios (HR) for VTE with 95% confidence intervals (CI). Age was used as

time-scale and the subjects' age at study enrolment was defined as entry-time, and exit-time was defined as age at date of VTE diagnosis, date of death, date of migration or date of study end. The exposure variable atrial fibrillation (yes/no) was included as a time-dependent variable, i.e. all subjects were initially classified with no atrial fibrillation at study entry, and the variable was updated in subjects who experienced an atrial fibrillation during follow-up. Hazard ratios of VTE according to time since diagnosis of atrial fibrillation (<6months and ≥6months) were calculated. The HRs were adjusted for potential confounders including sex, BMI, smoking status, diastolic blood pressure, cholesterol levels, self-reported CVD and diabetes. In addition, IRs and HRs for pulmonary embolism and DVT were calculated separately. The number of subjects included in the adjustment models varied slightly due to missing data for co-variates (<2% missing). The proportional hazard assumption was tested using Schoenfeld residuals. Statistical interactions between atrial fibrillation and sex were tested by including cross-product terms in the proportional hazards model. No statistical interactions between atrial fibrillation and sex were found.

Correct assessment of the temporal sequence of events was especially important in this study since atrial fibrillation potentially can be both the cause and the consequence of pulmonary embolism, and patients can present with the two conditions concomitantly. In the main analysis all incident VTEs that occurred ≥1 day after the diagnosis of atrial fibrillation were considered as potentially caused by the atrial fibrillation. In order to investigate whether the association was still present when the temporal sequence was unambiguous, we conducted additional sensitivity analysis where only VTE events that occurred more than 7 days after diagnosis of atrial fibrillation were included.

RESULTS

Overall, we identified 1604 (5.4%) subjects with validated diagnosis of incident atrial fibrillation. A total of 614 subjects (2.0%) had an incident VTE event during a median of 15.6 years (range: 1 day to 16.3 years) of follow-up. Among those with atrial fibrillation, 65 subjects (4.0%) experienced a subsequent VTE. Characteristics of the study participants at baseline are shown in table 1. Subjects who were diagnosed with atrial fibrillation during follow-up were on average almost 20 years older than those with neither atrial fibrillation nor VTE, and 6 years older than those with a VTE only (Table 1).

Characteristics of the VTE events are shown in table 2. Among patients with atrial fibrillation, 55% were pulmonary embolisms and 45% were deep vein thrombosis. In contrast, the corresponding proportions in those without atrial fibrillation were 37% and 67%, respectively (Table 2). The proportion of unprovoked VTE events was higher in those without atrial fibrillation (45%) than in those with atrial fibrillation (31%). Active cancer and immobilization were the most frequent provoking factors among subjects without atrial fibrillation (22.6% and 20.0%, respectively), while acute medical conditions and immobilization were most frequent among those with atrial fibrillation (32.3% and 30.8%, respectively).

Incidence rates and hazard ratios for VTE among subjects with and without atrial fibrillation during follow-up are displayed in Table 3 and Figure 2. Among the subjects with atrial fibrillation, 65 suffered a subsequent VTE. The incidence rate of VTE was highest during the first 6 months after the atrial fibrillation diagnosis (35 per 1000 person-years) (Figure 2), the risk was 8-fold higher in those with atrial fibrillation compared to those without atrial fibrillation (HR: 8.44, 95% CI: 5.61-12.69). Furthermore, the incidence rate of VTE in the period ≥6 months up to 15 years after atrial fibrillation was 6.3 per 1000 person-

years, and the risk of VTE was 43% increased (HR 1.43, 95% CI: 1.03-1.99). Adjustments for BMI, smoking, total cholesterol, diastolic blood pressure, self-reported CVD and diabetes slightly attenuated the risk estimates. Separate analysis of pulmonary embolism and DVT showed that the risk of both outcomes was remarkably high during the first 6 months after the atrial fibrillation diagnosis (Table 3). The multivariable HR was 11.17 (95% CI: 6.41-19.49) for pulmonary embolism and 6.01 (95% CI: 3.27-11.06) for DVT. The risk of pulmonary embolism remained 1.8-fold higher in those with atrial fibrillation in the period from 6 months throughout follow-up (HR 1.83, 95% CI 1.16-2.90), whereas there was apparently no association between atrial fibrillation and risk of DVT more than 6 months after the atrial fibrillation diagnosis (HR 1.04, 95% CI: 0.64-1.68).

