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ORIGINAL RESEARCH

RHYTHM DISORDERS AND ELECTROPHYSIOLOGY

Venous Thromboembolism in Patients With Atrial Fibrillation

A Systematic Review and Meta-Analysis of 4,170,027 Patients

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ABSTRACT

BACKGROUND Data on the association between atrial fibrillation (AF) and venous thromboembolism (VTE) are controversial.

OBJECTIVES The purpose of this study was to investigate the risk of VTE in patients with AF according to the time from AF diagnosis.

METHODS Systematic review of MEDLINE (PubMed), Embase, Cumulative Index to Nursing and Allied Health Literature (EBSCO host), Cochrane Central Register of Controlled Trials (2020) in the Cochrane Library, and World Health Organization Global Index Medicus databases and meta-analysis of observational studies. The risk of VTE, deep vein thrombosis (DVT) and pulmonary embolism (PE) was analyzed according to the time of AF onset: 1) short (≤3 months); 2) medium (≤6 months); and 3) long (>6 months) time groups.

RESULTS Eight studies were included with 4,170,027 patients, of whom 650,828 with AF. In the short-term group, AF was associated with the highest risk of either PE (HR: 9.62; 95% CI: 7.07-13.09; $I^2 = 0\%$) or DVT (HR: 6.18; 95% CI: 4.51-8.49, $I^2 = 0\%$). Even if to a lesser extent, AF was associated with a higher risk of VTE (HR: 3.69; 95% CI: 1.65-8.27; $I^2 = 79\%$), DVT (HR: 1.75; 95% CI: 1.43-2.14; $I^2 = 0\%$), and PE (HR: 4.3; 95% CI: 1.61-11.47; $I^2 = 68\%$) in the up to 6 months and long-term risk group >6 months groups (HR: 1.39; 95% CI: 1.00-1.92; $I^2 = 72\%$) and PE (HR: 1.08; 95% CI: 1.00-1.16; $I^2 = 0\%$).

CONCLUSIONS The risk of VTE is highest in the first 3 to 6 months after AF diagnosis and decreases over time. The early initiation of anticoagulation in patients with AF may reduce the risk of VTE. (JACC Adv 2023;2:100555) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

DVT = deep vein thrombosis

PE = pulmonary embolism

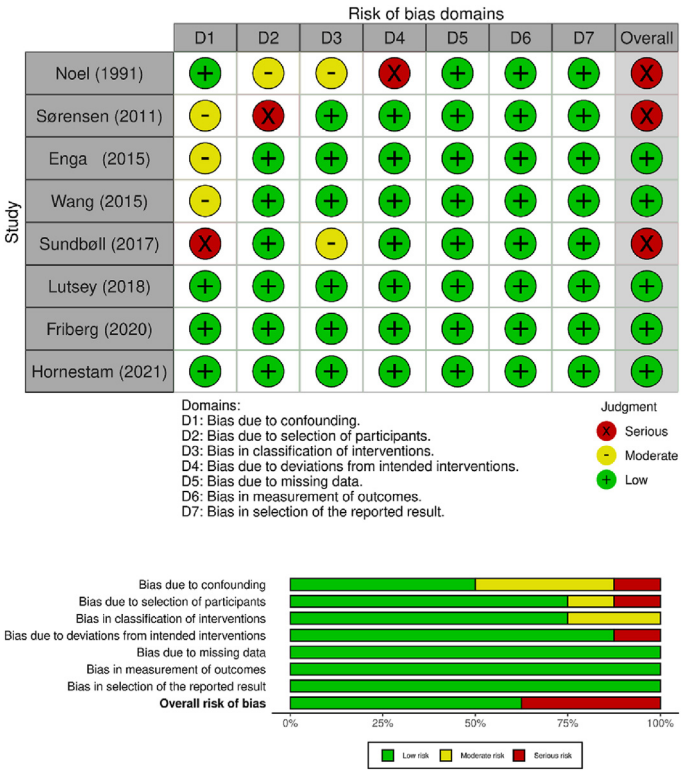
VTE = venous thromboembolism

Atrial fibrillation (AF) is associated with an increased risk of arterial thromboembolic events including ischemic stroke and systemic embolism, which may represent serious life threating complications for patients with AF. Hence, much effort has been dedicated to the improvement of stroke risk stratification to identify patients with AF requiring oral anticoagulation.

