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ORIGINAL ARTICLE

Outcomes following a negative computed tomography pulmonary angiography according to pulmonary embolism prevalence: a meta-analysis of the management outcome studies

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Essentials

- Computed tomographic pulmonary angiography (CTPA) is used to exclude pulmonary embolism.
- This meta-analysis explores the occurrence of venous thromboembolic events (VTE) after a CTPA.
- Occurrence of VTE after a negative CTPA is ˜8% in study subgroups with a prevalence of PE ≥ 40%.
- CTPA may be insufficient to safely rule out VTE as a stand-alone diagnostic test for this subgroup.

Summary. *Background:* Outcome studies have reported the safety of computed tomographic pulmonary angiography (CTPA) as a stand-alone imaging technique to rule out pulmonary embolism (PE). Whether this can be applied to all clinical probabilities remains controversial. *Objectives:* We performed a meta-analysis to determine the proportion of patients with venous thromboembolic events (VTE) despite a negative CTPA according to pretest PE prevalence. *Methods:* We searched MEDLINE, EMBASE and the Cochrane Library (January 1990 to May 2017) for outcome studies recruiting patients with suspected PE using CTPA as a diagnostic strategy. The primary outcome was the cumulative occurrence of VTE at 3 months following a negative CTPA. *Results:* Twenty-two different studies were identified. VTE was confirmed in 2.4% of patients (95% CI, 1.3–3.8%) either at the time of the index event or in the 3 months follow-up. Subgroup analyses suggested that the cumulative occurrence of VTE was related to pretest prevalence of PE, as VTE occurred in 1.8% (95% CI, 0.5–3.7%), 1.4% (95% CI, 0.7–2.3%), 1.0% (95% CI, 0.5–1.8%) and 8.1% (95% CI, 3.5–14.5%) of subgroups of patients with a PE prevalence < 20%, 20–29%, 30–39% and ≥ 40%, respectively. This was further confirmed using meta-regression analysis. *Conclusions:* The negative predictive value of CTPA for VTE varies according to pretest prevalence of PE, and is likely to be insufficient to safely rule out VTE as a stand-alone diagnostic test amongst patients at the highest pretest probability of VTE. Prospective studies are required to validate the appropriate diagnostic algorithm for this subgroup of patients.

Keywords: computed tomographic angiography; predictive value of tests; probability; pulmonary embolism; safety.

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Introduction

Acute pulmonary embolism (PE) is a relatively common reason for an emergency consultation and can have potential fatal consequences [1]. Thus, an accurate diagnostic modality is important to avoid the morbidity and mortality associated with delays in the diagnosis of PE. Computed tomographic pulmonary angiography (CTPA) has become an integral part of the diagnostic evaluation for

suspected PE. It is now the diagnostic modality most commonly ordered for patients requiring imaging testing [2]. In contrast with the V/Q scan, it allows direct visualization of the pulmonary arterial circulation. More importantly, multidetector CTPA showed excellent accuracy for PE when compared with conventional pulmonary angiography [3]. A negative CTPA has been shown to safely rule out the diagnosis of PE by several studies in which there was a low 3-month risk of venous thromboembolic events (VTE) in patients left untreated. Four meta-analyses confirmed that CTPA was associated with a high negative predictive value (NPV) ranging from 98.6% to 99.9% and concluded that no additional imaging is necessary for patients with suspected acute PE with a negative CTPA [4–7]. As a result, current guidelines recommend CTPA as a stand-alone imaging test for excluding PE [8].

However, ruling out PE in patients with a high clinical probability and a negative CTPA is still debated because of the possible lower NPV and higher false negative rates in this high-risk subgroup [9–12]. Indeed, the study population of previous outcome studies and meta-analyses most commonly had low-to-moderate clinical probability of PE, and few patients had high pretest clinical probability of PE within individual studies, precluding appropriately powered subgroup analyses for this subpopulation. As a result, the recent ESC/ERS guidelines pointed out that further investigations may be considered before withholding anticoagulation in this subset of patients [8], and whether patients with a negative CT and a high clinical probability should be further investigated thus remains controversial [2,8,9].

We thus aimed to assess whether a negative CTPA as a stand-alone imaging test is sufficient to safely withhold anticoagulation when the prevalence of PE increases.

Materials and methods

The methods for this meta-analysis are in accordance with 'Methodological guidelines for systematic review of randomized control trials in health care from the Postdam consultation on meta-analysis' [13]. No ethical approval was needed. The complete study protocol is available on PROSPERO (CRD42017081041).

Study objectives

The primary objective was to determine the proportion of patients with objectively confirmed VTE (deep vein thrombosis [[DVT], non-fatal PE, and fatal PE) at the time of the index event or occurring during the follow-up of non-anticoagulated patients following a negative CTPA according to the pretest probability of acute PE in outcome studies.

Search strategy and selection criteria

A literature search was performed to identify all published prospective outcome studies with a diagnostic strategy based on CTPA and a predefined diagnostic strategy used to confirm or exclude VTE during follow-up. MEDLINE, EMBASE and Cochrane Library were searched from January 1990 to 31 May 2017, using predefined search terms designed to provide maximum sensitivity in detecting outcome studies. A complete description of the search strategy is given in Data S1. Bibliographies of each included study as well as any review articles, systematic reviews, meta-analyses or text found were also searched for additional papers that may contain further studies. In addition, the grey literature was examined by hand from January 2012 to 31 May 2017 (Conference abstracts of the American Heart Association, American College of Cardiology, European Society of Cardiology, American Thoracic Society, American College of Chest Physicians, European Respiratory Society and British Thoracic Society). Articles written in any language were considered.

