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Impact of symptomatic atherosclerosis in patients with pulmonary embolism

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ABSTRACT

Background: Atherosclerosis is associated with increased cardiovascular mortality. Associations between venous thromboembolism and atherosclerosis were recently reported. We aimed to investigate the impact of symptomatic atherosclerosis on adverse outcomes in patients with pulmonary embolism (PE) and to identify significant differences among patients with PE stratified by symptomatic atherosclerosis.

Methods: Patients were selected by screening the nationwide inpatients sample for PE (ICD-code I26) stratified by symptomatic atherosclerosis (composite of coronary artery disease [ICD-code I25], myocardial infarction [ICD-code I21], ischemic stroke [ICD-code I63], and/or atherosclerotic arterial diseases [ICD-code I70]). We compared PE patients with (PE + Athero) and without (PE − Athero) symptomatic atherosclerosis and analysed the impact of symptomatic atherosclerosis on adverse outcomes.

Results: Overall, 213,995 patients with PE (54.2% females) were included in this analysis. Of these, 30,157 (14.1%) had symptomatic atherosclerosis with age-dependent incline. Deep vein thrombosis or thrombophlebitis (45.1% vs. 36.9%, $P < 0.001$) was more commonly observed in the PE − Athero group (Odds Ratio (OR) 0.713 [95% CI 0.695–0.731], $P < 0.001$). In-hospital mortality (12.1% vs. 9.6%, $P < 0.001$) and adverse in-hospital events (16.8% vs. 12.6%, $P < 0.001$) were affected by symptomatic atherosclerosis; both in-hospital mortality (OR 1.107 [95% CI 1.061–1.155], $P < 0.001$) and adverse in-hospital outcomes (OR 1.143 [95%CI 1.102–1.186], $P < 0.001$) were affected independently of age, gender, comorbidities, and reperfusion treatments.

Conclusions: Symptomatic atherosclerosis in patients with PE increased with age and was associated with a poorer outcome. Cardiovascular-atherosclerotic diseases might play a major role in thrombus formation in isolated PE.

1. Introduction

Venous thromboembolism (VTE), which comprises pulmonary embolism (PE) and deep venous thrombosis, and thromboembolic arterial diseases, such as acute myocardial infarction (MI), ischemic stroke, or peripheral artery disease (PAD), are generally considered as separate entities [1]. Venous thrombi are mainly composed of red blood cells and fibrin while arterial thrombi are mainly composed of platelets [2]. In recent years, studies have shown associations between VTE and atherosclerosis. Therefore, the hypothesis has been formulated that atherosclerotic diseases and VTE are linked diseases [1,3–7]. A higher prevalence of atherosclerotic lesions was reported in patients with idiopathic deep venous thrombosis in comparison to deep venous thrombosis patients with secondary deep venous thrombosis or to controls without deep venous thrombosis [7]. Additional studies observed a higher prevalence of aortic calcifications [8] and coronary artery calcium [6,9] in VTE patients compared to controls. Others identified a higher prevalence of deep venous thrombosis events in patients with PAD than in controls without PAD [10]. In contrast to these results, other studies failed to confirm a correlation between atherosclerosis and an increased risk for deep venous thrombosis [11] or VTE [12]. Most of the studies investigating links between VTE and atherosclerosis focused on VTE in general or deep venous thrombosis VTE, but studies regarding the potentially life-threatening PE VTE in this context are sparse.

Thus, the objectives of our study were to investigate the impact of symptomatic atherosclerosis on adverse outcomes in patients with PE and to identify differences between PE patients with and without additional symptomatic atherosclerosis.

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2. Methods and patients

We used the German nationwide inpatient statistics (diagnosis related groups [DRG] statistic) for this analysis (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2011–2014, own calculations). The Federal Statistical Office of Germany (Statistisches Bundesamt) gathers treatment data from all inpatient cases in Germany (processed according to the DRG system). Diagnoses are coded according to ICD-10-GM (International Classification of Diseases, 10th Revision with German Modification) and surgical or interventional procedures with OPS codes (surgery and procedures codes [Operationen- und Prozedurenschlüssel]).

Although the number of hospitals in Germany decreased from 2045 to 1980 between the years 2011 and 2014, covered patient files increased in this timeframe from 18.3 to 19.1 million per year.

For this analysis, all inpatients with a main diagnosis of PE (ICD-code I26) between 2011 and 2014 were selected. Patients' main diagnosis is defined as the diagnosis, which is mainly responsible for patients' hospitalization [13]. The included patients with PE were stratified according to presence of symptomatic atherosclerosis, defined as the presence of at least one of the following comorbidities coded in these patients: coronary artery disease (CAD, ICD-code I25), myocardial infarction (ICD-code I21), ischemic stroke (ICD-code I63), and/or atherosclerotic arterial diseases, including PAD, aortic atherosclerosis, and atherosclerosis of the renal arteries (ICD-code I70).

2.1. Study outcomes

The primary outcome of this study was all cause-death during hospitalization (in-hospital death). The secondary outcome encompassed adverse in-hospital outcomes, which included all causes of in-hospital deaths, cardio-pulmonary resuscitation (CPR, OPS code 8-77) and/or mechanical ventilation (MV, OPS codes 8-70 and 8-71). The tertiary endpoints included bleeding complications such as intracerebral, subarachnoid and gastrointestinal bleeding as well as the need for transfusions of blood products.

2.2. Definitions

Chronic lung diseases were defined as a composite of the following diseases: bronchial asthma, chronic obstructive lung disease, pulmonary arterial hypertension, and interstitial lung diseases. Renal insufficiency comprised diagnosis of all renal insufficiency stages. Coagulation abnormalities were defined as coagulopathies, haemophilia, purpura, and bleeding diathesis comprising disseminated intravascular coagulation. Right ventricular dysfunction (RVD) was defined as acute right ventricular dilatation in the imaging procedures.

2.3. Ethical aspects

Since this study did not involve direct access by the investigators of this study to individual patient data, approval by an ethics committee and informed patient consent were not required, in accordance with German law.

