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A more granular view on pulmonary embolism

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Citation

Mos, I. C. M. (2013, September 18). *A more granular view on pulmonary embolism*. Retrieved from <https://hdl.handle.net/1887/21764>

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Author: Mos, Inge Christina Maria

Title: A more granular view on pulmonary embolism

Issue Date: 2013-09-18

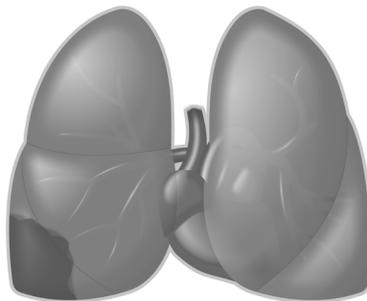
CHAPTER 5

Safety of ruling out acute pulmonary embolism by normal computed tomography pulmonary angiography in patients with an indication for computed tomography: systematic review and meta-analysis.

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J Thromb Haemost 2009; 7:1491-8



ABSTRACT

Introduction

Several outcome studies have ruled out acute pulmonary embolism (PE) by normal computed tomography pulmonary angiography (CTPA). We performed a meta-analysis in order to determine the safety of this strategy in a specific group of patients with a strict indication for CTPA, i.e. 'likely' or 'high' clinical probability for PE, an elevated D-dimer concentration, or both.

Methods

Studies that ruled out PE by normal CTPA, with or without subsequent normal bilateral compression ultrasonography (CUS), in patients with a strict indication for CTPA, were searched for in Medline, EMBASE, Web of Science and the Cochrane dataset. Primary endpoint was the occurrence of (fatal) thromboembolic events (VTE) in a 3-month follow-up period.

Results

Three studies were identified that excluded PE by CTPA alone (2020 patients) and three studies that performed additional CUS of the legs after normal CTPA (1069 patients). The pooled incidence of VTE at three months was 1.2% (95%CI 0.8-1.8%) based on a normal CTPA as a sole test and 1.1% (95%CI 0.6-2.0%) based on normal CTPA and negative CUS, resulting in a NPV of 98.8% (95%CI 98.2-99.2%) and 98.9% (95%CI 98.0-99.4%) respectively. This compares favorably with the VTE failure rate after normal pulmonary angiography (1.7%, 95%CI 1.0-2.7). Risk of fatal PE did not differ between both diagnostic strategies (0.6% vs. 0.5%).

Conclusion

A normal CTPA alone can safely exclude PE in all patients in whom CTPA is required to rule out this disease. There is no need for additional ultrasonography to rule out VTE in these patients.

INTRODUCTION

Computed tomography pulmonary angiography (CTPA) is currently the preferred thoracic imaging test for patients suspected of having pulmonary embolism (PE).¹ This is the result of the high negative predictive value (NPV) of CTPA that was shown to range from 98.7 to 99.9%.^{2,3} In addition, it has been demonstrated that there is no necessity of performing additional imaging, e.g. compression ultrasonography after a normal multidetector- row CTPA before excluding venous thromboembolic disease and withholding anticoagulant therapy.^{2,3} However, in these reports, patients with low, intermediate as well as patients with high clinical pretest probability for having PE were selected for CTPA. In several recent studies, it has been shown that acute PE can be ruled out without the need for radiological imaging tests in a specific patient population with 'low' or 'unlikely' clinical probability for PE in combination with a normal high-sensitive D-dimer test result.⁴⁻⁶ Since the NPV of a test is dependent on the prevalence of the disease in the tested population, the NPV of CTPA in patients in whom PE can not be ruled out by a clinical decision rule and a D-dimer test, i.e. with 'likely' or 'high' pretest probability for PE or an abnormal D-dimer test result (prevalence of PE 37-47%⁷), is likely to be less favorable than the NPV of CTPA in the overall population suspected of having PE (prevalence of PE 20-26%⁷). Furthermore, several studies have shown that despite of a negative CTPA, deep vein thrombosis (DVT) can be identified by compression ultrasonography (CUS) in patients with suspected PE.^{4,8,9}

Our objective was to perform a systematic review and meta-analysis to determine the safety of excluding acute PE on the basis of a normal CTPA alone for all patients with clinically suspected acute PE and a strict indication for CTPA to rule out PE, i.e. with a 'likely' or 'high' clinical probability or an elevated D-dimer concentration. In addition, we studied the additional value of CUS after a normal CTPA in this specific patient cohort.