However, many risk factors commonly detectable in patients with AF and accounting for the increased risk of arterial thrombotic events are also known to be associated also with the occurrence of venous thromboembolism (VTE), both pulmonary embolism (PE) and deep vein thrombosis (DVT). These factors include aging, sex, heart failure, diabetes, vascular disease, and ischemic stroke.[1] Indeed, patients aged over 75 years have a 5-fold increased risk of VTE compared to patients aged <50 years and the incidence of VTE in women younger than 55 years is higher than men.[2] Also, heart failure is associated with almost a 2-fold increase for VTE risk both in hospitalized and outpatients[3,4]; diabetes and vascular diseases increase the incidence of VTE by 2-fold, while in patients with previous stroke the incidence of DVT in the first 2 weeks ranges from 10% to 75%.[5-7]

It is therefore arguable that AF may be associated with an increased risk of VTE, but divergent data on this topic have been published. Our aim was to investigate by a systematic review and meta-analysis of observational studies the risk of VTE in patients with AF, by analyzing the overall risk of VTE either PE or DVT according to the time from AF diagnosis (ie, 3, 6, or >6 months).

FIGURE 1 Risk of Bias Evaluation of Eligible Studies Retrieved by Combined Strategy Searches Using the ROBINS-I Tool



ROBINS-I = Risk Of Bias In Non-randomised Studies-of Interventions.

METHODS

For searches strategy and study selection from December 1, 2021, to January 31, 2022, we researched MEDLINE (PubMed), Embase, Cumulative Index to Nursing and Allied Health Literature (EBSCO host), Cochrane Central Register of Controlled Trials (2020) in the Cochrane Library, and World Health Organization Global Index Medicus for potentially relevant results. The search strategy included "atrial fibrillation," "venous thromboembolism," "deep vein thrombosis," and "pulmonary embolism" as keywords and is detailed in Supplemental Table 1. The search strategy was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplemental Figure 1). Initial inclusion criteria were as follows: 1) English language; 2) full-text articles available; and 3) patients older than 18 years. Case reports/case series, as well as review or editorials/letters were excluded. Retrieved citations were screened by title and abstract independently. Three investigators (G.G, T.B, G.F.) independently assessed studies for possible inclusion. The same investigators independently extracted data on study designs, patient characteristics, and outcomes using a data extraction form. Full texts of potentially relevant citations were assessed for final decision of inclusion or exclusion, and disagreements were solved by a fourth investigator (D.P.).

TYPES OF STUDIES. We included only original research journal articles in English language with full text available. We included observational (both prospective and retrospective) cohort studies, and randomized controlled trials. We excluded cross-sectional and case-control studies, case reports,

TABLE 1 Summary of Study Endpoints in Each Study

First Author (Year)	Short-Term (Up to 3 mo)	Medium-Term (Up to 6 mo)	Long-Term (>6 mo)
Noel (1991)[12]	In-hospital VTE		
Sørensen (2011)[14]	PE, DVT, PE + DVT at 3 mo		PE, DVT, PE + DVT >3 mo
Enga (2015)[15]		PE, DVT, PE + DVT <6 mo	PE, DVT, PE + DVT >6 mo
Wang (2015)[10]			DVT and PE during a mean follow-up of 3.82 y
Sundbøll (2017)[11]	DVT and PE at 1 mo		DVT and PE at 1-5 y
Lutsey (2018)[13]		VTE ≤6 mo	VTE >6 mo
Friberg (2020)[16]			PE during a median follow-up of 7.6 y
Hornestam (2021)[17]	PE, DVT, PE + DVT at 1 mo	PE, DVT, PE + DVT at 3-6 mo	PE, DVT, PE + DVT at 1-5 y

DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

editorials/comments, letters, review and meta-analysis, and experimental studies not involving humans.