2.4. Statistics

The included patients with PE were stratified according to the coded information regarding the presence of symptomatic atherosclerosis into the group of PE patients with symptomatic atherosclerosis (PE + Athero) and the group of PE patients without symptomatic atherosclerosis (PE − Athero). We compared the two groups for common VTE risk factors, comorbidities, risk stratification markers, treatments, and outcomes, and tested the impact of symptomatic atherosclerosis on the different outcome parameters. Descriptive statistics for relevant baseline comparisons between PE patients with and without concomitant symptomatic atherosclerosis are provided as medians and interquartile ranges (IQR) or absolute numbers and corresponding percentages. Continuous variables in the two groups were tested for significant differences using the Wilcoxon-Mann-Whitney-*U* test and for categorical variables, the Fisher's exact or χ^2 test were used, as appropriate.

Univariate and multivariate logistic regression models were computed to investigate the impact of symptomatic atherosclerosis on the various study endpoints, risk stratification markers, and treatments. Tachycardia, RVD, and shock were used as established risk stratification markers in PE. In addition, the association between PE with and without additional deep venous thrombosis or thrombophlebitis (DVT) with symptomatic atherosclerosis, CAD, myocardial infarction, ischemic stroke as well as atherosclerotic arterial diseases including PAD, aortic atherosclerosis and atherosclerosis of the renal arteries were tested univariately in logistic regression models. Results were presented as Odds Ratios (OR) and corresponding 95% confidence intervals (CI).

The multivariate logistic regression models were performed with different adjustments to prove the independence of the associations regarding the following parameters:

- adjustment I: age and gender
- adjustment II: age, gender, obesity, surgery during in-hospital stay, cancer, heart failure, atrial fibrillation/flutter, chronic lung diseases, essential arterial hypertension, renal insufficiency, diabetes mellitus, coagulation abnormalities, systemic thrombolysis and surgical embolectomy. The multivariate logistic regression model was adjusted for age, gender, obesity, surgery during in-hospital stay, cancer, heart failure, atrial fibrillation, chronic lung diseases, essential arterial hypertension, renal insufficiency, diabetes mellitus, and coagulation abnormalities only when testing the independence of the reperfusion strategies (systemic thrombolysis and surgical embolectomy).
- adjustment III: age, gender obesity, surgery during in-hospital stay, cancer, heart failure, atrial fibrillation/flutter, chronic lung diseases, essential arterial hypertension, renal insufficiency, diabetes mellitus, coagulation abnormalities, RVD, tachycardia, syncope, and shock.
- adjustment IV: age, gender obesity, surgery during in-hospital stay, cancer, heart failure, atrial fibrillation/flutter, chronic lung diseases, essential arterial hypertension, renal insufficiency, diabetes mellitus, coagulation abnormalities, RVD, tachycardia, syncope, shock, and pneumonia.

We calculated Kaplan-Meier survival curves for PE + Athero and PE − Athero patients related to the in-hospital stay (observed for a maximum of 30 days) and compared the curve shapes with the log-rank test. Additionally, Cox proportional-hazards regression curves were plotted for both groups, and the difference of the survival for all these group variations was calculated with Cox regression models.

The analyses were performed on our behalf by the Research Data Center of the Federal Statistical Office and the Statistical Offices of the federal states (DRG Statistics 2011–2014, own calculations), in Wiesbaden (Germany). The aggregated statistics were provided on the basis of SPSS codes (SPSS® software, version 20.0, SPSS Inc., Chicago, Illinois), which were supplied to the Research Data Center. The SPSS® software (version 20.0; SPSS Inc., Chicago, Illinois, USA) was used for computerised analyses. P values of <0.05 (two-sided) were considered to be statistically significant.

3. Results

3.1. Patient characteristics

In total, 213,995 patients with PE (54.2% females) were included in this analysis. Of these patients, 30,157 (14.1%) had coded information on concomitant symptomatic atherosclerosis, while 183,838 (85.9%) did not (Fig. S1 in the Supplementary material). As expected, the proportion of PE patients with symptomatic atherosclerosis increased with advancing age (Fig. 1A).

Patient characteristics are shown in Table 1. Symptomatic atherosclerosis was less common in PE patients with DVT (univariate: OR 0.713 [95% CI 0.695–0.731], P < 0.001; adjustment II: OR 0.741 [95%CI 0.722–0.761], P < 0.001) and consequently all of the symptomatic atherosclerotic diseases such as CAD (univariate: OR 0.683 [95% CI 0.665–0.703], P < 0.001; adjustment II: OR 0.707 [95%CI 0.686–0.727], P < 0.001), ischemic stroke (univariate: OR 0.659 [95% CI 0.578–0.751], P < 0.001; adjustment II: OR 0.700 [95%CI 0.614–0.799], P < 0.001), and atherosclerotic arterial diseases including PAD, aortic atherosclerosis, and atherosclerosis of the renal arteries (univariate: OR 0.911 [95% CI 0.857–0.968], P = 0.003; adjustment II: 0.980 [95%CI 0.922–1.042], P = 0.523), were all found less often in PE patients with DVT using (univariate) logistic regression models. These results were confirmed in the multivariate analyses, except for atherosclerotic arterial diseases.

3.2. Risk stratification markers

All investigated risk stratification markers, particularly tachycardia (1.8% vs. 1.2%, P < 0.001), shock (3.5% vs. 2.5%, P < 0.001) and RVD (32.7% vs. 29.8%, P < 0.001), were more frequently found in PE + Athero patients (Table 1). In particular, RVD was more prevalent in PE + Athero patients compared to PE − Athero patients in life-decades 2 to 8 (Fig. 1B).

The univariate logistic regression models confirmed an impact of symptomatic atherosclerosis on RVD and shock with increased frequencies in PE + Athero patients compared to those without symptomatic atherosclerosis (Table 2). These results remained stable after multivariate adjustments for age and gender. After an additional adjustment for comorbidities and reperfusion therapies, symptomatic atherosclerosis was only associated with an increase in shock and remarkably with a decrease in RVD (Table 2).