The inclusion criteria for prospective outcome studies were the following: (i) detailed description of the inclusion and exclusion criteria for participants; (ii) selection of consecutive patients; (iii) diagnostic strategy based on CTPA; (iv) predefined diagnostic strategy used to confirm or exclude VTE during follow-up; (v) predefined clinical follow-up (i.e. office visits, telephone interviews or questionnaires) of at least 3 months duration; and (vi) systematic report of subsequent symptomatic VTE and the means of confirmation were available. Moreover, studies involving overlapping or duplicated cohorts of patients and publications specific to the pediatric population were excluded.

The abstracts and titles of all articles were independently reviewed by two authors (D.B. and S.J.). If pertinent, each reviewer retrieved and explored complete articles independently to make a final decision about their inclusion in the study. Disagreements were resolved by consensus or by consulting a third reviewer (S.P.). Throughout this process, the reviewers were blinded to authors' names, the journal and the year of publication of the papers. If studies that had been reported in multiple papers were identified, the analysis was limited to the largest cohort unless the necessary data had appeared only in another paper. A log of reasons for rejection of citations identified from the searches was kept. The agreement between the two primary reviewers was measured using the quadratic weighted kappa statistic.

Assessment of methodological quality

The methodological quality of the selected studies was systematically evaluated by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) assessment tool [14].

Data extraction

Information from all selected papers was independently extracted by two reviewers (D.B. and S.J.), including:

patients' characteristics; study design, methods and algorithms to diagnose/rule out PE; clinical probability assessment method; type of CTPA (single-row vs. multirow detector and number of detectors); overall prevalence of PE in the study population at the time of inclusion in the study; type and duration of follow-up; definition of DVT and PE recurrence; the number of patients with recurrent VTE during follow-up, including DVT, non-fatal PE and fatal PE; and whether the relationship between recurrent PE and death (i.e. fatal PE) was adjudicated by an independent committee. Whenever possible, the prevalence of acute PE at the time of inclusion in the study and the number of patients with recurrent VTE during follow-up were assessed within subgroups clearly identified in each study. In the case of missing data, corresponding authors were contacted.

Data analysis

We constructed a random-effects model [15], which accounts for within-study and between-study variability [16], to obtain a summary estimate and 95% confidence interval (CI) for the proportion of patients with objectively confirmed VTE at the time of the index event or occurring during the follow-up amongst patients with a negative CTPA from the abstracted numbers for each study. To calculate the overall proportion of VTE events that would be missed using CTPA as a stand-alone imaging test, we included DVT or PE objectively confirmed by an additional imaging test despite a negative CTPA during the index event, as well as objectively confirmed VTE that occurred during subsequent clinical follow-up. Patients who received anticoagulant therapy for reasons other than a VTE during follow-up or with an inconclusive CTPA were excluded from the analysis. These data were combined by using an approximation to the inverse variance approach, effectively weighting each study according to its sample size. Because the pooled proportion was expected to be close to the 0% margin, we used arcsine transformation to stabilize variance.

As we aimed to assess the NPV of CTPA according to baseline risk of PE, we planned *a priori* to conduct separate meta-analyses on the occurrence of DVT, non-fatal PE and fatal PE after a negative CTPA according to the prevalence of PE within the individual studies. The prevalence of PE in individual studies was thus extracted, unless the prevalence of PE and the occurrence of VTE were described in more than one subgroup within a study, in which case those subgroups were used for analyses. Using an unbiased approach, we assessed the proportion of VTEs and 95% CIs despite a negative CTPA in the different predefined prevalence subgroups ranging from $< 20\%$, 20–29%, 30–39% to $\geq 40\%$. The relationship between prevalence of PE at the time of the index event in each of these studies/subgroups and the proportion of VTEs despite a negative CTPA were further investigated using meta-regression analysis, with studies being weighted by the precision of their respective effect estimate. Finally, the overall sensitivity of CTPA was also assessed, using patients with a diagnosed VTE with CTPA or other methods at the time of the event or during follow-up as the denominator. Whenever possible, the point estimate (95% CI) was calculated as previously described for mean sensitivity [17].

Cochran's χ^2 test and the I^2 test for heterogeneity were used to assess between-study heterogeneity. Statistically significant heterogeneity was considered present at $P < 0.10$ and $I^2 > 50\%$. In addition to the prevalence of PE at the time of inclusion, we planned sensitivity analyses to investigate sources of heterogeneity in the main analysis, if any, according to the study design (single center vs. multicenter), the type of CTPA (single row vs. multirow), the year of study (before 2005, 2005–2010 or after 2010), the duration of follow-up (≤ 3 vs. > 3 months), whether inpatients were excluded and whether concomitant tests were used to exclude VTE at the time of index PE as part of the diagnostic algorithm. A sensitivity analysis was also performed using the fixed effect.

Publication bias was assessed visually using funnel plots. We assumed that the effect of publication bias should be minor if the plot of the magnitude of effect size in each study vs. its precision estimate (i.e. standard error) shows a roughly symmetrical funnel shape [18]. We also formally tested the presence of publication bias using the standard error-based and study size-based funnel plots and related asymmetry tests [19]. All analyses were performed with Review Manager (The Cochrane Collaboration, Oxford, England) and R (R Foundation for Statistical Computing, Vienna, Austria). The report was written according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [20].

Role of the funding source

No funding was received to perform this meta-analysis. All authors had full access to all the data and the final responsibility to submit the mansucript for publication.

Results

Literature search and agreement

A total of 3143 publications were retrieved from our literature search. Both primary reviewers finally agreed to include 22 articles in the final analysis [2,7,21–40] (quadratic weighted kappa 0.692 [95% CI, 0.543–0.840]). The reasons for exclusion are described in Fig. 1. Subgroup analyses based on prevalence of PE were available for five studies [2,21,26,33,39], enabling the identification of 29 PE prevalence subgroups.

