National Institute for Health and Care Excellence

Final

Venous thromboembolic diseases: diagnosis, management and thrombophilia testing

[A] Evidence reviews for D-dimer testing in the diagnosis of deep vein thrombosis and pulmonary embolism

NICE guideline NG158

Evidence reviews underpinning recommendations 1.1.12 to 1.1.14 in the guideline

March 2020

Final version

These evidence reviews were developed by the NICE Guideline Updates Team

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In people with suspected DVT, what is the diagnostic accuracy of age-adjusted D-dimer tests compared with D-dimer tests without age adjustment?

Introduction

The NICE guideline on venous thromboembolism (VTE) does not currently consider the use of age-adjusted D-dimer testing as an alternative to standard, non age-adjusted, D-dimer testing. D-dimer naturally increases within the body with age resulting in a higher rate of false-positives in older patients. Age adjusted D-dimer testing increases the threshold for a positive D-dimer reading in accordance with a person's age and therefore has cost-saving potential by reducing the number of people that unnecessarily undergo further investigation. This update will review the diagnostic accuracy of age-adjusted D-dimer tests compared with D-dimer tests without age adjustment in people with suspected DVT.

This review identified studies that fulfilled the conditions specified in Table 1. For full details of the review protocol, see appendix A.

PICO table

Table 1 PICO table for age -adjusted D-dimer testing for suspected DVT

Population	Adults (aged 18+) with clinically suspected DVT
Intervention	**Diagnostic accuracy studies:** • Age-adjusted D-dimer test • D-dimer test (without age adjustment – fixed test threshold) **Test and Treat RCTs:** • Age-adjusted D-dimer test
Comparator	**Diagnostic accuracy studies:** • Reference standard: Ultrasound, venography, MRI scan, CT scan, VTE event for 3 months or more follow-up **Test and treat RCTs:** • D-dimer test (without age adjustment – fixed test threshold)
Outcomes	**Diagnostic accuracy studies:** • Diagnostic accuracy metrics: Sensitivity/specificity, Positive and negative likelihood ratios **Test and treat RCTs:** • All-cause mortality • VTE-related mortality • Recurrence of VTE • Length of hospital stay

	• Quality of life
	• Post-thrombotic syndrome
	• Adverse events
	  ○ Total serious adverse events
	  ○ Major bleeding
	  ○ Clinically relevant non-major bleeding
	  ○ Intracranial haemorrhage
	  ○ Liver injury

Methods and process

This evidence review was developed using the methods and process described in developing NICE guidelines: the manual (2014). Methods specific to this review question are described in the review protocol in appendix A and the methods section in appendix B.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

Protocol deviation

Priority screening was not used for this review. All references returned by the search were screened at title and abstract level.

Clinical evidence

Included studies

A single systematic search was carried out for the 4 review questions in this evidence review to identify diagnostic accuracy studies, test-and-treat randomised controlled trials and systematic reviews of these studies, which found 4,342 references (see appendix C for literature search strategy). Evidence included in the original guideline was also reviewed, which added 14 references. In total, 4,356 references were identified for screening at title and abstract level. Based on title and abstract, 4,171 references were excluded and 168 references were ordered for full text screening.

Of the 168 references screened as full texts, 45 references were included for the 4 review questions based on their meeting the inclusion criteria specified in the review protocol (appendix A). Of the 45 included references, 3 presented data on age-adjusted D-dimer testing for suspected deep vein thrombosis and met the inclusion criteria for this review.

Note that the 22 included papers for the review question on point-of-care testing for suspected deep vein thrombosis also met the inclusion criteria for this review, as they included evidence on D-dimer tests that were not adjusted for age. The committee considered this evidence alongside that presented here.

A second set of searches, using the original search strategies, were conducted at the end of the guideline development process to capture papers published whilst the guideline was being developed. These searches returned 6,272 references in total for all the questions included in the update, and these were screened based on title and abstract. 30 references were identified for full text screening for the D-dimer review questions and 4 met the criteria for inclusion in this group of reviews, however, no additional relevant references were found that were relevant for this particular review question.

The clinical evidence study selection is presented as a diagram in appendix D.

For the full evidence tables and GRADE profiles for included studies, please see appendix E and appendix G respectively. The references of individual included studies are given in appendix K.

Excluded studies

The reasons for excluding studies at the full text stage are detailed in appendix J and the full references are listed in appendix K.

Summary of clinical studies included in the evidence review

The characteristics of the 3 studies that looked at age-adjusted D-dimer tests in suspected DVT are summarised in Table 2 and the relevant references from the review question on point-of-care testing for suspected deep vein thrombosis are summarised in Table 6, Table 7 and Table 8.

Table 2 Studies looking at age-adjusted D-dimer tests in suspected DVT

Author (year)	Study details	Index test	Reference standard
Gomez-Jabalera (2017)	Study type • Prospective cohort study Sample characteristics • Sample size 138 • % female 60.5% female • Mean age (SD) 71.6 years • % pre-test probability Well score low = 69.6% intermediate = 21% High = 9.4%.	• Laboratory D-dimer Hemos IL-500 • Age-adjusted D-dimer tested several formulas: Age x 10 ug/L Age x 15 ug/L Age x 20 ug/L Age x 25 ug/L Age x 30 ug/L We reported data for age x 10 ug/L as this is in line with formulas typically used in other studies.	• Ultrasonography whole leg compression ultrasonography of symptomatic leg by a B mode and pulsed Doppler in the common femoral vein, the popliteal vein, calf veins and great and small saphenous veins. The sonographic scanner used was a linear array at 5–7.5MHz
Oude (2015)	Study type • Prospective cohort study Sample characteristics • Sample size 290 • % female 60.3% • Mean age (SD) 56.6 (18.1-87.9) years	• Laboratory D-dimer Vidas (also reported innovance [on both CA-1500 and BCS systems separately), ACL-TOP, Tina-quant and Liatest but these were not extracted for this review) • Age-adjusted D-dimer Quantitative lab-based test: Vidas (also reported innovance [on both CA-1500 and BCS systems separately), ACL-TOP, Tina-quant and Liatest but these were not extracted for this review) Quantitative POC: pathfast (AQT90 also reported but was not	• Ultrasonography Real time B-mode compression ultrasonography with a 9 mHz linear array sonographic scanner.

Author (year)	Study details	Index test	Reference standard
		extracted for this review) • Point-of-care D-dimer Quantitative: Pathfast (also reported AQT90 but was not extracted for this review) Qualitative test: Simplify	
Prochaska (2017)	Study type • Prospective cohort study Sample characteristics • Sample size 500 • % female 55.6 • Mean age (SD) Median age 60.0 (interquartile range [IQR] 45.0, 72.0) • % pre-test probability Low-to-moderate (Wells score 0–2): 84.4 High (Wells score >2): 15.6 • % people with cancer 17.0	• Laboratory D-dimer Innovance from 04/2013 to 07/2014 and HemosIL HS from 08/2014 to the end of study. Cut-off: 0.5 mg/L fibrinogen equivalent unit (FEU) • Age-adjusted D-dimer age-dependent threshold applied to patients over 60 years (age/100mg/L)	• Ultrasound Compression duplex ultrasound

See appendix E for full evidence tables for the included studies.

Quality assessment of clinical studies included in the evidence review

See evidence tables in appendix E for quality assessment of individual studies, appendix F for forest plots and appendix G for full GRADE tables. Please refer to the evidence statement section for an overall summary of the evidence.

Economic evidence

Included studies

A single search was conducted to cover all review questions in this chapter. This search returned 817 records, of which 800 were excluded on title and abstract for this review question. The remaining 17 papers were screened using a review of the full text, and all were excluded.

An additional search was conducted at the end of the guideline development process to capture economic evidence published while the guideline was being developed. This was conducted as a single re-run search covering all questions in the guideline. This search returned 2,013 records in total, all of which were excluded on title and abstract for this review question.

Excluded studies

Details of the studies excluded at full-text review are given in appendix J, along with reasons for their exclusion. The full references are listed in appendix K.

Economic model

No *de novo* economic modelling was conducted for this review question on age-adjustment of D-dimer testing.

Evidence statements

Note that quality ratings were attached to likelihood ratios but not to sensitivity and specificity analyses because clinical decision thresholds were specified on this scale.

Main analyses

- Evidence suggests that a **negative** D-dimer result indicates a **moderate decrease** in the probability that a person with clinically suspected deep vein thrombosis has a deep vein thrombosis. This is the case irrespective of whether the result is adjusted for age (LR-=0.22 [0.08 to 0.47]) or unadjusted (LR-=0.22 [0.03 to 0.79]). (Low to moderate quality evidence from 3 prospective studies with 620 participants comparing age adjusted and unadjusted D-dimer tests)
- Evidence suggests that a **positive** D-dimer result indicates a **slight increase** in the probability that a person with clinically suspected deep vein thrombosis has a deep vein thrombosis. This effect is marginally larger when the result is adjusted for age (LR+=1.64 [1.25 to 2.18]) than unadjusted (LR+=1.35 [1.03 to 1.93]), although the confidence intervals overlap. (Low to moderate quality evidence from 3 prospective studies with 620 participants comparing age adjusted and unadjusted D-dimer tests)
- Evidence suggests that age-adjusted D-dimer tests offer increased specificity (44% [0.31, 0.57] vs 27% [0.12, 0.49]) but marginally reduced sensitivity (91% [0.84, 0.96] vs 96% [0.89, 0.99]) compared with unadjusted D-dimer tests, although the confidence intervals overlap. (Evidence from 3 prospective studies with 620 participants comparing age adjusted and unadjusted D-dimer tests)

Subgroup analyses

- Subgroup analyses in people with low-risk clinically suspected deep vein thrombosis suggests that a **negative** D-dimer result indicates a **moderate decrease** in the probability that a person with clinically suspected deep vein thrombosis (according to a 3-level Wells score) has a deep vein thrombosis. This is the case irrespective of whether the result is adjusted for age (LR-=0.26 [0.02 to 3.60]) or unadjusted (LR-=0.41 [0.03 to 5.87]). (Very low quality evidence from 1 prospective study with 96 participants comparing age adjusted and unadjusted D-dimer tests).
- Subgroup analyses in people with low-risk clinically suspected deep vein thrombosis suggests that a **positive** D-dimer result indicates a **slight increase** in the probability that a person with clinically suspected deep vein thrombosis has a deep vein thrombosis. This is the case irrespective of whether the result is adjusted for age (LR+=1.48 [1.06, 2.07]) or unadjusted (LR+=1.19 [0.87 to 1.63]). (Low to very-low quality evidence from 1 prospective study with 96 participants comparing age adjusted and unadjusted D-dimer tests).
- Subgroup analyses in people with moderate-risk clinically suspected deep vein thrombosis suggests that a **negative** D-dimer result indicates a **large decrease** in the probability that a person with clinically suspected deep vein thrombosis (according to a 3-level Wells score) has a deep vein thrombosis. This is the case irrespective of whether the result is adjusted for age (LR-=0.10 [0.01, 1.54]) or unadjusted (LR-=0.16 [0.01 to

2.59]). (Very low quality evidence from 1 prospective study with 29 participants comparing age adjusted and unadjusted D-dimer tests).

- Subgroup analyses in people with moderate-risk clinically suspected deep vein thrombosis suggests that a **positive** D-dimer result indicates a **slight increase** in the probability that a person with clinically suspected deep vein thrombosis (according to a 3-level Wells score) has a deep vein thrombosis. This is the case irrespective of whether the result is adjusted for age (LR+=1.90 [1.21, 2.98]) or unadjusted (LR+=1.38 [0.99, 1.89]). (Low quality evidence from 1 prospective study with 29 participants comparing age adjusted and unadjusted D-dimer tests).

The committee's discussion of the evidence

The joint discussion section for the use of age-adjusted D-dimer tests in people with DVT and PE is below in the review for age-adjusted D-dimer tests in people with PE.

Age-adjusted D-dimer testing for suspected pulmonary embolism (PE)

Review question

In people with suspected PE, what is the diagnostic accuracy of age-adjusted D-dimer tests compared with D-dimer tests without age adjustment?

Introduction

The NICE guideline on venous thromboembolism (VTE) does not currently consider the use of age-adjusted D-dimer testing as an alternative to standard, non age-adjusted, D-dimer testing. D-dimer naturally increases within the body with age resulting in a higher rate of false-positives in older patients. Age adjusted D-dimer testing increases the threshold for a positive D-dimer reading in accordance with a person's age and therefore has the potential to reduce the number of people that unnecessarily undergo further investigation. This update will review the diagnostic accuracy of age-adjusted D-dimer tests compared with D-dimer tests without age adjustment in people with suspected PE.

This review identified studies that fulfilled the conditions specified in Table 3. For full details of the review protocol, see appendix A.

PICO table

Table 3 PICO table for age -adjusted D-dimer testing for suspected PE

Population	Adults (aged 18+) with clinically suspected PE
Intervention	**Diagnostic accuracy studies:** • Age-adjusted D-dimer test • D-dimer test (without age adjustment – fixed test threshold) **Test and Treat RCTs:** • Age-adjusted D-dimer test
Comparator	**Diagnostic accuracy studies:** • Reference standard: CT scan, MRI scan, VQ scan, pulmonary angiography, VTE event during 3 months or more follow-up **Test and treat RCTs:** • D-dimer test (without age adjustment – fixed test threshold)
Outcomes	**Diagnostic accuracy studies:** • Diagnostic accuracy metrics: Sensitivity/specificity, Positive and negative likelihood ratios **Test and treat RCTs:** • All-cause mortality • VTE-related mortality • Recurrence of VTE • Length of hospital stay

	• Quality of life
	• Chronic thromboembolic pulmonary hypertension (CTEPH)
	• Adverse events
	  ○ Total serious adverse events
	  ○ Major bleeding
	  ○ Clinically relevant non-major bleeding
	  ○ Intracranial haemorrhage
	  ○ Liver injury

Methods and process

This evidence review was developed using the methods and process described in developing NICE guidelines: the manual (2014). Methods specific to this review question are described in the review protocol in appendix A and the methods section in appendix B.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

Protocol deviations

The protocol specified that only prospective studies were to be included in the review. However, no prospective studies that met the inclusion criteria were found. The committee agreed that retrospective studies that directly compared age-adjusted versus unadjusted D-dimer tests within the same study should also be included.

Priority screening was not used for this review. All references returned by the search were screened at title and abstract level.

Clinical evidence

Included studies

A single systematic search was carried out for the 4 review questions in this evidence review to identify diagnostic accuracy studies, test-and-treat randomised controlled trials and systematic reviews of these studies, which found 4,342 references (see appendix C for literature search strategy). Evidence included in the original guideline was also reviewed, which added 14 references. In total, 4,356 references were identified for screening at title and abstract level. Based on title and abstract, 4,171 references were excluded and 168 references were ordered for screening based on their full texts.

