**Should we reintroduce previous venous thromboembolism into the atrial fibrillation anticoagulation decision process? Results from a nationwide cohort study**

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**Abstract (247 words)**

**Background** In atrial fibrillation guidelines, previous venous thromboembolism (VTE) is not accounted for when deciding on whether or not to initiate oral anticoagulation.

**Objectives** To assess whether previous VTE was a prognostic factor for future thromboembolic events in patients with atrial fibrillation.

**Methods** Incident atrial fibrillation patients from 2000-2017 were defined and characterized using nationwide Danish health registries. Cox regression analyses were used to calculate hazard ratios (95% confidence interval) for the outcomes ‘ischemic stroke or systemic embolism’ and ‘ischemic stroke, systemic embolism, or VTE’ according to previous VTE status. Analyses were adjusted for components of CHA2DS2-VASc and time-varying use of oral anticoagulation.

**Results** The study population consisted of 246,313 patients with incident atrial fibrillation, of which 6,516 (2.6%) had previous VTE. Patients with previous VTE carried an overall similar adjusted risk of ‘ischemic stroke or systemic embolism’ compared with patients without previous VTE (reference), hazard ratio 0.99 (95% confidence interval 0.90-1.09). When analyzing a composite thromboembolic outcome of ‘ischemic stroke, systemic embolism, or VTE’, patients with previous VTE were at high-risk, hazard ratio 1.76 (95% confidence interval 1.64-1.90). Similar conclusions were found when stratifying by VTE subtype, among patients with low CHA2DS2-VASc scores, or when restricting to the non-anticoagulated subset of the study population.

**Conclusions** Patients with previous VTE carried similar risk of ‘ischemic stroke or systemic embolism’ compared with patients without previous VTE. Nonetheless, they remain a high-risk population compared with patients without previous VTE, mainly due to an excess risk of future VTE events.

**Abbreviations**

**CI** confidence interval

**HR** hazard rate ratio

**NOAC** non-vitamin K antagonist oral anticoagulant

**VTE** venous thromboembolism

**Introduction**

Atrial fibrillation is the most common cardiac arrhythmia with the proportions of pandemic.1 Stroke is the most feared complication of atrial fibrillation, but strokes can be effectively prevented by oral anticoagulation.2 Venous thromboembolism (VTE), comprising deep vein thrombosis and pulmonary embolism, is another common type of thrombosis.3 Several studies have demonstrated common coexistence of atrial fibrillation and VTE.4,5 In fact, thrombi forming in low-pressure vasculature such as the left atrium and the veins have constitutional similarities.6 7 This is consistent with the superiority of oral anticoagulation over antiplatelets for stroke prevention in atrial fibrillation.2

Patients with a history of VTE developing incident atrial fibrillation may therefore represent a high-risk category. Patients with a first-time VTE are treated with anticoagulants, but often only for a time-limited period of three to six months.8,9 Contemporary guidelines recommend using the CHA2DS2-VASc score for risk stratification purposes to guide decisions on anticoagulant treatment.10–12 In the current version of the CHA2DS2-VASc score, the ‘V’ component refers to Vascular disease defined by peripheral arterial disease, aortic plaque, or previous myocardial infarction. Thus, previous VTE is presently not considered in routine clinical thromboembolic risk assessment in atrial fibrillation, although the original derivation study actually included VTE in the definition of vascular disease.10,13 If VTE patients with completed anticoagulant treatment subsequently develop atrial fibrillation, the current risk stratification approach does not necessarily dictate a clear indication for anticoagulation, if not other stroke risk factors are evident.

Therefore, the aim of this cohort study was to explore whether history of VTE should be considered a prognostic factor for ischemic stroke and other thromboembolic outcomes in patients with incident atrial fibrillation.