Characteristics of included studies

The characteristics of selected studies are shown in Table 1. Overall, a VTE was diagnosed in 3923 out of 11 872 participants with an interpretable CTPA result, yielding an overall VTE prevalence of 33.0%. All studies were prospective and selected consecutive patients except for two studies that proceeded by randomization [35,37]. Eleven studies used at least a four-detector CT scanner (4–64 multi-slice CT scanner), whereas four studies used a single-detector helical CT scanner. Two studies used a single and multidetector scanner and in five studies the type of scanner was not specified. CTPA was most commonly performed as part of a diagnostic algorithm in patients with positive D-dimers or a non-low pretest clinical probability (n = 12) [6,7,21,23,24,26,29,31,38–41]. In five studies, venous ultrasound was systematically performed as part of the diagnostic algorithm [21,25,27,33,36]. Nine and five studies also used alternative imaging tests as per protocol and at the discretion of the physician, respectively. The follow-up period was 3 months, except for two studies that followed patients for 6–36 months [2,36]. Overall, all included studies had good methodological quality, although some methodological quality concerns were noted (Table S1).

Occurrence of VTE amongst patients with a negative CTPA

Amongst the 7863 patients with a negative CTPA included in the analysis, 148 patients had acute VTE confirmed by venous ultrasound (n = 113), V/Q scan (n = 3), angiography (n = 4) and an unspecified alternative imaging test (n = 28) at the time of the index PE. In addition, 74 patients experienced DVT (n = 26), non-fatal PE (n = 22), fatal PE (n = 22) and unspecified thromboembolism (n = 4) during follow-up, whereas 25 patients were lost to follow-up or experienced an unexplained death. Overall, the proportion of patients with a VTE at the time of the index event or during follow-up despite a negative CTPA was 2.4% (95% CI, 1.3–3.8%) (Fig. 2), with a sensitivity of CTPA of 94.6% (95% CI, 91.6–96.9%) (Figure S1). Visual inspection of the funnel plot suggested no publication bias (Fig. 3), which was confirmed using the Egger test (P = 0.17). Statistically significant heterogeneity was observed amongst included studies (I^2 = 92%, P < 0.01). Predefined sensitivity analyses confirmed that overall prevalence influenced the incidence of VTE ($P_{\text{interaction}}$ = 0.008, I^2 = 85% between pretest prevalence). This was confirmed by separate meta-analyses according to the overall prevalence of PE (Fig. 4), with VTE being confirmed in 8.1% (95% CI, 3.4–14.5%) of patients in the highest (> 40%) prevalence subgroup. This was further confirmed using meta-regression analysis (P = 0.0004) (Fig. 5). Conversely, subgroup analyses suggested that the incidence of VTE was consistent across other predefined subgroups (study design, publication date, CTPA type, outpatient/inpatient, and alternative test use), except for the follow-up duration subgroup analysis (Table S2; Figure S2–S7). A 'worst-case scenario', assuming the occurrence of recurrent VTE for patients lost to follow-up/unexplained death, yielded a rate of VTE despite a negative CPTA of 2.9% (95% CI, 1.9–4.1%), reaching 9.0% (95% CI, 3.6–16.4%) amongst patients with high pretest clinical probability (Figure S8). The fixed effect model yielded similar estimates.

Discussion

The present meta-analysis of management outcome studies confirms that a negative CTPA is an adequate criterion for excluding PE for most patients for whom imaging testing is required, as VTE is documented on average in 2.4% of patients with a negative CTPA. However, the NPV of CTPA varied according to the prevalence of PE, VTE being observed in up to 8% in the subgroup of patients with an overall prevalence of PE of ≥ 40%. These observations suggest that CTPA alone may be insufficient to safely rule out acute PE in high clinical probability patients and that complementary diagnostic strategies may be required to assess the subgroup of patients at higher pretest clinical probability.

Despite the existence of detailed consensus guidelines, challenges and controversies continue to exist regarding the most appropriate evaluation for suspected acute PE. CTPA has emerged as a prominent imaging technique for the exclusion or confirmation of PE amongst patients with positive D-dimers or high pretest clinical probability [8]. Many large-scale outcomes studies that included a diversity of study populations, pretest clinical probabilities, study designs and CTPA characteristics provided evidence in favor of CTPA as a stand-alone imaging test for excluding PE [33,34,37,38]. Although the rate of VTE during follow-up ranged from 0% to 3.7% in these studies, the upper confidence limits were as high as 5.8% because the sample size was sometimes limited. Previous meta-analyses showed that CTPA was associated with an NPV of ≥98% [6,9]. The present meta-analysis is consistent with these results and previous meta-analyses, with an overall rate of false negative results of 2.4%. Interestingly, its upper limit of its 95% CI is within the widely accepted safety margin of ~3%, which is based on the VTE incidence after a negative pulmonary angiography [42]. Indeed, the safety of a diagnostic algorithm is determined by the width, and more specifically the upper limit, of the confidence interval around the mean rates of VTE during follow-up.

