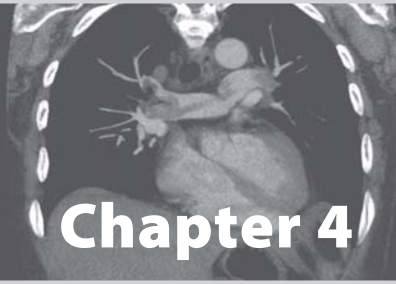
Pulmonary embolism : diagnostic management and prognosis
Klok, F.A.



Chapter 4

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

F.A. Klok†, I.C.M. Mos†, L.J.M. Kroft, A. de Roos, O.M. Dekkers and M.V. Huisman

†Equally contributed

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 in patients with a strict indication for CTPA by normal 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 three months follow-up period.

Results

Three studies were identified that excluded PE by CTPA alone (2020 patients) and three studies that performed additional bilateral compression ultrasonography (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 NPVs of 98.8% (95% CI 98.2-99.2%) and 98.9% (95% CI 98.0-99.4%) respectively. Risk of fatal PE did not differ between both diagnostic strategies (0.6% vs. 0.5%).

Conclusion

A normal CTPA alone safely excludes 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 acute 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 it is unnecessary to perform additional imaging tests after a normal multi-detector 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 reported that acute PE can be ruled 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 highly sensitive D-dimer test result.[4-6] Since the NPV of a test is dependent on the incidence 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 (incidence of PE 37-47%[7]), is likely to be less favorable than the NPV of CTPA in the overall population suspected of having PE (incidence of PE 20-26%[7]). Furthermore, several studies have shown that despite of a negative CTPA, non-symptomatic deep venous thrombosis (DVT) can be identified by compression ultrasonography (CUS) in a small proportion of 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. 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 predefined search terms. Search criteria included "pulmonary embolism" or "venous thromboembolism" or "venous thrombosis" and "computed tomography" or "spiral CT". 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 anticoagulant 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 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 patient selection, predefined endpoints, clear description of inclusion and exclusion criteria, and a clinical follow-up of more than one month. Two reviewers independently reviewed all identified studies. In case of disagreement, a third reviewer 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 cases of VTE 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 effects as well as in a random effects model. Because the criteria for the performance of CTPA in the included studies were comparable, the disease incidence 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 (CI) 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% CI of the fatal and non-fatal three months 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. 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 our predefined criteria, i.e. no clinical decision rule, D-dimer or CTPA performed, or performance of supplementary imaging tests before the CTPA. Three studies using CTPA without further imaging[5,12,13] and three studies that incorporated CUS after CTPA[4,8,9] were left for inclusion in this meta-analysis. No new articles were identified by reviewing the references of these six studies.

Quality and characteristics of the included studies

All six included studies were of a 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 to 60 years, the proportion of male gender ranged between 35% and 47% and the majority of patients were outpatients. Different clinical decision rules were used, i.e. the Geneva score, the revised Geneva score, the Wells rule or the Hyers criteria, in two or three level schemes.[14-18] 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. In two studies, patients were randomized between two diagnostic strategies, i.e. CTPA or ventilation 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%; Table 3). The overall proportion of inconclusive CT scan results was reported to be 1.8% (range 0.9-4.6%). The overall incidence of PE by positive CTPA in these cohorts was 28% (range 18-36%).

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 Pneumonlogie Développement
Ghanima[13]	Single center	Prospective, consecutive	Independent adjudication committee	3	0 (0)	Grant from the Eastern Norway Regional Health Authory
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, n=number.

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 three months follow-up period (Tables 3 and 4, Figure 1). 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). 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 CUS performed shortly after the CTPA (Tables 3 and 4). During three months follow-up, nine additional patients (9/1048; 1.1%, 95% CI 0.60-2.0) with initially normal CTPA and CUS results 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

Table 2. Patient characteristics of included studies.

Study	Number	Mean age (year ±SD)	Male (n, %)	History of VTE (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, VTE=venous thromboembolism, RGS=revised Geneva score, GS=Geneva score, MSCT=multi-detector row computed tomography, n=number, SD=standard deviation.

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.

