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The diagnostic and therapeutic management of pulmonary embolism

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Citation
Hulle, T. van der. (2018, January 10). *The diagnostic and therapeutic management of pulmonary embolism*. Retrieved from https://hdl.handle.net/1887/61127

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http://hdl.handle.net/1887/61127

Author: Hulle, T. van der
Title: The diagnostic and therapeutic management of pulmonary embolism
Issue Date: 2018-01-10

CHAPTER 4

Is a normal computed tomography pulmonary angiography safe to rule out acute pulmonary embolism in patients with a likely clinical probability?
- a patient-level meta-analysis -

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Thrombosis and Haemostasis 2017;117:1622-1629

ABSTRACT

Introduction

A normal computed tomography pulmonary angiography (CTPA) remains a controversial criterion for ruling out acute pulmonary embolism (PE) in patients with a likely clinical probability. We set out to determine the risk of VTE and fatal PE after a normal CTPA in this patient category and compare these risks to those after a normal pulmonary angiogram of 1.7% (95%CI 1.0-2.7%) and 0.3% (95%CI 0.02-0.7%).

Methods

A patient-level meta-analysis from 4 prospective diagnostic management studies that sequentially applied the Wells rule, D-dimer tests and CTPA to consecutive patients with clinically suspected acute PE. The primary outcome was the 3-month VTE incidence after a normal CTPA.

Results

A total of 6,148 patients were included with an overall PE prevalence of 24%. The 3-month VTE incidence in all 4,421 patients in whom PE was excluded at baseline was 1.2% (95%CI 0.48-2.6) and the risk of fatal PE was 0.11% (95%CI 0.02-0.70). In patients with a likely clinical probability the 3-month incidences of VTE and fatal PE were 2.0% (95%CI 1.0-4.1%) and 0.48% (95%CI 0.20-1.1%) after a normal CTPA. The 3-month incidence of VTE was 6.3% (95%CI 3.0-12) in patients with a Wells rule >6 points.

Conclusion

This study suggests that a normal CTPA may be considered as a valid diagnostic criterion to rule out PE in the majority of patients with a likely clinical probability, although the risk of VTE is higher in subgroups such as patients with a Wells rule >6 points for which a closer follow-up should be considered.

INTRODUCTION

Signs and symptoms of pulmonary embolism (PE) are highly variable and non-specific. As a result, PE is frequently considered, while in only approximately one fifth of patients the diagnosis is confirmed [1-3]. PE can only be demonstrated by an imaging test. This test, nowadays, is usually computed tomography pulmonary angiography (CTPA) due to several advantages over other imaging tests, i.e. widespread availability, small proportion of inconclusive test results, fast acquisition time and the possibility of establishing an alternative diagnosis [4, 5]. Disadvantages of CTPA include radiation exposure, risk of contrast-induced nephropathy or allergic reactions, unsuspected findings and increased healthcare costs [6, 7].

In order to reduce the need for imaging tests for suspected PE, diagnostic algorithms have been developed for patients with suspected PE without shock or hypotension, starting with a validated clinical decision rule (CDR) to predict the clinical probability for PE, followed by a quantitative D-dimer test and/or a CTPA [8]. In patients with a low, moderate or unlikely clinical probability according to a validated CDR (either the Wells score or the revised Geneva score) and a D-dimer concentration ≤500 μg/L or equal or below the age-adjusted D-dimer threshold in patients older than 50 years, PE can be safely excluded without further imaging tests in approximately one third of all patients [3, 9, 10]. In the remaining patients with either an unlikely clinical probability in combination with an elevated D-dimer concentration or a high or likely clinical probability CTPA is indicated [8]. This diagnostic strategy has been demonstrated to be safe with a 3-month venous thromboembolism (VTE) incidence of 0.34% (95% confidence interval (95%CI) 0.036-0.96%) in patients managed without CTPA and 1.2% (95%CI 0.8-1.8) in patients in whom PE was ruled out by CTPA [4, 11]. Importantly, it has been demonstrated that performing compression ultrasonography (CUS) of the lower extremities after a normal CTPA to rule out deep vein thrombosis (DVT) does not further diminish the risk of VTE during follow-up [4, 12-14]. Consequently, in daily clinical practice a normal CTPA alone is usually considered to be a valid diagnostic criterion to exclude PE [1-3, 15].