Of the 168 references screened as full texts, 45 references were included for the 4 review questions based on their meeting the inclusion criteria specified in the review protocol (appendix A). Of the 45 included references, 9 presented data on age-adjusted D-dimer testing for suspected pulmonary embolism and met the inclusion criteria for this review.

A second set of searches, using the original search strategies, were conducted at the end of the guideline development process to capture papers published whilst the guideline was being developed. These searches returned 6,272 references in total for all the questions included in the update, and these were screened based on title and abstract. 30 references were identified for full text screening for the D-dimer review questions and 4 met the criteria for inclusion in this review question. Therefore, in total, 13 references met the inclusion criteria for this review.

The clinical evidence study selection is presented as a diagram in appendix D.

Note that the 21 included papers for the review question on point-of-care testing for suspected pulmonary embolism also met the inclusion criteria for this review, as they included evidence on D-dimer tests that were not adjusted for age. The committee considered this evidence alongside that presented here.

For the full evidence tables and GRADE profiles for included studies, please see appendix E and appendix G respectively. The references of individual included studies are given in appendix K.

Excluded studies

The reasons for excluding studies at the full text stage are detailed in appendix J and the full references are listed in appendix K.

Summary of clinical studies included in the evidence review

The characteristics of the 14 studies that looked at age-adjusted D-dimer tests in suspected PE are summarised in Table 4 and the relevant references from the review question on point-of-care testing for suspected PE are summarised in Table 11 and Table 12.

Table 4 Studies looking at age-adjusted D-dimer tests in suspected PE

Author (year)	Study details	Index test	Reference standard
Dutton (2018)	Study type • Retrospective cohort study Sample characteristics • Sample size 329 • Median age (IQR) People with PE: 71 (64-82) People without PE: 71 (63-79) Study Location • UK	• Laboratory D-dimer Cut-off: 230 ng/mL ng/mL • Age-adjusted D-dimer; Cut-off: patient's age x 5 ng/mL	• CTPA or V/Q scan
Flores (2016)	Study type • Prospective cohort study Sample characteristics • Sample size 362 • Mean age (SD) People with PE: 65 (18) People without PE: 63 (15) • % pre-test probability Wells score People with PE Low: 21.4 Moderate: 54.1	• Laboratory D-dimer VIDAS; Cut-off: 500 ng/mL • Age-adjusted D-dimer VIDAS; Cut-off: patient's age x 10 ng/mL	• Composite reference standard

Author (year)	Study details	Index test	Reference standard
	High: 24.5 People without PE Low: 53.8 Moderate: 43.5 High: 2.6 Study Location • Spain		
Gupta (2014)	Study type • Retrospective cohort study Sample characteristics • Sample size 1055 • Mean age (SD) 52.8 (range 18 to 96) • % pre-test probability Wells score: median 4.5 (range 0 to 12.5) Study Location • US	• Laboratory D-dimer STA-Liatest; Cut-off: 500 ng/mL • Age-adjusted D-dimer STA-Liatest; Cut-off: age in years × 10 ng/mL	• Pulmonary angiography
Kozlowska (2017)	Study type • Retrospective cohort study Sample characteristics • Sample size 321 • Mean age (SD) 74.2 (range 51 to 101) Study Location • Poland	• Laboratory D-dimer VIDAS; Cut-off: 500 ng/ml • Age-adjusted D-dimer VIDAS; Cut-off: patient's age (years) × 10 ng/ml, for patients above the age of 50 years	• Composite reference standard
Kubak (2016)	Study type • Retrospective cohort study Sample characteristics • Sample size 822 • Mean age (SD) 64 (range 16 to 99) Study Location • Norway	• Laboratory D-dimer HemosIL D-dimer HS; Cut-off: 0.5 mg/L • Age-adjusted D-dimer HemosIL D-dimer HS; Cut-off: age/100 mg/L	• Pulmonary angiography
Laruelle (2013)	Study type • Retrospective cohort study Sample characteristics • Sample size	• Laboratory D-dimer Innovance; Cut-off: 0.5 µg/ml • Age-adjusted D-dimer Innovance; Cut-off: age in years multiplied by	• Composite reference standard

Author (year)	Study details	Index test	Reference standard
	165 • Mean age (SD) 83 (range 75 to 102) • % pre-test probability Geneva score Low: 24 Intermediate: 70 High: 6 Study Location • Belgium	0.01 µg/ml/year	
Lim (2018)	Study type • Retrospective cohort study Sample characteristics • Sample size 176 • Mean age (SD) 58.5 (16.8) Study Location • Austrailia	• Laboratory D-dimer normal <230 ng/mL • Age-adjusted D-dimer Cut-off: age x 5 ng/mL	• Pulmonary angiography
Parks (2018)	Study type • Retrospective cohort study Sample characteristics • Sample size 4845 • Mean age (SD) 52.2 Study Location • USA	• Laboratory D-dimer Hemosil D-Dimer HS automated latex enhanced immunoassay; Cut-off: normal <230 ng/mL • Age-adjusted D-dimer Hemosil D-Dimer HS automated latex enhanced immunoassay; Cut-off: age x 5 ng/mL	• CTPA
Polo (2014)	Study type • Retrospective cohort study Sample characteristics • Sample size 481 • Mean age (SD) 73.0 (16.1) Study Location • Italy	• Laboratory D-dimer Innovance; Cut-off: normal <490 ng/mL • Age-adjusted D-dimer Innovance; Cut-off: age x 10 ng/mL	• Pulmonary angiography
Senior (2019)	Study type • Retrospective cohort study	• Laboratory D-dimer HemosIL HS 500; Cut-off: positive result ≥500 ng/mL	• imaging confirmed diagnosis within 30 days

Author (year)	Study details	Index test	Reference standard
	Sample characteristics • Sample size 6655 • Mean age (SD) 67.3 (11.7) Study Location • Canada	• Age-adjusted D-dimer HemosIL; Cut-off: age x 10 ng/mL	
Sharp (2016)	Study type • Retrospective cohort study Sample characteristics • Sample size 31094 • Mean age (SD) 65.0 (10.9) Study Location • US	• Laboratory D-dimer Immunoturbidimetric assay; Cut-off: 500 ng/dL • Age-adjusted D-dimer Immunoturbidimetric assay; Cut-off: patient's age in years x 10	• Composite reference standard
Sheele (2018)	Study type • Retrospective cohort study Sample characteristics • Sample size 3117 • Mean age (SD) 65.9 (11.8) Study Location • US	• Laboratory D-dimer D-dimer type was not reported; Cut-off: positive result ≥500 µg FEU/l • Age-adjusted D-dimer D-dimer type was not reported; Cut-off: age x 10	• CT scan
Woller (2014)	Study type • Retrospective cohort study Sample characteristics • Sample size 923 • Mean age (SD) 67 (11.5) Study Location • US	• Laboratory D-dimer Stago latex agglutination; Cut-off: <500 ng/mL • Age-adjusted D-dimer Stago latex agglutination; Cut-off: patient age x 10 ng/mL	• Pulmonary angiography

See appendix E for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See evidence tables in appendix E for quality assessment of individual studies, appendix F for forest plots and appendix G for GRADE tables. Please refer to the evidence statement section for an overall summary of the evidence.

Economic evidence

Included studies

A single search was conducted to cover all review questions in this chapter. This search returned 817 records, of which 800 were excluded on title and abstract for this review question. The remaining 17 papers were screened using a review of the full text, and all were excluded.

An additional search was conducted at the end of the guideline development process to capture economic evidence published while the guideline was being developed. This was conducted as a single re-run search covering all questions in the guideline. This search returned 2,013 records in total, all of which were excluded on title and abstract for this review question.

Excluded studies

Details of the studies excluded at full-text review are given in Appendix J, along with reasons for their exclusion. The full list of references can be found in Appendix K.

Economic model

No *de novo* economic modelling was conducted for this review question on age-adjustment of D-dimer testing.

Evidence statements

Note that quality ratings were attached to likelihood ratios but not to sensitivity and specificity analyses because clinical decision thresholds were specified on this scale.

- Evidence suggests that a **negative** D-dimer result indicates a **large decrease** in the probability that a person with clinically suspected pulmonary embolism has a pulmonary embolism. This is the case irrespective of whether the result is adjusted for age (LR-=0.14 [0.11 to 0.18]) or unadjusted (LR-=0.12 [0.07 to 0.21]). (Low quality evidence from 13 retrospective studies with 48,379 participants comparing age adjusted and unadjusted D-dimer tests)
- Evidence suggests that a **positive** D-dimer result indicates a **slight increase** in the probability that a person with clinically suspected pulmonary embolism has a pulmonary embolism. This effect is marginally larger when the result is adjusted for age (LR+=1.38 [1.20 to 1.66]) than unadjusted (LR+=1.16 [1.07 to 1.31]), although the confidence intervals overlap.(Low quality evidence from 13 retrospective studies with 48,379 participants comparing age adjusted and unadjusted D-dimer tests)
- Evidence suggests that age-adjusted D-dimer tests offer marginally reduced sensitivity (96% [0.94, 0.97] vs 98% [0.98, 0.99]) and marginally increased specificity (30% [0.19, 0.43] vs 14% [0.08, 0.25]) compared to unadjusted D-dimer tests, although the confidence intervals for specificity overlap. (Evidence from 13 retrospective studies with up to 48,379 participants comparing age adjusted and unadjusted D-dimer tests)

The committee's discussion of the evidence

This section contains the joint committee discussion for the age-adjusted D-dimer recommendations for DVT and PE. The evidence review for the use of age-adjusted D-dimer in people with DVT is above.

Interpreting the evidence

The outcomes that matter most

Deep vein thrombosis and pulmonary embolism

The committee discussed the impact that true positive, false positive, true negative and false negative D-dimer results have on patients. People with true positive results go on to receive imaging (usually ultrasound) to confirm a DVT and/or PE diagnosis and then receive appropriate anti-coagulation therapy, people with false positive results undergo unnecessary imaging which may result in increased unnecessary anxiety and healthcare expense. People with false positive results may also undergo unnecessary anticoagulant treatment in the interim if imaging is not immediately available which may have serious side-effects, including major bleeding, although the committee agreed that the period of time that people received interim anticoagulant treatment was likely to be short in most cases. People with true negative results are correctly discharged and reassured that they do not have DVT, and people with false negative results are incorrectly discharged and go untreated with the risk of disease progression and complications, including death. If DVT is untreated this increases the risk of post-thrombotic syndrome and ulceration. A proportion of people with DVT may develop PE, which is associated with extra morbidity and mortality.

The committee were concerned with the potential for any test to increase false negative rates; small increases in false negatives are undesirable in a D-dimer test, meaning that the sensitivity of D-dimer tests is important. The committee considered that specificity is also important to avoid unnecessary anxiety, interim treatment and further imaging. However, the committee valued sensitivity (and negative LRs which are most affected by sensitivity) over specificity (and positive LRs) as it is of great importance that those people with VTE do not go undiagnosed.

The quality of the evidence

Deep vein thrombosis

The evidence comparing age-adjusted versus unadjusted D-dimer tests was of low to moderate quality and consisted of three prospective studies which all compared adjusted and unadjusted tests directly. Additionally, the committee advised that the reference standards used in these studies (ultrasonography and venography) are the best available tests yet are still not 100% accurate and this must be taken into account when considering diagnostic accuracy. However, it was agreed by the committee that the data were useful for informing decisions as the studies were prospective and directly compared age adjusted and unadjusted tests in the same participants, so biases are likely to be similar for both measures.

Although there was inconsistency in the data between studies, the committee agreed that the absolute diagnostic accuracy values were of less importance than those relative effects of age-adjusted versus unadjusted, and as these relative effects were comparable between studies it was agreed that the evidence should not be downgraded for inconsistency.

Pulmonary embolism

The committee noted that the quality of the evidence for age-adjusted versus unadjusted D-dimer tests was low, consisting of only retrospective studies and it was common for only those participants that were initially given a D-dimer test to go on to receive imaging. Consequently, those participants included in the study were likely to have been limited to those with a high clinical suspicion of PE and/or a positive D-dimer, because these people are more likely to receive imaging in clinical practice, rather than the population of interest to this review (all people suspected of PE). Additionally, it is unlikely that any of these studies were blinded (the reference standards were interpreted with knowledge of the D-dimer result).

However, it was agreed by the committee that although the data was retrospective it was still useful for informing decisions as the studies directly compared age adjusted and unadjusted tests in the same participants, so biases are likely to be similar for both measures. The retrospective nature meant that all studies included in the review were of high risk of bias. Additionally, there was a high level of inconsistency for the negative likelihood ratio and a very high level of inconsistency in the positive likelihood ratio for both age adjusted and unadjusted tests (LR- I^2 38.6%, 41.7%; LR+ I^2 99.6%, 99.8% respectively), meaning that there was also significant variability in the findings of the studies included in this review. However, although I^2 was greater than the specified limits, the committee were concerned with the relative difference between age-adjusted and unadjusted tests and this relative difference was homogenous between studies and so the results of these tests were not downgraded for inconsistency.

Benefits and harms

Deep vein thrombosis

The evidence suggested that age-adjusted D-dimer tests had marginally reduced sensitivity and increased specificity. The committee agreed the importance of avoiding false negatives and therefore the need for high sensitivity, however they noted that the confidence intervals for both the sensitivity and specificity estimates overlap and that the point estimates for sensitivity were much closer (96% versus 91%) than the point estimates for specificity (44% versus 27%). From a total sample of 473, this equated to an increase in 6 false negatives but a decrease in 63 false positives, for age-adjusted compared to unadjusted tests. Additionally, the committee also noted that the evidence was from just three studies and there was some uncertainty due to the relatively wide 95%CIs. However, both age-adjusted and unadjusted tests had very similar negative likelihood ratios (with the same point estimate) that indicated a moderate decrease in likelihood of DVT, suggesting similar efficacy when used to rule out DVT. Based on the clinical evidence and consideration of the costs to the individual and system of false negative and false positive results (see the section on cost effectiveness and resource use below), the committee agreed that the potential for a small increase in false negatives was justified by the benefits associated with the much larger reduction in false positives. This reduction in false positives was expected to lead to a reduction in anxiety, unnecessary imaging and interim anticoagulant treatment, which is associated with risk of major bleeding and other harms, and cost.