In the sensitivity analyses, 9 VTE events that occurred less than one week after onset of atrial fibrillation were excluded. Using this approach, the risk estimate for the first 6 months was somewhat attenuated, but still, atrial fibrillation was associated with a more than 5-fold higher risk of VTE (HR: 5.19, 95% CI: 3.14-8.60) and of pulmonary embolism (HR: 5.59, 95% CI: 2.60-12.1) after multivariable adjustments.

Incidence rates and hazard ratios of VTE according to different types of atrial fibrillation are shown in Table 4. All types of atrial fibrillation were associated with increased risk of VTE and followed essentially the same risk pattern as overall atrial fibrillation. Persistent atrial fibrillation exhibited the highest incidence rates and relative risk estimates, though the differences between the types of atrial fibrillation were not statistically significant (Table 4).

DISCUSSION

We found that patients with atrial fibrillation had increased risk of subsequent venous thromboembolism. The incidence rate and relative risk was especially high during the first 6 months after atrial fibrillation was diagnosed. Atrial fibrillation was associated with increased risk of both deep vein thrombosis and pulmonary embolism, during the first 6 months. In the period after 6 months there was no longer an association with DVT, whereas the risk of pulmonary embolism remained 80% higher in those with atrial fibrillation compared to those without atrial fibrillation. All sub-types of atrial fibrillation were associated with VTE, and displayed an essentially similar risk pattern.

Except for our population-based cohort study, only one previous register study has investigated the sequential relationship between atrial fibrillation and VTE. In coherence with our findings, Sørensen et al.[13] showed that the prevalence of atrial fibrillation/flutter was substantially higher in patients with VTE, and especially isolated pulmonary embolism, compared with population controls in a large registry-based case-control study. The association was particularly strong when a discharge diagnosis of atrial fibrillation was observed less than 3 months before the index date (OR 23.5 for isolated pulmonary embolism and 15.2 for isolated DVT) [13]. Several other observational studies support these findings. A history of atrial fibrillation was found in 20% of cases with pulmonary embolism, although the temporal sequence of the events had not been determined in these studies [10-12]. An Italian cross-sectional study of 11 236 patients with pulmonary embolism reported higher prevalence of heart diseases, including atrial fibrillation, among elderly (>60 years) patients with a diagnosis of isolated pulmonary embolism compared to those with pulmonary embolism and concurrent DVT [18]. Later case-control analysis of patients with unprovoked pulmonary embolism revealed that atrial fibrillation or flutter was 1.5-fold more prevalent in

patients with isolated pulmonary embolism compared to patients with pulmonary embolism and concurrent DVT [19].

In our study, atrial fibrillation exhibited higher risk estimates for pulmonary embolism than of DVT, particularly in the period more than 6 months after atrial fibrillation diagnosis. This finding supports the theory that isolated pulmonary embolism in atrial fibrillation patients may originate from right side intracardiac thrombi. Spontaneous echocontrast has been noted in the right atrium of patients with atrial fibrillation [6,7], and has been positively associated with perfusion defects assessed by pulmonary scintigraphy [20]. In a large Swedish autopsy study, an intracardiac thrombus was found in 12% of the subjects with pulmonary embolism compared with 6% in the matched controls [21]. Right side intracardiac thrombosis was identified as the only source of emboli in 4% of all patients with pulmonary embolism [21]. Later, right heart thrombi were confirmed by echocardiography in 4% of patients with acute pulmonary embolism [22]. In addition to intra-atrial stasis and thrombus formation, haemostatic changes promoting both platelet and coagulation activity are well-described in patients with atrial fibrillation [14,23,24].

The risk of both DVT and pulmonary embolism was particularly high during the first 6 months after diagnosis of atrial fibrillation. Several factors may explain this phenomenon. A delay in the initiation of rhythm and rate control along with hesitance to immediately introduce anticoagulant treatment may subject individuals to a higher risk in the early phase after diagnosis of atrial fibrillation. Moreover, circumstantial conditions such as concomitant hospitalization and other co-morbidities may contribute to excessive VTE risk in the initial phase.