3.3. Treatment and bleeding events

Although the use of systemic thrombolysis was higher in PE − Athero patients compared to PE + Athero patients (5.1% vs. 4.6%, P = 0.002), the PE + Athero patients had significantly more often bleeding events requiring blood-product transfusions (6.0% vs. 3.9%, P < 0.001) (Table 1). Systemic thrombolysis was particularly more often used in PE + Athero

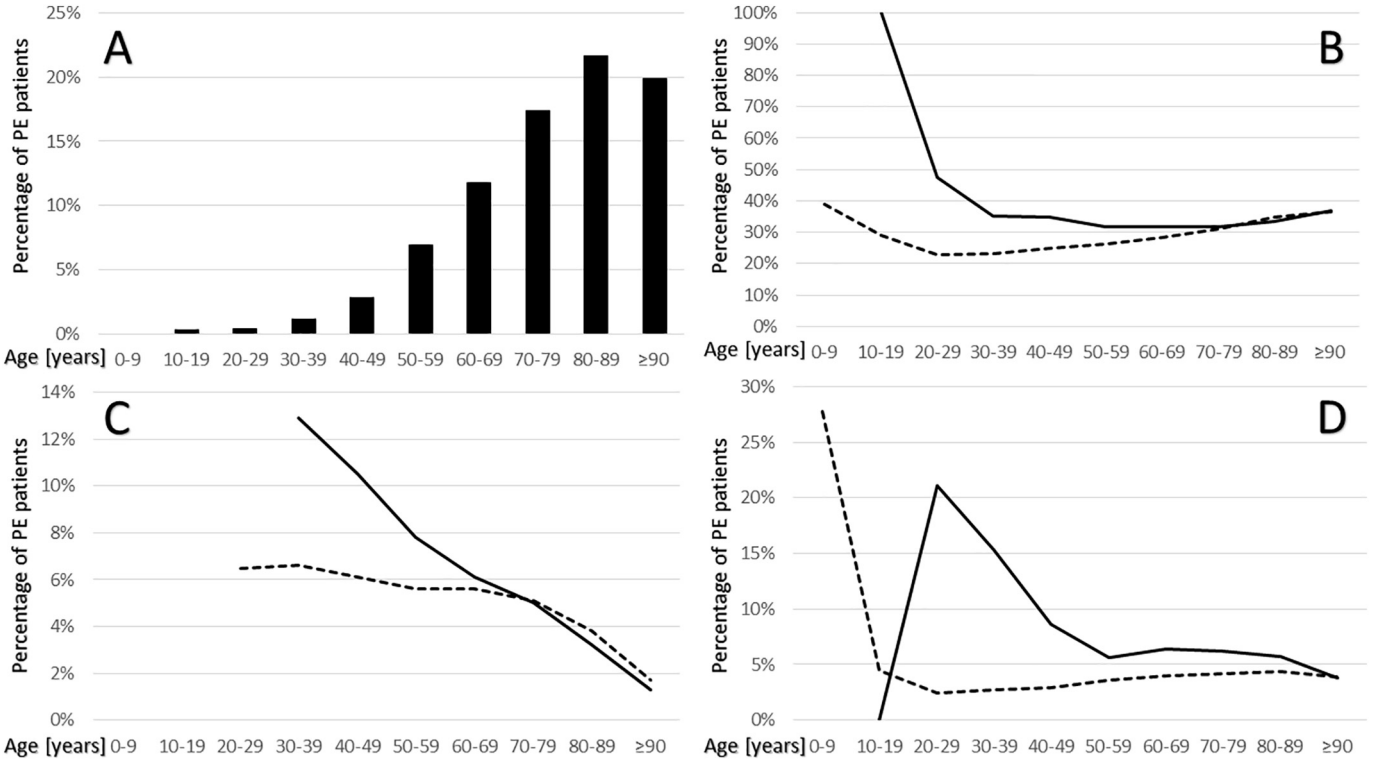

Fig. 1. Proportion of PE patients with symptomatic atherosclerosis in different age-groups (A), impact of symptomatic atherosclerosis on RVD (B), and the age-dependent differences in the treatments of systemic thrombolysis (C) as well as transfusion (D) stratified by symptomatic atherosclerosis (solid black line: PE patients with symptomatic atherosclerosis; dashed black line: PE patients without coded symptomatic atherosclerosis).

than in PE − Athero group patients younger than 60 years (Fig. 1C). In contrast, bleeding events such as intracerebral (Fig. 2C) and gastrointestinal bleeding (Fig. 2D) as well as transfusions of blood products (Fig. 1D) were all observed more often in most age-decades of PE + Athero patients compared to PE − Athero patients.

The multivariate logistic regression model (adjusted for age, gender, and comorbidities [adjustment II]) confirmed lower rates of reperfusion treatments (systemic thrombolysis and surgical embolectomy) in PE + Athero patients (Table 2).

Intracerebral bleeding events were significantly associated with PE + Athero independently of age, gender, comorbidities, and reperfusion treatments (adjustment II) (Table 2).

3.4. Primary and secondary study outcomes

In-hospital mortality (12.1% vs. 9.6%, $P < 0.001$) and adverse in-hospital events (16.8% vs. 12.6%, $P < 0.001$) were both higher in PE + Athero compared to PE-Arthero patients (Table 1). Frequency of in-hospital death (Fig. 2A) and adverse in-hospital outcome (Fig. 2B) both occurred more often in PE + Athero patients compared to PE − Athero in age-decades 4–8, but in patients aged 80 years and older PE − Athero patients revealed higher rates of primary and secondary study outcomes.

The multivariate logistic regression models showed an increase in all-cause mortality (OR 1.107 [1.061–1.155], $P < 0.001$) and adverse in-hospital outcomes (OR 1.143 [1.102–1.186], $P < 0.001$) due to the presence of symptomatic atherosclerosis independently of age, gender, comorbidities, and reperfusion treatments. These results remained stable in the fully adjusted models with additional adjustments for RVD, tachycardia, syncope, shock, and pneumonia (adjustment IV, Table 2).

The Kaplan-Meier plot as well as the Cox-proportional hazard plot depict the increased survival of PE − Athero patients compared to PE + Athero patients related to in-hospital stay (Fig. S2A and B in the Supplementary material). The difference between both curves was statistically significant (log rank test: $P < 0.001$). The Cox regression models statistically confirmed the survival benefit (Table S1 in the Supplementary material).

4. Discussion

Although VTE and thromboembolic arterial disease are generally considered as different entities, increased evidence underlines a potential link between venous and arterial thrombosis [1,3–7,9,14–22]. VTE and atherothrombosis share risk factors with common pathophysiological characteristics of inflammation, hypercoagulability, and endothelial injury [3]. However, most studies investigated links between VTE in general or DVT VTE with atherosclerosis, but study results about associations between life-threatening PE VTE and atherosclerosis are lacking. Thus, we aimed to investigate the impact of symptomatic atherosclerosis on the adverse outcomes in patients with PE and to identify significant differences between PE with and without additional DVTs in the German nationwide inpatient sample.