However, evidence on the safety of ruling out PE based on a normal CTPA in the subset of patients with a likely clinical probability of PE remains controversial. In the single post-hoc analysis of the Christopher study that investigated this issue, the 3-month VTE incidence after a negative CTPA was 1.7% (9 VTE events in 545 patients; 95%CI 0.9-3.1) in patients with a likely clinical probability compared to 0.7% (5 VTE events in 721 patients; 95%CI 0.3-1.6) in patients with an unlikely clinical probability (p-value for difference = 0.11) [1, 16]. Due to the limited evidence, in the recent guideline of the European Society of Cardiology (ESC) on the diagnosis and management of acute pulmonary embolism regarding ruling out PE in patients with a likely clinical probability are somewhat inconsistent [8]. In this ESC guideline, a class IIa recommendation (level of evidence: B) is

included stating that a normal CTPA may safely exclude PE in patients with a likely clinical probability, while in another paragraph a normal CTPA alone is recommended as a controversial criterion to rule out PE and further testing should be considered. Notably, the guideline does not provide any recommendation on which additional diagnostic strategy should be considered in case of a normal CTPA.

In order to address this issue, we evaluated the risk of VTE and fatal PE after a normal CTPA in patients with a likely clinical probability of PE by performing a patient-level meta-analysis of four large diagnostic management studies.

METHODS

Patients

Patient-level data were obtained from 4 previously published multicentre prospective diagnostic management studies of patients with clinically suspected acute PE, i.e. the Christopher study, the Prometheus study, the REPEAD study and the ADJUST-PE study [1-3, 15]. These studies were performed by our own collaboration network of several academic and non-academic hospitals in the Netherlands and had a highly comparable design as well as definition and assessment of outcomes. Also, the data of all studies are of high quality with nearly complete baseline and follow-up assessment. Study details are provided in Appendix A, available at https://th.schattauer.de. In all 4 studies, hemodynamically stable, predominantly outpatients with suspected acute PE were included. Exclusion criteria were age <18 years, treatment with therapeutic doses of anticoagulant treatment for >24 hours, life expectancy <3 months, pregnancy, a contra-indication for CTPA (i.e. allergy to intravenous contrast agents, renal insufficiency) and logistic reasons such as unavailability of CTPA, patient too ill to undergo CTPA, geographic inaccessibility precluding follow-up. In the Prometheus study, a history of PE was an additional exclusion criterion, and in the REPEAD study only patients with a history of PE were included. From the ADJUST-PE study, we only included patients from participating hospitals in the Netherlands who were all managed by the Wells score in the present analysis.

In all studies, an identical diagnostic management algorithm was used starting with the Wells CDR followed by quantitative D-dimer testing and/or CTPA, depending on the result of the Wells score. PE was excluded in case of an unlikely clinical probability (Wells score ≤4 points) in combination with a negative D-dimer test result. In the Christopher study, the Prometheus study and the REPEAD study a D-dimer threshold of 500 µg/L was used, whereas in the ADJUST-PE study the age-adjusted D-dimer threshold was applied, calculated by multiplying the patient's age by 10 in patients 50 years or older. In patients with either a likely clinical probability (Wells score >4 points) or a positive D-dimer test result, CTPA was performed and they were managed according to the CTPA result. All

studies were approved by the institutional review boards of participating hospitals and patients provided written informed consent where relevant.

All patients were prospectively followed for 3 months for the occurrence of symptomatic VTE (i.e. PE and/or DVT). Adjudication committees evaluated all episodes of suspected VTE and deaths. In case of clinically suspected PE or DVT, objective diagnostic tests were required. In case of death, information was obtained from the hospital records. In case of clinically suspected VTE, an objective clinical test was performed including CTPA or ventilation-perfusion scintigraphy for suspected PE and compression ultrasonography for suspected DVT [9, 8, 17]. Deaths were classified as caused by PE if PE was confirmed by autopsy, if PE was demonstrated by objective testing prior to death or if PE could not be confidently excluded as a cause of death. Independent adjudication committees evaluated and adjudicated all suspected VTE and deaths during follow-up. Both objectively confirmed (non-fatal) VTE and deaths caused by PE were included as outcome events.