Major strengths of this study include the large number of participants recruited from a general population, the well validated information on exposure and outcome, and

measurements of potential confounders. Putatively, atrial fibrillation can be both the cause and the consequence of pulmonary embolism, as a pulmonary embolism may trigger atrial fibrillation through right atrial distension, stress or hypoxia. The temporal sequence of diagnoses was well-assessed in our study, and in sensitivity analyses we found that atrial fibrillation was still associated with increased risk of VTE when the minimum time between the atrial fibrillation diagnosis and onset of VTE was more than one week. The study has some limitations that merit attention. Paroxysmal atrial fibrillation has been reported to be asymptomatic in a substantial amount of patients [25]. Thus, undetected paroxysmal episodes may still have preceded VTE, and thereby resulted in an underestimation of the risk estimates in our study. Potential confounders such as BMI and co-morbidities were assessed at baseline only, and these factors may have changed over time. Moreover, the observed association could potentially be confounded or mediated by concurrent development of other diseases such as congestive heart failure, infections, chronic obstructive pulmonary disease or chronic kidney disease. Unfortunately, we did not have information on use of oral anticoagulant therapy in patients with atrial fibrillation. However, a previous study from our hospital conducted in the period 1995-1998 reported that 70% of those discharged with a diagnosis of chronic atrial fibrillation were treated with oral anticoagulants and 20% with platelet inhibitors [26]. Oral anticoagulant treatment efficiently reduces the risk of VTE [27,28]. Therefore, it is likely that the true risk of VTE after atrial fibrillation is underestimated in our study, i.e. that the association between atrial fibrillation and VTE was even stronger in untreated patients.

In conclusion, patients with atrial fibrillation had higher risk of venous thromboembolism compared to subjects without atrial fibrillation, and the risk was particularly high for both deep vein thrombosis and pulmonary embolism during the first six months following a diagnosis of atrial fibrillation. After 6 months, atrial fibrillation was still

associated with increased risk of pulmonary embolism, but not with deep vein thrombosis. Our findings support the hypothesis that isolated pulmonary embolism may arise from intracardiac thrombi formed in patients with atrial fibrillation.

AUTHOR CONTRIBUTIONS

KFE: data analysis and writing of manuscript, IRH: data interpretation and revision of manuscript, EMH: data collection, interpretation and revision of manuscript, EBM: data collection and revision of manuscript, MLL: data collection and revision of manuscript, IN: data collection and revision of manuscript, TW: statistical support, SKB: data collection, interpretation and writing of manuscript, JBH: conception and design of study, data collection, interpretation and revision of manuscript.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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LEGENDS

Figure 1. Inclusion of study participants from the fourth (1994/95), fifth (2001/02) and sixth (2007/08) survey of the Tromsø study.

Figure 2: Hazard ratios (HR) with 95% confidence interval (CI) of venous thromboembolism (VTE) according to time periods after a diagnosis of atrial fibrillation. The Tromsø Study.

Table 1. Baseline characteristics of subjects without and with atrial fibrillation and/or venous thromboembolism (VTE) during follow-up. Values are given as absolute numbers with percentages in brackets or as means with standard deviation in brackets. The Tromsø Study.

	No atrial fibrillation or VTE during follow-up	**Atrial fibrillation during follow-up**	**VTE during follow-up**	**Atrial fibrillation and subsequent VTE during follow-up**
Subjects (n)	27815	1539	549	65
Sex (male) (%)	13066 (47.0)	863 (56.1)	252 (45.9)	31 (47.7)
Age (years)	45.2±14.0	63.8±11.7	57.8±14.2	66.0±9.5
BMI (kg/m^2)	25.2±3.9	26.9±4.3	26.9±4.4	27.6±3.9
Total cholesterol (mmol/l)	5.92±1.29	6.67±1.24	6.61±1.35	6.77±.1.11
Triglycerides (mmol/l)	1.53±1.04	1.76±.08	1.70±0.92	1.88±1.19
HDL (mmol/l)	1.49±0.41	1.51±0.44	1.51±0.42	1.55±0.37
Systolic blood pressure (mmHg)	132±20	152±24	143±23	151±25
Diastolic blood pressure (mmHg)	77±12	86±14	82±13	86±14
Smoking (%)	10122 (36.4)	413 (26.9)	174 (31.8)	22 (33.8)
Physical activity (%)	9236 (33.7)	297 (19.5)	119 (21.8)	8 (12.5)
Self-reported CVD (%)	1364 (4.9)	360 (23.5)	66 (12.0)	13 (20.0)
Self-reported diabetes (%)	448 (1.6)	81 (5.3)	15 (2.7)	4 (6.2)

Table 2. Characteristics of the incident VTE events (n=614) during follow-up. The Tromsø Study.