PARTICIPANTS/POPULATION. We included only studies that enrolled patients with and without AF reporting as outcomes at least one of the endpoints of the meta-analysis.

INTERVENTIONS/COMPARATOR. Our meta-analysis aims to compare patients with and without AF to investigate the potential role of AF as risk factor for venous thrombosis.

OUTCOME DOMAINS OF INTEREST. We investigated the risk of venous thrombosis in patients with and without AF. Endpoints of the study were the risk of develop VTE, DVT, and PE according to the time of onset after AF diagnosis as follows: 1) short (≤3 months); 2) medium (≤6 months); and 3) long (>6 months) time groups.

DATA EXTRACTION. From the included studies, we collected data on author name, year of publication, study design, mean age, proportion of women/men, total patients, proportion of comorbidities (hypertension, diabetes), type of VTE, proportion of anticoagulant treatments. All studies and outcomes data were collected in an electronic spreadsheet (Microsoft Excel). Studies with <200 patients and or 50 VTEs were excluded.

STUDY OUTCOMES. To evaluate the risk of VTE, PE, and DVT according to the time after the AF diagnosis. For this scope, the studies were divided into 3 groups: 1) short (0-3 months); 2) medium (≤6 months); and 3) long (>6 months) time groups. For the medium (≤6 months) group, the studies by Enga et al and Lutsey et al reported the incidence of VTE in the period ≤6 months also including 0 to 3 months, while for the study by Hornestam, we used the HR for the 3 to 6 months frame period.

QUALITY ASSESSMENT AND RISK OF BIAS EVALUATION. The quality of observational studies was assessed by the "Assessment Tool for Observational Cohort and Cross-Sectional Studies" developed by the National Heart, Lung, and Blood Institute. According to the answers obtained from a specific list of 14 questions, the studies were divided into high, medium and low quality by 2 raters (D.P. and D.M.). Specifically, 3 (+++) defined high quality and are assigned to the studies that positively answered all the 14 questions of the questionnaire. Two (++) defined medium-quality studies, assigned to studies that present 1 negative answer and 1 (+) defined low-quality studies that had more than 1 negative answer to the questionnaire.

ROBINS-I (Risk Of Bias In Non-randomised Studies-of Interventions) tool was also used to evaluate the risk of bias of observational studies (**Figure 1**).[8]

TABLE 2 Quality Assessment of the Studies

First Author (Year)	First Rater	Second Rater	Design
Noel (1991)[12]	++	++	Prospective
Sørensen (2011)[14]	++	+++	Retrospective
Enga (2015)[15]	+++	+++	Retrospective
Wang (2015)[10]	+++	+++	Retrospective
Sundbøll (2017)[11]	++	++	Retrospective
Lutsey (2018)[13]	+++	+++	Prospective
Friberg (2020)[16]	+++	+++	Retrospective
Hornestam (2021)[17]	++	+	Retrospective

+Low quality, ++fair quality, +++good quality.

TABLE 3 Characteristics of Studies Included in the Meta-Analysis

First Author (Year)	Setting	Design	Mean Age (y)	Male %	HT (%)	DM (%)
Noel (1991)[12]	Patients with stroke	P	75.9 (AF) 68 (CTRL)	48.4	-	-
Sørensen (2011)[14]	Nationwide population-based case-control study	R	29% 56-70	47.1	-	-
Enga (2015)[15]	Population living in Tromsø	R	46.4[a]	48.3	-	1.9
Wang (2015)[10]	Taiwan longitudinal Health Insurance Database 2000	R	71.6 (AF) 70.5 (CTRL)	55.8	61.3	17.2
Sundbøll (2017)[11]	Danish Civil Registration System	R	72.6	52.8	40 (AF) 25.8 (CTRL)	11 (AF) 7.9 (CTRL)
Lutsey (2018)[13]	ARIC	P	54.2	45.5	30.3	11.7
Friberg (2020)[16]	Retrospective registry study of a random sample of Swedish residents	R	74.4 (AF) 49.2 (CTRL)	48.6	51.1 (AF) 7.9 (CTRL)	18.2 (AF) 4.9 (CTRL)
Hornestam (2021)[17]	Swedish inpatient registry 1987-2013	R	70.41	57.4	29.9 (AF) 9.7 (CTRL)	12.8 (AF) 5.8 (CTRL)