Objectives of present study and statistical analysis

The primary objective of the current analysis was to determine the 3-month incidence of objectively diagnosed symptomatic VTE and fatal PE after a normal CTPA in patients with a likely clinical probability of acute PE assessed by the Wells score, who were not treated with anticoagulant therapy. Secondary objectives were to determine the 3-month incidence of VTE and fatal PE after exclusion of PE in the overall patient population, in the subgroup of patients in whom PE was excluded based on an unlikely clinical probability in combination with a negative D-dimer test, and in those with an unlikely clinical probability but a positive D-dimer test. For all analyses, only patients in whom PE was excluded at baseline, who did not receive anticoagulant treatment, and who were not lost to follow-up were included.

In addition, the original 3-level diagnostic algorithm was investigated in a post-hoc analysis, in which 3 different clinical probability categories are identified: a low (Wells score <2 points), an intermediate (Wells score 2-6 points) and a high clinical probability (Wells score >6 points) category [18]. By using this original diagnostic algorithm, PE is excluded without imaging test in case of a D-dimer concentration ≤500 µg/L in combination with a low or moderate clinical probability, while CTPA is indicated in the remaining patients. This analysis was performed since the recent ESC guideline considers a normal CTPA alone as a controversial criterion also in patients with a high clinical probability according to the 3-level diagnostic algorithm. Finally, we explored which patient characteristics at presentation were associated with the occurrence of VTE during 3 months of follow-up after PE was ruled out at baseline.

Patient characteristics and outcomes are reported for the total cohort and for the different clinical probability categories separately. For the purpose of this study and

to ensure comparability, we post-hoc applied the conventional D-dimer threshold of ≤500 µg/L to the patients included in the ADJUST-PE study, instead of the age-adjusted D-dimer threshold.

To estimate the 3-month VTE incidence after a normal CTPA at baseline in patients with a likely clinical probability, we used multilevel logistic regression modelling with a VTE diagnosis during follow-up as the outcome and no covariates. We specified a random effect for the intercept to account for the clustering of patients within studies. To express the 3-month VTE incidence, we estimated from this model the mean predicted 3-month probability of VTE during follow-up for patient with a likely clinical probability and a normal CTPA at baseline. Using a similar approach, we estimated the mean predicted 3-month incidence of VTE and fatal PE for the different management categories (i.e. patients with an unlikely clinical probability and a negative D-dimer test result, those with an unlikely clinical probability and an increased D-dimer but a normal CTPA, and the different management categories of the original 3-level diagnostic algorithm). D-dimer testing was not performed in a substantial proportion of patients with a Wells score of 4.5-6 points, because this test was not required by the original study protocols. We used multiple imputation to replace missing values within each study, 10 times and estimates were pooled across the imputed datasets using Rubin's rule [19]. Absolute numbers provided were derived from one of the imputed datasets.

The 3-month VTE incidence in the different management categories was compared to the 3-month VTE incidence of 1.7% (95%CI 1.0-2.7) and the incidence of fatal PE of 0.3% (95%CI 0.02-0.7) reported after a normal pulmonary angiography, traditionally the gold standard in PE diagnosis [20]. Consequently, we consider a strategy to be safe in case of a 3-month incidence of VTE and fatal PE that are equal or below these outcomes after a normal pulmonary angiography. In order to determine whether patient characteristics were associated with the occurrence of VTE during follow-up after a normal CTPA in patients with a likely clinical probability, odds ratios (OR) with 95%CI were calculated comparing patients without VTE during follow-up to those who developed VTE during follow-up using logistic regression analyses. An association was considered to be statistically significant in case of a P-value below 0.05. All statistical analyses were performed in R version 3.2.0, in particular using the *mice* and *lme4* packages (R foundation for Statistical Computing, www.R-project.org).