METHODS

Data sources

A literature search was performed to identify all published prospective outcome studies that excluded PE on the basis of a normal CTPA result. MEDLINE, EMBASE, Web of Science and the Cochrane dataset were searched using pre-defined search terms. Search criteria included "pulmonary embolism" or "venous thromboembolism" or "venous thrombosis" and "computed tomography" or "spiral CT", a complete overview of the search criteria is attached (appendix 1). Articles published from January 1990 till September 2008 were eligible for this analysis. Papers were not limited to the English language. All references of the included studies were reviewed for potential relevant articles.

Study outcome

Outcome of this meta-analysis was the NPV of CTPA and the safety of withholding anti-coagulant therapy based on a normal CTPA result in patients with a strict indication for CTPA, i.e. a clinical decision rule indicating 'likely' or 'high' probability, an elevated D-dimer concentration or both. Endpoints were objectively confirmed adverse thrombotic events subsequent to a normal CTPA, including all occurrences of venous thromboembolism (VTE), i.e. both deep vein thrombosis (DVT) and PE, and mortality attributable to PE.

Study selection and inclusion criteria

Mandatory for inclusion was a diagnostic strategy based on a clinical decision rule and a D-dimer test without additional imaging tests prior to CT scanning. In addition to studies that used CTPA as only imaging test, we also included studies that had used CUS of the legs following a normal CTPA to study the additional value of CUS for ruling out VTE. Further criteria for selection were: a prospective design, consecutive selection, predefined endpoints, clear description of inclusion and exclusion criteria and a clinical follow-up of more than one month. Two reviewers (I.M. and F.K.) independently reviewed all identified studies. In case of disagreement, a third reviewer (M.H.) was consulted.

Data abstraction

Data regarding study design, patient characteristics, diagnostic algorithm (clinical decision rule, D-dimer assay and CT modality), follow-up period, completeness of follow-up and endpoints were abstracted by two independent researchers. Guidelines proposed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group were followed to extract and present the data.¹⁰ Individual study quality was assessed by the following items: patient enrollment, outcome assessment, duration of follow-up, loss-to-follow-up and funding source.

Statistical analysis

We identified the reported number of objectively confirmed VTE's and in addition all deaths attributed to PE for each study. Patients who received anticoagulants for reasons other than VTE and patients who were lost to follow-up were excluded from the analysis. A meta-analysis was performed by pooling the proportions in a fixed effect as well as in a random effects model. Because the criteria for the performance of CTPA in the included studies were comparable, the disease prevalence was expected to be similar between the studies. For this reason pooling of the NPV was reasonable. The proportions were weighted according to the inverse of the squared standard error. Shown proportions and confidence intervals in the text represent a fixed effects model calculated proportion. Studies with CTPA alone and with additional CUS following a normal CTPA were pooled separately. For assessment of heterogeneity, I^2 was calculated for all comparisons.¹¹ We defined the upper

limit of the 95% confidence interval of the fatal and non-fatal 3-month thromboembolic rate after a normal invasive pulmonary angiography as the cut-off point for the safe exclusion of PE by CTPA, thereby comparing CTPA with the reference standard. For assessment of the effect of the additive use of CUS following a normal CTPA on mortality, the weighted relative risk of fatal PE was calculated. And finally the sensitivity for both diagnostic strategies was calculated. For statistical analysis SPSS version 16.0 and Comprehensive Meta-Analysis (version 2.0, Biostat, Englewood, New Jersey, USA) were used.

RESULTS

Study selection

The literature search revealed 1075 studies; 1052 studies were excluded after review of title and abstract and 23 studies were identified for more detailed evaluation. After full review, an additional 18 studies were excluded due to a diagnostic algorithm that did not meet predefined criteria, i.e. no clinical decision rule, D-dimer or CTPA performed, or performance of supplementary imaging before the CTPA. Three studies using CTPA without further imaging^{5,12,13} and three studies that incorporated CUS after to the CTPA^{4,8,9} were left for inclusion in this meta-analysis (Figure 1). No new articles were identified by reviewing the references of these included studies.

