Pulmonary embolism: investigation of the clinically assessed intermediate risk subgroup

¹D J WARREN, MRCP, FRCR and ²S MATTHEWS, MRCP, FRCR

¹Radiology Department, Royal Hallamshire Hospital and ²Northern General Hospital, Sheffield NHS Teaching Hospitals Trust, Sheffield, UK

Objectives: The simplified Wells pre-test probability scoring algorithm for pre-investigation evaluation of pulmonary emboli (PE) is a commonly utilised and validated assessment tool. We sought to identify whether use of a dichotomised scoring system altered the overall negative predictive value (NPV) in patients referred for CT pulmonary angiography (CTPA) assessment of suspected PE.

Methods: Prospective data collection of all patients referred for CTPA evaluation of suspected acute PE during a 3 year period was carried out. Pre-test risk stratification was performed according to simplified Wells criteria in conjunction with plasma D-Dimer (Bio-Pool and IL test) estimation. Retrospective dichotomisation was also performed.

Results: 2531 patients were investigated for suspected acute PE; acute thromboemboli were confirmed in 22.7%. The overall NPV for negative D-Dimer and intermediate pre-test probability (PTP) was 98.9% [95% confidence interval (CI) 96.3–99.7%]; with retrospective dichotomisation, the NPV for the PE unlikely group was 99.0% (95% CI 94.8–99.8%). Implementation of dichotomised scoring, excluding PE unlikely with negative D-Dimer cases from further imaging, would have yielded a 4% reduction in CTPA referral pathway imaging at our institution.

Conclusion: We demonstrate no significant difference between exclusion in the intermediate subgroup and the retrospectively dichotomised PE unlikely group and demonstrate the high negative predictive power of the Bio-Pool and IL tests in conjunction with the Wells PTP tool. Prior to implementation of new guidelines for exclusion of patients with suspected PE from further imaging, hospitals should audit their own practice and validate the D-Dimer assay utilised at their institution.

Received 25 October 2009

Revised 22 April 2010

Accepted 18 June 2010

DOI: 10.1259/bjr/17451818

© 2012 The British Institute of Radiology

The overall annual incidence of pulmonary emboli (PE) is quoted at 60–70 cases per 100 000 [1–3]. Associated with significant morbidity and mortality, prompt diagnosis and expeditious therapeutic intervention is of paramount importance for optimal patient management. Indiscriminate and often inappropriate D-Dimer assay evaluation coupled with frequently inexperienced clinical assessment of the presenting patient results in inappropriate referrals and reduced diagnostic yield. The challenge is to identify the patients referred for radiological assessment of suspected PE who actually have a thromboembolic event [4].

The British Thoracic Society (BTS) guidelines advise that the patient is fully evaluated by an experienced middle-grade doctor so that alternative diagnoses can be considered and a clinical probability documented; such practice should yield a 25% incidence of PE in investigated cases [1]. Numerous validated guidelines for initial assessment of PE identify the need for a clinical probability score using a validated scoring system and sensitive, appropriately taken, D-Dimer evaluation [1, 4–6].

With the improved diagnostic capability of modern helical CT, referring clinicians have lower thresholds

for patient referral for CT pulmonary angiography (CTPA) as it is deemed to offer an increasingly definitive detection of PE. However, increased CTPA examinations are associated with cost implications and increasing ionising radiation burden [7]. Patients referred for diagnostic work-up must be carefully selected to avoid unnecessary radiation and expenditure and to yield the desired prevalence of 25% or greater. Pivotaly, patients not requiring further diagnostic evaluation, as proposed by major guidelines [1, 4, 5], should be identified (if inappropriately referred) and safely excluded prior to any imaging [8].