As the studies included in this review only applied age-adjusted formulas for those participants aged over 50 years, the committee agreed that the recommendations should also be restricted to those over 50 years old, in the absence of evidence for other age groups. The committee did not recommend a specific formula due to inconsistencies with the formulas used in current practice and because this review did not look at evidence comparing different formulas. The committee did not recommend that use of age-adjustment be limited to laboratory tests as although the evidence considered was mostly limited to laboratory-based tests, the evidence was also applicable to quantitative point-of-care tests. The committee noted that people who were already taking anticoagulation at the point of enrolment were excluded from two of the three studies. However, these were the two smaller studies, with a combined sample size less than that of the remaining study and so the committee decided that these people were sufficiently represented in the evidence base that they could be covered by the recommendation.

Pulmonary embolism

Evidence suggested that age-adjusted D-dimer tests had reduced sensitivity to unadjusted tests. However, the committee agreed that this difference was very small (96% versus 98%) and that the sensitivity for both tests was very high. The committee noted that both age-adjusted and unadjusted tests have a negative likelihood ratio that indicated a large decrease in likelihood of PE, suggesting similar efficacy when used to rule out PE. Additionally, evidence suggested that age-adjusted tests had greater specificity and therefore have the potential to reduce the number of people receiving false positive results, and so may reduce unnecessary CTPA imaging and the radiation risk this poses.

The committee discussed the balance of benefits and harms associated with using this an age adjusted test for PE and agreed that increased specificity of age-adjusted testing in those patients aged over 50 years old came at only a very marginal reduction in sensitivity (with no change in the likelihood of PE for a negative test result between age adjusted and non-age adjusted tests). Taking this into account with the cost-effectiveness evidence and their decision regarding the use of age adjusted test in people with suspected DVT, the committee agreed to recommend that age adjustment be considered for PE too. The committee again advised that recommendations should be limited to participants aged over 50 years due to the absence of evidence for other age groups, and that they could not recommend a specific formula.

Cost effectiveness and resource use

Deep vein thrombosis and pulmonary embolism

The committee discussed the potential cost effectiveness of recommending age-adjusted D-dimer testing in people with suspected DVT or PE. It was determined that using an age-adjusted threshold would carry no additional upfront testing cost and could result in downstream cost savings because fewer patients without a DVT or PE would undergo unnecessary imaging.

For suspected DVT, the committee noted that the point estimate for the sensitivity for age-adjusted testing in people was lower than that of age-unadjusted testing. However, this difference was relatively small in absolute terms, and evidence shows that there was considerable overlap in confidence intervals of the two sensitivities. Therefore, the committee felt that the harm and additional costs associated with false negative results from age-adjusted testing is likely to be minimal at most, compared to the benefits of correct diagnoses in patients without a DVT.

For suspected PE, evidence from the clinical review indicated that the specificity of age-adjusted D-dimer testing was higher than that of age-unadjusted testing, so it is likely that a positive recommendation would result in cost savings due to a smaller number of patients without a PE undergoing unnecessary CT pulmonary angiogram. In addition, some health benefits may be achieved due to fewer patients unnecessarily being exposed to radiation. The committee noted that there was no appreciable difference in test sensitivities, and therefore using an age-adjusted test is unlikely to produce detrimental health effects through delayed treatment of patients with false negative test results.

The committee discussed the potential resource impact of the recommendation. It was concluded that increased use of age-adjusted D-dimer testing will result in cost savings, due to fewer unnecessary imaging tests. However, this saving is unlikely to be significant (less than £1 million), since a number of centres are already using age-adjusted D-dimer tests.

Other factors the committee took into account

Deep vein thrombosis and pulmonary embolism

The committee reviewed the evidence for point-of-care tests alongside the evidence for age-adjusted D-dimer tests and noted that an age-adjustment formula could only be applied to quantitative D-dimer tests. One study looked at the use of an age-adjusted formula for a quantitative point-of-care test and found that it had no effect on sensitivity or specificity. However, the committee could not see a reason why the adjustment would work differently for a lab-based test to a point-of-care test and so they decided recommend age adjustment be considered for both types of D-dimer test.

In addition to the retrospective evidence for the use of age-adjusted D-dimer tests in people with suspected PE, the committee were aware of the ADJUST-PE study, a prospective study that did not meet the inclusion criteria for this review as the administration of the reference standard was dependent on the result of the D-dimer test. The study compared diagnostic failure rates for age-adjusted and unadjusted D-dimer tests in practice and found similarly low rates of undiagnosed PE in those with negative D-dimer tests for both age-adjusted and unadjusted tests. The committee concluded that the results of the ADJUST-PE study agreed with the evidence presented in this review.

Point-of-care D-dimer testing for suspected deep vein thrombosis (DVT)

Review question

In people with suspected DVT, what is the diagnostic accuracy of point-of-care D-dimer tests compared with laboratory tests to identify DVT?

Introduction

The NICE guideline on venous thromboembolism (VTE) does not currently consider the use of point-of-care D-dimer tests as an alternative to standard, laboratory D-dimer tests. Point of care tests have the benefit of producing rapid results, reducing waiting times before subsequent testing is performed or VTE can be safely ruled out. Point of care tests therefore have the potential to improve the efficacy of healthcare settings where immediate laboratory facilities are not available

This update will review the diagnostic accuracy of point-of-care D-dimer tests compared with laboratory D-dimer tests in people with suspected DVT.

This review identified studies that fulfilled the conditions specified in Table 5. For full details of the review protocol see appendix A.

PICO table

Table 5 PICO table for point of care D-dimer testing for suspected DVT

Population	Adults (aged 18+) with clinically suspected DVT
Intervention	**Diagnostic accuracy studies:** • Point-of-care D-dimer test ‘Point of care’ is defined as testing at or near the place and time of patient contact (for example, in an emergency department or GP surgery) • Laboratory D-dimer test **Test and Treat RCTs:** • Point-of-care D-dimer test
Comparator	**Diagnostic accuracy studies:** • Reference standard: Ultrasound, venography, MRI scan, CT scan, VTE event during 3 months or more follow-up **Test and treat RCTs:** • Laboratory D-dimer test
Outcomes	**Diagnostic accuracy studies:** • Diagnostic accuracy metrics: Sensitivity/specificity, Positive and negative likelihood ratios

	Test and treat RCTs:
	• All-cause mortality
	• VTE-related mortality
	• Recurrence of VTE
	• Length of hospital stay
	• Quality of life
	• Post-thrombotic syndrome
	• Adverse events
	  ○ Total serious adverse events
	  ○ Major bleeding
	  ○ Clinically relevant non-major bleeding
	  ○ Intracranial haemorrhage
	  ○ Liver injury

Methods and process

This evidence review was developed using the methods and process described in developing NICE guidelines: the manual (2014). Methods specific to this review question are described in the review protocol in appendix A and the methods section in appendix B.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

In addition, the following principles were followed:

- Many studies contained within this review reported data on several different types of laboratory and/or point-of-care D-dimer tests. To avoid double counting of participants, a single point-of-care and a single laboratory test was retained from each study for each meta-analysis that was conducted. D-dimer tests were retained in the following order of prioritisation:
  - Those D-dimer tests referred to in Riley (2016) were prioritised over other forms of tests as these are more likely to represent current usage in clinical practice.
  - When the decision was between a second and first generation latex test, the second generation test was retained (according to Perrier 2004).
  - The tests reporting data on the greater number of participants
  - In the absence of any of the above criteria being applicable, a judgement was made (in discussion with the committee) to retain the D-dimer test more likely to be used in current clinical practice.
- A health technology assessment (HTA) systematic review was previously reported in the 2012 guideline (Goodcare, 2006). This review was assessed as high quality and fully applicable, and so the results of the review were incorporated directly into the evidence review (see appendix B for details of the methods used to incorporate published systematic reviews). The author of this review was contacted and provided NICE with the raw data and details of the quality assessment for each study. The following exclusion criteria were applied to ensure comparability with other included studies:
  - Non-prospective samples
  - Studies in which the application of the reference standard was dependent on the results of the index test (D-dimer)
  - Studies in which the test used was unclear and could not be classified as laboratory or point-of-care based.

- Each study from the HTA review was rated for risk of bias using quality assessment criteria supplied by the HTA authors. These were mapped on the QUADAS-2 domains used to assess risk of bias for the other studies in the review.
- Each study contained within the HTA review was assessed for directness based on restrictions to inclusion (limited data available). Reasons for marking down for directness included restricting the sample to those over 70 years old, only including participants of moderate/high pre-test probability of deep vein thrombosis, only including participants that had been referred for imaging.

Protocol deviation

Priority screening was not used for this review. All references returned by the search were screened at title and abstract level.

Clinical evidence

Included studies

A single systematic search was carried out for the 4 review questions in this evidence review to identify diagnostic accuracy studies, test-and-treat randomised controlled trials and systematic reviews of these study types, which found 4,342 references (see appendix C for literature search strategy). Evidence included in the original guideline was also reviewed, which added 14 references. In total, 4,356 references were identified for screening at title and abstract level. Based on the title and abstract not matching the review protocol 4,171 references were excluded, and 168 references were ordered for screening as full texts.

Of these 168 references, 45 references were included for the 4 review questions based on their meeting the inclusion criteria specified in the review protocol (appendix A). Of these 45 included references, 18 references were included for this review question. One systematic review (which was also included in the previous guideline) containing 41 studies presenting data on laboratory D-dimer tests and 21 studies presenting data on point-of-care D-dimer tests for suspected deep vein thrombosis. Three references presented data on point-of-care D-dimer testing, 10 references reported on laboratory D-dimer tests (and these were included for comparison with POC D-dimer tests) and 4 reported both.

A second set of searches, using the original search strategies, were conducted at the end of the guideline development process to capture papers published whilst the guideline was being developed. These searches returned 6,272 references in total for all the questions included in the update, and these were screened based on title and abstract. 30 references were identified for full text screening for the D-dimer review questions and 4 met the criteria for inclusion in this group of reviews, however, no additional relevant references were found that were relevant for this particular review question.

The clinical evidence study selection is presented as a diagram in appendix D.

For the full evidence tables and GRADE profiles for included studies, please see appendix E and appendix G respectively. The references for individual included studies are given in appendix K.

Excluded studies

The reasons for excluding studies at the full text stage are detailed in appendix J and the full references are listed in appendix K.

Expert testimony

The committee identified gaps in their knowledge concerning point-of-care testing, which were not filled by the included studies. Specifically, the committee were unclear about the extent to which quantitative, qualitative and semi-quantitative point-of-care tests are used in the UK and the practical differences between these tests in how they measure and classify D-dimer levels.

The committee invited expert testimony to provide additional information to help them interpret the results of the included studies. The expert witness was a lead scientist for point of-care testing programmes at the National External Quality Assessment Schemes (NEQAS) for Blood Coagulation, and was selected to give testimony due to the direct relevancy of this role to this review question, the known expertise of the expert witness in this matter (including the ability of the expert witness to address the gaps in committee knowledge identified above) and the high reputation of the scheme which is used for external quality assurance of testing by a large number of UK laboratories. A call for evidence was not considered appropriate due to the limited and non-subjective nature of the information required by the committee.

The expert witness presented evidence about the types of point-of-care tests being used in the UK and explained that qualitative tests were based on a colour read out that was required after a specific incubation period and that this meant there was a greater potential for human error with this type of test, leading to more variation in results. These tests were not used by any of the NEQAS registered labs. Semi- quantitative tests were rarely used in current practice, but there was still some historic use of these tests. However, although quantitative tests were the least prone to user error there was still some level of variability in results obtained between centres when they were supplied with the same samples to test using quantitative (both laboratory and point of care) methods. The majority of laboratories registered with the NEQAS used quantitative testing. The witness also agreed that there is no obvious biological reason that the tests would work differently when detecting D-dimer in people with DVT compared to people with PE as the test detects the same molecule in both cases. See appendix L for a more detailed summary of the expert witness testimony.

Summary of clinical studies included in the evidence review

The characteristics of the included studies are summarised in Table 6 (systematic review of lab-based D-dimer tests),Table 7 (cohort studies looking at laboratory based D-dimer tests) and Table 8 (cohort studies looking at point-of-care D-dimer tests).

Table 6 Systematic review looking at laboratory-based D-dimer tests in suspected DVT

Author (year)	Study details	Index tests	Reference standards
Goodacre (2006)	Study type • Systematic review Sample characteristics •data was extracted for 44 studies reporting data on laboratory based D-dimers, 9 reporting data on semi-quantitative point-of-care D-dimers, and 21 reporting data on qualitative point-of-care D-dimer tests.	• Laboratory D-dimer tests *VIDAS* *Sta-Liatest* *Miniquant* *Dimertest* *Tinaquant* *IL test* *Enzygnost* *Asserachrom*	•Ultrasonography • Venography • Composite (including CUS) • IPG

Author (year)	Study details	Index tests	Reference standards
	How was data extracted •2x2 table for individual studies were extracted from the raw data and combined with subsequent studies identified by this review Quality of systematic review •High	*Minutex* *Fibrinostika* • Point-of-care D-dimer tests *SimpliRED* *Nycocard* *Instant IA*	

Table 7 Cohort studies looking at laboratory-based D-dimer tests in suspected DVT

Author (year)	Study details	Index test	Reference standard
Anoop (2009)	Study type • Prospective cohort study Sample characteristics • Sample size 197 participants overall, 91 with suspected PE. • % female 66% female • Mean age (SD) Median 61 years (range: 19-96 years) • % pre-test probability 20.9% low; 79.1% intermediate	• Laboratory D-dimer MDA autodimer T3103 Cut-off: 0.50 µg FEU/ml	• Ultrasound Compression *ultrasound (HDI 5000) of common and superficial femoral veins, popliteal vein trifurcation and all three deep calf vein sets* • Pulmonary angiography *64-slice 0.625mm thickness CTPA (GE lightSpeed VCT) with Niopam 300 contrast, 74ml at 3 ml/s*
Baker (2010)	Study type • Prospective cohort study Sample characteristics • Sample size 112 • % female 42% female • Mean age (SD) 62 years • % pre-test probability 17% <2 Wells score 81.2% >2 Well score PTP not completed for 2 participants.	• Laboratory D-dimer STA-R Liatest D-dimer • Point-of-care D-dimer Biosite Triage, using an ELFA based D-dimer assay	• Ultrasonography