		Event rate	Lower limit	Upper limit	Relative weight
CTPA alone	van Belle[5]	1.3	0.8	2.0	72.00
	Righini[12]	1.4	0.6	3.3	19.98
	Ghanima[13]	0.9	0.2	3.5	8.03
	Fixed	**1.2**	**0.8**	**1.8**	
	Random	**1.2**	**0.8**	**1.8**	
CTPA followed by CUS	Anderson 2005[9]	0.2	0.0	3.4	25.00
	Anderson 2007[4]	0.8	0.3	2.0	33.51
	Perrier[8]	1.7	0.7	4.0	41.49
	Fixed	**1.1**	**0.6**	**2.1**	
	Random	**1.0**	**0.4**	**2.3**	

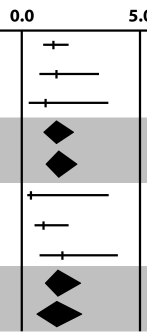


Figure 1. Pooled proportions (fixed as well as random effects model) of the confirmed venous thromboembolism event rate after a normal CTPA and after a normal computed tomography pulmonary angiography (CTPA) followed by a negative compression ultrasonography (CUS) of the legs.

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 as well (0.6% and 0.5%, Table 4), indicating a relative risk of 1.2. The use of a random effects model did not materially influences 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).

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.

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 is 98.8% (95% CI 98.2-99.2). Furthermore, the three months fatal recurrent risk after a normal CTPA in this particular patient population is very low (0.6%, 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 three months 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 three months 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 (0.6%, 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 three months of follow-up of CTPA alone was comparable to the NPV of CTPA followed by CUS (98.8% versus 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 higher 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 possible false negative CTPA results.[1] Nonetheless, no current evidence exists that additional imaging, e.g. CUS or ventilation perfusion scintigraphy, would prevent VTE in a three months 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 or D-dimer concentration cut-off points, 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 predefined criteria. Finally, demographic characteristics of the patients were comparable between all included studies. Even so, 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-dime 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 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 its 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 CUS of the legs to rule out VTE in these patients.

REFERENCES

1. Torbicki A, Perrier A, Konstantinides S, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J 2008; 29:2276-2315
2. Quiroz R, Kucher N, Zou KH, et al. Clinical validity of a negative computed tomography scan in patients with suspected pulmonary embolism: a systematic review. JAMA 2005; 293:2012-7
3. Hogg K, Brown G, Dunning J, et al. Diagnosis of pulmonary embolism with CT pulmonary angiography: a systematic review. Emerg Med J 2006; 23:172-8
4. Anderson DR, Kahn SR, Rodger MA, et al. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. JAMA 2007; 298:2743-53
5. van Belle A, Büller HR, Huisman MV, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA 2006; 295:172-9
6. Rodger MA, Bredeson CN, Jones G, et al. The bedside investigation of pulmonary embolism diagnosis study: a double-blind randomized controlled trial comparing combinations of 3 bedside tests vs ventilation-perfusion scan for the initial investigation of suspected pulmonary embolism. Arch Intern Med 2006; 166:181-7
7. Klok FA, Mos IC, Nijkeuter M, et al. Simplification of the revised Geneva score for assessing clinical probability of pulmonary embolism. Arch Intern Med 2008; 168:2131-6
8. Perrier A, Roy PM, Sanchez O, et al. Multidetector-row computed tomography in suspected pulmonary embolism. N Engl J Med 2005; 352:1760-8
9. Anderson DR, Kovacs MJ, Dennie C, et al. Use of spiral computed tomography contrast angiography and ultrasonography to exclude the diagnosis of pulmonary embolism in the emergency department. J Emerg Med 2005; 29:399-404
10. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283:2008-12
11. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327:557-60
12. Righini M, Le Gal G, Aujesky D, et al. Diagnosis of pulmonary embolism by multidetector CT alone or combined with venous ultrasonography of the leg: a randomised non-inferiority trial. Lancet 2008; 371:1343-52
13. Ghanima W, Almaas V, Aballi S, et al. Management of suspected pulmonary embolism (PE) by D-dimer and multi-slice computed tomography in outpatients: an outcome study. J Thromb Haemost 2005; 3:1926-32
14. Wicki J, Perneger TV, Junod AF, et al. Assessing clinical probability of pulmonary embolism in the emergency ward. Arch Intern Med 2001; 161:92–7
15. Le Gal G, Righini M, Roy PM, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med 2006; 144:165–71
16. Klok FA, Kruisman E, Spaan J, et al. Comparison of the revised Geneva score with Wells rule for assessing clinical probability of pulmonary embolism. J Thromb Haemost 2008; 6:40-4
17. Wells PS, Anderson DR, Rodgers M, et al. Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the model's utility with simpliRED D-dimer. Thromb Haemost 2000; 83:416–20
18. Hyers TM. Venous thromboembolism. Am J Respir Crit Care Med 1999; 159:1-14
19. van Beek EJ, Brouwerst EM, Song B, et al. Clinical validity of a normal pulmonary angiogram in patients with suspected pulmonary embolism-a critical review. Clin Radiol 2001; 56:838-42