A commonly utilised validated pre-test clinical probability (PTP) assessment tool is the Wells score [9]. The simplified Wells score incorporates seven variables from the patient's history and initial clinical assessment from which a clinical probability of PE is determined as either low, moderate (intermediate) or high (Table 1) [9, 10]. Used in conjunction with a sensitive D-Dimer assay PE can be safely excluded in patients with a negative D-Dimer estimation and low PTP [1, 4, 5, 8, 11–13]. The intermediate subgroup present a more challenging diagnostic enigma with variable recommendations pertaining to those with negative D-Dimer assays; in part, this is secondary to variable assay sensitivities. The BTS guidelines indicate that PE can safely be excluded with intermediate PTP in conjunction with a highly sensitive D-Dimer assay

Address correspondence to: Dr Daniel Warren, Radiology Department, Floor C, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK. E-mail: Daniel.Warren@sth.nhs.uk

Table 1. The simplified Wells score. Cumulative points total <2 implies low clinical pre-test probability of pulmonary emboli (PE), a total of 2–6 points represents moderate (intermediate) pre-test probability and >6 a high pre-test probability of PE [9]. Using a dichotomised scoring system PE “unlikely” represents a simplified Wells score of 4 or less vs PE “likely” score of greater than 4 points

Variable	Points assigned
Clinical signs and symptoms of deep vein thrombosis (DVT) (minimum of leg swelling and pain with palpation of deep veins)	3.0
An alternative diagnosis is less likely than pulmonary emboli	3.0
Heart rate >100 beats min ⁻¹	1.5
Immobilisation or surgery in the previous 4 weeks	1.5
Previous DVT/pulmonary embolus	1.5
Haemoptysis	1.0
Malignancy (on treatment, treated in the last 6 months or palliative)	1.0

[Vidas (bioMerieux, Marcy L’Etoile, France) or MDA (bioMerieux, Durham, NC)]; individual units should however validate the sensitivity and specificity of their particular D-Dimer assay and, as such, all patients with suspected PE, except those with low PTP and negative D-Dimer, are accepted for imaging at our institution. Dichotomisation of the Wells score into PE unlikely *vs* PE likely has been proposed to further increase the scoring system’s utility and permit safe exclusion from imaging in a larger subset of patients [4].

We sought to identify the incidence of PE in our practice, the prevalence of PE in the intermediate PTP subgroup and assess how use of a dichotomised PTP scoring system in conjunction with D-Dimer estimation altered the negative predictive value (NPV) of the assessment [10].

Methods

Data were prospectively collected for a consecutive cohort of patients referred for CTPA investigation of clinically suspected acute PE over a 3 year period between 2004 and 2007. The study population came from two large teaching hospitals within the same city, employing the same entrance criteria to the imaging pathway. All patients referred for investigation were either acute attendees at the emergency department or current hospital inpatients presenting with signs or symptoms of acute PE. This service review was performed following the implementation of new Trust guidelines for imaging in suspected cases of PE and initiated by the Trust Venous Thromboembolism Working Group.

A standard referral pro forma was completed by the referring clinician, detailing the patient’s name, age, location, presenting clinical history and a PTP score using the simplified Wells score (Table 1). Appropriately taken D-Dimer estimation and serum creatinine were also recorded; this information, along with patient clinical information, was available to the radiologist at the time of reporting. The PTP was documented to be low (Wells score <2), intermediate (score 2–6) or high (score >6); patients referred with low PTP and negative D-Dimer assay could be safely excluded from further imaging assessment [1, 4, 5]. A recent chest radiograph (within 24 h of symptoms or signs of acute PE) was reviewed to ensure alternative causes for presentation could be identified and evaluated to confirm that PE was still deemed “the most likely diagnosis”. All cases were discussed with either a registrar or consultant radiologist prior to acceptance for imaging.

The imaging pathway is detailed in Figure 1. Those patients referred for investigation of suspected acute PE who had concomitant leg signs, suggestive of possible deep venous thrombosis (DVT), underwent an initial leg venous Doppler study; a positive scan negated the need for further imaging evaluation. During the first year of data collection, lung perfusion studies were part of the imaging pathway, specifically for those patients with normal chest radiography but with either intermediate or high PTP. A normal perfusion scan excluded PE; where clinical doubt persisted or in the case of abnormal perfusion imaging the patient underwent a CTPA. Routine perfusion imaging was phased out of the CTPA referral pathway at our institution by the beginning of 2005, its ongoing routine use being reserved for patients with renal impairment or pregnancy (Figure 1).