The diagnostic algorithm, however, is largely influenced by the predicted pretest prevalence of PE as an inevitable consequence of the Bayes' theorem. Multiple studies confirmed the pivotal role of clinical prediction rules in classifying patients with suspected PE into distinct categories of pretest probability [8]. Amongst them, the Wells and the Geneva rules are simple and standardized and have

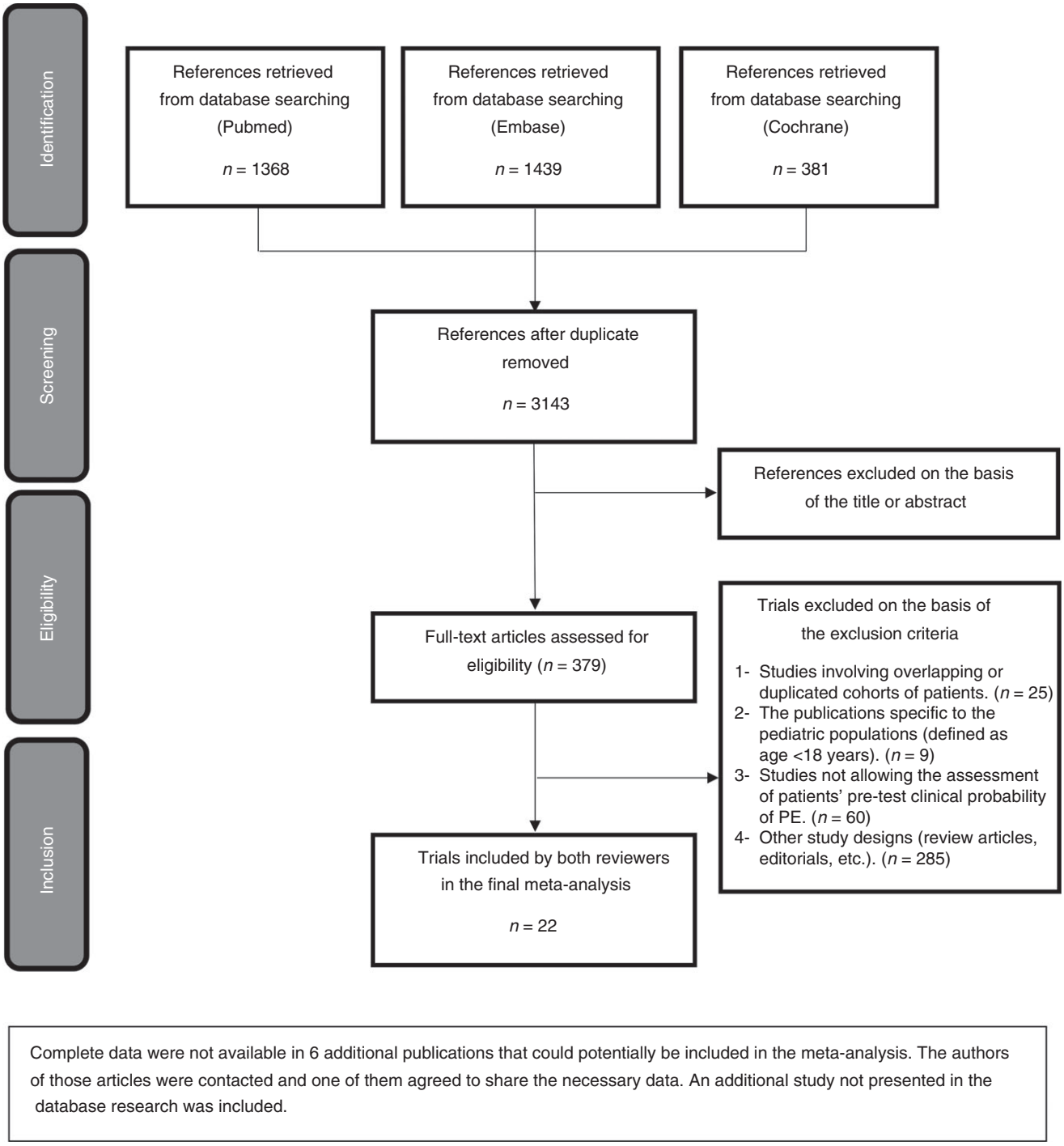

Fig. 1. Flow chart for literature search results. Independent reviewers included 22 different publications.

been validated in multiple prospective cohorts [43–46]. This has become a key step in the investigation of acute PE because the post-test probability of PE depends not only on the sensitivity of the proposed diagnostic test itself, but also on pre-test probability. Even in large-scale studies, the number of patients with high pretest clinical probability who remained non-anticoagulated following a negative CTPA was generally low, precluding appropriately powered subgroup analyses with narrow confidence intervals. When the subgroup of patients with a high (≥ 40%) prevalence of PE was pooled, VTE events were confirmed in 8% of them (with an upper confidence limit of 15%) following a negative CTPA, confirming our hypothesis that CTPA may be insufficient as a stand-alone imaging test to safely rule out acute VTE in these patients. This subgroup analysis was further supported by