The key findings of our study can be summarized as follows: i) the total numbers of PE patients with symptomatic atherosclerosis increased with advancing age, ii) symptomatic atherosclerosis was associated with isolated PE, iii) bleeding events were significantly more prevalent in PE + Athero patients independent of age, gender, comorbidities, and reperfusion treatments, and iv) adverse in-hospital outcomes and in-hospital mortalities were both higher in PE + Athero patients compared to PE − Athero patients. The increased risk for adverse in-hospital outcomes and in-hospital mortalities in PE + Athero patients was independent of sex, age, comorbidities, and important risk stratification markers such as shock, RVD, and tachycardia.

Atherosclerosis and related diseases with its complications are the most important causes of death worldwide [23]. Risk factors such as hypertension, obesity, smoking, dyslipidaemia, diabetes mellitus, and advanced age have been identified in the progression of atherosclerosis during an individuals' lifetime. In accordance with literature [24–26],

Table 1
Baseline characteristics, medical history, and presentation of the 213,995 patients with PE stratified according to the presence of symptomatic atherosclerosis.

Parameters	Symptomatic atherosclerosis (n = 30,157; 14.1%)	No symptomatic atherosclerosis (n = 183,838; 85.9%)	P-value
Age (years)	77.0 (71.0–83.0)	71.0 (57.0–79.0)	<**0.001**
Female gender*	13,921 (46.2%)	102,005 (55.5%)	<**0.001**
In-hospital stay (days)	9 (6–14)	8 (5–12)	<**0.001**
Obesity	2777 (9.2%)	15,109 (8.2%)	<**0.001**
VTE risk factors			
Surgery during in-hospital stay	13,264 (44.0%)	65,701 (35.7%)	<**0.001**
Cancer	2650 (8.8%)	20,209 (11.0%)	<**0.001**
Comorbidities			
Chronic (left) heart failure	10,094 (33.5%)	31,572 (17.2%)	<**0.001**
Chronic lung disease	7670 (25.4%)	29,328 (16.0%)	<**0.001**
Atrial fibrillation/flutter	6381 (21.2%)	20,187 (11.0%)	<**0.001**
Essential arterial hypertension	17,210 (57.1%)	77,838 (42.3%)	<**0.001**
Renal insufficiency	10,225 (33.9%)	29,503 (16.0%)	<**0.001**
Diabetes mellitus	8857 (29.4%)	26,949 (14.7%)	<**0.001**
Coagulation abnormalities	2079 (6.9%)	12,042 (6.6%)	**0.026**
Deep venous thrombosis or thrombophlebitis	11,131 (36.9%)	82,886 (45.1%)	<**0.001**
Pneumonia	7342 (24.3%)	45,296 (24.6%)	0.273
Risk stratification			
Tachycardia	543 (1.8%)	2236 (1.2%)	<**0.001**
Right ventricular dysfunction	9847 (32.7%)	54,860 (29.8%)	<**0.001**
Shock	1045 (3.5%)	4526 (2.5%)	<**0.001**
Treatment			
Systemic thrombolysis	1400 (4.6%)	9321 (5.1%)	**0.002**
Surgical embolectomy	28 (0.09%)	253 (0.14%)	**0.047**
Outcomes/clinical conditions			
Adverse in-hospital event	5066 (16.8%)	23,098 (12.6%)	<**0.001**
All cause in-hospital death	3645 (12.1%)	17,721 (9.6%)	<**0.001**
Mechanical ventilation	2753 (9.1%)	11,075 (6.0%)	<**0.001**
Cardio-pulmonary resuscitation	1598 (5.3%)	8436 (4.6%)	<**0.001**
Intracerebral bleeding	77 (0.3%)	244 (0.1%)	<**0.001**
Subarachnoid bleeding	15 (0.05%)	56 (0.03%)	0.090
Gastrointestinal bleeding	328 (1.1%)	1295 (0.7%)	<**0.001**
Transfusion of blood constituents	1805 (6.0%)	7122 (3.9%)	<**0.001**

Abbreviations: PE indicates for pulmonary embolism; DVT, deep venous thrombosis; VTE, venous thromboembolism.
Data in bold indicates P values of <0.05.
* Information available for n = 213,989 patients.

and as expected, we identified an age-dependent increase of symptomatic atherosclerotic diseases in patients with PE.

It is well known that atherosclerosis, the underlying cause of the majority of clinical cardiovascular events, is typically present for decades before the onset of clinical cardiovascular events or symptoms and initial manifestation of clinical atherosclerotic cardiovascular diseases is often a fatal event (sudden cardiac death, massive myocardial infarction, or disabling stroke) [26]. Our study results demonstrated that the presence of symptomatic atherosclerosis was related to poorer outcomes in patients with PE with a higher rate of adverse in-hospital events and especially a higher frequency of in-hospital deaths. The increased risk for adverse in-hospital outcomes and in-hospital mortality for PE + Athero patients was independent of sex, age, comorbidities, and reperfusion treatments as well as important risk stratification markers such as shock, RVD, syncope, and tachycardia (Table 2). It is well established that clinical parameters of the Pulmonary Embolism Severity Index (PESI) [27], parameters of risk stratification tools such as the ESC 2014 guideline algorithm [28], the Bova score [29], and the modified FAST score [30], all have a prognostic impact on the 30 day mortality. Key roles regarding risk stratification involved RVD [28] and myocardial injury [28]. Thus, we tried to analyse the independence of our findings regarding these parameters (RVD and scores/algorithm). Table S2 in the Supplementary material provides an overview about the parameters of the risk stratification tools. Missing adjustments regarding some parameters of the PESI [27], such as hypoxia, respiratory rate, temperature, and altered mental status could not adequately addressed and the missing adjustments for these parameters, as well as cardiac troponins and NT-Pro B-type natriuretic peptides (NT-proBNP) are main limitations of our study. Nevertheless, we were able to adjust the multivariate logistic regression model for most of the PESI [27], Bova score [29] and modified FAST score [30] parameters and additionally, for a large number of comorbidities which are relevant for in-hospital outcomes. The large number of outcomes enabled us to include a huge number of variables in the multivariate logistic regression model. This is a major strength of our study because smaller studies with small numbers of outcome events can only adjust for a limited number of parameters and therefore cannot provide large evidence regarding independence of their prognostic findings.