Two D-Dimer assays were utilised during the study period: the IL test D-Dimer (Instrumentation Laboratory, Bedford, MA) (cut-off 230 ng ml⁻¹) and the Bio-Pool Autodimer (Trinity Biotech, Bray, Ireland) (cut-off 189 ng ml⁻¹). D-Dimer estimation was performed within 24 h of onset of clinical signs or symptoms. Retrospective dichotomisation of the patients into PE unlikely (equivalent of simplified Wells score ≤4) *vs* likely (score >4) was possible as the dichotomised version of the Wells score utilises the simplified Wells scoring criteria (Table 1).

Statistical analysis included assessment of NPV of D-Dimer in conjunction with the alternative PTP scoring systems and calculation of 95% confidence intervals (CIs) was carried out by a general method based on constant χ^2 boundaries [14].

Results

During the 3 year study period a total of 2531 patients were accepted for investigation of suspected acute PE. The age range was 16–98 years and there was a female preponderance (1471 females *vs* 1060 males).

The pre-test simplified Wells probability score was recorded in 2453 cases (96.92%) and of the 7 variables in the clinical decision rule (Table 1) the most frequently cited (1969 cases, 77.8% of the total population) was “an alternative diagnosis is less likely than PE”. A majority of cases, 77.6%, were deemed to be intermediate PTP (pre-test score 2–6).

A total of 2221 patients underwent CTPA examination during the study period. Of the 310 patients who did not undergo CTPA, 247 patients had isotope lung scanning alone and 63 patients had lower limb venous Doppler study only. Of the patients who underwent initial isotope

Figure 1. Referral pathway for CT pulmonary angiography (CTPA) investigation of patients with suspected acute pulmonary embolus at our institution. BP, blood pressure; CXR, chest radiography; DVT, deep vein thrombosis; HR, heart rate; PE, pulmonary emboli; PTP, pre-test probability.

perfusion imaging on the assessment pathway only 24% were excluded from further imaging, the remainder proceeded to CTPA.

Acute thromboemboli were confirmed in 575 cases, a prevalence of 22.72% of the scan population (age range 17–96 years). 63 of the confirmed cases were patients presenting with clinical signs of PE and associated symptoms suggestive of lower limb DVT; Doppler ultrasound of the lower leg confirmed DVT, thus negating the need for further imaging. The remaining 512 cases were confirmed with CTPA examination. Acute thromboembolic events were absent in the remaining 1956 cases, of which 3 were deemed to have inconclusive studies.

The incidence of acute thromboembolic events was greatest in the intermediate PTP subgroup. The PTP score was provided in 564 of the 575 confirmed cases, of which 425 scored an intermediate PTP score (73.9% of confirmed cases); 28 confirmed cases (4.9%) were deemed to have a low PTP. Using retrospective dichotomisation there were 178 cases where PE PTP was classed as unlikely and 386 cases where PE was thought likely.

An alternative diagnosis is less likely than PE was the most frequently cited variable in the PTP score and of the 1969 cases where this was cited 472 actually had an acute thromboembolic event (24.0%). 431 cases gained an intermediate PTP score by solely citing “an alternative diagnosis is less likely than PE”; of these cases only 76 actually

had a confirmed acute event (17.6%). Conversely, of 501 cases where a PTP score was documented but did not include 3 points for an alternative diagnosis is less likely than PE, 99 cases were demonstrated to have an acute thromboembolic event (20.0%).