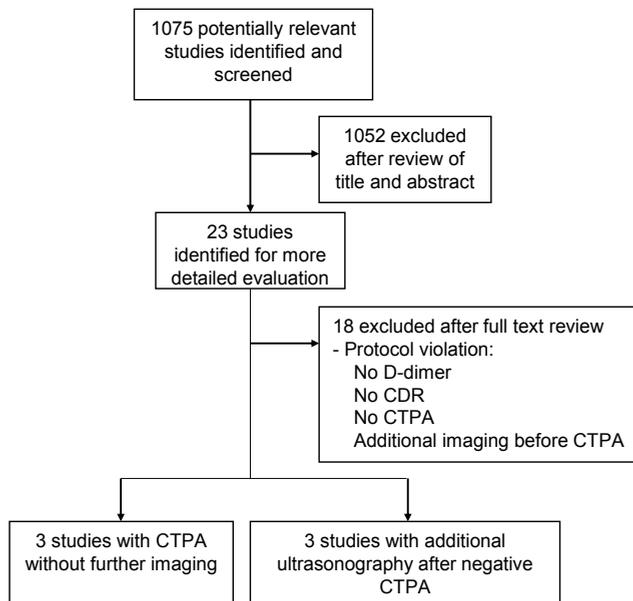


Figure 1. Flow diagram of study selection. CDR: clinical decision rule; CTPA: computed tomography pulmonary angiography.

Quality and characteristics of included studies

All six included studies were of prospective design with consecutive patient enrolment. The duration of follow-up was three months in all studies and loss to follow-up varied between 0.0 and 1.3% (Table 1). The demographic characteristics of patients in the studies were comparable (Table 2). Mean age varied from 50.2 to 60 years, the proportion of male gender ranged between 35 and 46% and the majority of patients were outpatients (Table 2). Different clinical decision rules were used, i.e. the Geneva score¹⁴, the revised Geneva score^{15,16}, the Wells rule¹⁷ or the Hyers criteria¹⁸, in a two or three level scheme (Table 2). Also, different quantitative D-dimer tests were used: VIDAS D-dimer assay (BioMérieux, Marcy- l'Etoile, France), STA Liatest (Diagnostica Stago, Asnières, France), SimpliRED (Agen Biomedical Limited, Acaccia Ridge, Australia), Tinaquant assay (Roche Diagnostica, Mannheim, Germany) and an immunoturbimetric latex agglutination assay (IL-Test, Instrumentation Laboratory, Lexington, MA). Furthermore, the use of single- or multi detector row CT modalities varied between the studies (Table 2). In two studies, patients were randomized between two diagnostic strategies, i.e. CTPA or ventilation

Table 1. Study quality assessment.

Study	Study design	Patient enrollment	Outcome assessment	Duration of follow-up (months)	Lost to follow-up (n, %)	Funding source
van Belle ⁵	Multicenter	Prospective, consecutive	Radiologist and adjudication committee; blinded	3	4 (0.1)	Unrestricted grants from the participating hospitals
Righini ¹²	Multicenter, RCT	Prospective, consecutive	Independent and adjudication committee; blinded	3	1 (0.1)	Grant from the Swiss National Research Foundation, from the Projects Hospitaliers de Recherche Clinique and from Pneumologie Développement
Ghanima ¹³	Single center	Prospective, consecutive	Independent adjudication committee	3	0 (0)	Grant from the Eastern Norway Regional Health Authority
Anderson 2005 ⁹	Multicenter	Prospective, consecutive	Laboratory, radiologist and adjudication committee; blinded	3	11 (1.3)	Grant from Heart and stroke foundation of Nova Scotia
Anderson 2007 ⁴	Multicenter, RCT	Prospective, consecutive	Radiologists and adjudication committee; blinded	3	7 (1.0)	Grant from the Canadian Institutes of Health Research
Perrier ⁸	Multicenter	Prospective, consecutive	Independent adjudication committee	3	4 (1.2)	Grant from the Hirsch Fund of the University of Geneva

RCT: randomized controlled trial.

Table 2. Patient characteristics of included studies.