**Methods**

*Study design and data sources*

This was a register-based cohort study based on linked individual-level data from nationwide Danish registries using a unique personal identification number given to all Danish residents at birth or emmigration.14 We obtained data from: 1) the Civil Registration System holding information about age, sex, vital- and emigration status15, 2) the National Patient Register storing information about all discharge diagnosis for hospitalized patients since 197716, and 3) the National Prescriptions Registry, which holds information on all claimed prescriptions from Danish pharmacies since 1995.17

*Study population*

The study population included all patients with incident non-valvular atrial fibrillation from 2000 through 2017. Patients with inconsistent identification data as well as patients who immigrated within one year prior to atrial fibrillation diagnosis, or who had a history of cancer were excluded, see **Figure 1** for details.

*Exposure*

The exposure was a history of VTE (deep vein thrombosis or pulmonary embolism) prior to the atrial fibrillation diagnosis. Specifically, previous VTE was defined as an in- or outpatient diagnosis (primary or secondary) given in combination with an imaging procedure (ultrasound or computed tomography scan). This ensures a positive predictive value of the VTE diagnosis of 91%.18 Furthermore, patients with previous VTE were subcategorized into deep vein thrombosis and pulmonary embolism. In case of a history of both such diagnoses, the patient was categorized as having pulmonary embolism. Also, VTE was subdivided as provoked and unprovoked as previously defined according to the medical history preceding the most recent VTE.19

*Covariates*

﻿The CHA2DS2-VASc is the preferred stroke risk stratification tool in international guidelines, and components from the score were included as covariates. This includes information about Congestive heart failure, Hypertension, Age ≥75 years [doubled], Diabetes mellitus, previous Stroke, systemic embolism, or transient ischemic attack [doubled], Vascular disease [previous myocardial infarction, peripheral artery disease, or aortic plaque], Age 65-74 years, and Sex category [female]. Components were defined at the time of atrial fibrillation diagnosis using a combination of International Classification of Disease (ICD) and Anatomical Therapeutic Classification (ATC) codes. Oral anticoagulant treatment was assessed by claimed prescriptions from the National Prescription Registry. An overview of the relevant codes and variable definitions is available in **Online Table 1**.

*Outcome*

The primary outcome was a combined thromboembolic outcome including a diagnosis of ischemic or unspecified stroke, or systemic embolism. The positive predictive value of an ischemic stroke diagnosis in the Danish National Patient Register is >85%.20,21 Unspecified stroke was included in the combined outcome definition because the majority of strokes coded as unspecified stroke have been shown to be of ischemic origin.21

Another prespecified composite outcome was a combination of ‘ischemic stroke, systemic embolism, or VTE’, since oral anticoagulation also prevents VTE, and the risk of this outcome is likely to differ between patients with and without a history of VTE. A diagnosis of VTE during follow-up was defined as a primary in- or outpatient diagnosis given in combination with a relevant imaging procedure.18

Few patients in Denmark have an autopsy performed (4%) and the exact cause of death is therefore often unknown.22 To encompass fatal cases of thromboembolism not coded in registries, death was included in a composite outcome definition in a secondary analysis.

*Statistics*

Baseline characteristics were calculated overall and according to history of VTE as number of patients and with proportions for categorical values and with median and inter-quartile range, for continuous variables. Cumulative incidences of outcome were estimated using the cumulative incidence function taking into account competing risk of death for the primary outcomes of ‘ischemic stroke or systemic embolism’ and ‘ischemic stroke, systemic embolism, or VTE’,23 and by use of Kaplan Meier for the composite outcome including death. Patients were followed from time of atrial fibrillation diagnosis until the outcome of interest, emigration, death, end of follow-up (maximum three years) or study end (October 30, 2017), which ever came first. Results after 1-year follow-up were likewise calculated and presented only in the supplementary material. Incidence rates per 100-person years were calculated only for subgroup of patients free from anticoagulation at baseline with additional censoring at the time of initiation of oral anticoagulation, to allow for comparison with previous studies reporting on incidence rates for an untreated population.24 We applied time-to-event analysis using Cox regression analysis with time since atrial fibrillation diagnosis as the underlying time-axis to calculate hazard rate ratios (HRs) for outcomes. Hazard ratios were calculated as crude and after adjustment for CHA2DS2-VASc components with age modelled as a cubic spline and with indicator for anticoagulant treatment included as a time-varying covariate. Additionally, prespecified subgroup analyses were performed for ‘low-risk’ patients defined as a CHA2DS2-VASc score of 1 or 2 for women and 0 or 1 for men, as well as with the VTE cohort divided by VTE subtype (deep vein thrombosis vs. pulmonary embolism and provoked vs. unprovoked). A crude and adjusted Cox regression analysis was repeated for the subset of patients not using oral anticoagulation, with additional censoring at the time of initiation of oral anticoagulation. Some supplementary analyses were also performed. 1) Repeating the main analyses but restricting follow-up to a maximum of 1 year, and 2) a Cox regression analyses also including death in a composite outcome definition.