D-Dimer estimation was provided in 84.08% of the scan population. It was not apparent until subsequent selected data review whether the D-Dimer had been appropriately taken, considering exclusion criteria such as prolonged bed rest, long-term warfarin therapy and renal impairment. 246 cases were documented to have a negative D-Dimer; 5 of these cases were removed from further evaluation as on review of notes it was found that they were on long-term warfarin when the D-Dimer was measured; warfarin falsely suppresses the D-Dimer level and thus calculation of D-Dimer in such cases is inaccurate and should be avoided. Of the five cases removed four did have evidence of acute PE: two were intermediate PTP score, the other two high PTP score. 148 of the remaining 241 patients with negative D-Dimer were scored as intermediate PTP. Two cases with negative D-Dimer were confirmed to have acute thromboembolic events: both intermediate PTP, one patient with concomitant leg signs had confirmed DVT, the other was a confirmed segmental PE.

Within the 1964 patients in the intermediate PTP subgroup 283 did not have a pre-test D-Dimer calculation;

a further 2 patients were known to be on long-term warfarin (confirmed PE cases). For the remaining 1679 patients in the intermediate PTP subgroup the overall NPV for negative D-Dimer and intermediate PTP was 98.9% (95% CI 96.3–99.7%) (Table 2). With retrospective dichotomisation there were 946 PE unlikely cases *vs* 1507 PE likely. Within the 946 PE unlikely subgroup there were 178 confirmed thromboembolic events; D-Dimer estimations were available for 823 of the 946 cases and were known in 166 of the 178 confirmed cases. 102 patients within the unlikely subgroup had negative pre-test D-Dimer assays (including one false negative D-Dimer); the resultant NPV for negative D-Dimer in the PE unlikely group was 99.0% (95% CI 94.8–99.8%).

Despite a low PTP and concomitant negative D-Dimer, a CTPA was performed in 13 cases where there was persistent clinical concern; all were negative for PE.

During the 3 year study period the incidence of confirmed cases of acute thromboembolic events was consistent and did not show significant annual variation: 23.3% during the first year, 21.8% second year and 23.3% during the final year.

Discussion

Multidetector CTPA is now established as the imaging modality of choice for evaluation of suspected PE. It provides a rapid, non-invasive assessment of the pulmonary arterial system down to the subsegmental level, with provision to assess for alternative causes of the patient's acute presentation [15]. It is imperative that diagnostic algorithms for assessment of PE be adhered to and optimised to ensure unnecessary imaging investigation is avoided, thus minimising avoidable patient radiation exposure and resultant cost implications. The BTS standards of care committee guidelines (2003) for the management of suspected acute PE state that "proper use of D-Dimer tests in the context of wise clinical assessment will result in radiological confirmation of PE in at least 25% of cases" [1]. Our results are encouraging with a PE prevalence of 22.72% of the scan population, and no significant year-on-year variation. At our institution, to date, we have only excluded patients with low PTP and negative D-Dimer from further imaging assessment.

Various PTP assessment tools exist. The BTS guidelines were based on a pragmatic clinical decision rule that included more risk factors than the originally described Wells score [16]. The PIOPED II investigators also recommend clinical assessment be made prior to any imaging, noting that "physicians experienced with pulmonary embolism have shown similar results with

empirical assessment and with clinical probability assessment scoring indexes" [5, 17]. Furthermore, in patients where the clinical PTP is non-high or unlikely, D-Dimer estimation should be obtained.

D-Dimers are fibrin degradation products released following the almost immediate fibrinolytic response to thrombus formation [18]. The role of D-Dimer estimation in patients with suspected acute thromboembolic events is its negative predictive power. An elevated D-Dimer unrelated to thrombus formation may be seen in patients with sepsis or malignancy, in association with markedly elevated C-reactive protein levels, following surgery, in elderly patients *per se* and those who have undergone prolonged hospitalisation [19–22]; in such patients reliance upon clinical evaluation and diagnostic imaging studies is more valuable. Conversely, the requesting clinician must be alert to occasions when the D-Dimer value may be falsely suppressed, including those receiving heparin treatment [23] or warfarin therapy [24–26], and measurement in patients receiving such anticoagulation should be viewed with caution.