RESULTS

Study characteristics

The four studies available for the present analysis concerned a total of 7,975 patients. From the REPEAD study, 234 patients were overlapping with the Christopher or Pro-

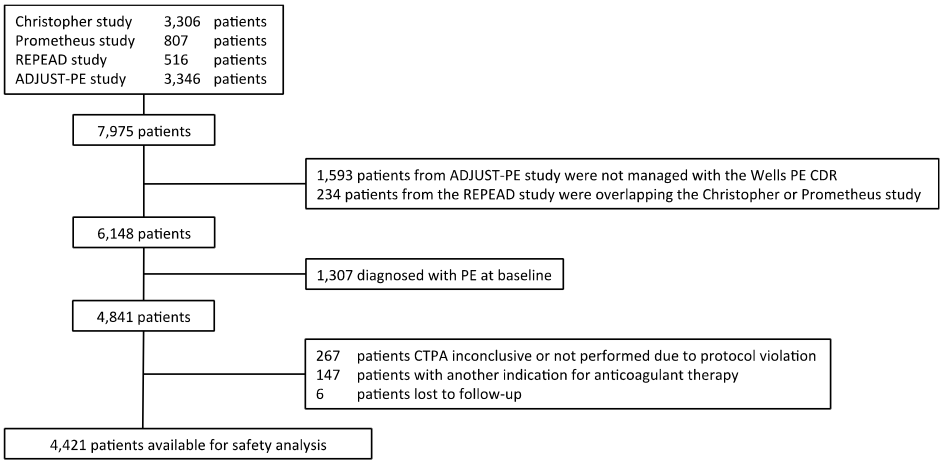
metheus study and therefore excluded from the present analysis. From the ADJUST-PE study, we included only the 1,753 patients from Dutch hospitals in whom the Wells PE CDR was used, leaving 6,148 patients with clinically suspected acute PE available for the present analysis (**Table 1**). Baseline characteristics for the individual studies are provided in Appendix B (available at https://th.schattauer.de). The PE prevalence at baseline varied from 19% to 39% between the four studies and the corresponding mean predicted PE prevalence at baseline was 24% (95%CI 18-32). In 267 patients (4.3%) CTPA was inconclusive or not performed although indicated; CTPA was not performed in 187 patients in the ADJUST-PE study as the result of a D-dimer concentration between the conventional and the age-adjusted D-dimer threshold; 147 patients (2.4%) received anticoagulant treatment for reasons other than VTE and follow-up of 6 patients (0.1%) was incomplete, leaving 4,421 patients available for the analysis (**Figure 1**). The 3-month VTE incidence in all patients in whom PE was excluded at baseline was 1.2% (42 events in 4421 patients; 95%CI 0.48-2.6) and the 3-month incidence of fatal PE was 0.11% (8 events in 4421 patients; 95%CI 0.02-0.70).

Table 1. Baseline characteristics for the evaluated subgroups.

Characteristic n, (%)	Total cohort n=6148	Pre-test probability category of PE	
		Unlikely n=4254	Likely n=1894
Mean age (SD)	57 (17)	56 (18)	58 (17)
Male sex	2581 (42)	1780 (42)	801 (42)
COPD	742 (12)	524 (12)	218 (12)
Heart failure	447 (7.3)	313 (7.4)	134 (7.1)
Estrogen use	576 (9.4)	424 (10)	152 (8.0)
Inpatient	804 (13)	393 (9.2)	411 (22)
Duration of complaints ≥7 days	1523 (25)	1026 (25)	461 (24)
Wells items			
Clinical signs of DVT	262 (4.3)	28 (0.7)	234 (12)
Alternative diagnosis less likely than PE	3342 (54)	1556 (37)	1786 (94)
Heart rate >100 bpm	1472 (24)	615 (14)	857 (45)
Surgery or immobilization <4 weeks	1158 (19)	381 (9.0)	777 (41)
History of VTE	993 (16)	387 (9.1)	606 (32)
Hemoptysis	301 (4.9)	187 (4.4)	114 (6.0)
Active cancer	885 (14)	462 (11)	423 (22)
PE at baseline	1307 (21)	551 (13)	756 (40)

Note: PE: pulmonary embolism; SD standard deviation; COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; bpm: beats per minute; n: number, VTE: venous thromboembolism.

Figure 1. Flowchart patient selection.



Note: PE: pulmonary embolism; CDR: clinical decision rule; CTPA: computed tomography pulmonary angiography.