Table 1 Characteristics of included studies

Study	Number of patients	Patient enrolment	Outpatients (%)	Overall PE prevalence (%)	CTPA indication	CDR	D-dimer test in algorithm	Single-slice CT/ MSCT	Alternative tests in algorithm	Follow-up (months)	Number of lost to follow-up
Blachere 2000 [27]	179	Consecutive	16	35·8	All patients	Clinician opinion	–	4-slice CT	DVUS, V/Q, PA	3	0
Musset 2002 [33]	1041	Consecutive	77	38·6	All patients	Hyers	–	Single-slice CT	DVUS, V/Q, PA	3	13
Bourriot 2003 [36]	117	Consecutive	0	54·3	All patients	Clinician opinion	Asserachrom D-Di	4-slice CT	DVUS	6–36	5
Kucher 2003 [31]	191	Consecutive	100	55·6	D-dimer + or high clinical probability	Clinical opinion	VIDAS	Unknown	DVUS, V/Q, PA	3	0
Friera 2004 [28]	209	Consecutive	58	33·3	All patients	Clinical opinion	–	Single-slice CT	DVUS, V/Q, PA	3	6
Anderson 2005 [26]	869	Consecutive	100	16·8	D-dimer + or intermediate/ high clinical probability	Wells	Agen/IL-Test	Unknown	DVUS, PA	3	11
Ghanima 2005 [29]	432	Consecutive	Unknown	30·9	D-dimer + or high clinical probability	Hyers	STA-Liatest	4-slice CT	DVUS, V/Q, PA	3	0
Perrier 2005 [21]	756	Consecutive	100	40·0	D-dimer + or high clinical probability	Geneva score	VIDAS	4-slice/16-slice CT	DVUS, V/Q, PA	3	4
Stein 2006 [2]	1090	Consecutive	89	34·4	All patients	Wells	–	4-slice/8-slice/16-slice CT	CTV	6	1
Tillie-Leblond 2006 [25]	197	Unknown	0	24·9	All patients	Geneva score	–	Single-slice CT/ MSCT	DVUS	3	0
Perez de Llano 2006 [22]	88	Consecutive	Unknown	45·7	All patients	Geneva score/ Wicki score	–	Single-slice CT	–	3	0
Van Belle 2006 [38]	3306	Consecutive	82	32·8	D-dimer + or likely clinical probability	Wells	VIDAS/Tina-quant	Single-slice CT/ MSCT	DVUS, V/Q	3	4
Subramaniam 2007 [23]	494	Consecutive	Unknown	21·7	D-dimer + or intermediate/ high clinical probability	Unknown	Unknown	Single-slice CT	–	3	8
Righini* 2008 [37]	1819	Randomized	100	33·1	D-dimer + or high clinical probability	Revised Geneva score	VIDAS	16–64-slice CT	DVUS, V/Q, PA	3	2
Galipienzo 2010 [30]	386	Consecutive	100	24·7	All patients	Wells	–	16-slice CT	DVUS, PA	3	0
Douma 2011 [40]	807	Consecutive	80	31·4	D-dimer + or likely clinical probability	Wells/revised Geneva score/ simplified Wells/simplified revised Geneva	VIDAS/Tina-quant/STA-Lia	4-slice/16-slice/ 64-slice CT	V/Q	3	1

Table 1 (Continued)

Study	Number of patients	Patient enrolment	Outpatients (%)	Overall PE prevalence (%)	CTPA indication	CDR	D-dimer test in algorithm	Single-slice CT/ MSCT	Alternative tests in algorithm	Follow-up (months)	Number of lost to follow-up
Pesavento 2011 [24]	804	Consecutive	62	31·7	D-dimer + or likely clinical probability	Simplified Wells score	Biopool Autodimer assay	64-slice CT	–	3	0
Mos 2014 [34]	516	Consecutive	89	42·5	D-dimer + or likely clinical probability	Wells	VIDAS/Tina-quant/STA-Lia	Unknown	–	3	1
Szucs-Farkas 2014 [35]	504	Randomized	50	16·4	All patients	Revised Geneva score	VIDAS	16-slice CT	DVUS, V/Q	3	46
Righini* 2014 [7]	3324	Consecutive	100	29·1	D-dimer + or high/likely clinical probability	Revised Geneva score/simplified Wells/simplified Geneva	VIDAS/Tina-quant/STA-Lia/ Cobas H232/D-dimer HS500/ Innovance	Unknown	–	3	4
Moores 2016 [32]	134	Consecutive	Unknown	74·5	High clinical probability	Wells	Unknown	64-slice CT	DVUS, V/Q	3	0
van der Hulle 2017 [39]	3465	Consecutive	86	26·3	D-dimer +	YEARS	VIDAS/Tina-quant/STA-Lia/ Innovance	Unknown	–	3	5

CDR, clinical decision risk score; CT, computed tomography; CTPA, computed tomographic pulmonary angiography; PE, pulmonary prevalence; MSCT, multi-slice computed tomography; DVUS, deep venous ultrasound; CTV, venous-phase multidetector computed tomographic venography; PA, pulmonary angiography; V/Q, ventilation-perfusion lung scintigraphy. *Data from the two Righini studies [7,37] were extracted from the data presented in another article [41]

Study	Events	Total	Proportion	95%–CI	Weight (fixed)	Weight (random)
Blachere 2000	3	120	0.025	[0.005; 0.071]	1.5%	4.2%
Musset 2002	68	636	0.107	[0.084; 0.134]	8.1%	5.0%
Kucher 2003	0	68	0.000	[0.000; 0.053]	0.9%	3.6%
Burriot 2003	24	93	0.258	[0.173; 0.359]	1.2%	3.9%
Friera 2004	1	115	0.009	[0.000; 0.047]	1.5%	4.1%
Anderson 2005	15	422	0.036	[0.020; 0.058]	5.4%	4.9%
Ghanima 2005	5	224	0.022	[0.007; 0.051]	2.8%	4.6%
Perrier 2005	8	300	0.027	[0.012; 0.052]	3.8%	4.7%
Stein 2006	27	315	0.086	[0.057; 0.122]	4.0%	4.8%
Tillie–Leblond 2006	6	154	0.039	[0.014; 0.083]	2.0%	4.4%
Perez de Llano 2006	3	98	0.031	[0.006; 0.087]	1.2%	4.0%
Van Belle 2006	18	1436	0.013	[0.007; 0.020]	18.3%	5.1%
Subramaniam 2007	8	423	0.019	[0.008; 0.037]	5.4%	4.9%
Righini 2008	0	131	0.000	[0.000; 0.028]	1.7%	4.2%
Douma 2011	7	425	0.016	[0.007; 0.034]	5.4%	4.9%
Pasavento 2011	1	367	0.003	[0.000; 0.015]	4.7%	4.8%
Galipienzo 2012	1	242	0.004	[0.000; 0.023]	3.1%	4.6%
Szucs–Farkas 2014	1	410	0.002	[0.000; 0.014]	5.2%	4.9%
Mos 2014	7	249	0.028	[0.011; 0.057]	3.2%	4.6%
Righini 2014	1	183	0.005	[0.000; 0.030]	2.3%	4.5%
Moores 2016	7	134	0.052	[0.021; 0.105]	1.7%	4.3%
Van der Hulle 2017	11	1318	0.008	[0.004; 0.015]	16.8%	5.1%
Fixed effect model		7863	0.021	[0.018; 0.024]	100.0%	––
Random effects model			0.024	[0.013; 0.038]	––	100.0%

