

# Atrial fibrillation is related to lower incidence of deep venous thrombosis in patients with pulmonary embolism

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**Background:** Atrial fibrillation (AF) is an established risk factor of left atrial thrombosis and systemic embolism. Traditionally pulmonary embolism (PE) is a recognized complication of deep vein thrombosis (DVT). However, whether AF is responsible for right atrial thrombosis and leads to PE has not been examined.

**Methods:** We retrospectively analyzed medical records of patients with confirmed diagnosis of PE with AF (study group) from 2002–2015. Patients with PE without AF, matched by age and sex, served as controls (control group). The CHA<sub>2</sub>DS<sub>2</sub>-VASc and CHADS<sub>2</sub> scores were classified into two categories, low-intermediate (<2 points) and high-risk (≥2 points).

**Results:** A total of 330 patients (110 in study group and 220 in control group). The study group had significantly lower incidence of newly diagnosed DVT (21% vs. 44%, P<0.001), previous history of DVT (6% vs. 17%, P=0.006) and recent surgery or trauma (10% vs. 23%, P=0.004) compared to the control group. When stratified by the CHADS<sub>2</sub> score, 49 patients (44.5%) were considered low-intermediate risk. This proportion significantly differed when stratified using CHA<sub>2</sub>DS<sub>2</sub>-VASc, in which 13 patients (13.6%) were considered low-intermediate risk, P<0.001.

**Conclusions:** The incidence of DVT was much lower in the study group, suggesting the possibility of clots originated from the right heart that may increase the risk of PE. The CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system might be more sensitive for prediction and stratification of the PE in AF patients than the CHADS<sub>2</sub> score.

**Keywords:** Atrial fibrillation (AF); pulmonary embolism (PE); deep vein thrombosis (DVT); CHA<sub>2</sub>DS<sub>2</sub>-VASc score; CHADS<sub>2</sub> score

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## Introduction

Pulmonary embolism (PE) is a potentially life-threatening condition, affecting a significant proportion of hospitalized patients (1). In Iceland, its incidence was reported to be

0.05%, whereas in Chinese populations estimated to be between 0.09% to 1.12% (1,2). PE is a known manifestation of venous thromboembolism (VTE). Approximately 70% to 80% of PE events are thought to be secondary to deep venous thromboses (DVTs) rather than a separate clinical

entity (3,4). Risk factors for VTE are previous VTE, recent surgery or trauma, advanced age, prolonged immobilization, cancer, thrombophilia, acute myocardial infarction or stroke, congestive heart failure, etc. (1,2,5-8). However, these factors have variable predictive values of DVT and PE.

The association between left atrial appendage thrombosis and systemic embolism in atrial fibrillation (AF) patients is well recognized. Recent studies have pointed out the theoretical potential for a similar phenomenon for the right atrial appendage (RAA), which might also lead to thrombosis that could elevate the risk of PE (9,10). Thus, RAA thrombi have been detected in AF patients with PE reported as a complication of electrical and pharmacologic cardioversion of AF (11-13). However, there is little information on incidence of potential risk factors of PE in AF populations. Therefore, we conducted a retrospective study to investigate the most common risk factors and clinical characteristics of PE patients with and without AF.

## Methods

### Study population

This study complied fully by the declaration of Helsinki and was specifically approved by the Dalian Medical University Ethics Committee (Ethical Approval ID: YJ-KY-FB-2015-20). The study population included patients presenting to The First Affiliated Hospital of Dalian Medical University. They were identified by searching through hospital medical records with a coded diagnosis of PE with and without AF. From 2002 to 2015, total 10,540 and 1,709 patients were found with primary diagnosis of AF and PE respectively. Patients having 12-lead ECG or Holter evidence with previous history of AF and confirmed PE were categorized into the study group. Age and sex-matched PE patients without AF were enrolled into the control group. A case to control ratio of 1:2 was used.