Study	Number	Mean age (year ±SD)	Male (n, %)	History of VT (n, %)	Cancer (n, %)	Surgery, immobilization or trauma (n, %)	Outpatient (n, %)	CDR (2- or 3-level scheme) [†]	Single/ multi slice CT	D-Dimer assay
van Belle ⁵	3306	53 ±18	1409 (43)	480 (15)	476 (14)	610 (19)	2701 (82)	Wells (2)	Single / MSCT	VIDAS / Tinaquant
Righini ¹²	901*	60 ±19	410 (46)	121 (14)	72 (8.0)	59 (6.5) [#]	901 (100)	RGS (3)	MSCT	VIDAS
Ghanima ¹³	432	58	201 (47)	43 (10)	31 (7.2)	38 (8.8)	432 (100)	Hyers criteria (3)	MSCT	STA-Lia
Anderson 2005 ⁹	858	50 ±18	300 (35)	77 (9.0)	58 (6.8)	160 (19)	858 (100)	Wells (3)	Single	SimpliRED/IL test [*]
Anderson 2007 ⁴	694*	53 ±19	259 (37)	64 (9.2)	67 (9.7)	161 (23) [#]	619 (90)	Wells (2)	Single / MSCT	Local practice
Perrier ⁸	756	60 ±19	302 (40)	142 (19)	75 (9.9)	146 (19)	756 (100)	GS (3)	MSCT	VIDAS

*Only patients included in the CT-group after randomization; [#]number of patients with recent immobilization not mentioned; [†]two level scheme: likely/less likely; three level scheme: low, intermediate and high clinical probability; [‡]immunoturbimetric latex agglutination assay. CDR: clinical decision rule; RGS: revised Geneva score; GS: Geneva score; MSCT: multi-detector-row computed tomography; n: number; SD: standard deviation.

perfusion scintigraphy and CTPA or CUS preceding CTPA.^{4,12} Only the patients randomized to CTPA were included in this analysis. Overall, the fraction of patients who had an indication for CTPA was 70% (range 35-93%). The overall proportion of inconclusive CT scan results was reported to be 1.8% (range 0.9-4.6%). The overall prevalence of PE by positive CTPA in these cohorts was 28% (range 18-36%).

Meta-analysis

Three studies were identified that excluded PE in symptomatic patients with an indication for CT-scanning based on a normal CTPA without additional imaging tests. Of all 2020 patients with an initial normal CTPA result, 25 (1.2%, 95%CI 0.80-1.8) were diagnosed with VTE in a 3-month follow-up period (Tables 3 and 4, Figure 2). Of these, 12 (12/2020; 0.60%, 95%CI 0.40-1.1) were classified as fatal PE. Markedly, only in two of these 12 patients, an autopsy was performed and PE was objectively identified as cause of death. The NPV for symptomatic VTE in three months following a negative CTPA in patients with an indication for CTPA was 98.8% (95% CI 98.2-99.2).

Table 3. Outcome of negative CT scans of the included studies.

Study	Patients (n)	CTPA performed (n, %)	Inconclusive CTPA result (n, %)	CTPA positive for PE (n, %)	CTPA negative for PE (n, %)	Resulting study population [†] (n)	VTE in follow-up (by immediate CUS according to protocol/symptomatic)	Fatal PE (certain/possible) (n/n)
CTPA alone								
van Belle ⁵	3306	2249 (68)	20 (0.9)	647 (30)	1505 (67)	1435	-/18	2/5
Righini ¹²	838 [‡]	558 (67)	15 (2.7)	179 (32)	364 (65)	364 [*]	-/5	0/3
Ghanima ¹³	432 [‡]	329 (76)	15 (4.6)	93 (28)	221 (67)	221	-/2	0/2
CTPA followed by CUS								
Anderson 2005 ⁹	858	300 (35) [*]	8 [‡] (1.7)	59 (20)	241 (80)	241 [†]	11/0	0/0
Anderson 2007 ⁴	694	646 (93)	10 (1.5)	115 (18)	531 (82)	531	7/4	0/2
Perrier ⁸	756 [‡]	524 (69)	13 (2.5)	187 (36)	324 (62)	297	3/5	0/2

*In the follow-up of the complete study population without PE, one patient was lost to follow-up and 30 patients used anticoagulant therapy for other reasons than PE (the fraction of the latter patients in the normal CTPA cohort was not reported); [‡]this number does not include study patients in case of protocol violation, lost to follow-up or use of oral anticoagulants for other reasons than VTE; [†]only CT scans performed in case of either 'high' clinical probability or elevated D-dimer test in combination with 'low' or 'intermediate' clinical probability; [‡]number of inconclusive CTPA results for all performed CT scans in this study (n=467); [†]total number of patients with normal CTPA, complete follow-up and without anticoagulant therapy; [‡]of the total study population, PE was ruled out by other means than by CTPA in 26 patients (CT indicated but not performed or inconclusive CTPA result followed by additional imaging; the fraction of the latter patients in the normal CTPA cohort was not reported). PE: pulmonary embolism; VTE: venous thromboembolism; CUS: compression ultrasonography.