Heterogeneity: $I^2 = 92\%$, $\tau^2 = 0.0085$, $P < 0.01$

0 0.05 0.1 0.15 0.2 0.25 0.3 0.35

Fig. 2. Weighted meta-analysis with fixed- and random-effect models for thromboembolic events during the 3 months' follow-up after a negative CTPA.

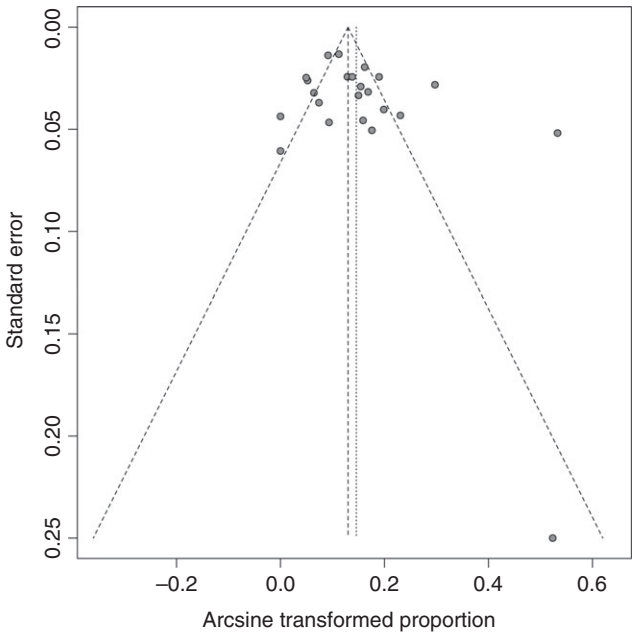

Fig. 3. Study of publication bias: funnel plot for the primary outcome of the meta-analysis (occurrence of thromboembolic events during follow-up). Visual inspection of the funnel plot does not suggest a publication bias.