**Results**

After exclusions, 246,313 patients with incident atrial fibrillation were included, of which 2.6% (6,516) had a history of VTE (see **Figure 1 for** patient selection process details). Compared with patients without previous VTE, patients with previous VTE were older (median age 76.4 vs. 73.9 years) and had a higher prevalence of comorbidity, in particular congestive heart failure (32.7 vs 26.6%), vascular disease (22.2 vs 18.5%) and previous ischemic stroke (19.0 vs. 16.8%). The higher comorbidity burden among patients with previous VTE was also reflected in a slightly higher mean CHA2DS2-VASc score (3.4 vs 3.1). A recent prescription of oral anticoagulation use was most frequent among VTE patients (43.3 vs 19.3%). In the VTE group, 68.4% had a history of deep vein thrombosis, 45.4% a history of pulmonary embolism, and 13.8% a history of both. Among those with a history of VTE, 59.4% were categorized as provoked and 40.6% as unprovoked.

*Cumulative incidence and incidence rates*

**Figure 2** shows crude cumulative incidence curves taking into account competing risk of death. Risk of ischemic stroke or systemic embolism were similar irrespective of VTE history (**Figure 2a**), with a 3-year risk just below 8%. When including VTE in a composite thromboembolic outcome definition, patients with a history of VTE were at highest risk with a cumulative incidence of approximately 15% (**Figure 2b**).

**Table 2** presents incidence rates per 100-person after three years of follow-up for patients not using anticoagulation at baseline. For the outcome of ischemic stroke or systemic embolism, rates were overall higher in patients with previous VTE compared with patients with no VTE (4.78 vs. 3.38). Rates were also numerically higher irrespective of VTE subtype compared with patients with no history of VTE, and highest for the subgroup of patients with provoked VTE (5.95). Among patients with low CHA2DS2-VASc scores rates were similar (0.78 vs. 0.80). When including VTE in the composite thromboembolic outcome definition, patients with a history of VTE exhibited markedly higher incidence rates than patients without history of VTE (9.01 vs. 3.89), and incidence rates were also higher irrespective of VTE subtype and among patients with low CHA2DS2-VASc scores

*Cox regression*

Results from the Cox regression analyses after three years of follow-up are presented in **Table 3**, both crude and after adjustment for oral anticoagulation and CHA2DS2-VASc components.

We observed comparable hazard rates of ‘ischemic stroke or systemic embolism’ in patients with and without previous VTE, adjusted HR 0.99 (0.90-1.09). Findings were generally similar in analyses stratified by VTE subgroups. When restricting to patients with low CHA2DS2-VASc scores, history of VTE was associated with a higher rate of ‘ischemic stroke or systemic embolism’, HR 1.33 (0.96-1.85).

When assessing the outcome of ‘ischemic stroke, systemic embolism, or VTE’, we found consistently higher hazard rates both among the entire population, adjusted HR 1.76 (1.64-1.90), and across all specified subgroups in patients with a history of VTE compared with patients with no history of VTE, see **Table 3**.

**Table 4** contain the results from a Cox regression analysis restricted to the subset of the study population who were free from anticoagulation. Here, a history of VTE was associated with a higher hazard ratio of ‘ischemic stroke or systemic embolism’ in the crude analysis [HR 1.30 (1.08-1.58)], but not in the adjusted analysis [HR 1.03 (0.85-1.25)].