Incidence of VTE and fatal PE in the different management categories

A total of 4,254 patients (69%) had an unlikely clinical probability and 1,894 patients (31%) a likely clinical probability. The baseline PE prevalences in these groups were 13% and 40% (**Table 1**), respectively. Of the 4,254 patients with an unlikely clinical probability, 1,586 patients (37%) had a D-dimer concentration ≤500 µg/L and could be managed without CTPA. In patients managed without CTPA, the 3-month VTE incidence was 0.71% (7 events in 1583 patients; 95%CI 0.40-1.3) and no fatal PE occurred in these patients (**Table 2**). In the remaining 2,668 patients with an unlikely clinical probability but an increased D-dimer and a normal CTPA, the 3-month incidence of VTE was 0.85% (14 events in 1792 patients; 95%CI 0.36-2.0) and of fatal PE 0.12% (3 events in 1792 patients; 95%CI 0.01-1.4).

The 3-month VTE incidence after a normal CTPA in patients with a likely clinical probability varied from 0.5% to 5.8% across the individual studies, for an overall 3-month VTE incidence of 2.0% (21 events in 1046 patients; 95%CI 1.0-4.1; **Figure 2A**), and a 3-month incidence of fatal PE of 0.48% (5 events in 1046 patients; 95%CI 0.20-1.1; **Figure 2B**). Of the 21 patients with VTE during follow-up, 9 had active cancer (47%) while only 241 of the 1,024 (24%) without VTE during follow-up had active cancer (OR 2.6; 95%CI 1.1-6.3). Also, patients with VTE during follow-up more frequently had had signs and symptoms of DVT at initial presentation: 5 of the 21 patients with VTE during follow-up (24%) versus 81 of the 1,025 patients without VTE during follow-up (7.9%) (OR 4.1; 95%CI 1.4-12) (**Table 3**). Three of the 5 patients with clinical signs of DVT at baseline and VTE during follow-up underwent compression ultrasonography of the lower extremities at baseline, of which 2 were negative for DVT and 1 demonstrated DVT. The latter patient was adju-

Table 2. The 3-month risk of VTE (A) and fatal PE (B) after PE was ruled out at baseline.

A: The 3-month risk of VTE

Diagnostic criterion	3-month risk of VTE %, (95%CI)	
Clinical probability	**Unlikely**	**Likely**
Wells score	**≤4**	**>4**
Normal D-dimer (Threshold ≤500 µg/L)	0.71 (0.40-1.3)	-
Normal CTPA	0.85 (0.36-2.0)	2.0% (1.0-4.1)

B: The 3-month risk of fatal PE

Diagnostic criterion	3-month risk of fatal PE %, (95%CI)	
Clinical probability	**Unlikely**	**Likely**
Wells score	**≤4**	**>4**
Normal D-dimer (Threshold ≤500 µg/L)	NA[1]	-
Normal CTPA	0.12% (0.01-1.4)	0.48% (0.20-1.1)

Note: PE: pulmonary embolism; CTPA: computed tomography pulmonary embolism; [1]not estimatable due to zero events.

dicated as a failure of the algorithm. Of two other patients with clinical signs of DVT at baseline information on whether CUS had been performed could not be retrieved.

Of the 21 patients with VTE during follow-up, 13 patients were diagnosed with PE (±DVT) and 8 patients with DVT. Regarding the time between initial presentation and VTE during follow-up, 9 (4 with PE, 5 with DVT) were diagnosed within 1 month after presentation, 6 (4 with PE and 2 with DVT) were diagnosed between 1 and 2 months after presentation and 6 (5 with PE and 1 with DVT) were diagnosed more than 2 months after presentation. Of the 12 patients with VTE more than 1 month after initial presentation, 8 patients (67%) had active cancer and 9 were diagnosed with PE (±DVT).