### PE: diagnosis and validation

Cases of PE were collected from medical records of patients and confirmed based established criteria. These included clinical signs and symptoms of dyspnea, chest pain, cyanosis, and pre-syncope confirmed by radiological evidence using computer tomography pulmonary angiography (CTPA), spiral computed tomography or perfusion-ventilation. The

presence or absence of risk factors for PE was examined: DVT (diagnosed by compression ultrasonography or venography), recent surgery or trauma (previous 8 weeks) and active malignancy. In this study, the majority of patients received CTPA or spiral computed tomography. For patients with severe disease in whom we were unable to perform radiological testing, they satisfied of the following: the clinical signs and symptoms suggestive of PE, high D-dimer >500, hypoxemia with  $\text{PaO}_2 \leq 80$  mmHg, with or without electrocardiographic signs of S1Q3T3, and the presence of signs of DVT.

Five independently trained personnel were assigned to review the medical data. To avoid bias, they were blinded to the study objectives. All information on study endpoints were validated by medical records and adjudicated by an independent review panel.

### Study variables

Variables that were obtained at the baseline from discharge medical records were demographic and clinical details. Clinical variables included the most common risk factors of PE, including the new diagnosis of DVT, previous history of DVT, history of recent surgery or trauma within the preceding 8 weeks of presentation to hospital, active malignancy, pulmonary diseases and smoking. The  $\text{CHA}_2\text{DS}_2\text{-VASc}$  and  $\text{CHADS}_2$  scores were also determined. The  $\text{CHADS}_2$  score include the following components: congestive heart failure (1 point), hypertension (1 point), age  $\geq 75$  years (1 point), diabetes mellitus (1 point), and previous stroke/transient ischemic accident (2 points), while  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score include: congestive heart failure (1 point), hypertension (1 point), age  $\geq 75$  years (2 points), diabetes mellitus (1 point), previous stroke/transient ischemic accident (2 points), vascular disease (1 point), age 65–75 years (1 point) and female gender (1 point) were calculated at the study entry for each patient (14,15). Both the  $\text{CHADS}_2$  and  $\text{CHA}_2\text{DS}_2\text{-VASc}$  scores include categories of 0= low risk, 1= intermediate risk, and  $\geq 2$ = high risk (14,15). In order to evaluate better predictability for predicting the risk of PE in study group,  $\text{CHADS}_2$  and  $\text{CHA}_2\text{DS}_2\text{-VASc}$  scores were classified into two categories: low-intermediate risk (<2 points) and high-risk ( $\geq 2$  points).

Drug history was also obtained from the pharmacy and discharge records. This included antithrombotic therapy with oral anticoagulants.

**Table 1** Comparison of demographic and clinical characteristics of PE with and without AF

Variables	Study group, PE with AF (n=110)	Control group, PE without AF (n=220)	P
Sex			0.907
Female	54 (49.1)	110 (50.0)	
Male	56 (50.9)	110 (50.0)	
Age	70.2±9.3	70.05±9.5	0.850
Classification of AF			
Paroxysmal AF	34 (30.9)		
Persistent AF	76 (69.1)		
PE risk factors			
Newly diagnosed DVT	23 (20.9)	97 (44.1)	<0.001
Previous history of DVT	7 (6.4)	38 (17.3)	0.006
Recent surgery or trauma	11 (10.0)	50 (22.7)	0.004
Active malignancy	18 (16.4)	19 (8.6)	0.042
Smoking	13 (11.8)	27 (12.2)	1.000
Pulmonary diseases	35 (31.8)	64 (29.1)	0.613
CHADS <sub>2</sub> and CHA <sub>2</sub> DS <sub>2</sub> -VASc components			
Age stratified			0.850
<65	29 (26.4)	56 (25.4)	
65–74	42 (38.1%)	86 (39.1)	
≥75	39 (35.4%)	78 (35.4)	
CHF	43 (39.1)	19 (8.6)	<0.001
Hypertension	58 (52.7)	117 (53.1)	1.000
Diabetes	15 (13.6)	33 (15.0)	0.869
Stroke/TIA	33 (30.0)	39 (17.7)	0.016
Vascular disease	40 (36.4)	61 (27.7)	0.128
Warfarin therapy			
Warfarin taken	16 (14.5)		
Warfarin untaken	94 (85.5)		
LVEF	55.4±7.9	57.1±6.4	0.075

Data are expressed as percentage and mean ± standard deviation. AF, atrial fibrillation; DVT, deep vein thrombosis; CHF, congestive heart failure; TIA, transit ischemic stroke; LVEF, left ventricular ejection fraction.