An association between atherosclerosis and DVT was confirmed in several studies [7,10,18,31]. Prandoni et al. [7], reported a higher frequency of carotid plaques as an indicator of atherosclerosis in patients with previous idiopathic DVT in comparison to those without DVT [7]. Other studies found that aortic calcifications [8] and coronary artery calcium [6,9] were more prevalent in VTE patients than in controls. The concept of linked diseases was proved in the study by Libertiny et al. [10], demonstrating a higher prevalence of DVT events in patients with PAD than in controls [10]. In contrast, other studies failed to confirm a correlation between atherosclerosis and an increased risk of VTE [11,12]. Interestingly, our study identified a lower frequency of symptomatic atherosclerosis in PE patients with DVT, which might indicate a different pathomechanism in the development of PE patients with and without DVT. In about 65% of the PE events, the clot in the pulmonary artery bed is the result of DVT rather than a separate clinical entity [28,32]. For PE without underlying DVTs (isolated PE), data from clinical studies suggest a key role of co-morbidities such as cancer [33], and especially cardiovascular diseases with an association to atherosclerosis like atrial fibrillation [34,35], myocardial infarction [34], and heart failure [34,35] in the pathogenesis of thrombus formation. Several pathomechanisms were proposed to explain the absence of peripheral thrombi, such as cardiac thrombus formation, embolization of the complete deep-vein thrombus, and thrombus development de novo in the lungs due to local inflammatory processes and driven coagulation or reduced cardiac outputs [35–40]. Right cardiac stasis due to reduced cardiac output might also lead to intracardiac thrombus formation with an elevated risk of PE [34,39,41]. The results of our study confirm an association between atherosclerotic diseases and isolated PE and support the hypothesis that cardiovascular atherosclerotic diseases, especially those with cardiac dysfunction (heart failure, CAD, and myocardial infarction) might play a role in thrombus formation in PE patients without DVT [34,40,42,43]. However, while not all patients in the German nationwide sample underwent lower limb ultrasound testing for DVT, this finding should be considered with caution, although it has to be expected that symptomatic DVTs have been detected in the vast majority of cases. Studies investigating the outcomes of isolated PE vs. PE with concomitant DVT showed conflicting results [44,45]. Most studies indicate a poorer outcome for PE patients with concomitant DVT [45–49], but not all [35,50]. Becattini et al. [44], provided evidence in their large meta-analysis involving >7500 patients, that a concomitant DVT in PE was associated with an increased risk of death within 30 days after PE diagnosis [44]. This higher short-term mortality might be driven by larger thrombus burdens in these patients with concomitant DVT [44]. In this context, another limitation of our study requires consideration: There was a lack of data regarding the left ventricular ejection fraction in our patients, especially in those with coded information on heart failure. It would be of interest to determine whether the left ventricular function is a significant predictor and co-founder for the poor outcome in PE patients with symptomatic atherosclerosis.

Table 2
Impact of symptomatic atherosclerosis on risk stratification markers, outcomes, and treatments in patients with PE (univariate and multivariate logistic regression model).

	Univariate regression model		Multi-variate regression model with adjustment I[a]		Multi-variate regression model with adjustment II[b]		Multi-variate regression model with adjustment III[c]		Multi-variate regression model with adjustment IV[d]	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Risk stratification markers										
RV dysfunction	1.140 (1.111–1.170)	<**0.001**	1.063 (1.035–1.092)	<**0.001**	0.919 (0.893–0.946)	<**0.001**	0.900 (0.875–0.926)	<**0.001**	0.900 (0.875–0.926)	<**0.001**
Shock	1.422 (1.328–1.523)	<**0.001**	1.376 (1.282–1.476)	<**0.001**	1.162 (1.076–1.254)	<**0.001**	1.152 (1.069–1.241)	<**0.001**	1.152 (1.069–1.241)	<**0.001**
Outcomes/clinical conditions										
Adverse in-hospital outcome	1.405 (1.359–1.452)	<**0.001**	1.182 (1.143–1.223)	<**0.001**	1.143 (1.102–1.186)	<**0.001**	1.149 (1.106–1.195)	<**0.001**	1.150 (1.106–1.195)	<**0.001**
All-cause death	1.289 (1.241–1.339)	<**0.001**	1.028 (0.989–1.069)	0.160	1.107 (1.061–1.155)	<**0.001**	1.115 (1.066–1.166)	<**0.001**	1.113 (1.064–1.164)	<**0.001**
Cardio-pulmonary resuscitation	1.163 (1.101–1.229)	<**0.001**	1.127 (1.065–1.192)	<**0.001**	1.219 (1.146–1.297)	<**0.001**	1.196 (1.122–1.275)	<**0.001**	1.196 (1.122–1.275)	<**0.001**
Intracerebral bleeding	1.926 (1.490–2.489)	<**0.001**	1.816 (1.394–2.366)	<**0.001**	1.734 (1.322–2.274)	<**0.001**	1.691 (1.290–2.218)	<**0.001**	1.693 (1.291–2.221)	<**0.001**
Subarachnoid bleeding	1.633 (0.924–2.888)	0.092	2.156 (1.182–3.935)	**0.012**	1.701 (0.918–3.149)	0.091	1.697 (0.917–3.141)	0.092	1.700 (0.918–3.146)	0.091
Gastrointestinal bleeding	1.550 (1.372–1.751)	<**0.001**	1.300 (1.148–1.472)	<**0.001**	1.045 (0.920–1.188)	0.498	1.045 (0.919–1.187)	0.504	1.046 (0.920–1.189)	0.491
Treatment										
Systemic thrombolysis	0.912 (0.861–0.965)	**0.002**	1.042 (0.982–1.105)	0.173	0.882 (0.830–0.938)	<**0.001**	0.896 (0.840–0.955)	**0.001**	0.896 (0.840–0.955)	**0.001**
Surgical embolectomy	0.674 (0.456–0.997)	**0.048**	1.040 (0.694–1.558)	0.850	0.509 (0.337–0.768)	**0.001**	0.500 (0.330–0.756)	**0.001**	0.501 (0.331–0.759)	**0.001**
Transfusion of blood components	1.580 (1.498–1.666)	<**0.001**	1.584 (1.500–1.673)	<**0.001**	1.263 (1.190–1.341)	<**0.001**	1.232 (1.161–1.308)	<**0.001**	1.238 (1.166–1.315)	<**0.001**

Data in bold indicates P values of <0.05.