	No atrial fibrillation % (n)	Atrial fibrillation % (n)
Venous thromboembolism	549	65
Age at VTE diagnosis (years, mean (SD))	67 (14)	77 (10)
Sex (% men)	252 (45.9)	31 (47.7)
Deep vein thrombosis	345 (62.8)	29 (44.6)
Pulmonary embolism	204 (37.2)	36 (55.4)
Unprovoked	246 (44.8)	20 (30.8)
Clinical risk factors		
Estrogen[a]	37 (6.7)	1 (1.5)
Pregnancy/puerperium[a]	6 (1.1)	-
Heredity[b]	20 (3.6)	-
Other medical conditions[c]	11 (20.0)	24 (36.9)
Provoking factors		
Surgery	86 (15.7)	12 (18.5)
Trauma	39 (7.1)	5 (7.7)
Acute medical conditions[d]	63 (11.5)	21 (32.3)
Cancer	124 (22.6)	12 (18.5)
Immobility[e]	110 (20.0)	20 (30.8)
Other[f]	23 (4.2)	4 (6.2)

[a] Only women included in analysis
[b] VTE in first degree relative before aged 60 years.
[c] Includes other diseases within the previous year (myocardial infarction, ischemic stroke, heart failure, inflammatory bowel disease, chronic infections, chronic obstructive pulmonary disease, or myeloproliferative disorders).
[d] Includes myocardial infarction, ischemic stroke or major infectious disease.
[e] Immobility includes bed rest>3days, longtime travels with car, boat, train or by air >4 hours within last 14 days, or other type of immobilization.
[f] Other provoking factor described by a physician in the medical record (e.g. intravascular catheter).

Table 3. Incidence rates and hazard ratios for total VTE, pulmonary embolism and DVT in subjects developing atrial fibrillation during follow-up compared to subject without atrial fibrillation. The Tromsø Study.

	Person-Years	Events	Crude IR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95%CI)
Total VTE					
No atrial fibrillation	358845	549	1.5 (1.4-1.7)	Ref	Ref
<6 months after atrial fibrillation	712	25	35.1 (23.7-51.9)	8.44 (5.61-12.69)	8.09 (5.37-12.18)
≥6 months after atrial fibrillation	6369	40	6.3 (4.6-8.6)	1.43 (1.03-1.99)	1.35 (0.98-1.89)
Pulmonary embolism					
No atrial fibrillation	358845	204	0.6 (0.5-0.7)	Ref	Ref
<6 months after atrial fibrillation	712	14	19.6 (11.6-33.2)	11.84 (6.80-20.63)	11.17 (6.41-19.49)
≥6 months after atrial fibrillation	6369	22	3.5 (2.3-5.3)	1.96 (1.24-3.10)	1.83 (1.16-2.90)
DVT					
No atrial fibrillation	358845	345	1.0 (0.9-1.1)	Ref	Ref
<6 months after atrial fibrillation	712	11	15.4 (8.6-2.8)	6.20 (3.37-11.39)	6.01 (3.27-11.06)
≥6 months after atrial fibrillation	6369	18	2.8 (1.8-4.4)	1.08 (0.66-1.75)	1.04 (0.64-1.68)

[a] using age as time-scale and adjusted for sex.

[b] using age as times-scale and adjusted for sex, BMI, smoking, total cholesterol, diastolic blood pressure, self-reported CVD and diabetes.

Table 4. Incidence rates and hazard ratios for venous thromboembolism (VTE) according to type of atrial fibrillation. The Tromsø Study.

	Person-Years	VTE events	Crude IR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95%CI)
Paroxysmal atrial fibrillation					
No atrial fibrillation	358845	549	1.5 (1.4-1.7)	Ref	Ref
<6 months after atrial fibrillation	297	8	26.9 (13.4-53.7)	6.67 (3.30-13.47)	6.59 (3.26-13.32)
≥6 months after atrial fibrillation	2666	17	6.4 (4.0-10.3)	1.43 (0.88-2.34)	1.41 (0.86-2.31)
Persistent atrial fibrillation					
No atrial fibrillation	358845	549	1.5 (1.4-1.7)	Ref	Ref
<6 months after atrial fibrillation	278	11	39.5 (21.8-71.4)	9.01 (4.93-16.49)	8.18 (4.47-14.98)
≥6 months after atrial fibrillation	2686	19	7.0 (4.5-11.1)	1.56 (0.98-2.49)	1.41 (0.88-2.25)
Other atrial fibrillation					
No atrial fibrillation	358845	549	1.5 (1.4-1.7)	Ref	Ref
<6 months after atrial fibrillation	137	6	43.9 (19.7-97.7)	11.0 (4.87-24.64)	10.8 (4.82-24.40)
≥6 months after atrial fibrillation	1016	4	3.9 (1.5-10.4)	0.96 (0.36-2.59)	0.96 (0.36-2.56)