Author (year)	Study details	Index test	Reference standard
Boeer (2009)	Study type • Prospective cohort study Sample characteristics • Sample size 79 • % female 50.6% female • Mean age (SD) 61 years (range 22 - 95)	• Laboratory D-dimer Extracted: Tinaquant (evaluated on Architect c8000 system) Also reported but not extracted: Auto Dimer (evaluated on Architect c8000 system) Quantia D-dimer (evaluated on Architect c8000 system) D-Dimer HS(evaluated on ACL-TOP system) Innovance (evaluated on BCS system) D-Dimer plus (evaluated on BCS system)	• Ultrasonography *Limited data on the procedure and protocol for performing reference standard.*
Dempfle (2006)	Study type • Prospective cohort study Sample characteristics • Sample size 637; 560 used in the analysis (77 excluded) • % female 61.3% female • Mean age (SD) 57.7 (SD 17.2) years	• Laboratory D-dimer VIDAS (also reported tinaquant but was not extracted for this review) • Point-of-care D-dimer Cardiac D-dimer (Roche)	• Ultrasonography *Diagnosis determined by venous duplex sonography, including CUS and colour Doppler visualization of the veins of the symptomatic leg. According to the study protocol, the minimal requirement for B-mode ultrasonography was a high resolution real time scanner equipped with a 5 Mhz electronically focused linear-array transducer. Ultrasonography devices with better specifications could be used. The single criterion indicating the presence of venous thrombosis was the failure to fully compress the venous lumen, despite firm compression with the transducer probe. The following sites were examined: i) the common femoral vein at the inguinal ligament in supine position, ii) the popliteal vein at the popliteal fossa, down to the point of the trifurcation in the prone position. In case of anatomical abnormalities of the trifurcation of the anterior and posterior tibial and peroneal vein, the thrombus should involve the most upper vein junction. In case of a negative ultrasound this was to be documented by pictures of non-compressed and fully compressed veins at the popliteal fossa (popliteal vein) and inguinal ligament*
Diamond (2005)	Study type • Prospective cohort	• Laboratory D-dimer Tinaquant	• *Venous duplex imaging* *Examinations were performed using the ATL HDI 5000 scanner (Philips Medical Systems, Andover, MA). The common femoral, deep*

Author (year)	Study details	Index test	Reference standard
	study Sample characteristics • Sample size 148 • % female 49.5% • Mean age (SD) 57.2 • % people with previous VTE 12.8% previous DVT		*femoral, femoral, popliteal, posterior tibial, peroneal, gastrocnemius, and soleus veins were scanned in the transverse and longitudinal plane. Duplex criteria for a diagnosis of acute DVT included visualization of thrombus on B-mode, lack of venous compressibility, and the absence of doppler flow signals distal to the site of suspected thrombosis.*
Gomez-Jabalera (2017)	Study type • Prospective cohort study Sample characteristics • Sample size 138 • % female 60.5% female • Mean age (SD) 71.6 years • % pre-test probability Well score low = 69.6% intermediate = 21% High = 9.4%	• Laboratory D-dimer Hemos IL-500 • Age-adjusted D-dimer tested several formulas: Age x 10 ug/L Age x 15 ug/L age x 20 ug/L Age x 25 ug/L Age x 30 ug/L We reported data for age x 10 ug/L	• Ultrasonography *Following the analysis, experienced personnel performed a whole leg compression ultrasonography of the symptomatic leg by a B mode and pulsed Doppler in the common femoral vein, the popliteal vein, calf veins and great and small saphenous veins. The sonographic scanner used was a linear array at 5–7.5MHz (SonoSite M-Turbo ultrasound).20 The DVT diagnosis was established if one or more deep veins in the leg were not completely compressible or there were not any phasic flow signs with respiratory movements of calf compression.*
Ilkhanipour (2004)	Study type • Prospective cohort study Sample characteristics • Sample size 365 • % female	• Laboratory D-dimer Quantitative ELISA assay with a previously established threshold value of 500 ug/L or greater for a positive result	• *Ultrasonography* *All patients underwent duplex ultrasound examination of the symptomatic leg by experienced vascular technologists who were blinded to the results of the clinical assessment and ELISA D-dimer values. Sonography was performed using a 128 XP scanner (Acuson, Mountain View, CA) with a 5-MHz linear array probe.*

Author (year)	Study details	Index test	Reference standard
	65% female • Mean age (SD) 54 years • % pre-test probability 35% low risk 43% intermediate risk 22% high risk		
Kong (2016)	Study type • Prospective cohort study Sample characteristics • Sample size 255, all ischemic stroke patients • % female With DVT: 68 Without DVT: 61 • Mean age (SD) With DVT 45.2% female Without DVT: 62.5% female	• Laboratory D-dimer INNOVANCE (SYSMEX CA-7000 System) with a detection limit of 0.05mg/L	• *Ultrasonography* *Colour Doppler Ultrasonography (CDUS) was performed in all the included patients to assess the incidence of DVT. Further, real-time B-mode ultrasonography (with compression) was performed with a 7.5-MHz (higher frequency) or a 5.0-MHz transducer.*
Luxembourg (2012)	Study type • Prospective cohort study Sample characteristics • Sample size 216 • % female 57% female • Mean age (SD) 51 years • % pre-test probability 46% low 38%	• Laboratory D-dimer Vidas (N=215), also reported Liatest (N=216), HemosIL (N=191), HemosIL-DDHS (N=189), Innovance on BCS system (n =195) but these were not reported for this review	• Ultrasonography *complete CUS (cCUS) of the symptomatic leg(s) which means that the femoral, popliteal, tibial, fibular as well as calf muscle veins (gastrocnemius and soleal muscular veins) were examined by moving the transducer distally from the groin to the ankle level.*

Author (year)	Study details	Index test	Reference standard
	intermediated 17% high • % people with cancer 17%		
Michiels (2016)	Study type • Prospective cohort study Sample characteristics • Sample size 1330	• Laboratory D-dimer VIDAS ELISA D-dimer assay	• Ultrasonography *All participants underwent both d-dimer and CUS Positive CUS = DVT positive Negative CUS and <500 D-dimer = DVT negative, Negative CUS and >500 D-dimer = repeat CUS after 5-7 days.*
Neale (2004)	Study type • Prospective cohort study Sample characteristics • Sample size 187 • % female 54% female	• Laboratory D-dimer Auto-dimer: Latex-agglutination test • Point-of-care D-dimer SimpliRED (also reported Simplify)	• Venography *contrast venography*
Oude (2015)	Study type • Prospective cohort study Sample characteristics • Sample size 290 • % female 60.3% • Mean age (SD) 56.6 (18.1-87.9) years	• Laboratory D-dimer Vidas (also reported innovance [on both CA-1500 and BCS systems separately), ACL-TOP, Tina-quant and Liatest but these were not extracted for this review) • Age-adjusted D-dimer Quantitative lab-based test: Vidas (also reported innovance [on both CA-1500 and BCS systems separately), ACL-TOP, Tina-quant and Liatest but	• Ultrasonography *Real time B-mode compression ultrasonography with a 9 mHz linear array sonographic scanner*

Author (year)	Study details	Index test	Reference standard
		these were not extracted for this review) Quantitative POC: pathfast (AQT90 also reported but was not extracted for this review) • Point-of-care D-dimer Quantitative: Pathfast (also reported AQT90 but was not extracted for this review) Qualitative test: Simplify	
Prochaska (2017)	Study type • Prospective cohort study Sample characteristics • Sample size 500 • % female 55.6 • Mean age (SD) Median age 60.0 (interquartile range [IQR] 45.0, 72.0) • % pre-test probability Low-to-moderate (Wells score 0–2): 84.4 High (Wells score >2): 15.6 • % people with cancer 17.0	• Laboratory D-dimer Innovance from 04/2013 to 07/2014 and HemosIL HS from 08/2014 to the end of study. Cut-off: 0.5 mg/L fibrinogen equivalent unit (FEU) • Age-adjusted D-dimer age-dependent threshold applied to patients over 60 years (age/100mg/L)	• Ultrasound *Compression duplex ultrasound*
Yamada (2015)	Study type • Prospective cohort study	• Laboratory D-dimer latex photometric immunoassay (LPIA) at a	• Ultrasonography *Venous ultrasonography: Aplio (Toshiba Medical Systems Corporation) and SSD-5500 (Hitachi Aloka Medical, Ltd.) diagnostic*

Author (year)	Study details	Index test	Reference standard
	Sample characteristics • Sample size 525 • % female 44.4% female • Mean age (SD) 64 (SD 14) years • % people with cancer 18.3%	cut-off point of 1.0 µg/mL	*ultrasound systems*

Table 8 Cohort studies looking at point-of-care D-dimer tests in suspected DVT

Author (year)	Study details	Index test	Reference standard
Baker (2010)	Study type • Prospective cohort study Sample characteristics • Sample size 112 • % female 42% female • Mean age (SD) 62 years • % pre-test probability 17% <2 Wells score 81.2% >2 Well score PTP not completed for 2 participants.	• Laboratory D-dimer STA-R Liatest D-dimer • Point-of-care D-dimer Biosite Triage, using an ELFA based D-dimer assay	•Ultrasonography
Dempfle (2006)	Study type • Prospective cohort study Sample characteristics • Sample size 637; 560 used in the analysis (77 excluded) • % female 61.3% female • Mean age (SD) 57.7 (SD 17.2) years	• Laboratory D-dimer VIDAS (also reported tinaquant but was not extracted for this review) • Point-of-care D-dimer Cardiac D-dimer (Roche)	•Ultrasonography
Di Nisio (2006)	Study type • Prospective cohort study Sample characteristics • Sample size 2,066 • % people with cancer	• Point-of-care D-dimer SimpliRED	•Ultrasonography In cases of negative CUS, serial testing was performed 1 week later and if still negative, the person was followed-up for 3 months for VTE occurrence.

Author (year)	Study details	Index test	Reference standard
	11%		
Neale (2004)	Study type • Prospective cohort study Sample characteristics • Sample size 187 • % female 54% female	• Laboratory D-dimer Auto-dimer: Latex-agglutination test • Point-of-care D-dimer SimpliRED (also reported Simplify)	• Venography contrast venography
Oude (2015)	Study type • Prospective cohort study Sample characteristics • Sample size 290 • % female 60.3% • Mean age (SD) 56.6 (18.1-87.9) years	• Laboratory D-dimer Vidas (also reported innovance [on both CA-1500 and BCS systems separately), ACL-TOP, Tina-quant and Liatest but these were not extracted for this review) • Age-adjusted D-dimer Quantitative lab-based test: Vidas (also reported innovance [on both CA-1500 and BCS systems separately), ACL-TOP, Tina-quant and Liatest but these were not extracted for this review) Quantitative POC: pathfast (AQT90 also reported but was not extracted for this review) • Point-of-care D-dimer Quantitative: Pathfast (also reported AQT90 but was not extracted for this review) Qualitative test: Simplify	•Ultrasonography Real time B-mode compression ultrasonography with a 9 mHz linear array sonographic scanner
Subramaniam (2006a)	Study type • Prospective cohort study Sample characteristics • Sample size 312 • % female 62.5% female	• Point-of-care D-dimer Simplify D-dimer	•Ultrasonography *Diagnosis of DVT made using duplex compression (acuson Sequoia 512 sonographic imaging system). The common femoral vein, superficial femoral vein, popliteal vein, and trifurcation, and all three deep calf vein sets were examined.*

Author (year)	Study details	Index test	Reference standard
	• Mean age (SD) 55.8 years • % pre-test probability 48.4% unlikely modified wells criteria. • % people with previous VTE 12.8% previous VTE		
Subramaniam (2006b)	Study type • Prospective cohort study Sample characteristics • Sample size 453 • % female 64.9% female • Mean age (SD) 55.8 years • % pre-test probability 61.8% unlikely DVT on Hamilton score • % people with previous VTE 0% previous lower limb DVT	• Point-of-care D-dimer Simplify	•Ultrasonography *Duplex compression carried out by experienced ultra sonographers and senior radiology registrars (third- and fourth- year) under the supervision of consultant radiologists. Interpreted blind to D-dimer results.*

See appendix E for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See evidence tables in appendix E for quality assessment of individual studies, appendix F for forest plots and appendix G for GRADE tables. Please refer to the evidence statement section for an overall summary of the evidence.

Economic evidence

Included studies

A single search was conducted to cover all review questions in this chapter. This search returned 817 records, of which 800 were excluded on title and abstract for this review question. The remaining 17 papers were screened using a review of the full text, and all were excluded.

An additional search was conducted at the end of the guideline development process to capture economic evidence published while the guideline was being developed. This was conducted as a single re-run search covering all questions in the guideline. This search returned 2,013 records in total, all of which were excluded on title and abstract for this review question.

Excluded studies

Details of the studies excluded at full-text review are given in appendix J, along with reasons for their exclusion.

Economic model

For the review question on point-of-care versus laboratory D-dimer testing, the committee indicated that, alongside test accuracy data, recommendation making would be facilitated by information on absolute numbers of patients with each testing outcome (i.e. true positives, false negatives, true negatives, and false positives), as well as estimates of costs involved in the testing process. To provide this information, a simple cost-consequences analysis was developed. A full cost-utility analysis was felt to be inappropriate as cost effectiveness is likely to be heavily dependent on the long-term health outcomes and costs associated with false negative results (patients who have a DVT but are incorrectly diagnosed). Since randomised evidence of sufficient quality on the consequences of an intentionally untreated DVT is unlikely to exist, such an analysis would not be feasible without substantial speculation on the downstream outcomes for these patients.

The main results of the cost-consequences analysis in terms of the test outcomes and costs per 1000 people are presented below. Table 9 shows the incremental number of true positives, false negatives, true negatives and false positives for each point-of-care testing strategy versus laboratory testing as well as the incremental total costs with and without primary care costs. A more detailed description of the model is provided in appendix I.

Table 9 Incremental test outcomes and costs (with 95% credible intervals) per 1000 people with suspected DVT for different types of D-dimer point-of-care tests versus laboratory testing

	Overall POC	Quantitative POC	Semi-quantitative POC	Qualitative POC
Test outcomes				
True positive	-4 (-7 to -1)	3 (1 to 5)	-2 (-5 to 1)	-7 (-11 to -3)
False negative	4 (1 to 7)	-3 (-5 to -1)	2 (-1 to 5)	7 (3 to 11)
True negative	138 (66 to 207)	-9 (-163 to 151)	0 (-131 to 131)	193 (122 to 260)
False positive	-138 (-207 to -66)	9 (-151 to 163)	0 (-131 to 131)	-193 (-260 to -122)
Total costs				
Excluding primary care	-£1,331 (-£10,777 to £8,721)	£13,709 (-£864 to £29,418)	£7,960 (-£3,772 to £20,140)	-£11,559 (-£18,596 to -£5,085)
Including primary care	-£20,166 (-£30,296 to -£9,527)	-£3,770 (-£19,706 to £12,951)	-£9,644 (-£22,402 to £3,627)	-£30,900 (-£38,712 to -£23,489)

Evidence statements

Clinical evidence statements

Note that quality ratings were attached to likelihood ratios but not to sensitivity and specificity analyses because clinical decision thresholds were specified on this scale.