Otherwise, results were broadly similar to the main analysis using the entire population with adjustment for differences in anticoagulant treatment, except that among patients with low CHA2DS2-VASc scores, history of VTE was not associated with higher rates of stroke or systemic embolism neither in the crude or adjusted model. For the composite outcome ‘ischemic stroke, systemic embolism, or VTE’, patients with previous VTE had higher hazard rates both overall and across all subgroups.

*Supplementary analyses*

Results and conclusions were widely similar when restricting follow-up time to only one year, see **Online Tables 2-4**. After three years of follow-up patients with previous VTE had a higher cumulative incidence for the composite outcome of ischemic stroke, systemic embolism, VTE, or death, (see **Online Figure 1**). Results from a Cox regression analysis are presented in **Online Table 5**. Patients with a history of VTE exhibited higher rates of the composite outcome both overall and across all subgroup analyses compared with patients without previous VTE.

**Discussion**

In this nationwide cohort of patients with atrial fibrillation, we found similar risk of ischemic stroke or systemic embolism following a diagnosis of atrial fibrillation for patients with and without a history of VTE. When including VTE in the outcome definition, patients with a history of VTE were a high-risk population for the composite outcome compared with patients without previous VTE, even after taking differences in CHA2DS2-VASc levels and use of oral anticoagulation into account.

The CHA2DS2-VASc score is a globally adopted anticoagulation treatment decision tool, but has also been criticized for its simplistic and reductionist design, incorporating only some known common or validated thromboembolic risk factors associated with atrial fibrillation, and mainly in a dichotomized fashion.25 Interestingly, the original CHA2DS2-VASc derivation study initially included VTE in the definition of vascular disease,10 but has since been left out and does not appear in any of the major guidelines’ definitions of vascular disease as defined by CHA2DS2-VASc.8,11,12,26

Since oral anticoagulation is currently indicated for most patients with atrial fibrillation, large contemporary unselected and untreated cohorts of atrial fibrillation patients no longer exist. To assess whether patients with a history of VTE should be considered a high-risk category among patients with atrial fibrillation, we therefore conducted several different analyses, both using the entire population with adjust for differences in anticoagulant treatment as well as the anticoagulation-free subpopulation. First, we reported crude incidence rates for the sub-population not treated with oral anticoagulation knowing that such patients are unlikely to be a random subset of the atrial fibrillation population. This analysis revealed higher rates of thromboembolism and VTE for patients with versus without a history of VTE. According to this analysis, a patient’s history of VTE seems an easily accessible marker of thromboembolic risk that should be considered when making clinical risk assessments. Importantly, we had no information on the reasons for withholding anticoagulation.

The pathophysiology of VTE and atrial fibrillation-related embolism share the same theoretical basis, with erythrocyte-rich thrombi forming in low-pressure vasculature.7 Although risk profiles for atherothrombotic and venous thrombi are different,27 there is also a clear overlap in that patients with a history of VTE are at high risk of future atherothrombotic events. Nonetheless, we found conflicting prior evidence regarding whether patients with a history of VTE were a high-risk category with respect to ischemic stroke or systemic embolism. In the anticoagulation-free subpopulation, patients with a history of VTE had higher rates of ischemic stroke or systemic embolism, but the association diminished after adjustment for CHA2DS2-VASc components. However, in the analysis using the entire population with adjustment for anticoagulation use, we found no differences. This indicates that any excess risk of ischemic stroke or systemic embolism for patients with a history of VTE seem adequately captured using the existing risk components of CHA2DS2-VASc. However, an inevitable added benefit is likely to be concomitant protection against VTE, which is also effectively treated and prevented with anticoagulation.28,29

Atrial fibrillation itself may be a direct but relatively obscured cause of pulmonary embolism. While many thrombi form in the left atrial appendage, the importance of the right atrial appendage may have been neglected.30,31 Indeed, atrial fibrillation is more prevalent among patients presenting with pulmonary embolism but without deep vein thrombosis than in those with both conditions.32 This supports the theory that atrial fibrillation can directly cause pulmonary embolism and that including VTE in clinical risk stratification for atrial fibrillation patients seems sensible.5,33,34 Hence, when we included VTE in a composite thromboembolic outcome definition, patients with a history of VTE appeared as a high-risk population compared with patients without previous VTE.