[a]Weighted mean.

AC = anticoagulant treatment; AF = atrial fibrillation; CTRL = control; DM = diabetes mellitus; DVT = deep venous thrombosis; HT = hypertension; PE = pulmonary embolism; VTE = venous thromboembolism.

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STATISTICAL ANALYSES. Meta-analyses for each endpoint (VTE, DVT, and PE) at the 3 different time points (0-3, ≤6, and >6 months), separately were performed based on random effect models, using the logarithm of HRs and 95% CI as outcome. According to Higgins et al,[9] we performed Bayesian meta-analysis with informative priors, since some analyses were based on a limited number of studies. When not reported (in the studies by Wang et al[10] and Sundbøll et al,[11] HRs and their standard errors were calculated on the basis of the number of subjects, number of events and mean follow-up per group based on Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022, Cochrane, 2022). Heterogeneity was evaluated by calculating the I^2 index. Low, moderate, and high heterogeneity was defined as an I^2 of <25%, 25% to 75%, and >75%, respectively. Publication bias was evaluated by funnel plots (Supplemental Figure 2). Analyses were performed using the R software (R development Core Team, 2021, version 4.1.2).

PROSPERO REGISTRATION. This systematic review has been registered at PROSPERO: International prospective register of systematic reviews (CRD42021288296).

ETHICAL REVIEW, PATIENT, AND PUBLIC INVOLVEMENT. Given the study type (review and meta-analysis article), an ethical approval was not required. Patients were not involved in the design and the development of this study.

RESULTS

STUDY CHARACTERISTICS AND QUALITY ASSESSMENT. PRISMA flow diagram showing study selection is reported in Supplemental Figure 1. After screening, 8 studies were included in the meta-analysis[10-17]: 2 prospective[12,13] and 6 retrospective studies.[10,11,14-17] Four studies reported data about short-term (<3 months) and 4 about medium term risk of VTE, and 7 studies about long-term (>6 months) (**Table 1**). The quality assessment showed an overall good quality (**Table 2**).

Risk of bias was performed using the ROBINS-I tool for observational studies. Analysis of risk of bias showed an overall low-moderate risk of bias (**Figure 1**). The most serious risk of bias was represented by the risk of residual confounding which was considered as serious in 1 study[11] and moderate in 3 studies (**Figure 1**). Only 1 study showed a serious risk of potential selection bias[1] and another one a serious risk of deviations from intended interventions[12] (**Figure 1**).

RESULTS OF INDIVIDUAL STUDIES. Clinical characteristics of each study are shown in **Table 3**. A total of 4,170,027 patients, of whom 650,828 (15.6%) with AF

TABLE 3 Continued

AC (%)	Total Cohort	AF Total	CTRL Total	VTE AF	VTE CTRL	PE AF	PE CTRL	DVT AF	DVT CTRL
-	539	88	451	20	40	-	-	-	-
-	651,313	22,379	628,934	12,209	97,335	4,489	40,793	3,248	56,542
-	29,419	1,604	27,815	65	459	36	204	29	345
-	57,095	11,458	45,637	186	353	68	103	118	250
33.2 (AF) 0.4 (CTRL)	623,924	103,989	519,935	-	-	-	-	-	-
23.5	15,129	2,048	13,081	68	613	17	173	51	440
40.3	1,442,028	46,018	1,396,010	-	-	765	11,667	-	-
41.2	1,350,580	463,244	887,336	-	-	-	-	-	-

were included in the meta-analysis. The mean age ranged from 46.4 to 75.9 years, while the proportion of men ranged from 45.5% to 57.4%. Hypertension and diabetes proportions ranged from 29.9% to 61.3% and from 1.9% to 17.2%, respectively (Table 3). Data about anticoagulation treatment are available only for 4 out 8 studies[11,13,16,17] with a wide variability of treatment proportions, ranging from 23.5% to 41.2% of patients.