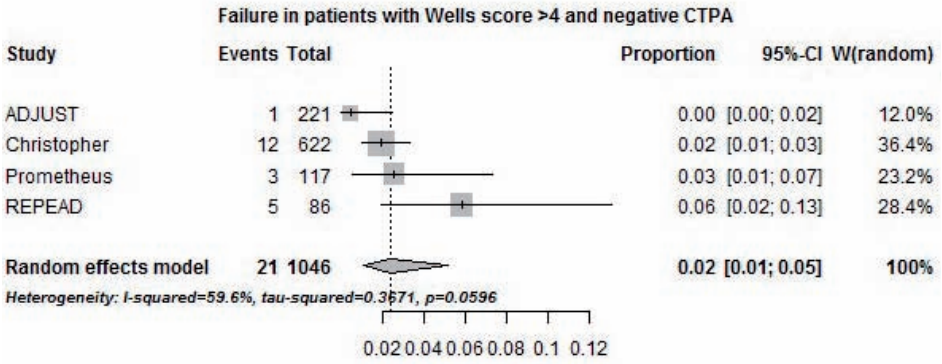
The 3-level diagnostic algorithm

When the 3-level diagnostic algorithm would have been applied, 2,314 patients (38%) would have been categorized in the low clinical probability category, 3,538 patients (58%) in the moderate clinical probability and 296 patients (4.8%) in the high clinical probability category, with PE baseline prevalences of 7.9%, 27% and 56% respectively. Baseline characteristics for the different subgroups are available in Appendix C (https://th.schattauer.de).

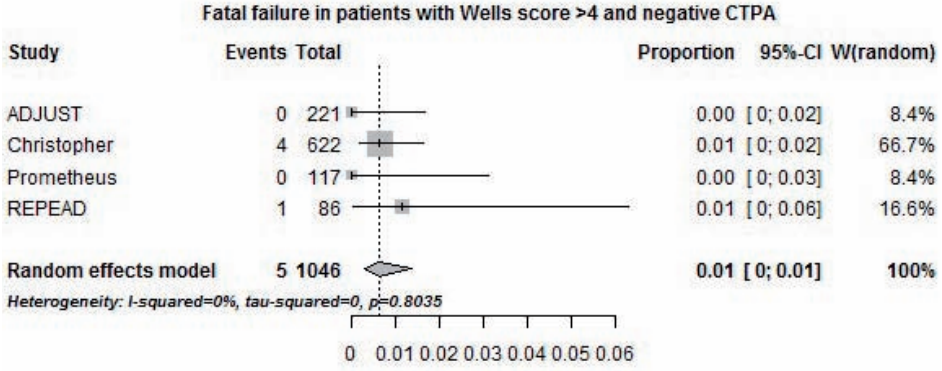
The 3-month VTE risk in patients managed without CTPA based on a low clinical probability and a D-dimer test ≤500 µg/L was 0.44% (3 events in 965 patients; 95%CI 0.17-1.2) and no fatal PE occurred among these patients. In patients with a low clinical probability and a D-dimer concentration >500 µg/L the 3-month VTE risk was 0.54% (5 events in 920 patients; 95%CI 0.23-1.3) and the 3-month risk of fatal PE was 0.11% (1 events in 920 patients; 95%CI 0.02-0.76) after a negative CTPA. In patients with an intermediate clinical probability, the 3-month VTE risk was 2.8% (18 events in 784 patients; 95%CI 1.7-4.7) after a D-dimer concentration ≤500 µg/L and 1.2% (21 events in 1645 patients; 95%CI 0.26-5.2) after a D-dimer concentration >500 µg/L and a negative CTPA. The corresponding 3-month risks of fatal PE were 0.29% (1 events in 784 patients; 95%CI

Figure 2. The 3-month risk of (A) VTE and fatal PE (B) after a normal CTPA in patients with a likely clinical probability.

A: The 3-month risk of VTE



B: The 3-month risk of fatal PE



Note: VTE: venous thromboembolism; PE: pulmonary embolism; CTPA: computed tomography pulmonary angiography.

0.07-1.1) and 0.29% (5 events in 1645 patients; 95%CI 0.09-0.92) respectively. In patients with a high clinical probability, the 3-month VTE risk after negative CTPA was 6.3% (7 events in 111 patients; 95%CI 3.0-12.6) and a 3-month risk of fatal PE was 0.90% (1 event in 111 patients; 95%CI 0.13-6.1).

DISCUSSION

The key findings of our study are the 3-month incidence of VTE of 2.0% and the risk of fatal PE of 0.48% after a normal CTPA as single imaging test in patients with a likely clinical probability of PE according to the Wells rule. In order to determine whether these

Table 3. Characteristics of patients with a likely clinical probability in whom PE was ruled out and had VTE during follow-up.