Guidelines vary on who can safely be excluded from further diagnostic imaging in an intermediate or unlikely PTP subgroup in association with negative D-Dimer, predominantly due to a range of D-Dimer assays with variable sensitivities. Using Vidas D-Dimer assay or Tinaquant assay (Roche Diagnostica, Mannheim, Germany) the Christopher study group excluded the PE unlikely and normal D-Dimer subgroup from further imaging evaluation [4]; for the intermediate subgroup further diagnostic imaging can be avoided if a highly sensitive D-Dimer assay is used [13]: the BTS highlights Vidas and MDA as two such assays [1]. The safety of any protocol resulting in exclusion from further imaging is based on the ultimate incidence of thromboembolic events, *i.e.* the false negative rate [21]. Keeling et al [27] recommended that, for exclusion of further imaging in suspected DVT, the combined NPV of D-Dimer and PTP should be over 98%; Michiels et al [28] suggested that the post-test incidence of venous thromboembolism be less than 1%. A post-test incidence of 1–2% is similar to that following a negative catheter pulmonary angiogram (3 month rate 1.7%; 95% CI 1.0–2.7%) [29] or a negative CTPA (3 month incidence 1.3%, 95% CI 0.7–2.0%) [4, 21].

In our study, the overall NPV of D-Dimer in conjunction with the simplified Wells PTP score for PE within the intermediate PTP subgroup was 98.9% (95% CI 96.3–99.7%). With retrospective dichotomisation the NPV for the PE unlikely subgroup was 99.0% (95% CI 94.8–99.8%); no statistically significant difference in NPV was observed between the two subgroups. The 95% CI was seen to be wider in the PE unlikely group; however,

Table 2. Outcome of D-Dimer assays when combined with an intermediate pre-test probability simplified Wells score

	IL-test assay (n=794)	Bio-Pool assay (n=885)	Combined assays (n=1679)
Sensitivity (%) (95% CI)	100 (98.0–100)	99.0 (96.6–99.7)	99.5 (98.1–99.9)
Specificity (%) (95% CI)	12.8 (12.2–12.8)	15.7 (15.0–15.9)	14.3 (13.9–14.4)
Negative predictive value (%) (95% CI)	100 (95.5–100)	98.2 (93.7–99.5)	98.9 (96.3–99.7)
Positive predictive value (5%) (95% CI)	24.5 (24.0–24.5)	25.8 (25.1–26.0)	25.2 (24.8–25.2)

CI, confidence interval.

this group encompasses the low PTP (Wells score <2) patients, many of whom would have been excluded from further assessment at the time of initial clinical work-up and thus will not have been referred for radiological investigation, thus skewing the overall data for this subset. Gardiner et al [30] evaluated eight D-Dimer assays for the exclusion of DVT in conjunction with a Wells PTP (low or high), using the same cut-off values as we employed; the Bio-Pool autodimer had a NPV of 98% and IL test D-Dimer assay 100%, very similar to those achieved within the intermediate subgroup assessed in our study (Table 2).

Owing to the varied performance and sensitivities of D-Dimer assays they must be assessed on a local basis to determine sensitivity and specificity [1]. There is a lack of standardisation among the numerous commercially available assays; various assays have differing negative and positive predictive values. The negative predictive power for any given assay is higher in the outpatient setting than for inpatients and also alters according to the prevalence of thromboemboli in the study population [30]. The lack of assay standardisation highlights the necessity for individual units to assess D-Dimer sensitivity locally and establish appropriate cut-off values for their particular assay. The negative predictive power of both D-Dimers used in this study in conjunction with either the unlikely group as per the dichotomised scoring system or intermediate probability (simplified Wells) suggests excellent results.