Main analyses

- Evidence suggests that a **negative** D-dimer result indicates a **large decrease** in the probability that a person with clinically suspected deep vein thrombosis has deep vein thrombosis for both point-of-care and laboratory-based tests respectively (LR-=0.19 [0.15 to 0.24] and LR-=0.16 [0.14 to 0.19]). (Low- quality evidence from 37 prospective studies comprising 9,811 participants looking at point-of-care tests and very-low to low-quality evidence from 53 prospective studies comprising 10,163 participants looking at laboratory based tests).
- Evidence suggests that a **positive** point-of-care based D-dimer result indicates a **moderate increase** in the probability that a person with clinically suspected deep vein thrombosis has deep vein thrombosis (LR+=2.38 [2.05 to 2.79]) and that a **positive** laboratory-based D-dimer result indicates a **slight increase** in probability (LR+=1.78 [1.62 to 1.97]). (Very-low to low- quality evidence from 37 prospective studies comprising 9,811 participants looking at point-of-care tests and very-low to low-quality evidence from 53 prospective studies comprising 10,163 participants looking at laboratory based tests).
- Evidence suggests that point-of-care D-dimer tests offer lower sensitivity (88% [0.84 to 0.91] vs 93% [0.91 to 0.94]) but higher specificity (63% [0.57 to 0.69] vs 48% [0.43. 0.53]) compared with laboratory-based tests, although the confidence intervals for sensitivity touch. (Evidence from 37 prospective studies comprising 9,811 participants looking at point-of-care tests and evidence from 53 prospective studies comprising 10,163 participants looking at laboratory based tests).
- Evidence suggests that a **negative** quantitative point-of-care based D-dimer result indicates a **very large decrease** in the probability that a person with clinically suspected deep vein thrombosis has deep vein thrombosis. This is the case irrespective of whether

the test is adjusted for age (LR-=0.04 [0.00 to 0.68]) or unadjusted (LR-=0.04 [0.00 to 0.68]). (Moderate quality evidence from 1 prospective study comprising 275 participants).

- Evidence suggests that a **positive** quantitative point-of-care based D-dimer result indicates a **slight increase** in the probability that a person with clinically suspected deep vein thrombosis has deep vein thrombosis. This is the case irrespective of whether the test is adjusted for age (LR+=1.88 [1.65 to 2.15] or unadjusted (LR+=1.88 [1.65 to 2.15]). (Moderate quality evidence from 1 prospective study comprising 275 participants).

Sensitivity analyses excluding studies at high risk of bias

- Evidence suggests that a **negative** point-of-care based D-dimer result indicates a **moderate decrease** in the probability that a person with clinically suspected deep vein thrombosis has deep vein thrombosis (LR-=0.20 [0.15 to 0.24]) and that a **negative** laboratory-based D-dimer result indicates a **slight decrease** in probability (LR-=0.15 [0.12 to 0.19]). (Low quality evidence from 36 prospective studies comprising 9,710 participants looking at point-of-care tests and low-quality evidence from 51 prospective studies comprising 9,559 participants looking at laboratory based tests).
- Evidence suggests that a **positive** point-of-care based D-dimer result indicates a **moderate increase** in the probability that a person with clinically suspected deep vein thrombosis has deep vein thrombosis (LR+=2.43 [2.09 to 2.84]) and that a **positive** laboratory-based D-dimer result indicates a **slight increase** in probability (LR+=1.78 [1.62 to 1.97]). (Low quality evidence from 36 prospective studies comprising 9,710 participants looking at point-of-care tests and very-low quality evidence from 51 prospective studies comprising 9,559 participants looking at laboratory based tests).

Subgroup analyses

- Subgroup analyses where point-of-care tests were separated into qualitative, quantitative and semi-quantitative tests suggest that a **negative** D-dimer result indicates a **moderate decrease** in the probability that a person with clinically suspected deep vein thrombosis has a deep vein thrombosis when using a qualitative (LR-=0.22 [0.16, 0.28]), a **large decrease** when using a semi-quantitative (LR-=0.18 [0.14, 0.24]) test, and a **very large decrease** when using a quantitative point of care test (LR-=0.07 [0.03, 0.15]). (Very-low quality evidence from 26 prospective studies comprising 7791 participants looking at qualitative point-of-care tests, high quality evidence from 3 prospective studies comprising 936 participants looking at quantitative point-of-care tests and high quality evidence from 9 prospective studies comprising 1,359 participants looking at semi-quantitative point-of-care tests).
- Subgroup analyses where point-of-care tests were separated into qualitative, quantitative and semi-quantitative tests suggest that a **positive** D-dimer result indicates a **slight increase** in the probability that a person with clinically suspected deep vein thrombosis has a deep vein thrombosis when using a quantitative (LR+=1.88 [1.41, 2.65]) or semi-quantitative (LR+=1.79 [1.42, 2.35]) point of care test, and a **moderate increase** in probability when using a qualitative point of care test (LR+=2.75 [2.31, 3.28]). (Very-low quality evidence from 26 prospective studies comprising 7791 participants looking at qualitative point-of-care tests, low quality evidence from 3 prospective studies comprising 936 participants looking at quantitative point-of-care tests and very-low quality evidence from 9 prospective studies comprising 1,359 participants looking at semi-quantitative point-of-care tests).
- Subgroup analyses where point-of-care tests were separated into qualitative, quantitative and semi-quantitative tests suggest that qualitative tests offer lower sensitivity (85% [0.81,0.89]) than quantitative (97% [0.94 to 0.98]) tests and marginally lower sensitivity

than semiquantitative (91% [0.88 to 0.95]) tests, although the confidence intervals for the qualitative and semi-quantitative tests overlap. Qualitative tests offer increased specificity (69% [0.63 to 0.74]) than semiquantitative (48% [0.35 to 0.62]) tests, and marginally increased specificity than quantitative (47% [0.31 to 0.64]) tests, although the confidence intervals overlap for semi-quantitative and quantitative, and qualitative and quantitative tests. (Evidence from 26 prospective studies comprising 7791 participants looking at qualitative point-of-care tests, evidence from 3 prospective studies comprising 936 participants looking at quantitative point-of-care tests and evidence from 9 prospective studies comprising 1,359 participants looking at semi-quantitative point-of-care tests).

- Subgroup analyses in people with cancer suggests that a **positive** qualitative point-of-care based D-dimer result indicates a **slight increase** in the probability that a person with clinically suspected deep vein thrombosis has deep vein thrombosis (LR+=1.82 [1.56 to 2.11]) and a **negative** test indicates a **large decrease** (LR-=0.15 [0.06 to 0.39]). (Low quality evidence from 3 prospective study comprising 384 participants).
- Subgroup analyses in people with low-moderate probability of DVT (according to a 3-level Wells score) suggests that a **negative** D-dimer result indicates a **moderate decrease** in the probability that a person with clinically suspected deep vein thrombosis has a deep vein thrombosis. This is the case irrespective of whether the result is laboratory based (LR-=0.33 [0.14 to 0.66]) or qualitative point of care (LR-=0.21 [0.14 to 0.29]). (Low quality evidence from 4 prospective studies comprising 855 participants looking at laboratory tests and moderate quality evidence from 6 prospective studies comprising 2739 participants looking at point of care tests).
- Subgroup analyses in people with low-moderate probability of DVT (according to a 3-level Wells score) suggests that a **positive** laboratory based D-dimer result indicates a **slight increase** in the probability that a person with clinically suspected deep vein thrombosis has a deep vein thrombosis (LR+=1.47 [1.13, 1.96]) and that a **positive** qualitative point of care D-dimer result indicates a **moderate increase** (LR+=3.20 [2.44 to 4.20]). (Low quality evidence from 4 prospective studies comprising 855 participants looking at laboratory tests and very-low quality evidence from 6 prospective studies comprising 2739 participants looking at point of care tests).
- Subgroup analyses in people with high probability of DVT (according to a 3-level Wells score) suggests that a **negative** laboratory-based D-dimer result indicates a **moderate decrease** in the probability that a person with clinically suspected deep vein thrombosis has a deep vein thrombosis (LR-=0.46 [0.03, 1.92]) a **negative** qualitative point of care test indicates a **large decrease** (LR-=0.14 [0.07 to 0.26]). (Low quality evidence from 2 prospective studies comprising 142 participants looking at laboratory tests and moderate quality evidence from 6 prospective studies comprising 614 participants looking at point of care tests).
- Subgroup analyses in people with high probability of DVT (according to a 3-level Wells score) suggests that a **positive** laboratory-based D-dimer result indicates a **slight increase** in the probability that a person with clinically suspected deep vein thrombosis has a deep vein thrombosis (LR+=1.28 [0.80, 1.79]) and that a **positive** qualitative point of care test indicates a **moderate increase** (LR+=2.08 [1.69, 2.61]). (Very-low quality evidence from 2 prospective studies comprising 142 participants looking at laboratory tests and low quality evidence from 6 prospective studies comprising 614 participants looking at point of care tests).

Expert witness testimony

- Directly applicable evidence from expert witness testimony suggested that although 99% of laboratories that are registered with NEQAS use quantitative tests there is some historical use of semi-quantitative tests for D-dimer. Additionally, the expert testimony suggested that there is no obvious biological reason that the tests would work differently when detecting D-dimer in people with DVT compared to people with PE as the test detects the same molecule in both cases.

Economic evidence statements

In patients with suspected DVT, evidence from the de novo cost-consequences model developed for this guideline suggests that compared to laboratory testing:

- Overall, point-of-care D-dimer testing results in a small statistically significant increase (4 per 1,000 people) in the number of false negative results and a large statistically significant decrease (138 per 1,000) in the number of false positive results. Excluding primary care costs, the overall point-of-care testing strategy is less costly than laboratory testing (-£1,331 [-£10,777 to £8,721)]). When primary costs are included, the overall point-of care testing strategy becomes significantly less costly (-£20,166 [-£30,296 to -£9,527]).
- In a subgroup analysis, quantitative point-of-care D-dimer testing results a small statistically significant decrease (3 per 1,000 people) in the number of false negative results and a small increase (9 per 1,000 people) in the number of false positive results (not statistically significant at the 5% level). Excluding primary care costs, the quantitative point-of-care testing strategy is more costly than laboratory testing (£13,709 [-£864 to £29,418]). When primary costs are included, the quantitative point-of-care testing strategy becomes less costly than laboratory testing (-£3,770 [-£19,706 to £12,951]).
- In a subgroup analysis, semi-quantitative point-of-care D-dimer testing results in a small increase (2 per 1,000 people) in the number of false negative results and no difference in the number of false positive results, although neither of these findings is statistically significant at the 5% level. Excluding primary care costs, the semi-quantitative point-of-care testing strategy is more costly than laboratory testing (£7,960 [-£3,772 to £20,140]). When primary costs are included, the semi-quantitative point-of care testing strategy becomes less costly than laboratory testing (-£9,644 [-£22,402 to £3,627]).
- In a subgroup analysis, qualitative point-of-care D-dimer testing results a small statistically significant increase (7 per 1,000 people) in the number of false negative results and a large statistically significant decrease (193 per 1,000 people) in the number of false positive results. The qualitative point-of-care testing strategy is significantly less costly than laboratory testing both when primary care costs are excluded (-£11,559 [-£18,596 to -£5,085]) and when primary care costs are included (-£30,900 [-£38,712 to -£23,489]).

The committee's discussion of the evidence

The joint discussion section for the use of the point-of-care D-dimer test in people with DVT and PE is below in the review for point-of-care D-dimer test in people with PE.

Point-of-care D-dimer testing for suspected pulmonary embolism (PE)

Review question

In people with suspected PE, what is the diagnostic accuracy of point-of-care D-dimer tests compared with laboratory tests to identify PE?

Introduction

The NICE guideline on venous thromboembolism (VTE) does not currently consider the use of point-of-care D-dimer tests as an alternative to standard, laboratory D-dimer tests. Point of care tests have the benefit of producing rapid results, reducing waiting times before subsequent testing is performed or VTE can be safely ruled out. Point of care tests therefore have the potential to improve the efficacy of healthcare settings where immediate laboratory facilities are not available.

This update will review the diagnostic accuracy of point-of-care D-dimer tests compared with laboratory D-dimer tests in people with suspected PE.

This review identified studies that fulfilled the conditions specified in Table 10. For full details of the review protocol, see appendix A.

PICO table

Table 10 PICO table point of care D-dimer testing for suspected PE

Population	Adults (aged 18+) with clinically suspected PE
Intervention	**Diagnostic accuracy studies:** • Point-of-care D-dimer test • Laboratory D-dimer test **Test and Treat RCTs:** • Point-of-care D-dimer test
Comparator	**Diagnostic accuracy studies:** • Reference standard: CT scan, MRI scan, VQ scan, pulmonary angiography, VTE event during 3 months or more follow-up **Test and treat RCTs:** • Laboratory D-dimer test
Outcomes	**Diagnostic accuracy studies:** • Diagnostic accuracy metrics: Sensitivity/specificity, Positive and negative likelihood ratios **Test and treat RCTs:** • All-cause mortality • VTE-related mortality • Recurrence of VTE

	• Length of hospital stay
	• Quality of life
	• Chronic thromboembolic hypertension
	• Chronic thromboembolic pulmonary hypertension (CTEPH)
	• Adverse events
	    ○ Total serious adverse events
	    ○ Major bleeding
	    ○ Clinically relevant non-major bleeding
	    ○ Intracranial haemorrhage
	    ○ Liver injury

Methods and process

This evidence review was developed using the methods and process described in developing NICE guidelines: the manual (2014). Methods specific to this review question are described in the review protocol in appendix A and the methods section in appendix B.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

Protocol deviation

Priority screening was not used for this review. All references returned by the search were screened at title and abstract level.

Clinical evidence

Included studies

A single systematic search was carried out for the 4 review questions in this evidence review to identify diagnostic accuracy studies, test and treat randomised controlled trials and systematic reviews of these study types, which found 4,342 references (see appendix C for literature search strategy). Evidence included in the original guideline was also reviewed, which added 14 references. In total, 4,356 references were identified for screening at title and abstract level. Based on title and abstract, 4,171 were excluded and 168 references were ordered for screening based on their full texts.

Of the 168 references screened as full texts, 45 references were included for the 4 review questions based on their meeting the inclusion criteria specified in the review protocol (appendix A). Of the 45 included references, 6 presented data on point-of-care D-dimer testing for suspected pulmonary embolism and met the inclusion criteria for this review. 15 studies reported on laboratory D-dimer results and these were included to compare with point-of-care D-dimers.