Baseline characteristics n, (%)	Patients in whom PE was excluded and no PE during follow-up n=1025	Patients who developed VTE during 3-month follow-up after a negative CTPA n=21	Odds ratio (95%CI)
Mean age (SD)	58 (17)	57 (17)	N.A.
Male sex	397 (39)	5 (24)	0.49 (0.18-1.4)
COPD	147 (14)	2 (9.5)	0.64 (0.15-2.8)
Heart failure	81 (7.9)	2 (9.5)	1.3 (0.3-5.9)
Estrogen use	67 (6.5)	3 (14)	2.7 (0.77-9.7)
Inpatient	229 (22)	5 (24)	1.1 (0.39-3.0)
Duration of complaints ≥7 days	237 (23)	4 (19)	0.80 (0.26-2.4)
Wells items			
Clinical signs of DVT	81 (7.9)	5 (24)	**4.1 (1.4-12)**
Alternative diagnosis less likely than PE	968 (94)	19 (90)	0.43 (0.10-1.9)
Heart rate >100 bpm	474 (46)	9 (43)	0.92 (0.38-2.2)
Surgery or immobilization <4 weeks	419 (41)	11 (52)	1.9 (0.76-4.8)
History of VTE	297 (29)	8 (38)	1.5 (0.62-3.7)
Hemoptysis	55 (5.4)	1 (4.8)	0.95 (0.13-7.3)
Active cancer	241 (24)	9 (43)	**2.6 (1.1-6.3)**

Note: PE: pulmonary embolism; VTE: venous thromboembolism; CI: confidence interval; n: number of patients; CTPA: computed tomography pulmonary angiography; SD: standard deviation; COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; bpm: beats per minute; N.A: not applicable.

results support ruling out PE by a normal CTPA alone, several considerations should be taken into account.

First and most importantly, the incidence of VTE of 2.0% as well as the incidence of fatal PE of 0.48% after a normal CTPA in patients with a likely clinical probability identified in our study compare well to the same incidences after a normal pulmonary angiography - 1.7% (95%CI 1.0-2.7) for VTE and 0.3% (95%CI 0.02-0.7) for fatal PE - which is the gold standard in PE diagnosis [20].

Second, although our results demonstrate that the VTE incidence after a negative CTPA is higher in patients with a likely clinical probability compared to the incidences observed in patients with an unlikely clinical probability, this has to be interpreted as an inevitable consequence of Bayes' theorem. Since the sensitivity of CTPA - as for all other relevant available diagnostic tests for PE - is known to be slightly less than 100%, a higher clinical probability results in a slight decrease of the negative predictive value. Therefore and in general, the overall PE prevalence in study population should always be taken into account when interpreting the VTE incidence after PE had been ruled out.

In our study, the PE prevalence in patients with a likely clinical probability was 40%. In the studies included in the meta-analysis of van Beek and colleagues in which the safety of a normal pulmonary angiography was investigated, the PE prevalence varied from 20% to 33% [20]. Consequently, it can be reasonably expected that the VTE incidence after a normal pulmonary angiogram in our patients with a likely clinical probability, in whom the PE prevalence of 40% was notably higher, would have exceeded the 1.7% reported in this meta-analysis. Moreover, a recent SSC recommendation suggested using a diagnostic safety threshold in PE studies that is dependent on the disease prevalence at baseline [21]. According to the suggested formula, the safety threshold for studies with a baseline PE prevalence of 40% is 2.0%, which is in line with our findings.

We acknowledge that when focussing on the small subgroup of patients with a high clinical probability according to the Wells rule (less than 5% of total study population), the 3-month VTE incidence is non negligible. Importantly, there is no diagnostic test after CTPA available that has been shown to improve the patient's prognosis, except for CUS in patients who also have symptoms of DVT [4]. Our results thus demonstrate that clinicians should be alert on the occurrence of VTE at follow-up after a normal CTPA in these latter patients.

In our view, an individualized patient management is much preferred over performing additional diagnostic tests in all patients, since it is highly unlikely that such a strategy will lead to an acceptable yield, when performed in all patients.