### Statistical analysis

Data were expressed as frequencies and percentages. Continuous variables were summarized with mean +/- standard deviation and statistical comparison was made by Student's *t*-test. The Chi square test was used to compare significant differences between two categories of CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores. Statistical significance was considered at P<0.05. All statistical analyses were performed by SPSS version 23 (SPSS IBM).

### Results

In a total of 10,540 patients of the hospital, 110 patients (1.1%) satisfied the inclusion criteria of diagnosed PE and AF for the study group (mean age 70.2±9.3 years). For the control group, 220 patients with diagnosis of PE without AF were matched (mean age 70.05±9.5 years). *Table 1* lists the demographic and clinical characteristics of this study population.

#### Risk factors of PE

Among the most common risk factors of PE, the study group had significantly lower incidence of newly diagnosed DVT (20.9% vs. 44.1%, P<0.001), previous history of DVT (6.4% vs. 17.3%, P=0.006) and recent surgery or trauma (10.0% vs. 22.7%, P=0.004) as compared to control group (*Table 1*).

#### CHA<sub>2</sub>DS<sub>2</sub>-VASc vs. CHADS<sub>2</sub> score

The CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores are established score systems for stratification of stroke risk in AF patients (*Table 1*). The distribution of the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring systems are display in *Tables 2,3*, respectively. Using the CHADS<sub>2</sub> score, the most frequent score was 1 (30.9%) and 49 patients (44.5%) were placed in the low-intermediate risk (<2 points) category. By contrast, using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, the most frequent was 3 (22.7%) in study group. CHA<sub>2</sub>DS<sub>2</sub>-VASc arranged 13 (11.6%) patients (P<0.001) (*Table 3*). CHA<sub>2</sub>DS<sub>2</sub>-VASc score redistributed 36 (73.4%) patients in the CHADS<sub>2</sub> low-intermediate risk category as high-risk (≥2 points) category, an indication for prescription of anticoagulant medications. These findings suggest that the CHA<sub>2</sub>DS<sub>2</sub>-VASc score has better predictability for predicting the low- and high-risk PE

**Table 2** Distributions of the CHA<sub>2</sub>DS<sub>2</sub>-VASc and CHADS<sub>2</sub> scores

CHADS <sub>2</sub> score	N (%)	CHADS <sub>2</sub> redistribution to CHA <sub>2</sub> DS <sub>2</sub> -VASc score	CHA <sub>2</sub> DS <sub>2</sub> -VASc	N (%)
0	15 (13.6)	0: 4 (26.6) 1: 5 (33.3) 2: 4 (26.6) 3: 2 (13.3)	0	4 (3.6)
1	34 (30.9)	1: 4 (11.7) 2: 12 (35.2) 3: 14 (41.1) 4: 4 (11.7)	1	9 (8.2)
2	21 (19.1)	2: 3 (14.2) 3: 7 (33.3) 4: 7 (33.3) 5: 4 (19.0)	2	19 (17.3)
3	23 (20.9)	3: 2 (8.6) 4: 7 (30.4) 5: 11 (47.8) 6: 3 (13.0)	3	25 (22.7)
4	10 (9.1)	5: 2 (20.0) 6: 6 (60.0) 7: 2 (20.0)	4	18 (16.3)
5	6 (5.4)	6: 2 (33.3) 7: 3 (50.0) 8: 1 (16.6)	5	17 (15.4)
6	1 (0.9)	8: 1 (100.0)	6	11 (10.0)
			7	5 (4.5)
			8	2 (1.8)

Values represent the CHADS<sub>2</sub> score redistribution applying the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. CHADS<sub>2</sub> = congestive heart failure (1 point), hypertension (1 point), age ≥75 years (1 point), diabetes mellitus (1 point) and previous stroke/transient ischemic accident (2 points); CHA<sub>2</sub>DS<sub>2</sub>-VASc = congestive heart failure (1 point), hypertension (1 point), age ≥75 years (2 points), diabetes mellitus (1 point), previous stroke/transient ischemic accident (2 points), vascular disease (1 point), age 65–75 years (1 point) and female gender (1 point).