[a] Adjustment I: adjusted for age and gender.

[b] Adjustment II: adjusted for age, gender, obesity, surgery during in-hospital stay, cancer, heart failure, atrial fibrillation/flutter, chronic lung diseases, essential arterial hypertension, renal insufficiency, diabetes mellitus, coagulation abnormalities, systemic thrombolysis, and surgical embolectomy. The multivariate logistic regression model was adjusted for age, gender, obesity, surgery during in-hospital stay, cancer, heart failure, atrial fibrillation/flutter, chronic lung diseases, essential arterial hypertension, renal insufficiency, diabetes mellitus, and coagulation abnormalities only when testing the independence of the reperfusion strategies (systemic thrombolysis and surgical embolectomy).

[c] Adjustment III: adjusted for age, gender, obesity, surgery during in-hospital stay, cancer, heart failure, atrial fibrillation/flutter, chronic lung diseases, essential arterial hypertension, renal insufficiency, diabetes mellitus, coagulation abnormalities, RVD, tachycardia, syncope, and shock.

[d] Adjustment IV: adjusted for age, gender, obesity, surgery during in-hospital stay, cancer, heart failure, atrial fibrillation/flutter, chronic lung diseases, essential arterial hypertension, renal insufficiency, diabetes mellitus, coagulation abnormalities, RVD, tachycardia, syncope, shock, and pneumonia.

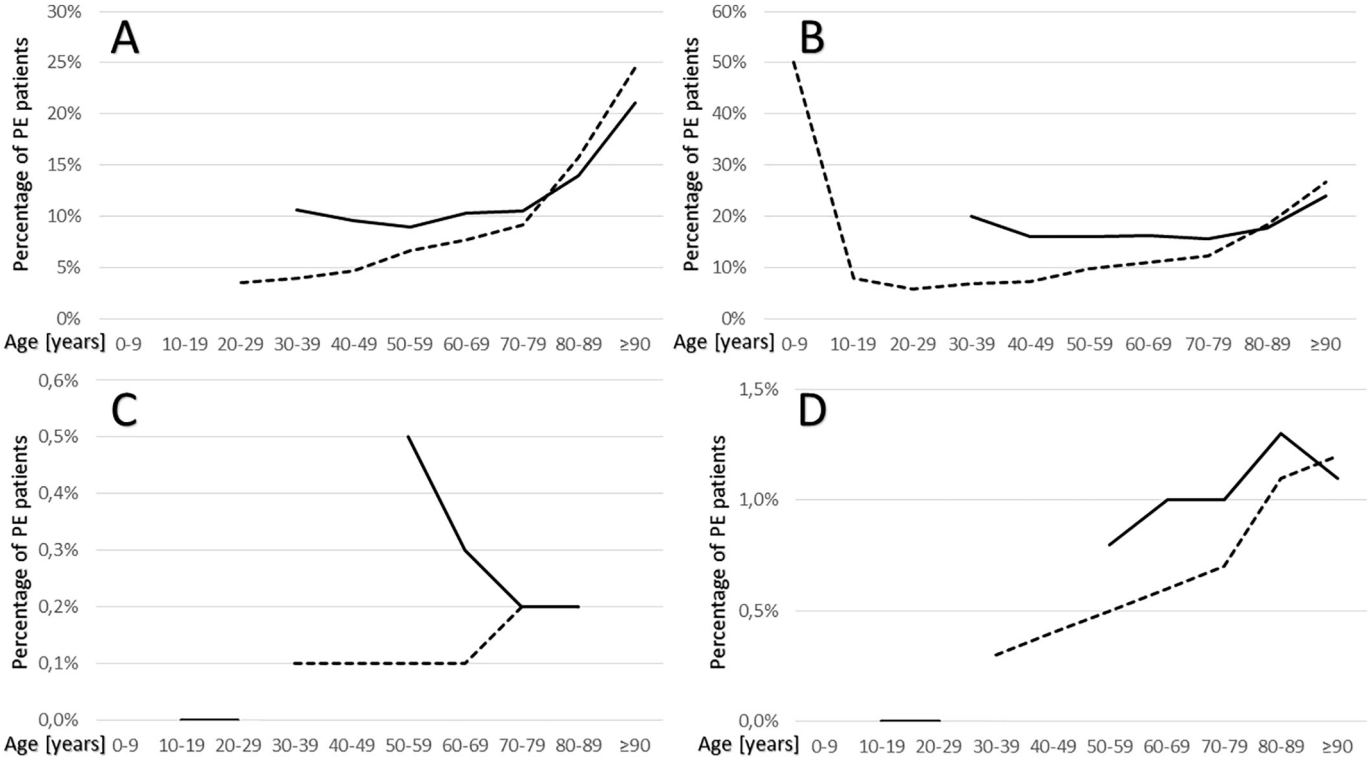

Fig. 2. Impact of symptomatic atherosclerosis on all-cause in-hospital death (A), adverse in-hospital events (B), intracerebral bleeding events (C) as well as gastro-intestinal bleeding events (D) (solid black line: PE patients with symptomatic atherosclerosis; dashed black line: PE patients without coded symptomatic atherosclerosis).

PE patients with atherosclerosis revealed higher rates of bleeding complications presumably driven by additional antiplatelet medication, whereby the bleeding events were independent of reperfusion treatments (systemic thrombolysis and surgical embolectomy).

There are further limitations of our study that require consideration. The analysis is based on ICD discharge codes, which might lead to incomplete data due to underreporting/undercoding or miscoding. Therefore, the focus of our study was on clear endpoints, such as in-hospital mortality and complications, which are very unlikely to be miscoded or not coded. This study includes in-hospital results and cannot address long-term outcomes.