Active cancer and signs of DVT were shown to be predictive of developing VTE during follow-up. The first patient category has an intrinsic very high risk of VTE, with an overall OR varying from 4.1 to 6.7 compared to patients without cancer resulting in an annual risk varying from 0.5 to 20% [22-24]. Consequently, the question arises whether VTE in cancer patients after a normal CTPA could be newly formed VTE rather than initially missed VTE. With regard to the latter category, at least 3 of the 5 patients with a negative CTPA but clinical signs of DVT and a VTE during follow-up were subjected to CUS at baseline. A negative CUS did not prevent the occurrence of VTE, which supports previous studies, indicating that baseline CUS after negative CTPA in patients without signs of DVT does not further diminish the VTE incidence during follow-up [4, 12-14]. Of note, a positive baseline CUS may be regarded as a somewhat doubtful criterion for failure of the PE algorithm since the algorithm aims to rule out PE and not symptomatic DVT. Moreover, CT venography might be considered as an additional test after a normal CTPA, since the PIOPED 2 study demonstrated an improvement of the sensitivity by adding this test to a 4 to 16-row CTPA [25]. However, it should be emphasized that the PIOPED 2 study was a diagnostic accuracy study. In a clinical outcome study the key question is the incidence of recurrent VTE during follow-up in those patients with initially normal diagnostic tests. By design, this question could not be answered by the PIOPED-2 study and as a result the true value of adding CT venography with respect to clinical outcome at 3 months

is still uncertain. Moreover, the CTPA technology used in the PIOPED-2 study, i.e. 4 to 16-row CTPA, has become outdated since in current clinical practice 254-row CTPA is used with resulting higher sensitivity. Therefore, future studies are required in order to determine whether our findings still reflect current daily clinical practice.

Recently, another study investigated the safety of excluding PE based on a normal CTPA alone [26]. In this observational study, 134 patients with a high clinical probability (Wells rule score >6 points) but a normal CTPA were described. Of these patients, 48 patients (36%) underwent additional testing, either CUS or ventilation/perfusion-scanning, after which 4 patients were diagnosed with DVT and 2 with PE. It should be noted that it is unclear how these patients were selected and whether these 4 patients with DVT had symptoms suggesting of DVT. Likely, this was based on their symptoms and other clinical characteristics. These patients represented a highly selected subgroup from a total cohort of 3237 patients (1.5%). Together with 2 symptomatic PE diagnoses during follow-up, the hypothetical 3-month VTE incidence after a normal CTPA would have been 5.2% (7/134; 95%CI 1.5-9.0). These results are quite in line with our findings and underline our suggested strategy of a stricter follow-up of patients with a high clinical probability but a normal CTPA and considering additional testing only in selected patients.

Strengths of our study are the large number of included patients, the availability of patient-level data from 4 large prospective studies and the highly comparable study designs of all included studies. Additionally, it should be noted that in three of the included studies single row and 4-row CTPA were used, of which the sensitivity is known to be relatively low compared to nowadays multi-row CTPA [1, 2, 15]. Therefore, the safety of a normal CTPA reported in this study may even be an underestimation of the safety of the multi-row CTPA machines currently used in clinical practice, further supporting our conclusion. The major limitation of our study is the fact that we only evaluated 4 studies and did not perform a full systematic review and meta-analysis of all available literature, but rather used data from 4 homogeneous studies. Also, differences in the CT imaging quality between the individual studies were present among the individual studies and we could not retrieve information on CUS examinations of 2 of the 5 patients with a likely probability of PE and symptoms suggestive of DVT at baseline, who were diagnosed with VTE during follow-up after a normal CTPA. Nonetheless, we do not dispute the clear indication for CUS in those particular patients. Last, the post-hoc analysis of the group of patients with an intermediate clinical probability (Wells score 2-6 points) may have introduced differential verification bias since patients with a Wells score of 4.5-6 points underwent CTPA regardless of their D-dimer result. Consequently, we may have overestimated the failure rate in patients with an intermediate probability and a negative D-dimer due to false-positive CTPA results and PE that would have resolved without anticoagulant treatment otherwise.

In conclusion, our study suggests that the risk of VTE and fatal PE after a normal CTPA in patients with a likely clinical probability is comparable to these risks after a normal pulmonary angiogram. Therefore, a normal CTPA alone may be considered as a valid diagnostic criterion to rule out PE in the majority of patients with a likely clinical probability of PE assessed by the Wells rule. Nevertheless, the risk of fatal PE after a normal CTPA alone is relatively high, particularly in patients with concomitant signs of DVT, active cancer and those with a Wells rule >6 points. Consequently, clinicians should consider a closer follow-up in selected patients preferably with a personalised approach. Further studies are required to determine whether the modern multi-row CTPA result in a higher accuracy than the 4 to 64-row CTPA used in the included studies.

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