During follow-up, 12,548 VTE, 5,375 PE, and 3,446 DVT in the AF group and 98,800 VTE, 52,940 PE, and 57,577 DVT in the non-AF group occurred (Table 3). Diagnostic strategies for VTE are reported in the Supplemental Table 2.

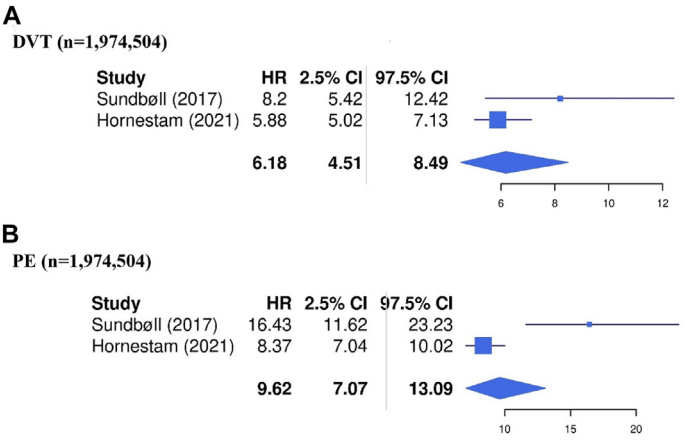
SHORT-TERM (0-3 MONTHS) RISK OF VTE. Two studies[11,17] reported data on DVT and PE, including 1,974,504 patients. AF resulted as strong risk factor for DVT and PE (HR: 6.18; 95% CI: 4.51-8.49; $I^2 = 0\%$, and HR: 9.62; 95% CI: 7.07-13.09; $I^2 = 0\%$, respectively) (Figures 2A and 2B). Funnel plots for short-term outcomes are reported in the Supplemental Figure 2A.

MEDIUM TERM (<6 MONTHS) RISK OF VTE. Three studies[13,15,17] reported data on VTE including 1,395,128 patients (Figure 3A). AF was associated with VTE risk (HR: 3.69; 95% CI: 1.65-8.27; $I^2 = 79\%$). Two studies[15,17] reported data on DVT and PE, separately including 1,379,999 patients. AF resulted as a risk factor for DVT and PE (HR: 1.75; 95% CI: 1.43-2.14; $I^2 = 0\%$, and HR: 4.30; 95% CI: 1.61-11.47; $I^2 = 68\%$) (Figures 3B and 3C, respectively). Funnel plots for 6-month outcomes are reported in Supplemental Figure 2B.

LONG-TERM RISK (>6 MONTHS) FOR VENOUS THROMBOSIS. Four studies[10,13,15,17] reported data on VTE including 1,452,223 patients. The pooled HR for AF as risk factor for VTE during long-term follow-up was 1.39 (95% CI: 1.00-1.92; $I^2 = 72\%$) (Figure 4A).