A second set of searches, using the original search strategies, were conducted at the end of the guideline development process to capture papers published whilst the guideline was being developed. These searches returned 6,272 references in total for all the questions included in the update, and these were screened based on title and abstract. 30 references were identified for full text screening for the D-dimer review questions and 4 met the criteria for inclusion in this group of reviews, however, no additional relevant references were found that were relevant for this particular review question.

The clinical evidence study selection is presented as a diagram in appendix D.

For the full evidence tables and GRADE profiles for included studies, please see appendix E and appendix G respectively. The references of individual included studies are given in appendix K.

Excluded studies

The reasons for excluding studies at the full text stage are detailed in appendix J and the full references are listed in appendix K.

Expert witness testimony

The committee identified gaps in their knowledge and invited expert witness testimony to provide additional information to help them interpret the included studies. See the corresponding section in the DVT review above for a summary of this testimony and the reasons for choosing the expert witness, and appendix L for full details of the expert witness testimony.

Summary of clinical studies included in the evidence review

The characteristics of the studies that looked at point-of-care D-dimer tests in suspected PE are summarised in summarised in Table 11 and the studies looking at laboratory-based D-dimer tests in suspected PE are summarised in Table 12.

Table 11 Cohort studies looking at point-of-care D-dimer tests in suspected PE

Author (year)	Study details	Index test	Reference standard
Ginsberg (1995)	Study type • Prospective cohort study Sample characteristics • Sample size 86 • Mean age (SD) 51 (range 17 to 90) Study location • Canada	• Point-of-care D-dimer SimpliRED assay; Cut-off: positive test if any agglutination was observed; negative test if no agglutination was observed	• Composite reference standard
Ginsberg (1998)	Study type • Prospective cohort study Sample characteristics • Sample size 1177 • Mean age (SD) 53.4 (range 20 to 94) • % pre-test probability Low: 60 Moderate: 32 High: 8 Study Location • Canada	• Point-of-care D-dimer SimpliRED; Cut-off: normal if absence of erythrocyte agglutination; abnormal if presence of erythrocyte agglutination	• Composite reference standard

Author (year)	Study details	Index test	Reference standard
Gosselin (2012)	Study type • Prospective cohort study Sample characteristics • Sample size 1012 • Mean age (SD) Median age from 52 to 70 (range 18 to 94) • % pre-test probability Wells pre-test probability scores Low: 60.2 Moderate: 34.7 High: 5.1 Study Location • US, Germany	• Point-of-care D-dimer Stratus R CS Acute Care TM; heparin or citrate plasma blood samples; Cut-off: 450 mg/L FEU Data was reported for diagnostic accuracy for heparin and citrate samples. However only data from the citrate sample was used in the analysis to avoid double counting.	• Composite reference standard
Kline (2001)	Study type • Prospective cohort study Sample characteristics • Sample size 380 • Mean age (SD) People with PE: 55.6 (16.9) People without PE: 49.2 (16.2) Study Location • US	• Point-of-care D-dimer SimpliRED; Cut-off: strong-positive and weak-positive agglutination were considered abnormal	• Composite reference standard
Lucassen (2015)	Study type • Prospective cohort study Post-hoc analysis Sample characteristics • Sample size 598 • Mean age (SD) 48 Study Location • The Netherlands	• Laboratory D-dimer Either ELISA or latex assay; Cut-off: not reported • Point-of-care D-dimer Simplify Clearview; Cut-off: positive >80 ng mL-1	• Composite reference standard
Subedi (2009)	Study type • Prospective cohort study Sample characteristics • Sample size 47 • Mean age (SD) Not reported Study Location • UK	• Point-of-care D-dimer SimpliRED; Cut-off: positive; negative	• Pulmonary angiography

Table 12 Cohort studies looking at laboratory-based D-dimer tests in suspected PE

Author (year)	Study details	Index test	Reference standard
Anoop (2009)	Study type • Prospective cohort study Sample characteristics • Sample size 91 • Mean age (SD) Median 61 years (range: 19-96 years) • % pre-test probability 20.9% low; 79.1% intermediate Study Location • UK	• Laboratory D-dimer MDA autodimer T3103 Cut-off: 0.50 µg FEU/ml	• Pulmonary angiography 64-slice 0.625mm thickness CTPA (GE lightSpeed VCT) with Niopam 300 contrast, 74ml at 3 ml/s
Arnautovic-Torlak (2014)	Study type • Prospective cohort study Sample characteristics • Sample size 80 • Mean age (SD) 59.83 (16.40) Study Location • Bosnia and Herzegovina	• Laboratory D-dimer New method of immunoturbidimetry (BCSX System); Cut-off: >500 ng/L	• CT scan
Burkill (2002)	Study type • Prospective cohort study Sample characteristics • Sample size 101 • Mean age (SD) 58 Study Location • UK	• Laboratory D-dimer Semi-quantitative Accuclot TM; Cut-off: positive result ≥0.25 mg/l	• CT scan • Pulmonary angiography
de Moerloose (1996)	Study type • Prospective cohort study Sample characteristics • Sample size 195 • Mean age (SD) 60 (range 19 to 95) Study Location • Switzerland	• Laboratory D-dimer VIDAS quantitative ELISA; Cut-off level: 500 ng/ml	• Composite reference standard

Author (year)	Study details	Index test	Reference standard
de Monye (2002)	Study type • Prospective cohort study Sample characteristics • Sample size 287 • Mean age (SD) 50 (18) Study Location • The Netherlands	• Laboratory D-dimer Vidas R Cut-off: 500 ng/ml Note: also reported Tinaquant R; Cut-off: 0.5 µg/ml (excluded from analysis to avoid double-counting)	• Composite reference standard
Goldhaber (1993)	Study type • Prospective cohort study Sample characteristics • Sample size 173 • Mean age (SD) Abnormal pulmonary angiogram: 57.6 (17.1) Normal pulmonary angiogram: 58.2 (16.6) Study Location • US	• Laboratory D-dimer Asserachrom; Cut-off: 500 ng/mL	• Pulmonary angiography
Gupta (2009)	Study type • Prospective cohort study Sample characteristics • Sample size 627 • Mean age (SD) 46.9 (range 15 to 94) • % pre-test probability Geneva score Low: 44.8 Intermediate: 52.6 High: 2.6% Study Location • US	• Laboratory D-dimer Advanced D-dimer; Cut-off: 1.2 mg/L	• Pulmonary angiography
King (2008)	Study type • Prospective cohort study Sample characteristics • Sample size 201 • Mean age (SD) Median age 61 years Study Location • US	• Laboratory D-dimer STA Liatest; Cut-off: positive ≥0.21 µg/mL	• CT scan

Author (year)	Study details	Index test	Reference standard
Lichey (1991)	Study type • Prospective cohort study Sample characteristics • Sample size 74 • Mean age (SD) 59.2 Study Location • Germany	• Laboratory D-dimer ELISA D-dimer by a quantitative enzyme-immunoassay Note: Also reported a D-dimer test by latex agglutination assay; Cut-off: 1000 ng/mL (excluded from analysis to avoid double-counting)	• Composite reference standard
Nilsson (2002)	Study type • Prospective cohort study Sample characteristics • Sample size 84 • Mean age (SD) PE: 59.0 (14) No PE: 49.5 (15) Study Location • Sweden	• Laboratory D-dimer Tinaquant R; Cut-off: 0.5 mg/l	• Pulmonary angiography
Pappas (1993)	Study type • Prospective cohort study Sample characteristics • Sample size 169 • Mean age (SD) Not reported Study Location • US	• Laboratory D-dimer D-Di test; Cut-off: negative result if no agglutination (approximately equivalent to 250 ng/mL of D-D or 500 FEU)	• Group 1: V/Q scan Group 2: V/Q scan and pulmonary angiography
Quinn (1994)	Study type • Prospective cohort study Sample characteristics • Sample size 36 • Mean age (SD) Not reported Study Location • Austrailia	• Laboratory D-dimer Dimertest II ELISA; Cut-off: 220 ng/mL	• Pulmonary angiography
Quinn (1999)	Study type • Prospective cohort study Sample characteristics • Sample size 103 • Mean age (SD) 59 (range 16 to 87)	• Laboratory D-dimer Asserachrom D-Di ELISA; Cut-off: 500 ng/mL Note: Study also reported outcomes of 5 latex agglutination assays (excluded from the analysis to avoid double-counting)	• Pulmonary angiography

Author (year)	Study details	Index test	Reference standard
	Study Location • US		
Taman (2016)	Study type • Prospective cohort study Sample characteristics • Sample size 98 • Mean age (SD) 50 (range 17 to 88) Study Location • Egypt	• Laboratory D-dimer STA Liatest; Cut-off: normal value <0.5 ug/ml; positive test ≥0.5 ug/ml	• Pulmonary angiography
Youssf (2014)	Study type • Prospective cohort study Sample characteristics • Sample size 30 • Mean age (SD) 49.1 (10.1) Study Location • Egypt	• Laboratory D-dimer ELFA technique (Enzyme Linked Fluorescent Assay); Cut-off: positive ≥500 ng/ml; negative <500 ng/ml	• Pulmonary angiography

See appendix E for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See evidence tables in appendix E for quality assessment of individual studies, appendix F for forest plots and appendix G for full GRADE tables. Please refer to the evidence statement section for an overall summary of the evidence.

Economic evidence

Included studies

A single search was conducted to cover all review questions in this chapter. This search returned 817 records, of which 800 were excluded on title and abstract for this review question. The remaining 17 papers were screened using a review of the full text, and all were excluded.

An additional search was conducted at the end of the guideline development process to capture economic evidence published while the guideline was being developed. This was conducted as a single re-run search covering all questions in the guideline. This search returned 2,013 records in total, all of which were excluded on title and abstract for this review question.

Excluded studies

Details of the studies excluded at full-text review are given in appendix J, along with reasons for their exclusion.

Economic model

For the review question on point-of-care versus laboratory D-dimer testing, the committee indicated that, alongside test accuracy data, recommendation making would be facilitated by information on absolute numbers of patients with each testing outcome (i.e. true positives, false negatives, true negatives, and false positives), as well as estimates of costs involved in the testing process. To provide this information, a simple cost-consequences analysis was developed. A full cost-utility analysis was felt to be inappropriate as cost effectiveness is likely to be heavily dependent on the long-term health outcomes and costs associated with false negative results (patients who have a PE but are incorrectly diagnosed). Since randomised evidence of sufficient quality on the consequences of an intentionally untreated PE is unlikely to exist, such an analysis would not be feasible without substantial speculation on the downstream outcomes for these patients.

The main results of the cost-consequences analysis in terms of the test outcomes and costs per 1000 people are presented below. Table 13 shows the incremental number of true positives, false negatives, true negatives and false positives for each point-of-care testing strategy versus laboratory testing as well as the incremental total costs with and without primary care costs. A more detailed description of the model is provided in appendix I.

Table 13 Incremental test outcomes and costs (with 95% credible intervals) per 1000 people with suspected PE for different types of D-dimer point-of-care tests versus laboratory testing

	Overall POC	Quantitative POC	Qualitative POC
Test outcomes			
True positive	-2 (-10 to 4)	4 (0 to 7)	-5 (-13 to 1)
False negative	2 (-4 to 10)	-4 (-7 to 0)	5 (-1 to 13)
True negative	151 (-6 to 296)	-38 (-168 to 90)	198 (66 to 326)
False positive	-151 (-296 to 6)	38 (-90 to 168)	-198 (-326 to -66)
Total costs			
Excluding primary care	-£14,374 (-£37,279 to £10,115)	£19,017 (-£2,189 to £41,566)	-£28,226 (-£47,727 to -£8,115)
Including primary care	-£33,725 (-£59,124 to -£6,331)	£1,374 (-£22,667 to £26,316)	-£48,021 (-£70,243 to -£25,043)

Evidence statements

Clinical evidence statements

Note that quality ratings were attached to likelihood ratios but not to sensitivity and specificity analysis because clinical decision thresholds were specified on this scale.

Main analyses

- Evidence suggests that a **negative** D-dimer result indicates a **large decrease** in the probability that a person with clinically suspected pulmonary embolism has a pulmonary embolism for both laboratory-based (LR-=0.19 [0.14 to 0.26]) and point-of-care (LR-=0.20 [0.07 to 0.44]) D-dimer tests. (Low quality evidence from 19 prospective studies on laboratory based D-dimer tests comprising 2,819 participants and very-low quality evidence from 6 studies on point-of-care D-dimer tests comprising 2,976 participants).

- Evidence suggests that a **positive** point-of-care based D-dimer result indicates a **moderate increase** in the probability that a person with clinically suspected pulmonary embolism has a pulmonary embolism (LR+=2.21 [1.77 to 2.76]). (Very-low quality evidence from 6 prospective studies comprising 2,976 participants).
- Evidence suggests that a **positive** laboratory-based D-dimer result indicates a **slight increase** in the probability that a person with clinically suspected pulmonary embolism has a pulmonary embolism (LR+=1.67 [1.36 to 2.14]). (Very-low quality evidence from 19 prospective studies comprising 2,819 participants).
- Evidence suggests that point of care D-dimer tests offer similar sensitivity (89% [0.73, 0.96] vs 92% [0.88, 0.94]) but marginally higher specificity (60% [0.50, 0.69] vs 44% [0.32. 0.58]) compared with laboratory-based tests, although the confidence intervals overlap. (Evidence from 6 prospective studies comprising 2,976 participants looking at point-of-care tests and evidence from 19 prospective studies comprising 2,819 participants looking at laboratory-based tests).

Sensitivity analyses removing studies at high risk of bias

- Evidence suggests that a **negative** laboratory based D-dimer result indicates a **moderate decrease** in the probability that a person with clinically suspected pulmonary embolism has pulmonary embolism (LR-=0.23 [0.15 to 0.33]) and that a **negative** point of care D-dimer result indicates a **large decrease** in probability (LR-=0.19 [0.05 to 0.50]). (Moderate quality evidence from 6 prospective studies comprising 937 participants looking at laboratory-based tests and very low quality evidence from 5 prospective studies comprising 2,378 participants looking at point-of-care tests).
- Evidence suggests that a **positive** laboratory based D-dimer result indicates a **slight increase** in the probability that a person with clinically suspected pulmonary embolism has pulmonary embolism (LR+=1.68 [1.23 to 2.53]) and that a **positive** point of care D-dimer result indicates a **moderate increase** in probability (LR+=2.20 [1.66 to 2.91]). (Very low quality evidence from 6 prospective studies comprising 937 participants looking at laboratory-based tests and very low quality evidence from 5 prospective studies comprising 2,378 participants looking at point-of-care tests).