While the overall benefit of oral anticoagulation for stroke prevention in atrial fibrillation is well established,2 there are no randomized trials investigating head-to-head comparison of different antithrombotic treatment strategies across CHA2DS2-VASc score levels. Decisions on whether or not to initiate oral anticoagulation in the setting of atrial fibrillation therefore relies essentially on the patient’s estimated risk of thromboembolism if left untreated. Above a certain risk threshold, the downsides of oral anticoagulation - essentially bleeding risk - are expected to be outweighed by the protective effect on thromboembolism. It has been estimated that if a population carries a risk of ischemic stroke above the equivalent of 0.9 events per 100-person years, non-vitamin K antagonist oral anticoagulants (NOACs) are likely to offer a net clinical benefit.35,36 In this study, untreated patients with low CHA2DS2-VASc scores of 0 and 1 for men and 1 and 2 for women exhibited incidence rates of ischemic stroke or systemic embolism below this threshold (see Table 2). However, the suggested treatment threshold does not consider the inevitable concomitant benefit of VTE prevention, and even among these low risk patients, a history of VTE was a clear marker of subsequent ischemic stroke, systemic embolism, or VTE. Also, NOACs may also have an advantage over warfarin for preventing VTE, adding further support to contemporary guideline recommendations advocating NOACs over warfarin in atrial fibrillation.29

*Limitations*

The use of nationwide administrative registries allowed for a large study cohort, thus minimizing the impact of random variation. A validation study found a positive predictive value of a diagnosis of atrial fibrillation to be high (>90%) in these registries.37 The positive predictive value of incident VTE is 91% with the applied definition, but lower for patients with a history of VTE (82%), since any future VTE in this subgroup are recurrent events, for which the positive predictive value is lower (82%).18 Hence, this could lead to a small relative overestimation of rates of VTE in the population with previous VTE compared with those without VTE, but unlikely to be enough to explain the observed, rather substantial, differences in rates of VTE following a diagnosis of atrial fibrillation. The diagnosis of ischemic stroke has been validated with a positive predictive value of >80%, which is unlikely to be associated with history of VTE. Information bias is therefore not a likely sole explanation for the comparative study results.

Patients were followed in nationwide registries, which minimized the potential selection bias arising from loss to follow-up. Some deaths due to ischemic stroke or pulmonary embolism are not recorded as such in the administrative registries due to very low autopsy rates in Denmark.22 Hence, we also included death in the outcome definition in a supplementary analysis. The uncertainty of causes of death in the registries precluded the conduction of an adequate competing risk analysis, since only deaths due to non-thromboembolic events are considered competing events in this setting.38–40

*Conclusion*

Patients with incident atrial fibrillation and previous VTE carried an overall similar risk of ‘ischemic stroke or systemic embolism’ compared with patients without previous VTE. Nonetheless, patients with atrial fibrillation with a history of VTE are a high-risk population compared with patients without a history of VTE, mainly due to an excess risk of future VTE events. History of VTE may be a useful parameter for routine clinical thromboembolic risk stratification in patients with atrial fibrillation.

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**Figure legends**

**Central illustration**

Patients with incident atrial fibrillation were divided according to history of venous thromboembolism. Patients with and without history of venous thromboembolism carried similar risk of ischemic stroke or systemic embolism. Nonetheless, the combined thromboembolic burden was greatest among patients with a history of venous thromboembolism due to an excess incidence of future venous thromboembolic events.

**Figure 1**

Flowchart depicting the patient population selection process

**Figure 2**

Three-year cumulative incidence of a) ‘ischemic stroke or systemic embolism’ and b) ‘ischemic stroke, systemic embolism, or VTE’ in patients with incident atrial fibrillation according to history of VTE