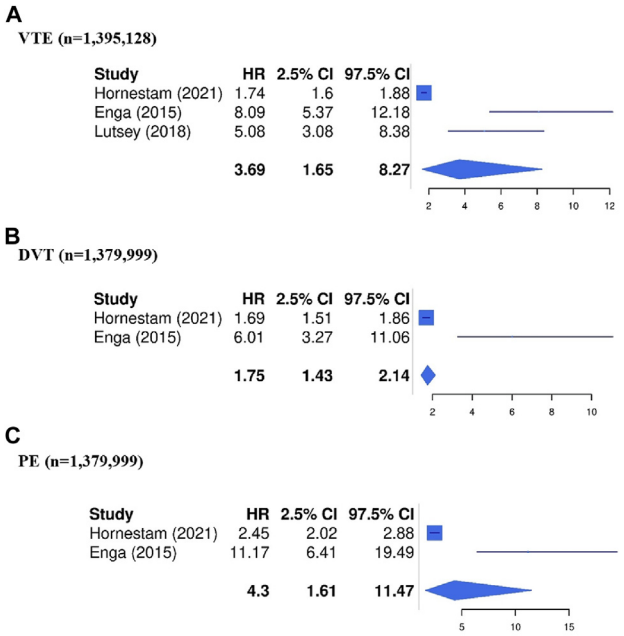
Five studies[10,11,13,15,17] reported data on DVT including 2,076,147 patients. AF was not associated

FIGURE 2 Short Term Risk of Deep Vein Thrombosis and Pulmonary Embolism



Short term (0-3 months) risk of deep vein thrombosis **(A)** and pulmonary embolism **(B)**. DVT = deep vein thrombosis; PE = pulmonary embolism.

FIGURE 3 Medium Risk of Venous Thromboembolism, Deep Vein Thrombosis, and Pulmonary Embolism



6-month risk of venous thromboembolism **(A)**, deep vein thrombosis **(B)**, and pulmonary embolism **(C)**. DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

with DVT during long-term follow-up (HR: 1.24; 95% CI: 0.98-1.56; $I^2 = 61\%$) (**Figure 4B**).

Finally, 6 studies[10,11,13,15-17] reported data on PE during long-term follow-up, including 3,518,175 patients. The pooled HR for AF as risk factor for PE was 1.08 (95% CI: 1.00-1.16; $I^2 = 0\%$) (**Figure 4C**).

Funnel plots for long-term outcomes are reported in the Supplemental Figure 2C.

DISCUSSION

This meta-analysis of observational studies provides evidence that the risk of VTE is highest in the first 3 months after AF diagnosis and decreases over time, although remaining evident in studies with long-follow-up over 6 months (**Central Illustration**). Indeed, we found a 6- to 9-fold increase in the risk of DVT or PE in the short-term period.

The highest risk of VTE in the short-term period may rely on several different reasons. This period is coincidentally also the one with the highest risk of thromboembolic stroke,[18] due to a low quality of anticoagulation in the first 90 days for patients started on vitamin K antagonists.[19] Indeed, low-quality anticoagulation or delayed anticoagulant administration may result in an increased risk of venous thrombotic events in addition to the arterial ones. This is also suggested by the study by Friberg et al[16] that considered oral anticoagulation as potential confounder for the association between AF and VTE. Indeed, despite <50% of patients were taking oral anticoagulants, anticoagulation was associated with lower risk of VTE vanishing the association between AF and VTE seen at the univariable analysis.[16] In addition, different oral anticoagulant treatments may influence the risk of VTE. Thus, in the study by Lutsey et al[20] including 117,912 patients with AF starting oral anticoagulation, the risk of VTE changed according to different anticoagulant drugs. The risk of incident VTE was lower among new users of dabigatran, compared to vitamin K antagonist (HR: 0.55;

95% CI: 0.47-0.66) and apixaban (HR: 0.51; 95% CI: 0.39-0.68), but similar among new users of rivaroxaban (HR: 1.01; 95% CI: 0.87-1.19).[20] In addition, in the indirect head-to-head direct oral anticoagulant comparisons, VTE risk was lower among patients started on dabigatran [HR: 0.48; 95% CI: 0.36-0.64)] and apixaban (HR: 0.61; 95% CI: 0.47-0.78) compared to rivaroxaban users.[20]

In the first months after AF diagnosis, there could also be an increased detection of VTE in patients monitored for the new-onset arrhythmia, coincidentally to that occurs for the high rate of cancer detection in the first 90 days after AF detection.[21] In this context, cancer is a risk factor responsible for an increased VTE risk in AF,[16] and a recent meta-analysis showed that direct oral anticoagulants are more effective than warfarin for the treatment of VTE in patients with AF and cancer (risk ratio: 0.37; 95% CI: 0.22-0.63).[22]

In addition, new-onset AF, especially when symptomatic or associated with hemodynamic instability, may lead to an increased rate of hospitalization[23] and subsequent immobilization accounting for an increased risk of in-hospital VTE.