An alternative diagnosis is less likely than PE was thought to be the case in 77.8% of the scan population, the actual confirmed acute thromboembolic event incidence was 22.7%; in many cases (431), this was the sole criterion upon which the patient's PTP was calculated (only 17.6% of whom actually had a confirmed PE/DVT). The wide discrepancy between the suspected principal clinical diagnosis and confirmed thromboembolic incidence demonstrates the difficulty in clinical assessment of this patient subgroup and supports the role of clinical evaluation being performed by at least an experienced middle-grade doctor [1]. Ironically, in 501 cases where a PTP was documented and an alternative diagnosis is less likely than PE was not thought to be the case, 20% of cases had confirmed acute thromboembolic events.

During the last decade CT has replaced ventilation/perfusion scintigraphy as the imaging modality of choice for investigation of suspected PE: CT being widely available, offering increased diagnostic sensitivity and demonstrating alternate causes for a patient's presentation [31]. Risk stratification and safe exclusion of patients from further imaging is paramount to ensure optimisation of resources and negate unnecessary CT examinations [32]. During this service evaluation, perfusion imaging was removed from routine use in our assessment pathway as only 24% of patients who underwent a perfusion scan were excluded from further imaging evaluation. The high rate of abnormal perfusion imaging in patients with a normal chest radiograph reflects the high incidence of lung disease secondary to occupational exposure and smoking in our region. In an attempt to expedite a definitive diagnosis, increase diagnostic provision "out-of-hours", minimise cost and in-line with the BTS guidelines which state "CTPA is now the recommended initial lung imaging modality for non-massive

PE" [1] the Trust algorithm was changed accordingly, as depicted in Figure 1.

In our Trust we have now moved to the dichotomised scoring method and, as such, patients with an appropriately taken negative D-Dimer estimation and unlikely PTP are not routinely further investigated unless there is persistent clinical concern. Had this policy been operational during the 3 year study period the number of CTPA investigations performed could have been reduced accordingly by up to 4% (102/2531), with the effect that the overall actual PE incidence in the scanned population would move toward the desired 25% suggested by the BTS (23.7%). Although we did not demonstrate a significant difference in NPV between exclusion at the unlikely or intermediate PTP in conjunction with a negative D-Dimer, we have adopted the lower exclusion score (unlikely) as follow-up data are not known for our study group and also an alternate D-Dimer assay is currently being trialled at our institution.

The data presented herein lack follow-up outcome measures. Subramaniam et al [33] however conducted a prospective management study and concluded that negative helical CTPA examination excludes clinically significant PE as a stand-alone imaging investigation; Quiroz et al [34] concluded in their systematic review that "the clinical validity of using a CT scan to rule out pulmonary embolism is similar to that reported for conventional pulmonary angiography". Moores et al [35], in their meta-analysis, reviewed a total of 4657 patients in 23 studies with negative CTPA who did not receive anticoagulation; the 3 month thromboembolic event rate was 1.4% (95% CI 1.1–1.8%), similar to that observed after negative conventional pulmonary angiography, and concluded that "it appears to be safe to withhold anticoagulation after negative CTPA results" [35].

Conclusion

Despite an apparent increase in demand for imaging of acute PE we demonstrate an essentially unaltered year-on-year imaging incidence during a 3 year time period, with an overall prevalence of 22.72%, slightly below the target figure of 25% recommended by the BTS. It is imperative that when D-Dimer assays are used in conjunction with a validated clinical decision rule to exclude patients from further imaging that a highly sensitive assay be employed. We demonstrate the high sensitivity and negative predictive power of the Bio-Pool and IL tests in conjunction with the Wells PTP tool, with no demonstrable difference between exclusion in the intermediate subgroup and the retrospectively dichotomised PE unlikely group. Dichotomisation of the Wells scoring system further simplifies the pre-test risk stratification and permits safe exclusion of more patients from additional imaging assessment than the traditional simplified Wells criteria, with resultant beneficial financial and resource implications.

Prior to implementation of new guidelines for exclusion of patients from further imaging, in suspected cases of acute PE, hospitals should validate the particular D-Dimer assay utilised at their institution [1].