Subgroup analyses

- Subgroup analyses where point-of-care tests were separated into qualitative and quantitative suggest that a **negative** D-dimer result indicates a **moderate decrease** in the probability that a person with clinically suspected pulmonary embolism has a pulmonary embolism when using a qualitative (LR-=0.27 [0.11. 0.52]), and a **very large decrease** when using a quantitative (LR-=0.03 [0.00, 0.21]) test (Very-low quality evidence from 5 prospective studies comprising 2288 participants looking at qualitative point-of-care tests and moderate quality evidence from 1 prospective study comprising 1177 participants looking at quantitative point-of-care tests).
- Subgroup analyses where point-of-care tests were separated into qualitative and quantitative suggest that a **positive** D-dimer result indicates a **moderate increase** in the probability that a person with clinically suspected pulmonary embolism has a pulmonary embolism when using a qualitative (LR-=2.35 [1.73, 2.96]) and a **slight increase** when using a quantitative (LR-=1.63 [1.53, 1.75]) test (Very-low quality evidence from 5 prospective studies comprising 2288 participants looking at qualitative point-of-care tests and moderate quality evidence from 1 prospective study comprising 1177 participants looking at quantitative point-of-care tests).
- Sub-group analyses where point-of-care tests were separated into qualitative and quantitative suggest that qualitative tests offer lower sensitivity (83% [0.68,0.92]) than

quantitative (99% [0.92 to 1.00]), but increased specificity (65% [0.59 to 0.69]) than quantitative (40% [0.36 to 0.43]), although the confidence intervals for sensitivity touch. (Evidence from 5 prospective studies comprising 2288 participants looking at qualitative point-of-care tests, evidence from 1 prospective study comprising 1177 participants looking at quantitative point-of-care tests).

- Subgroup analyses in people with low probability of PE (according to a 3-level Wells score) suggests that a **negative** D-dimer result indicates a **moderate decrease** in the probability that a person with clinically suspected pulmonary embolism has pulmonary embolism. This is the case irrespective of whether the result is laboratory based (LR-=0.28 [0.02 to 4.10]) or point of care (LR-=0.27 [0.13 to 0.60]). (very-low quality evidence from 1 prospective study comprising 281 participants looking at laboratory tests and moderate quality evidence from 1 prospective study comprising 703 participants looking at point of care tests).
- Subgroup analyses in people with low probability of PE (according to a 3-level Wells score) suggests that a **positive** laboratory based D-dimer result indicates a **slight increase** in the probability that a person with clinically suspected pulmonary embolism has a pulmonary embolism (LR+=1.24 [1.00, 1.54]) and that a **positive** point of care D-dimer result indicates a **moderate increase** (LR+=3.30 [2.58 to 4.21]). (very-low quality evidence from 1 prospective study comprising 281 participants looking at laboratory tests and high quality evidence from 1 prospective study comprising 703 participants looking at point of care tests).
- Subgroup analyses in people with moderate probability of PE (according to a 3-level Wells score) suggests that a **negative** D-dimer result indicates a **moderate decrease** in the probability that a person with clinically suspected pulmonary embolism has a pulmonary embolism. This is the case irrespective of whether the result is laboratory based (LR-=0.08 [0.01 to 1.30]) or point of care (LR-=- 0.38 (0.26, 0.58]). (very-low quality evidence from 1 prospective study comprising 330 participants looking at laboratory tests and moderate quality evidence from 1 prospective study comprising 382 participants looking at point of care tests).
- Subgroup analyses in people with moderate probability of PE (according to a 3-level Wells score) suggests that a **positive** D-dimer result indicates a **slight increase** in the probability that a person with clinically suspected pulmonary embolism has a pulmonary embolism. This is the case irrespective of whether the test is laboratory-based (LR+=1.45 [1.30, 1.62]) or point of care (LR+=1.66 [1.42 to 1.93]). (low quality evidence from 1 prospective study comprising 330 participants looking at laboratory tests and high quality evidence from 1 prospective study comprising 382 participants looking at point of care tests).
- Subgroup analyses in people with moderate probability of PE (according to a 3-level Wells score) suggests that a **negative** laboratory-based D-dimer result indicates a **moderate decrease** in the probability that a person with clinically suspected pulmonary embolism has a pulmonary embolism (LR-=0.55 [0.08 to 3.75]) and that a **negative** point of care test indicates a **large decrease** (LR-=0.15 [0.06 to 0.41]). (Very-low quality evidence from 1 prospective study comprising 16 participants looking at laboratory tests and high quality evidence from 1 prospective study comprising 92 participants looking at point of care tests).
- Subgroup analyses in people with high probability of PE (according to a 3-level Wells score) suggests that a **positive** D-dimer result indicates a **slight increase** in the probability that a person with clinically suspected pulmonary embolism has a pulmonary embolism. This is the case irrespective of whether the test is laboratory-based (LR+=1.26 [0.67, 2.35]) or point of care (LR+=1.69 [1.13 to 2.53]). (Very-low quality evidence from 1

prospective study comprising 16 participants looking at laboratory tests and moderate quality evidence from 1 prospective study comprising 92 participants looking at point of care tests).

Expert witness testimony

Directly applicable evidence from expert witness testimony suggested that although the majority of laboratories that are registered with NEQAS use quantitative tests there is some historical use of semi-quantitative tests for D-dimer. Additionally, the expert testimony suggested that there is no obvious biological reason that the tests would work differently when detecting D-dimer in people with DVT compared to people with PE as the test detects the same molecule in both cases.

Economic evidence statements

In patients with suspected PE, evidence from the de novo cost-consequences model developed for this guideline suggests that compared to laboratory testing:

- Overall, point-of-care D-dimer testing results in a small increase (2 per 1,000 people) in the number of false negative results and a large decrease (151 per 1,000) in the number of false positive results, although neither of these findings is statistically significant at the 5% level. Excluding primary care costs, the overall point-of-care testing strategy is less costly than laboratory testing (-£14,374 [-£37,279 to £10,115]). When primary costs are included, the overall point-of care testing strategy becomes significantly less costly (-£33,725 [-£59,124 to -£6,331]).
- In a subgroup analysis, quantitative point-of-care D-dimer testing results a small decrease (4 per 1,000 people) in the number of false negative results and a moderate increase (38 per 1,000 people) in the number of false positive results, although neither of these findings is statistically significant at the 5% level. Excluding primary care costs, the quantitative point-of-care testing strategy is more costly than laboratory testing (£19,017 [-£2,189 to £41,566]). When primary costs are included, the difference in costs between quantitative point-of-care testing and laboratory testing is reduced (£1,374 [-£22,667 to £26,316]).
- In a subgroup analysis, qualitative point-of-care D-dimer testing results a small increase (5 per 1,000 people) in the number of false negative results and a large decrease (198 per 1,000 people) in the number of false positive results, although neither of these findings is statistically significant at the 5% level. The qualitative point-of-care testing strategy is significantly less costly than laboratory testing both when primary care costs are excluded (-£28,226 [-£47,727 to -£8,115]) and when primary care costs are included (-£48,021 [-£70,243 to -£25,043]).

The committee’s discussion of the evidence

This section contains the joint discussion for the point-of-care D-dimer test recommendations for DVT and PE. The evidence review for the use of the point-of-care D-dimer test in people with DVT is above.

Interpreting the evidence

The outcomes that matter most

Deep vein thrombosis and pulmonary embolism

The committee discussed the impact that true positive, false positive, true negative and false negative D-dimer results have on patients. People with true positive results go on to receive imaging to confirm a VTE diagnosis and then receive appropriate anti-coagulation therapy, people with false positive results undergo unnecessary imaging which may result in increased unnecessary anxiety and healthcare expense. People with false positive results may also undergo unnecessary anticoagulant treatment in the interim if imaging is not immediately available which may have serious side-effects, including major bleeding. However, the committee agreed that the period of time that people received interim anticoagulant treatment was likely to be short in most cases. People with true negative results are correctly discharged and reassured that they do not have VTE, and people with false negative results are incorrectly discharged and go untreated with the risk of disease progression and complications, including death. A proportion of people with an untreated DVT may develop PE, which is associated with extra morbidity and mortality. If DVT is untreated this increases the risk of post-thrombotic syndrome and ulceration.

The committee were concerned with the potential for any test to increase false negative rates; small increases in false negatives are undesirable in a D-dimer test, meaning that the sensitivity of D-dimer tests is important. The committee considered that specificity is also important as it is costly to conduct imaging and these are accompanied by a radiation risk, however the committee valued sensitivity (and negative LRs which are most affected by sensitivity) over specificity (and positive LRs) as it is of great importance that those people with VTE do not go undiagnosed.

The quality of the evidence

Deep vein thrombosis and pulmonary embolism

The committee noted that the evidence for DVT varied in its quality and quantity between laboratory and the different types of point-of-care tests, ranging from low to high quality evidence from just three studies for quantitative point-of-care tests and very low to low quality evidence from 58 studies for laboratory tests. For PE, the quality ranged from low to very-low from 19 studies for laboratory tests and very-low from just 6 studies looking at point-of-care tests (only 1 study looked at both point-of-care and laboratory tests in the same study).

The evidence for both DVT and PE suffered from serious to very-serious inconsistency. Additionally, studies for quantitative point-of-care tests were generally more recent than studies looking at other D-dimer tests. However, the committee noted that for DVT, studies that compared both a laboratory and a point-of-care test in the same participants demonstrated very similar findings to the overall analysis. Consequently, the committee agreed that the data likely reflected a true difference between tests rather than one that might be explained by other differences between the studies. Only one study used quantitative point-of-care testing in people with PE and no studies looked at this and laboratory D-dimer testing in the same study. As a result, the committee agreed that the was less certainty of the diagnostic accuracy of quantitative point-of-care tests for people with PE.

For DVT, there was a serious overall risk of bias for qualitative point-of-care and laboratory studies. For PE, there was a very serious overall risk of bias for laboratory tests and a serious risk of bias for point of care tests. The main reasons for this included the reference standards being interpreted with knowledge of the D-dimer results (or lack of reporting as to whether this was the case) and a lack of reporting of the timing of the index test in relation to the reference standard.

The committee identified some gaps in their knowledge relating to the use of qualitative, semi-quantitative and quantitative point-of-care tests, namely which tests were commonly used in current clinical practice, how qualitative test are interpreted and how much variation is seen in results with quantitative tests. To address these issues the committee invited expert witness testimony on these points from a Lead scientist for Point of care testing programmes at the National External Quality Assessment Schemes for Blood Coagulation (see above for a summary of the expert witness testimony and appendix L for more details)

The committee agreed that the testimony was directly applicable to the review question and provided a useful overview of how point-of-care tests are used in current practice. However, the committee were concerned with the relatively high level of variation in results between labs for quantitative tests that was reported in the expert witness testimony and the effect that this could have on the accuracy of classification of people into D-dimer positive and negative groups.

The committee again noted the high degree of heterogeneity associated with the evidence for point-of-care tests identified in this review, but they noted that this was the also case with laboratory D-dimer tests for DVT and PE. This heterogeneity remained when sensitivity analyses were carried out to remove studies at high risk of bias. When looking at quantitative, semi-quantitative and qualitative point of care tests separately heterogeneity remained very high for positive LRs and specificity, but not for negative LRs and sensitivity. The committee noted that the heterogeneity for the quantitative negative LR and sensitivity, and semi-quantitative negative LR was zero (I^2 =0).

For D-dimer testing in people with suspected PE, there was minimal heterogeneity in negative LRs and sensitivity for laboratory tests, but the heterogeneity was much higher for the positive LR and specificity for laboratory tests and for both LRs and sensitivity and specificity for point-of-care tests. Sensitivity analyses removing studies at high risk of bias did not reduce the heterogeneity in the point-of-care test results. The heterogeneity was not reduced substantially by separating the studies into a qualitative subgroup, probably because this only removed the single quantitative study. Heterogeneity could not be determined for the single quantitative study and no semi-quantitative studies were included in the evidence base.

Taking the expert witness testimony into account, the committee noted that the heterogeneity in results seen for qualitative tests could be due to the need to read the test at exactly the right time to get a valid result and that this would be likely to lead to greater imprecision than for fully quantitative tests that are more automated and therefore have reduced scope for user error and interpretation of results.

The committee discussed the imprecision in the in the evidence for point-of-care and laboratory tests. They noted that the 95% CIs for the negative LR and sensitivity for laboratory D-dimer tests for suspected DVT and PE were narrow and therefore there was less uncertainty about the effect estimate. For point-of-care testing for suspected DVT the point estimate of sensitivity was marginally lower (0.88 versus 0.93 for laboratory tests) and the 95% CI were a little wider, and this was reflected in the marginally higher negative LR and its wider 95% CI. Imprecision was judged to be not serious for both point-of-care and laboratory tests for the negative and positive LRs for suspected DVT. When subgroup analyses were carried out dividing the point-of-care studies by type of test the qualitative tests imprecision remained not serious for the negative LRs and qualitative positive LR, but became serious for the quantitative and semi-quantitative positive LRs reflecting the wider 95% CIs around the positive LRs and the corresponding specificity results. For point-of care testing for suspected PE there was similar trend with a marginally lower point estimate for sensitivity and marginally higher for the negative LR both with wider 95% CIs than laboratory testing. In the subgroup analyses for qualitative point-of-care tests imprecision was serious for both negative and positive LRs reflecting wide 95% CIs around the sensitivity and specificity point estimates, but imprecision was not serious for the quantitative test results (that came from a single study).

The committee agreed that the size of the 95% CIs around the negative LRs and sensitivity for point-of-care and lab-based tests were particularly important as the committee needed to be sure that people who were D-dimer positive were likely to be identified and could be treated appropriately. The committee also noted the large evidence base for the use of point-of-care D-dimer tests for DVT and this increased their confidence in the overall estimation of diagnostic accuracy. Although there was less evidence for D-dimer testing in PE, the expert witness thought it was very unlikely that D-dimer tests would work differently in someone with a PE compared to DVT because they share a common biological effect on D-dimer levels and therefore the committee agreed that they could extrapolate the results from point-of-care D-dimer tests for DVT to people with PE. This increased the confidence the committee had in the evidence base for PE.

Benefits and harms

Deep vein thrombosis and pulmonary embolism

For people with suspected VTE, waiting for results of a D-dimer test can be a cause of distress and anxiety, and the dangerous nature of a PE means that a quick diagnosis is very important. Point-of-care tests present a potential solution to this by providing almost immediate results, eliminating the anxiety and treatment delays that these people experience when they have to wait for extended periods of time before finding out their test result. This is particularly useful when there are no onsite laboratory facilities.