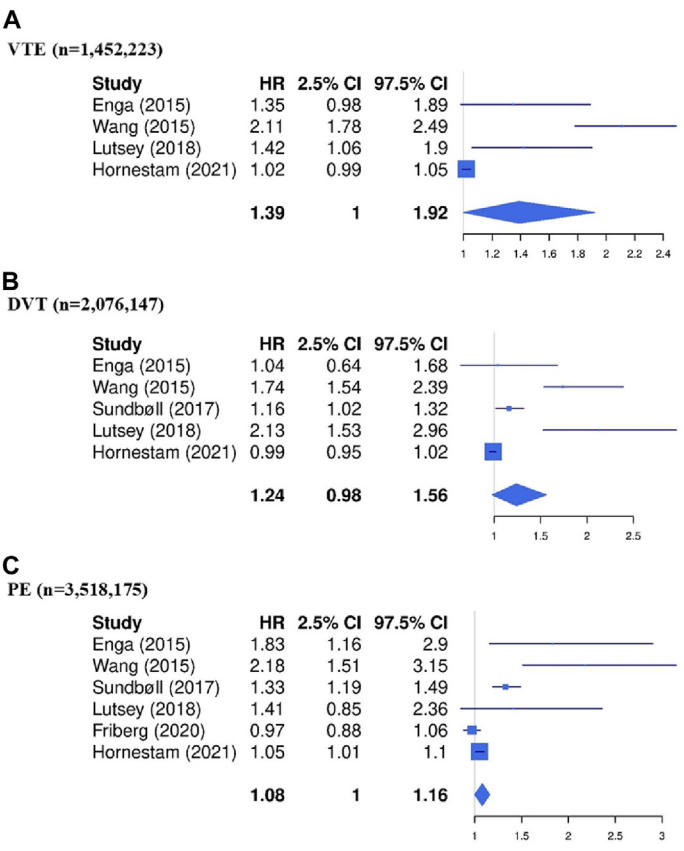
Among patients with AF, VTE seems to parallel the risk of thromboembolic stroke in the first period after detection, highlighting the role of cardiovascular comorbidities in increasing thrombotic risk both in the arterial and venous system.[24] This is also suggested by a previous study showing that the risk of unprovoked PE increases with the number of cardiovascular risk factors, and associates with the severity of PE.[25] Among others, hypertension, diabetes, and obesity seem to have a stronger impact on the risk of VTE.[26,27] The mechanisms through which cardiovascular risk factors may increase the risk of VTE in patients with AF may be related to the induction of a prothrombotic state[28] by increasing clotting and platelet activation,[29,30] and endothelial dysfunction that seem to be highest shortly after AF onset and lowered by sinus rhythm restoration by effective cardioversion.[31,32]

Indeed, after a patient is diagnosed with AF, physicians should actively search and address potentially modifiable risk factors for VTE, especially in the first 3 to 6 months. This is support of a more holistic or integrated care approach to AF management, which has been associated with improved clinical outcomes[33] and advocated in guidelines.[34]

STUDY LIMITATIONS. Our analysis has limitations including the relatively low number of studies addressing the short-term risk of VTE. This result, therefore, should be confirmed in larger studies. However, the risk of bias of studies included in the meta-analysis was generally low. Also, a formal analysis according to the type of oral anticoagulation was not possible as few studies reported data on anticoagulants and in all cases the proportion of patients taking oral anticoagulants was <50%. Other limitations include that VTE diagnosis was based on International Classification of Diseases codes in most studies and none of the included studies reported D-dimer levels.