5. Conclusions

Symptomatic atherosclerosis in patients with PE increased with advancing age and was accompanied by poorer outcomes. Symptomatic atherosclerosis was associated with isolated PE (without DVT) and cardiovascular atherosclerotic diseases might play a role in thrombus formation of PE patients without DVT.

Disclosure of interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.12.019.

References

[1] G. Agnelli, C. Becattini, Venous thromboembolism and atherosclerosis: common denominators or different diseases? J. Thromb. Haemost. 4 (2006) 1886–1890.
[2] V. Fuster, L. Badimon, J.J. Badimon, J.H. Chesebro, The pathogenesis of coronary artery disease and the acute coronary syndromes (1), N. Engl. J. Med. 326 (1992) 242–250.
[3] S.Z. Goldhaber, H. Bounameaux, Pulmonary embolism and deep vein thrombosis, Lancet 379 (2012) 1835–1846.
[4] I.J. Hansen-Krone, K.F. Enga, I. Njolstad, J.B. Hansen, S.K. Braekkan, Heart healthy diet and risk of myocardial infarction and venous thromboembolism. The Tromso Study, Thromb. Haemost. 108 (2012).
[5] S.Z. Goldhaber, Risk factors for venous thromboembolism, J. Am. Coll. Cardiol. 56 (2010) 1–7.
[6] P. Prandoni, Links between arterial and venous disease, J. Intern. Med. 262 (2007) 341–350.
[7] P. Prandoni, F. Bilora, A. Marchiori, E. Bernardi, F. Petrobelli, A.W. Lensing, et al., An association between atherosclerosis and venous thrombosis, N. Engl. J. Med. 348 (2003) 1435–1441.
[8] S. Rafi, F.F. van Doormaal, K.P. van Lienden, P.W. Kamphuisen, V.E. Gerdes, Venous thrombo-embolism and aortic calcifications; more evidence on the link between venous and arterial thrombosis, Thromb. Res. 124 (2009) 381–382.
[9] C. Hong, F. Zhu, D. Du, T.K. Pilgram, G.A. Sicard, K.T. Bae, Coronary artery calcification and risk factors for atherosclerosis in patients with venous thromboembolism, Atherosclerosis 183 (2005) 169–174.
[10] G. Libertiny, L. Hands, Deep venous thrombosis in peripheral vascular disease, Br. J. Surg. 86 (1999) 907–910.
[11] P.B. van der Hagen, A.R. Folsom, N.S. Jenny, S.R. Heckbert, E.S. O'Meara, L.M. Reich, et al., Subclinical atherosclerosis and the risk of future venous thrombosis in the Cardiovascular Health Study, J. Thromb. Haemost. 4 (2006) 1903–1908.
[12] L.M. Reich, A.R. Folsom, N.S. Key, L.L. Boland, S.R. Heckbert, W.D. Rosamond, et al., Prospective study of subclinical atherosclerosis as a risk factor for venous thromboembolism, J. Thromb. Haemost. 4 (2006) 1909–1913.
[13] Internet page of the InEK GmbH – Institut für das Entgeltsystem im Krankenhaus: Deutsche Kodierrichtlinien, Druckversion A4 (PDF), https://www.g-drg.de/inek_site_de/layout/set/standard/Media/Files/G-DRG-System/G-DRG-System_2018/Deutsche_Kodierrichtlinien_2018_Druckversion_A4_PDF 2018 (Date of visit: 2nd Oct 2018).
[14] F.D. Mili, W.C. Hooper, C. Lally, H. Austin, Family history of myocardial infarction is a risk factor for venous thromboembolism among whites but not among blacks, Clin. Appl. Thromb. Hemost. 19 (2012) 410–417.
[15] B. Zoller, X. Li, J. Sundquist, K. Sundquist, Venous thromboembolism does not share strong familial susceptibility with coronary heart disease: a nationwide family study in Sweden, Eur. Heart J. 32 (2011) 2800–2805.
[16] T. Zhu, I. Martinez, J. Emmerich, Venous thromboembolism: risk factors for recurrence, Arterioscler. Thromb. Vasc. Biol. 29 (2009) 298–310.
[17] A. Tripodi, A. Branchi, V. Chantarangkul, M. Clerici, G. Merati, A. Artoni, et al., Hypercoagulability in patients with type 2 diabetes mellitus detected by a thrombin generation assay, J. Thromb. Thrombolysis 31 (2011) 165–172.
[18] H.T. Sorensen, E. Horvath-Puho, L. Pedersen, J.A. Baron, P. Prandoni, Venous thromboembolism and subsequent hospitalisation due to acute arterial cardiovascular events: a 20-year cohort study, Lancet 370 (2007) 1773–1779.
[19] G.D. Lowe, Common risk factors for both arterial and venous thrombosis, Br. J. Haematol. 140 (2008) 488–495.
[20] W. Ageno, C. Becattini, T. Brighton, R. Selby, P.W. Kamphuisen, Cardiovascular risk factors and venous thromboembolism: a meta-analysis, Circulation 117 (2008) 93–102.
[21] P. Prandoni, Venous thromboembolism and atherosclerosis: is there a link? J. Thromb. Haemost. 5 (Suppl. 1) (2007) 270–275.
[22] D. Green, Risk of future arterial cardiovascular events in patients with idiopathic venous thromboembolism, Hematology Am. Soc. Hematol. Educ. Program (2009) 259–266.
[23] G.A. Roth, M.D. Huffman, A.E. Moran, V. Feigin, G.A. Mensah, M. Naghavi, et al., Global and regional patterns in cardiovascular mortality from 1990 to 2013, Circulation 132 (2015) 1667–1678.
[24] H.C. McGill Jr., C.A. McMahan, E.E. Herderick, G.T. Malcom, R.E. Tracy, J.P. Strong, Origin of atherosclerosis in childhood and adolescence, Am. J. Clin. Nutr. 72 (2000) 1307S–13015S.
[25] N. Okumiya, K. Tanaka, K. Ueda, T. Omae, Coronary atherosclerosis and antecedent risk factors: pathologic and epidemiologic study in Hisayama, Japan, Am. J. Cardiol. 56 (1985) 62–66.
[26] D. Lloyd-Jones, R. Adams, M. Carnethon, G. De Simone, T.B. Ferguson, K. Flegal, et al., Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee, Circulation 119 (2009) 480–486.
[27] D. Aujesky, D.S. Obrosky, R.A. Stone, T.E. Auble, A. Perrier, J. Cornuz, et al., Derivation and validation of a prognostic model for pulmonary embolism, Am. J. Respir. Crit. Care Med. 172 (2005) 1041–1046.
[28] S.V. Konstantinides, A. Torbicki, G. Agnelli, N. Danchin, D. Fitzmaurice, N. Galie, et al., ESC guidelines on the diagnosis and management of acute pulmonary embolism, Eur. Heart J. 2014 (2014) 35 (3033-69, 69a-69k).
[29] C. Bova, O. Sanchez, P. Prandoni, M. Lankeit, S. Konstantinides, S. Vanni, et al., Identification of intermediate-risk patients with acute symptomatic pulmonary embolism, Eur. Respir. J. 44 (2014) 694–703.
[30] L. Hobohm, K. Hellenkamp, G. Hasenfuss, T. Munzel, S. Konstantinides, M. Lankeit, Comparison of risk assessment strategies for not-high-risk pulmonary embolism, Eur. Respir. J. 47 (2016) 1170–1178.
[31] P. Prandoni, Venous and arterial thrombosis: two aspects of the same disease? Eur. J. Intern. Med. 20 (2009) 660–661.
[32] A. Torbicki, A. Perrier, S. Konstantinides, G. Agnelli, N. Galie, P. Pruszczyk, et al., Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC), Eur. Heart J. 29 (2008) 2276–2315.
[33] T. Schwartz, A. Hingorani, E. Ascher, N. Marks, A. Shiferson, D. Jung, et al., Pulmonary embolism without deep venous thrombosis, Ann. Vasc. Surg. 26 (2012) 973–976.
[34] H.T. Sorensen, E. Horvath-Puho, T.L. Lash, C.F. Christiansen, R. Pesavento, L. Pedersen, et al., Heart disease may be a risk factor for pulmonary embolism without peripheral deep venous thrombosis, Circulation 124 (2011) 1435–1441.
[35] K. Keller, J.H. Prochaska, M. Coldewey, S. Gobel, A. Ullmann, C. Junger, et al., History of deep vein thrombosis is a discriminator for concomitant atrial fibrillation in pulmonary embolism, Thromb. Res. 136 (2015) 899–906.
[36] K. van Langevelde, A. Sramek, P.W. Vincken, J.K. van Rooden, F.R. Rosendaal, S.C. Cannegieter, Finding the origin of pulmonary emboli with a total-body magnetic resonance direct thrombus imaging technique, Haematologica 98 (2013) 309–315.
[37] G. Gex, E. Gerstel, M. Righini, L.E.G. G, D. Aujesky, P.M. Roy, et al., Is atrial fibrillation associated with pulmonary embolism? J. Thromb. Haemost. 10 (2012) 347–351.
[38] L. Chapoutot, D. Metz, E. Canivet, B. Maillier, F. Torossian, J.L. Pommier, et al., Mobile thrombus of the right heart and pulmonary embolism: diagnostic and therapeutic problems. Apropos of 12 cases, Arch. Mal. Coeur Vaiss. 86 (1993) 1039–1045.
[39] M. Ogren, D. Bergqvist, H. Eriksson, B. Lindblad, N.H. Sternby, Prevalence and risk of pulmonary embolism in patients with intracardiac thrombosis: a population-based study of 23,796 consecutive autopsies, Eur. Heart J. 26 (2005) 1108–1114.
[40] M. de Divitiis, H. Omran, R. Rabahieh, B. Rang, S. Illien, R. Schimpf, et al., Right atrial appendage thrombosis in atrial fibrillation: its frequency and its clinical predictors, Am. J. Cardiol. 84 (1999) 1023–1028.