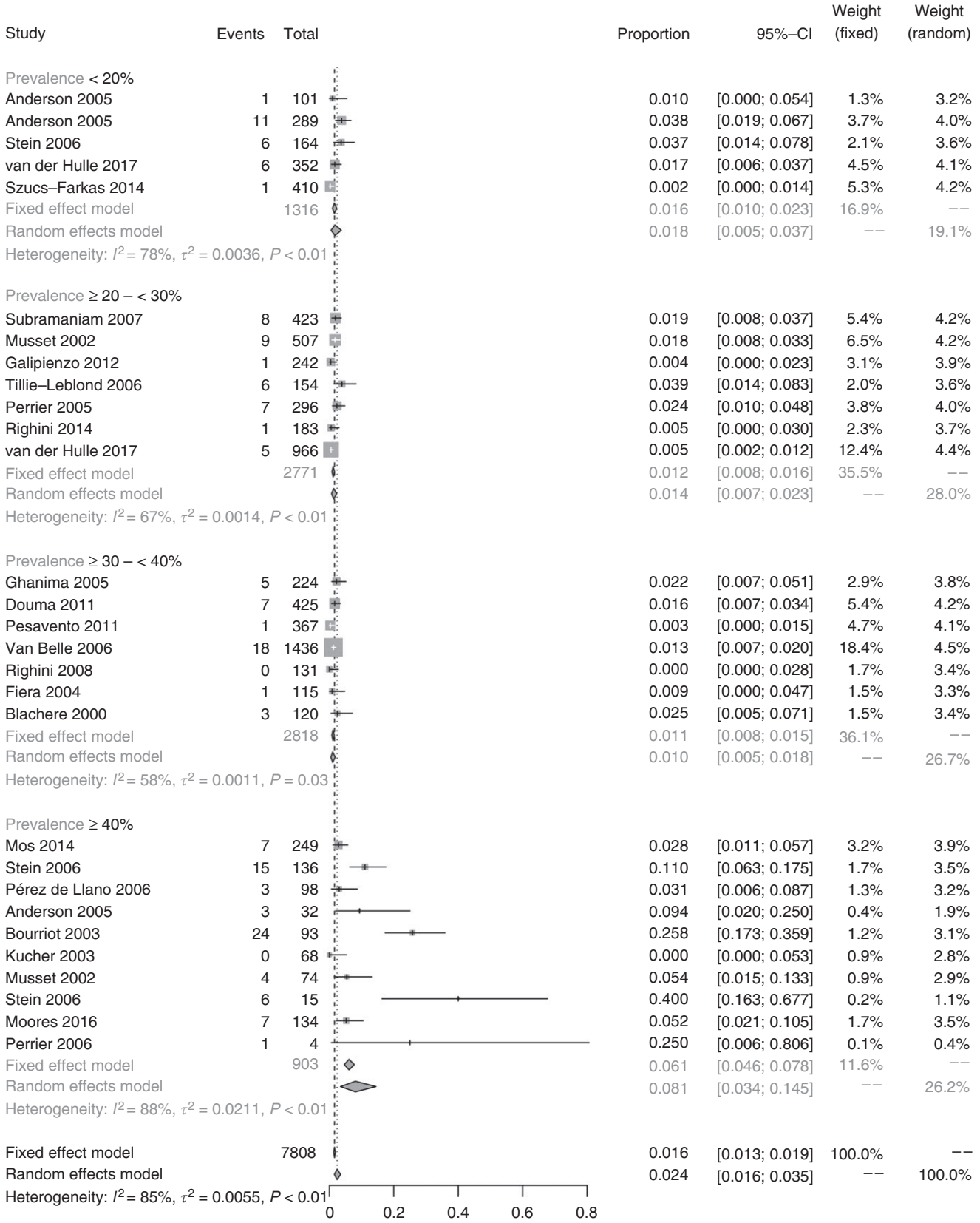

Fig. 4. Subgroup analysis according to the prevalence of pulmonary embolism (0–20%, 20–30%, 30–40% and > 40%). Confidence interval (CI) at 95%.

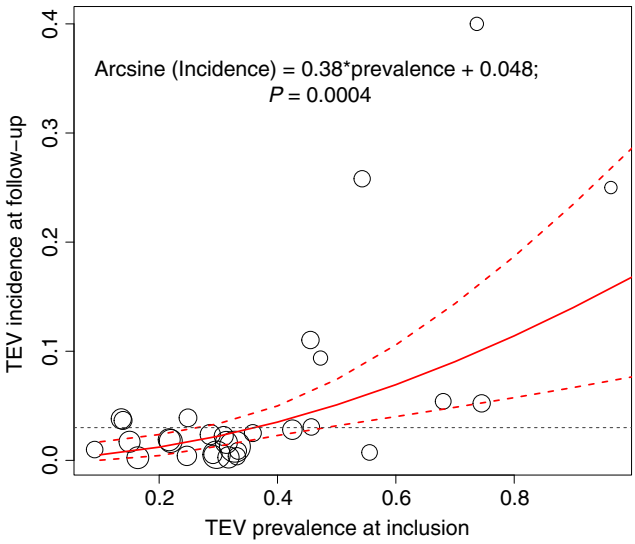

Fig. 5. Meta-regression (arcsine function). Occurrence of venous thromboembolism (VTE) at the time of the index event or in the 3-month follow-up according to prevalence of VTE at inclusion. Proportional representation of the different subpopulations according to sample size. The dotted lines represent the 95% confidence interval for the regression. [Color figure can be viewed at wileyonlinelibrary.com]

a meta-regression analysis documenting the increasing proportion of patients with VTE as the initial PE prevalence increased.

The influences of clinical probability on the predictive value of CTPA were previously highlighted in the PIOPED II study [2]. In patients with a low clinical probability of PE as assessed by the Wells rule, a negative CT had a high NPV for PE (96%) when compared with a composite reference standard that was used to diagnose or rule out PE, whereas this was only 60% in those with a high pretest probability. This disparity in the accuracy of CTPA compared with a reference standard vs. long-term clinical outcomes has been noted for over a decade and has been attributed to the fact that CTPA probably misses small, isolated, subsegmental emboli when compared with V/Q scan [47]. Our results are also consistent with a recent patient-level meta-analysis of four pivotal outcome studies [34,38,40,48] in which the 3-month risk of VTE was 0.54% (95% CI, 0.2–1.3%) and 1.2% (95% CI, 0.3–5.2%) amongst patients with a low and intermediate pretest probability (in addition to elevated D-dimers), whereas the 3-month risk of VTE was 6.3% (95% CI, 3.0–12.6%) amongst patients with high pretest probability [49]. Interestingly, the PE baseline prevalence within these subgroups was 8%, 27% and 56%, respectively. In both studies, the proportion of patients with VTE documented despite a negative CTPA markedly increased in the highest prevalence subgroup only. This is not surprising considering the exponential changes in post-test probability as prevalence fluctuates, especially at extremes of pretest probability and likelihood ratios (Figure S9). Therefore, the epidemiology of PE should be taken into account when elaborating diagnostic strategies for VTE, as suggested in a recent communication [50].

Importantly, two-thirds of the VTEs observed in the studies included in the meta-analysis despite a negative CTPA were confirmed at the time of the index event. Whether these VTEs were clinically relevant is thus a valid question. Some studies incorporated more confirmatory tests (e.g. venous ultrasound) within their diagnostic algorithm in the case of negative CTPA, especially for patients with a high clinical probability. Because we considered DVT to be a marker for PE, as DVT is a manifestation of the same disease, more intensive screening may have introduced differential detection bias within this high-risk population. Not surprisingly, the systematic use of alternative tests tended to be associated with a higher proportion of VTE amongst patients with a negative CTPA in our predefined subgroup analysis. On the other hand, VTE occurring during follow-up may also represent unrelated events with newly formed rather than initially missed VTE, especially in cancer patients at high risk of thrombotic diseases. Nonetheless, the observed NPV within the high pretest clinical probability subgroup is unlikely to be an overestimation of clinically relevant events because the majority of the events were diagnosed as concomitant DVT and symptomatic VTE during follow-up. Moreover, the proportion of 'missed' VTEs diagnosed at baseline vs. during follow-up was fairly consistent across the different pretest clinical probability subgroups.

Importantly, the studies included in the present meta-analysis used both single- and multi-detector CT scanners. The latter obviously produce images with less movement artefacts, better arterial contrast filling and more details.