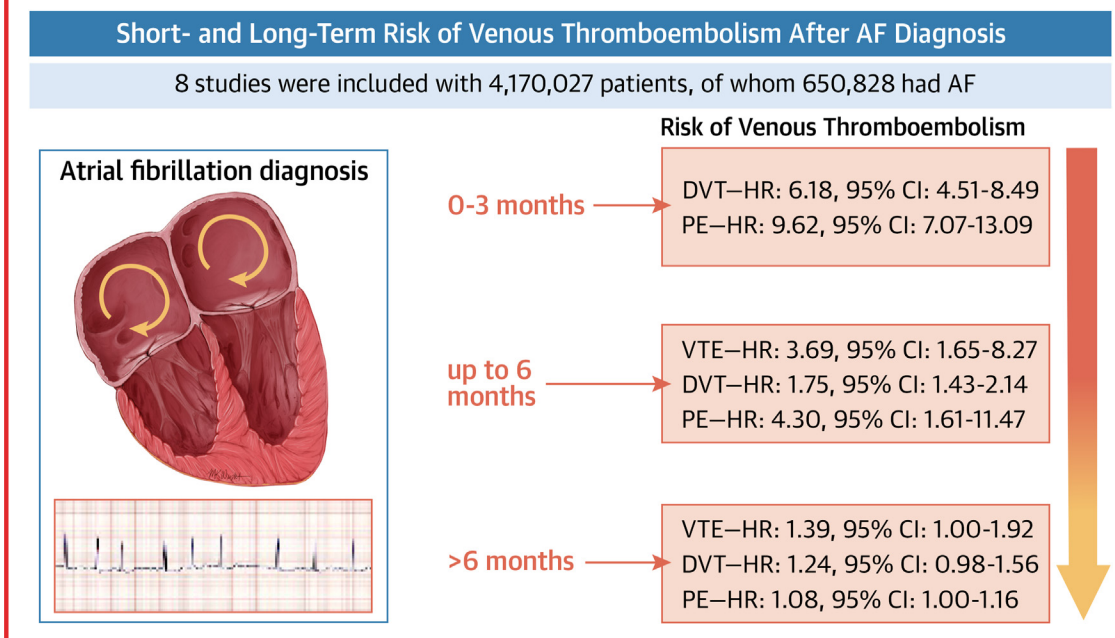
An unexplored issue is if the risk of VTE is also present in patients considered as "truly low-risk" for stroke (ie, those with CHA_2DS_2-VASc 0-1) not taking oral anticoagulants.

FIGURE 4 Long-Term Risk of Venous Thromboembolism, Deep Vein Thrombosis, and Pulmonary Embolism



Long term risk of venous thromboembolism **(A)**, deep vein thrombosis **(B)**, and pulmonary embolism **(C)**. Abbreviations as in Figure 3.

CENTRAL ILLUSTRATION **Summary of the HRs of Venous Thromboembolism, Either Deep Venous Thrombosis or Pulmonary Embolism, According to Time Since Diagnosis of Atrial Fibrillation**



AF = atrial fibrillation; DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

CONCLUSIONS

Patients diagnosed with AF have an increased risk of VTE, which is more evident in the first months. The early initiation of anticoagulation in patients with AF may reduce not only the risk of thromboembolic stroke/systemic embolism but also that of VTE.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: AF is associated with an increased risk of arterial thromboembolic events, which may represent serious life threating complications but data about VTE are lacking.

COMPETENCY IN PATIENT CARE: The risk of VTE is highest in the first 3 to 6 months after AF diagnosis and decreases over time.

TRANSLATIONAL OUTLOOK: The early initiation of anticoagulation and a narrow follow-up in patients with AF may reduce the risk of VTE.

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KEY WORDS **atrial fibrillation, deep vein thrombosis, pulmonary embolism, venous thromboembolism**

APPENDIX **For supplemental tables and figures, please see the online version of this paper.**