References

- British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. *Thorax* 2003;58:470–83.
- Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. *Thromb Haemost* 2000;83:657–60.
- Heit JA, Melton LJ 3rd, Lohse CM, Petterson TM, Silverstein MD, Mohr DN, et al. Incidence of venous thromboembolism in hospitalized patients vs. community residents. *Mayo Clin Proc* 2001;76:1102–10.
- Van Belle A, Büller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW, et al. Christopher Study Investigators. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-Dimer testing, and computed tomography. *JAMA* 2006;295:172–9.
- Stein PD, Woodard PK, Weg JG, Wakefield TW, Tapson VF, Sostman HD, et al. PIOPED II Investigators. Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II Investigators. *Radiology* 2007;242:15–21.
- Cacciola RR, Cacciola E, Polosa R. D-Dimer in the diagnostic workup of suspected pulmonary embolism: additional clinical value of pre-test probability. *Chest* 2005;127:1467–8; Author reply 1468.
- Ghaye B, Dondelinger RF. When to perform CTA in patients suspected of PE? *Eur Radiol* 2008;18:500–9.
- Goekoop RJ, Steeghs N, Niessen RW, Jonkers GJ, Dik H, Castel A, et al. Simple and safe exclusion of pulmonary embolism in outpatients using quantitative D-Dimer and Wells' simplified decision rule. *Thromb Haemost* 2007;97:146–50.
- Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, et al. Derivation of a simple clinical model to categorize patient's probability of pulmonary embolism: increasing the models utility with the SimpliRED D-Dimer. *Thromb Haemost* 2000;83:416–420.
- Gibson NS, Sohne M, Kruip MJ, Tick LW, Gerdes VE, Bossuyt PM, et al. Christopher Study Investigators. Further validation and simplification of the Wells clinical decision rule in pulmonary embolism. *Thromb Haemost* 2008;99:229–34.
- Kruip MJ, Slob MJ, Schijen JH, van der Heul C, Büller HR. Use of a clinical decision rule in combination with D-Dimer concentration in diagnostic workup of patients with suspected pulmonary embolism: a prospective management study. *Arch Intern Med* 2002;162:1631–5.
- Ten Wolde M, Hagen PJ, Macgillavry MR, Pollen IJ, Mairuhu AT, Koopman MM, et al. Advances in New Technologies Evaluating the Localization of Pulmonary Embolism Study Group. Non-invasive diagnostic work-up of patients with clinically suspected pulmonary embolism; results of a management study. *J Thromb Haemost* 2004;2:1110–17.
- Roy PM, Colombet I, Durieux P, Chatellier G, Sors H, Meyer G. Systematic review and meta-analysis of strategies for the diagnosis of suspected pulmonary embolism [Review]. *BMJ* 2005;331:259.
- Fleiss JL. Statistical methods for rates and proportions (2nd edn). New York, NY: John Wiley & Sons, 1981.
- Remy-Jardin M, Pistolesi M, Goodman LR, Gefter WB, Gottschalk A, Mayo JR, et al. Management of suspected acute pulmonary embolism in the era of CT angiography: a statement from the Fleischner Society. *Radiology* 2007;245:315–29.
- Wells PS, Ginsberg JS, Anderson DR, Kearon C, Gent M, Turpie AG, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. *Ann Intern Med* 1998;129:997–1005.
- Wicki J, Perneger TV, Junod AF, Bounameaux H, Perrier A. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. *Arch Intern Med* 2001;161:92–97.
- Fancher TL, White RH, Kravitz RL. Combined use of rapid D-Dimer testing and estimation of clinical probability in the diagnosis of deep vein thrombosis: systematic review. *BMJ* 2004;329:821.
- Brotman DJ, Segal JB, Jani JT, Petty BG, Kickler TS. Limitations of D-Dimer testing in unselected inpatients with suspected venous thromboembolism. *Am J Med* 2003;114:276–82.