Table 4. Random and fixed model proportions of study endpoints.

Model	VTE in FU after normal CTPA without CUS	Fatal PE in FU after normal CTPA without CUS	Positive echo directly subsequent to normal CTPA followed by CUS	VTE in FU after normal CTPA and negative CUS	Fatal PE in FU after normal CTPA and negative CUS
Fixed	1.2	0.6	2.4	1.1	0.5
95% CI	0.8-1.8	0.4-1.1	1.6-3.7	0.6-2.0	0.2-1.1
Random	1.2	0.6	2.0	1.0	0.5
95% CI	0.8-1.8	0.4-1.1	0.7-5.2	0.4-2.3	0.2-1.1
I ²	0.000	0.000	78.98	29.35	0.000

PE: pulmonary embolism; VTE:venous thromboembolism; FU: follow-up; CI: confidence interval; CTPA: computed tomography pulmonary angiography; CUS: compression ultrasonography.

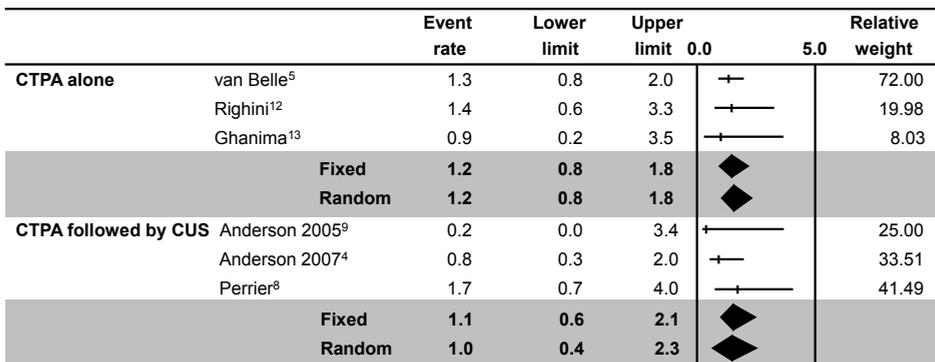


Figure 2. Pooled proportions (fixed as well as random effects model) of confirmed venous thromboembolism event rate after a normal computed tomography pulmonary embolism (CTPA) and after a normal CTPA followed by a negative compression ultrasonography (CUS) of the legs.

In the three studies that included CUS of the legs subsequent to a normal CTPA, 1069 symptomatic patients with an indication for CTPA and eventually a normal CTPA were identified. Twenty-one cases of DVT (21/1069; 2.4%, 95%CI 1.6-3.7) were identified by compression ultrasonography performed shortly after the CTPA (Tables 3 and 4). During 3-month follow-up, nine additional patients (9/1048; 1.1%, 95% CI 0.60-2.0) with initially normal CTPA and a normal CUS were diagnosed with symptomatic VTE. Four of these 1048 patients in whom VTE was excluded and who were not treated with anticoagulants, died (4/1048; 0.50%, 95%CI 0.20-1.1) possibly as a consequence of PE. The NPV for symptomatic VTE in three months after a normal CTPA followed by CUS was 98.9% (95% CI 98.0-99.4). Therefore, the NPV of CTPA alone was equal to the NPV of CTPA followed by CUS (98.8% vs. 98.9%).

The pooled proportions of fatal PE in follow-up were comparable (0.6% and 0.5%, Table 4), indicating a relative risk of 1.2. The use of a random effects model did not materially influence the study results (Table 4). The pooled sensitivity for detecting PE by CTPA alone was 97.3% (95%CI 96.1-98.2), the sensitivity for detecting PE of CTPA combined with additional CUS was 97.4% (95%CI 95.1-98.6).