**Table 3** Comparing the CHA<sub>2</sub>DS<sub>2</sub>-VASc and CHADS<sub>2</sub> scoring systems in study group

Scoring systems	Mean SD	Categories	
		Low-intermediate risk, <2 points	High risk, ≥2 points
CHADS <sub>2</sub>	2±1.4	49 (44.5%)	61 (55.4%)
CHA <sub>2</sub> DS <sub>2</sub> -VASc	3.6±1.8	13 (11.6%)	97 (88.1%)

P<0.001,  $\chi^2=29.106$ . The proportion of patients in high-risk category (≥2 points) was significantly higher for CHA<sub>2</sub>DS<sub>2</sub>-VASc than that of CHADS<sub>2</sub> score.

patients as compared to CHADS<sub>2</sub>. CHA<sub>2</sub>DS<sub>2</sub>-VASc score (≥2 points) might be associated with high-risk factor of PE in patients with AF.

### Anticoagulation therapy

In terms of anticoagulation use in our study group, 94 patients (85.5%) did not receive any, whereas 16 patients (14.5%) were warfarin taken with a mean international normalized ratio (INR) of 1.87±0.85. Despite the fact that 97 patients (88.1%) had a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of ≥2, only 16 (16.4%) patients received warfarin therapy. Out of the 16 patients who had warfarin therapy, ten had poor INR control within therapeutic range (≥2).

### Discussion

The main findings of this study are that (I) PE patients with AF had significantly lower incidence of newly and previous history of DVT, and lower history of recent surgery or trauma when compared to patients with PE patients without AF; and (II) The CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system remained a better predictive tool for the high-risk of PE patients with AF, as compare to CHADS<sub>2</sub>.

### Relationship between AF and PE

Previous studies have reported that peripheral thrombus could not be identified in up to 50% of PE patients (16,17). van Langevelde *et al.* found peripheral thrombus in only 44% of PE patients by advanced magnetic resonance imaging technique. The pulmonary emboli was suggested to be arose from the site other than the deep vein systems, such as thrombi of a right cardiac origin or *de novo*

formation in the lung arteries (17).

In the present study, the incidence of DVT was significantly lower in the study group compared to the control group, and when compared with previous studies (16,17). The absence of thrombus secondary to DVTs for the PE event in the study group is consistent with the notion of additional causal factors, as reported previously. Thus, Keller *et al.* demonstrated that AF was the strongest discriminative condition and might play a role in the pathophysiology of PE without DVT (18). Sorensen *et al.* reported the AF patients in the preceding 3 months were associated with markedly increase risk of PE without coexisting peripheral DVT (19), which is consistent to our results.

Other studies have also reported a strong relationship between AF and PE (9-11,20-22). In the Tromsø study, patients with AF had an eight-fold risk for subsequent VTE particularly PE during first 6 months after AF diagnosis (HR =8.44, 95% CI, 5.61–12.69) (9). Similarly, Wang *et al.* found the incidence of PE was significantly higher in AF group than non-AF group (21). The thrombogenic tendency had been explained and observed in both atria of AF patients as a cause of stroke and PE in several studies (11,21,23-25). Right atrium spontaneous echo contrast has been noted in AF patients without DVT, which could directly lead to pulmonary artery occlusion and consequent development of PE (24). Autopsy and echocardiographic studies also illustrated clot formation in the right atrium, predominantly at the RAA, in patients with AF (11,25,26). Their findings pointed out that right intra-cardiac thrombosis might be as common as left intra-cardiac thrombosis (26), despite the different anatomical characteristics of right and left atrium (11). Furthermore, some studies showed that the most of the right cardiac thrombi occurred in the RAA in patients with AF (10,11,26). Thus, AF patients might have an origin for clots in the right heart particularly appendage and linked to a potential causal and preceding risk factor of PE in absence of DVT.