[41] F. Haddad, R. Doyle, D.J. Murphy, S.A. Hunt, Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure, Circulation 117 (2008) 1717–1731.
[42] K.M. Flegel, When atrial fibrillation occurs with pulmonary embolism, is it the chicken or the egg? CMAJ 160 (1999) 1181–1182.
[43] M.J. Weigner, L.R. Thomas, U. Patel, J.G. Schwartz, A.J. Burger, P.S. Douglas, et al., Early cardioversion of atrial fibrillation facilitated by transesophageal echocardiography: short-term safety and impact on maintenance of sinus rhythm at 1 year, Am. J. Med. 110 (2001) 694–702.
[44] C. Becattini, A.T. Cohen, G. Agnelli, L. Howard, B. Castejon, J. Trujillo-Santos, et al., Risk stratification of patients with acute symptomatic pulmonary embolism based on presence or absence of lower extremity DVT: systematic review and meta-analysis, Chest 149 (2016) 192–200.
[45] D. Jimenez, D. Aujesky, L. Moores, V. Gomez, D. Marti, S. Briongos, et al., Combinations of prognostic tools for identification of high-risk normotensive patients with acute symptomatic pulmonary embolism, Thorax 66 (2011) 75–81.
[46] D. Jimenez, D. Aujesky, G. Diaz, M. Monreal, R. Otero, D. Marti, et al., Prognostic significance of deep vein thrombosis in patients presenting with acute symptomatic pulmonary embolism, Am. J. Respir. Crit. Care Med. 181 (2010) 983–991.
[47] J. Wicki, A. Perrier, T.V. Perneger, H. Bounameaux, A.F. Junod, Predicting adverse outcome in patients with acute pulmonary embolism: a risk score, Thromb. Haemost. 84 (2000) 548–552.
[48] D. Jimenez, D. Kopecna, V. Tapson, B. Briese, D. Schreiber, J.L. Lobo, et al., Derivation and validation of multimarker prognostication for normotensive patients with acute symptomatic pulmonary embolism, Am. J. Respir. Crit. Care Med. 189 (2014) 718–726.
[49] C. Kabrhel, I. Okechukwu, P. Hariharan, J.K. Takayesu, P. MacMahon, F. Haddad, et al., Factors associated with clinical deterioration shortly after PE, Thorax 69 (2014) 835–842.
[50] P. Girard, O. Sanchez, C. Leroyer, D. Musset, G. Meyer, J.B. Stern, et al., Deep venous thrombosis in patients with acute pulmonary embolism: prevalence, risk factors, and clinical significance, Chest 128 (2005) 1593–1600.