- Wilson DB, Gard KM. Evaluation of an automated, latex-enhanced turbidimetric D-Dimer test (advanced D-Dimer) and usefulness in the exclusion of acute thromboembolic disease. *Am J Clin Pathol* 2003;120:930–7.
- Wells PS. Integrated strategies for the diagnosis of venous thromboembolism. *J Thromb Haemost* 2007;5:41–50.
- Gaffney PJ, Creighton LJ, Callus M, Thorpe R. Monoclonal antibodies to cross linked fibrin degradation products (XL-FDP). II. Evaluation in a variety of clinical conditions. *Br J Haematol* 1988;68:91–6.
- Siragusa S, Terulla V, Pirrelli S, Porta C, Falaschi F, Anastasio R, et al. A rapid D-Dimer assay in patients presenting at the emergency room with suspected acute venous thrombosis: accuracy and relation to clinical variables. *Haematologica* 2001;86:856–61.
- MacCallum PK, Rudnicka AR, Rumley A, Meade TW, Lowe GD. Low-intensity warfarin reduces thrombin generation and fibrin turnover, but not low-grade inflammation, in men at risk of myocardial infarction. *Br J Haematol* 2004;127:448–50.
- Lip GY, Lowe GD, Metcalfe MJ, Rumley A, Dunn FG. Effects of warfarin therapy on plasma fibrinogen, von Willebrand factor, and fibrin D-Dimer in left ventricular dysfunction secondary to coronary artery disease with and without aneurysms. *Am J Cardiol* 1995;76:453–8.
- Li-Saw-Hee FL, Blann AD, Lip GY. Effects of fixed low-dose warfarin, aspirin-warfarin combination therapy, and dose-adjusted warfarin on thrombogenesis in chronic atrial fibrillation. *Stroke* 2000;31:828–33.
- Keeling DM, Mackie IJ, Moody A, Watson HG. The Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. The diagnosis of deep vein thrombosis in symptomatic outpatients and the potential for clinical assessment and D-Dimer assays to reduce the need for diagnostic imaging. *Br J Haematol* 2004;124:15–25.
- Michiels JJ, Gadisseur A, van der Planken M, Schroyens W, De Maeseneer M, Hermesen JT, et al. Different accuracies of rapid enzyme-linked immunosorbent, turbidimetric, and agglutination D-Dimer assays for thrombosis exclusion: impact on diagnostic work-ups of outpatients with suspected deep vein thrombosis and pulmonary embolism. *Semin Thromb Hemost* 2006;32:678–93.
- Van Beek EJ, Brouwerst EM, Song B, Stein PD, Oudkerk M. Clinical validity of a normal pulmonary angiogram in patients with suspected pulmonary embolism: a critical review. *Clin Radiol* 2001;56:838–42.
- Gardiner C, Pennaneac'h C, Walford C, Machin SJ, Mackie IJ. An evaluation of rapid D-Dimer assays for the exclusion of deep vein thrombosis. *Br J Haematol* 2005;128:842–8.
- Burge AJ, Freeman KD, Klapper PJ, Haramati LB. Increased diagnosis of pulmonary embolism without a corresponding decline in mortality during the CT era. *Clin Radiol* 2008;63:381–6.
- Goldhaber SZ. Multislice computed tomography for pulmonary embolism: a technological marvel. *N Engl J Med* 2005;352:1812–14.

33. Subramaniam RM, Blair D, Gilbert K, Coltman G, Sleight J, Karalus N. Withholding anticoagulation after a negative computed tomography pulmonary angiogram as a stand-alone imaging investigation: a prospective management study. *Intern Med J* 2007;37:624–30.
34. Quiroz R, Kucher N, Zou KH, Kipfmüller F, Costello P, Goldhaber SZ, et al. Clinical validity of a negative computed tomography scan in patients with suspected pulmonary embolism: a systematic review. *JAMA* 2005; 293:2012–17.
35. Moores LK, Jackson WL Jr, Shorr AF, Jackson JL. Meta-analysis: outcomes in patients with suspected pulmonary embolism managed with computed tomographic pulmonary angiography. *Ann Intern Med* 2004;141:866–74.