#### ***CHA<sub>2</sub>DS<sub>2</sub>-VASc vs. CHADS<sub>2</sub> score for prediction of PE***

CHA<sub>2</sub>DS<sub>2</sub>-VASc and CHADS<sub>2</sub> scores are well-recognized scores for stratification of stroke risk in AF patients. Of these, where 90% of thrombus is originated from left atrial appendage and CHA<sub>2</sub>DS<sub>2</sub>-VASc score has demonstrated better predictability (27). Most components of these stroke risk scoring systems are also risk factors for PE (8,26,28-32). However, for prediction of RAA thrombosis and incidence

of PE, very few studies have been done to determine better predictability between CHA<sub>2</sub>DS<sub>2</sub>-VASc and CHADS<sub>2</sub> scores in AF patients. Saliba *et al.* had found that high CHA<sub>2</sub>DS<sub>2</sub>-VASc score is directly associated with increased risk of PE among AF patients (32). Consistent with these findings, our study revealed that the CHA<sub>2</sub>DS<sub>2</sub>-VASc low-intermediate risk category had lower 13 (11.6%) *vs.* 49 (44.5%) and high-risk category had higher 97 (88.1%) *vs.* 61 (55.4%) proportion of patients compared to CHADS<sub>2</sub> score. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score is recommended for risk stratification of stroke in the 2014 guidelines of ESC and CCS as compared to classical CHADS<sub>2</sub> score (33,34). The results of our study support the notion that CHA<sub>2</sub>DS<sub>2</sub>-VASc is a useful and suitable scoring system than CHADS<sub>2</sub> score regarding prediction and stratification for the PE in patient with AF.

#### ***Anticoagulation***

In our center, warfarin is common anticoagulant agent prescribed. Warfarin was only observed in 16 patients (14.5%). In 97 patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score of  $\geq 2$  (88.1%), only 16 (16.4%) received warfarin therapy. Of these, ten did not reach the target INR, which might underlie the high incidence of PE in the study group. Similar reports have been published that the use of anticoagulant was very low in Chinese hospitalized AF patients and in Chinese community based studies, even among high risk (CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$ ) individuals (35-37). Public awareness and health education for thromboembolic event prevention with anticoagulant according to risk scores and current guidelines in AF patients are needed in China.

However, warfarin has been the mainstay anticoagulant agent for ischemic stroke and thromboembolic event prevention and could reduce the risk of stroke by 64% in AF patients (38). At the meantime, the application of anticoagulant was suggested to be highly beneficial and could reduce about 33% the risk of PE and 39% all-cause mortality rates in AF patients (32). Our results further supported that anticoagulation in high risk AF patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc  $\geq 2$  are important not only for stroke prevention, but also for PE. Moreover, in many cases closure of left atrial appendage has been concerned to overcome the warfarin contraindications in AF patients (27,39). Whether RAA closure could reduce the incidence of PE and bleeding complications in AF patients remains further elucidation.

### Limitations

The design of this work is a retrospective study carried out in a single hospital with a relatively small sample size. We have compared several factors to elucidate direct conclusion but due to nature of our study, it is not possible to draw direct conclusions on the causal association of AF and PE. In addition, our study did not have the power to explain that PE itself causes AF, where acute onset AF patients were excluded from study group. Further studies are warranted to conduct more details investigations.

### Conclusions

The incidence of DVT in patients with PE and AF is lower than those without AF. These findings are consistent with the notion that the thrombi burden may not arise solely from the deep vein systems, but possibly from the right heart or are formed *de novo* within the large arteries. The CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system might be more sensitive for risk prediction and stratification of the PE in AF patients.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* This study complied fully by the declaration of Helsinki and was specifically approved by the Dalian Medical University Ethics Committee (Ethic Approval ID: YJ-KY-FB-2015-20).

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