Increases in CTPA accuracy are thus expected with new technologies. Surprisingly, previous meta-analysis suggested that the risk of subsequent VTE was similar following a negative single-slice and multidetector-row CTPA [4]. Consistent with this observation, our predefined subgroup analysis suggested a comparable incidence of VTE after a negative CTPA irrespective of the type of CTPA performed (Table S2). This potentially reflects the fact that multidetector CTPA may detect non-clinically-relevant PEs that are not necessarily associated with increased thromboembolic risk during follow-up [51,52]. It is noteworthy, however, that the proportion of patients with a confirmed VTE despite a negative CTPA tended to be influenced by the publication year, which might be explained by changes in study population (e.g. lower prevalence of PE) and study design (e.g. less alternative tests), as well as higher sensitivity of modern multi-slice CT scans. Further studies are thus required to assess whether our findings reflect current daily clinical practice. Similarly, subgroup analysis suggested the possible interaction between follow-up duration and the incidence of subsequent VTE, with a higher incidence of events with longer follow-up periods. However, only two studies had a follow-up duration greater than 3 months [2,36]. A high number of VTE diagnoses were made based on an alternative imaging technique within these two studies, and no VTE diagnosis was made after the initial 3-month follow-up, suggesting that follow-up duration had a limited influence on the incidence of VTE after a negative CTPA. Finally, some methodological concerns were observed for most of the included studies. It is noteworthy, however, that the QUADAS tool was primarily developed for the quality assessment of diagnostic accuracy rather than outcome studies in which the index test (in this case CTPA) is not systematically compared with a reference standard [53].

Taken together, these data suggest that a negative CTPA is an adequate criterion for excluding PE in patients with a non-high clinical probability of PE, but complementary diagnostic strategies may be required to assess the small subgroup of patients at higher pretest clinical probability. The addition to the diagnostic algorithm may be ultrasonography of the lower limbs. This remains to be confirmed, however, because it has been shown in high-quality randomized controlled trials that screening for asymptomatic DVT in addition to a negative CTPA did not reduce the risk of overall and fatal recurrences in patients with diverse pretest probabilities of PE (i.e. all patients) [6]. Conversely, the disappointing 60% NPV of CTPA in patients deemed to have a high pretest probability was improved to 82% with the addition of computed tomography venography, prompting the authors of the PIOPED2 study to recommend combined testing in these patients [2]. It is noteworthy that several patients with a high clinical probability of PE possibly had signs and/or symptoms of DVT that prompted an ultrasound of the lower limbs, regardless of the CTPA result. Therefore, our results should be interpreted as a failure of CTPA to diagnosis VTE as a stand-alone imaging test amongst patients within the high clinical probability population, rather than a failure of the diagnostic strategy. Future prospective studies are thus required to validate an appropriate diagnostic algorithm for these patients at risk of VTE despite a negative CTPA. This is especially relevant because recent studies confirmed the lower global incidence of major hemorrhagic complications with direct oral anticoagulants [54,55], so that clinicians might require a more accurate diagnostic algorithm for PE when balancing the current risks of unnecessary anticoagulation vs. leaving 'missed' VTE non-anticoagulated. Until then, the present results should caution clinicians in the case of discrepancy between clinical judgment and CTPA results [56,57], and further testing may be considered in the case of high pretest clinical probability. It is noteworthy, however, that a minority of patients (likely $< 5\%$) present with a baseline preclinical risk of PE of $> 40\%$ [49]. At the present stage, individualized management is thus preferred over performing additional imaging tests in all patients.

In conclusion, the NPV of CTPA amongst patients requiring imaging tests for suspected acute PE is reasonably high, supporting current guidelines that recommend CTPA as a stand-alone imaging test in these patients. However, the NPV of CTPA largely varied according to the pretest clinical probability of acute PE, as VTE was confirmed despite a negative CTPA in ~8% of study subgroups with a prevalence of PE of $\geq 40\%$. Taken together, these data suggest that a negative CTPA is an adequate criterion for excluding PE in patients with a low-to-moderate clinical probability of PE but may be insufficient for the small subgroup of patients with high pretest clinical probability. Future prospective studies are required to confirm these results and validate appropriate diagnostic algorithms to safely rule out PE for this subset of patients.

Addendum

D. Belzile and S. Jacquet completed the literature search, data collection, data analysis and data interpretation, and drafted the first version of the manuscript. L. Bertoletti and Y. Lacasse contributed to study design, data interpretation and the revision of the manuscript. C. Lambert contributed to the literature search. J. C. Lega contributed to study design, data analysis, data interpretation and the revision of the manuscript. S. Provencher contributed to the study design, literature search, data analysis and data interpretation and revised the manuscript.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig. S1. CTPA sensitivity for pulmonary embolism.
Fig. S2. Study follow-up subgroup analysis.
Fig. S3. Study design subgroup analysis
Fig. S4. Publication year subgroup analysis.
Fig. S5. CTPA type subgroup analysis.
Fig. S6. Study patient type subgroup analysis.
Fig. S7. Study alternative tests subgroup analysis.
Fig. S8. Worst-case scenario.
Fig. S9. Relation between pre- and post-test probabilities for various positive (upper left half) and negative (lower right half) likelihood ratios.
Data S1. Methods.
Table S1. Methodological quality assessment.
Table S2. Subgroup analysis tests for interaction.
Table S3. VTE occurrence amongst patients with a negative CTPA – prevalence subgroups.
Table S4. VTE occurrence amongst patients with a negative CTPA – follow-up duration subgroups.
Table S5. VTE occurrence amongst patients with a negative CTPA – study design subgroups.
Table S6. VTE occurrence amongst patients with a negative CTPA – publication date subgroups.
Table S7. VTE occurrence amongst patients with a negative CTPA – CTPA type subgroups.
Table S8. VTE occurrence amongst patients with a negative CTPA – patient localization subgroups.
Table S9. VTE occurrence amongst patients with a negative CTPA – alternative tests use subgroups.

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