DISCUSSION

The main finding of this study is that the NVP of CTPA to rule out PE in a patient population with an indication for CT scanning to exclude acute PE is 98.8% (95% CI 98.2-99.2). Furthermore, the 3-month mortality risk of PE after a normal CTPA in this particular patient population is very small (0.60%, 95%CI 0.40-1.1). An invasive pulmonary angiography is the reference standard for the diagnosis of PE.¹ The upper limit of the 95% confidence interval of the 3-month VTE rate after normal pulmonary angiography is 2.7%.¹⁹ Using this fraction as the upper posttest probability limit above which it is no longer safe to rule out PE by a diagnostic test, our data show that a normal CTPA alone is a valid criterion for the safe exclusion of acute PE, even in this specific population. Furthermore, the 3-month PE associated mortality rate after a normal invasive pulmonary angiography is 0.3% (95%CI 0.02-0.7%) which is comparable with the pooled mortality rate observed in our study (0.60%, 95%CI 0.40-1.1).¹⁹

Our analysis of the three studies that included CUS after a normal CTPA allowed us to test the additional value of CUS for ruling out VTE. In these three studies, the proportion of patients with CUS proved DVT in spite of a normal CTPA result was low (2.4%). Furthermore, the NPV for symptomatic VTE in 3 months of follow-up of CTPA alone was comparable to the NPV of CTPA followed by CUS (98.8 and 98.9%). In accordance with this finding, the VTE-related mortality risk was not different between both diagnostic strategies.

Some additional observations require comment. We intended to study the performance of CTPA in all patients in whom this imaging modality is required to rule out PE. For this reason, our study patients had an overall moderate probability for having PE (28%). It could be reasoned that the NPV of the CTPA is lower in more selected patients with a high clinical probability than in the population that we studied in this report. Of note, in the recent guidelines of the European Society of Cardiology on the diagnosis of acute PE, the safe exclusion of PE in a high clinical probability population by a normal CTPA result alone is being debated because of the possible false negative CTPA result.¹ Nonetheless, no current evidence exists that additional imaging, e.g. CUS or ventilation perfusion scintigraphy, would prevent VTE in a 3-month follow-up period in this small selected group of patients. In our analysis it was not possible to study this issue in more detail, since none of the included studies had reported the incidence of symptomatic VTE after normal CTPA result alone in a selection of high probability patients only. In addition, the distinction of patients with a high clinical probability for PE is clinically unpractical since this would imply a different diagnostic strategy for the same (normal) CTPA result, as it would be unpractical and unnecessary to distinguish patients with a 'low' from patients with a 'less likely' clinical probability for the interpretation of a normal D-dimer test result. Furthermore, the best threshold, i.e. clinical decision rule cut-off or

D-dimer concentration cut-off, for defining a high risk population in whom negative CTPA does not safely rule out PE is unknown.

We consider our results to be representative because our findings are based on a pooled analysis of a large cohort of over 3000 patients. Second, the analyzed studies were of high quality with a prospective design, including consecutive patients and using standardized diagnostic tests. Third, follow-up time was consistent in all studies (three months) and all endpoints were well-defined and confirmed by objective tests by pre-defined criteria. Finally, demographic characteristics of the patients were comparable between all included studies.

This meta-analysis has some limitations. Inherent to the design of a meta-analysis, pooling observational or non-randomized data could lead to biases. Specifically for our analysis, different clinical decision rules, D-dimer assays and CT-scanners were used between the included studies. The distinct use of the clinical decision rules, with either 2- (PE 'likely' or 'unlikely') or 3-level schemes ('low', 'intermediate' or 'high' probability of PE), resulted in differences in the fraction of patients who were eligible for CTPA without the need for D-dimer testing. Nevertheless, quantitative, highly sensitive D-dimer tests were used in all 6 included studies and all patients with an abnormal D-dimer test result underwent CTPA. Thus, the different use of clinical decision rules did not affect the overall proportion of patients that was finally selected for CTPA. Also, we could not correct for differences between the performances of single- and multi-detector-row CT scanners. In addition, all included studies reported a low number of inconclusive CTPA results (1.8%). We excluded these cases from our analysis. Finally, by study design, we could not objectively assess whether the reported VTE-related mortality was actually caused by an acute PE. Definite cause of death was only determined by autopsy in 11% of the fatal cases. As a consequence, our mortality rates are likely to be overestimated.

In summary, the NPV and safety of excluding acute PE in patients with an indication for CTPA, i.e. 'likely' or 'high' clinical probability, an elevated D-dimer concentration or both, by a normal CTPA without further imaging tests is comparable to the NPV and safety of a normal invasive pulmonary angiography. Furthermore, a strategy including CUS of the legs following a normal CTPA did not improve diagnostic performance. The clinical implication of our findings is that anticoagulant therapy can safely be withheld in all patients with suspected PE after using CDR and D-dimer testing, and a normal CTPA. In our view, there is no need for additional compression ultrasonography of the legs to rule out VTE in these patients.

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