For people with suspected DVT, the sensitivity of point-of-care D-dimer tests is marginally lower than laboratory-based tests but the specificity is higher and the negative LRs for both types of test are associated with a large decrease in the probability of having the disease. However, an analysis where qualitative, quantitative and semi-quantitative tests for DVT were considered separately showed that qualitative point-of-care tests have lower sensitivity than quantitative and semi-quantitative tests, which have comparable specificity to laboratory-based tests. Quantitative tests have marginally higher sensitivity than laboratory tests.

Evidence suggested that point-of-care tests had a similar sensitivity and marginally increased specificity compared to laboratory-based tests for PE and this is reflected in the negative LRs which had a negative result associated with a large decrease in the probability of having the disease for both types of test. However, when the point-of-care tests were separated into qualitative and quantitative tests, the evidence suggested that qualitative tests had marginally reduced sensitivity and increased specificity compared to laboratory tests and a negative result was associated with a moderate decrease in the probability of having the disease. In contrast, the specificity of quantitative tests was reduced compared to lab-based tests but the sensitivity was higher, with a smaller negative LR associated with a very large decrease in the probability of having the disease. However, the evidence came from a single study and the 95% CIs overlapped for both sensitivity and specificity.

Overall, the evidence from prospective diagnostic accuracy studies suggests that for both DVT and PE, the sensitivity of point-of-care D-dimer tests is marginally lower than laboratory-based tests, but that specificity is higher. For both DVT and PE, a negative laboratory test suggested a large decrease in likelihood of DVT/PE and a negative quantitative point of care test suggested a very large decrease in the likelihood of DVT/PE. Although there was more uncertainty surrounding the negative likelihood ratios for point of care tests, these findings suggest that these tests are comparable to laboratory-based tests at ruling out DVT/PE. However, the committee noted that the studies looked at the final diagnosis (i.e. did patient have a DVT or PE) rather than carrying out a direct comparison of D-dimer results from laboratory and point-of-care testing and so some degree of uncertainty about the relative effectiveness of these tests remains.

Based on the evidence from the included studies, the committee agreed that point-of-care tests have comparable diagnostic test accuracy to laboratory tests. They noted that in cases where laboratory testing is not available on site, and cannot be accessed rapidly (within a few hours), there is a benefit to the person with suspected VTE of having access to point-of-care test because this will enable them to obtain a faster D-dimer test result, a faster diagnosis and treatment where needed. Taking the clinical evidence and the cost - effectiveness results into account (see the cost-effectiveness section below), they made recommendations to consider a point of care test if laboratory facilities are not immediately available, reflecting the mainly very low quality of the results available and the uncertainty surrounding the evidence, and that where this test is offered it should be quantitative.

The committee noted that from the expert witness testimony that 99% of NEQAS registered laboratories in the UK already use quantitative tests, but that there is some historical use of semi-quantitative tests. The committee agreed to restrict the point-of-care tests to quantitative tests due to the greater sensitivity of this test compared to qualitative and semi-quantitative tests. They committee wanted to ensure that qualitative point-of-care tests were not used because they have lower sensitivity and greater variability in interpretation. Semi-quantitative tests were not recommended because they are rarely used in current practice and quantitative tests had higher sensitivity.

The committee noted that laboratory testing for VTE is the default approach in current practice, although some primary care centres are able to carry out point-of-care testing. Hospitals typically have on-site laboratories capable of interpreting and returning D-dimer results within an hour, however in primary care settings and those hospitals without on-site laboratories, there are extended waiting periods for D-dimer results. The committee noted that point-of-care tests are currently used less frequently for suspected PE than suspected DVT in primary care settings.

They agreed that if laboratory testing is available then it should be used in preference to a quantitative point-of-care test because although quantitative point-of-care tests have a higher sensitivity and lower negative LR than laboratory tests, the 95% CIs touch for DVT and overlap for PE and the 95% CIs for specificity overlap with that for laboratory tests for both DVT and PE. In addition, the committee did not believe that in practice, laboratory tests would have lower sensitivity than quantitative point of care tests, and that the evidence suggesting this was likely due to point of care and laboratory tests typically not being compared in the same study. Finally, the committee noted that rigorous quality assurance processes are in place in laboratory settings and they are expected to have more experienced staff performing the tests.

Cost effectiveness and resource use

Deep vein thrombosis and pulmonary embolism

The committee considered evidence from the *de novo* cost-consequences model in their discussion of the cost effectiveness of point-of-care D-dimer testing. They noted that, compared to laboratory D-dimer testing, qualitative point-of-care testing produces substantially more true negative results, but also slightly more false negative results (7 more per 1,000 suspected DVT patients and 5 more per 1,000 suspected PE patients). Qualitative point-of-care testing also produces a cost saving due to fewer false positive results requiring further imaging tests. In addition, further cost savings are made in a primary care setting, since timelier results from point-of-care tests mean that less GP time is required, and fewer patients require interim treatment while awaiting test results.

However, despite these benefits, the committee felt that qualitative point-of-care testing could not be recommended, due to the higher number of false negative results compared to laboratory testing. This is because the consequences of a false negative result are potentially much more severe than those of a false positive result. In the case of a false negative result, a patient with a DVT or PE remains untreated, which can result in adverse health consequences and potentially considerable downstream costs, which the model does not account for. In contrast, a false positive result leads to a patient without a DVT or PE undergoing further imaging tests. While this produces patient anxiety and additional costs, it is unlikely to have serious health consequences.

There were no diagnostic test accuracy studies for semi-quantitative point-of-care D-dimer tests in people with suspected PE. For suspected DVT, the cost-consequences model showed no statistically significant differences in the number of false negative and false positive results between semi-quantitative point-of-care testing and laboratory testing. If primary care costs were included in the analysis, the additional acquisition cost of point-of-care D-dimer tests were offset by savings due to fewer false positive results requiring further imaging tests. However, the committee noted that semi-quantitative tests are rarely used in current practice and did not wish to recommend them because they had lower sensitivity than quantitative tests.

For the comparisons of quantitative point-of-care D-dimer testing with laboratory testing, the committee observed that numbers of false negative and false positive outcomes were broadly similar and subject to considerable uncertainty. The exception was that quantitative point-of-care testing for suspected DVT achieved a statistically significant reduction in false negative results, but the committee noted that the absolute difference in the number of events was very small. Cost outcomes showed that quantitative D-dimer tests produce higher costs than laboratory tests when primary care costs are excluded (primarily due to the more expensive acquisition cost of the D-dimer tests). However, in primary care settings where laboratory testing is not immediately available, point-of-care tests can provide more rapid results that reduce the need for additional GP time and unnecessary interim anticoagulation treatment while awaiting D-dimer test results. When these cost offsets in primary care were taken into account in the analysis, the difference in total costs between quantitative point-of-care testing and laboratory testing was much reduced. In the case of suspected DVT, the cost-consequences model showed that using quantitative point-of-care testing in primary care where laboratory facilities are not immediately available may even be cost saving but this finding was associated with a high degree of uncertainty.

The committee discussed the practicality of conducting each type of test in primary and secondary care. Conducting a laboratory test in secondary care is generally a streamlined process, with results available in around 40 minutes. Similarly, a point-of-care test can produce results in around 30 minutes. However, in primary care settings where laboratory facilities are often not immediately available, it can take 24 hours to obtain results for a laboratory D-dimer test. The committee considered the balance of factors and agreed that recommending one test over another purely on the basis of diagnostic accuracy would not be appropriate, given the level of uncertainty in the evidence, but felt it was important to highlight that the cost effectiveness of a point-of-care testing strategy depends on the setting of care.

Results of the cost-consequences analysis showed that quantitative point-of-care D-dimer tests are generally comparable to laboratory tests in terms of accuracy and although they have a higher acquisition cost, they may produce cost offsets in a primary care setting and result in faster appropriate treatment. Therefore, the committee felt that quantitative point-of-care testing should be considered where laboratory facilities are not immediately available.

The committee discussed the potential resource impact of their recommendations. Point-of-care testing may incur an upfront cost, since surgeries will need to buy analyser equipment in order to carry out quantitative tests. However, the committee noted that, in many cases, such equipment is provided by manufacturers free of charge, so surgeries only have to pay for consumables. Moreover, based on experience the committee was aware that some primary care centres are already using point-of-care testing but was unable to estimate what proportion of centres are currently using point-of-care testing on a national level.

Other factors the committee took into account

Deep vein thrombosis and pulmonary embolism

The committee reviewed the evidence for point-of-care tests alongside the evidence for age-adjusted D-dimers and noted that an age-adjustment formula could be applied to quantitative D-dimer tests, but not to qualitative and semi-quantitative point-of-care tests due the nature of the adjustment. The committee decided not to restrict the use of age-adjusted formulas to laboratory tests as they could see no reason why they would not work in the same way for quantitative point-of-care tests as for laboratory-based D-dimer tests.

Appendices

Appendix A – Review protocols

Review protocol for the diagnostic accuracy of age-adjusted D-dimer tests in suspected DVT

Field (based on PRISMA-P)	Content
Review question	In people with suspected DVT, what is the diagnostic accuracy of age-adjusted D-dimer tests compared with D-dimer tests without age adjustment?
Type of review question	Diagnostic
Objective of the review	The surveillance review highlighted that many false positive results were obtained with D-dimer tests, especially in older people. It has been suggested that use of age-adjusted D-dimer in PE may be more appropriate, and lead to fewer false-positives. Therefore guidance is required on this for PE. Following stakeholder consultation of the draft scope the same question for clinically suspected DVT was added to the scope.
Eligibility criteria – population	Adults (18+ years) with clinically suspected DVT
Eligibility criteria – intervention(s)/index test(s)	**Diagnostic accuracy studies:** **Index tests** • Age-adjusted D-dimer test 'Age-adjusted' means that the threshold for a positive test is dependent on the age of the patient • D-dimer test (without age adjustment – fixed test threshold) **Test and Treat RCTs:** **Intervention:**

	• Age-adjusted D-dimer test 'Age-adjusted' means that the threshold for a positive test is dependent on the age of the patient
Eligibility criteria – comparator(s)/control or reference (gold) standard	**For diagnostic accuracy studies:** • Reference standard: Ultrasound, venography, MRI scan, CT scan, VTE event during 3 months or more follow-up **Test and treat RCTs:** **Comparator:** • D-dimer test (without age adjustment – fixed test threshold)
Outcomes and prioritisation	**For diagnostic accuracy studies:** • Diagnostic accuracy metrics: Sensitivity/specificity, Positive and negative likelihood ratios **For test and treat RCTs:** • All-cause mortality • VTE-related mortality • Recurrence of VTE • Length of hospital stay • Quality of life o Generic and disease-specific measures will be reported o Overall score will be reported (data on subscales will not be reported) • Post-thrombotic syndrome • Adverse events o Total serious adverse events (as defined by the European medicines agency) will be reported if data is available. o Major bleeding (as defined by International Society on Thrombosis and Haemostasis)

	○ Clinically relevant non-major bleeding (as defined by International Society on Thrombosis and Haemostasis) ○ Intracranial haemorrhage ○ Liver injury
Eligibility criteria – study design	• Prospective diagnostic accuracy studies • Test and treat RCTs
Other inclusion exclusion criteria	• English language papers included only. • Diagnostic accuracy studies that do not report sufficient information to allow a 2*2 table (TP, FP, TN, FN) to be constructed will be excluded • Diagnostic accuracy studies where performance of index test depends of the result of the reference test (or vice versa) will be excluded. • Studies with the purpose of establishing optimal D-dimer thresholds • Retrospective studies • Studies using different reference standards across participants • Case-controlled studies
Proposed sensitivity/sub-group analysis	• Analysis will be stratified by pre-test probability (e.g. in groups categorised by Well's score) where data is available. • People with cancer. • People who have restricted movement. • People with leg trauma • People with chronic infection / HIV • People with previous VTE • People with delayed clinical presentation (7 days or more)

	• People with obesity III (a BMI of 40 kg/m^2 or more). • People who have stage 3 to 5 chronic kidney disease.
Selection process – duplicate screening/selection/ analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See Appendix B

Information sources – databases and dates	• Sources to be searched
	    ○ Clinical searches - Medline, Medline in Process, PubMed, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA.
	    ○ Economic searches - Medline, Medline in Process, PubMed, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied.
	• Supplementary search techniques
	    ○ None identified
	• Limits
	    ○ Studies reported in English
	    ○ Study design RCT, SR and Observational filter will be applied (as agreed)

	○ Animal studies will be excluded from the search results ○ Conference abstracts will be excluded from the search results
Identify if an update	This is a new question for the update of the guideline, therefore no previous search has been undertaken for this question.
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10087
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C of the evidence review
Data collection process – forms/duplicate	A standardised evidence table format will be used and published as appendix E (clinical evidence tables) or I (economic evidence tables) of the evidence review (where relevant).
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or I (economic evidence tables) of the evidence review (where relevant).
Methods for assessing bias at outcome/study level	See Appendix B
Criteria for quantitative synthesis (where suitable)	See Appendix B
Methods for analysis – combining studies and exploring (in)consistency	See Appendix B

Meta-bias assessment – publication bias, selective reporting bias	See Appendix B
Assessment of confidence in cumulative evidence	See Appendix B
Rationale/context – Current management	For details please see the introduction to the evidence review
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NICE Guidelines Updates Team and chaired by Susan Bewley in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guidelines Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods section of the evidence review.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
PROSPERO registration number	N/A

Review protocol for the diagnostic accuracy of point-of-care D-dimer tests in suspected DVT

Field (based on PRISMA-P	Content
Review question	In people with suspected DVT, what is the diagnostic accuracy of point-of-care D-dimer tests compared with laboratory tests to identify DVT?
Type of review question	Diagnostic
Objective of the review	This was identified as an issue by the GP reference panel during the scoping process. POINT-OF-CARET D-dimer tests was not specifically addressed in the original guideline; clearer guidance is required on whether a POINT-OF-CARET D-dimer test is suitable for use (i.e. does it have comparable diagnostic usefulness as laboratory D-dimer tests?)
Eligibility criteria – population	Adults (18+ years) with clinically suspected DVT
Eligibility criteria – intervention(s)/ index test(s)	**Diagnostic accuracy studies:** **Index tests:** • Point of care D-dimer test (including qualitative, semi quantitative and quantitative tests - these categories of tests will be reported and analysed separately) 'Point of care' is defined as testing at or near the place and time of patient contact (for example, in an emergency department or GP surgery) • Laboratory tests for D-dimer **Test and Treat RCTs:** **Intervention:**

	• Point of care D-dimer test (including qualitative, semi quantitative and quantitative tests, these categories of tests will be reported and analysed separately)
Eligibility criteria – comparator(s)/control or reference (gold) standard	**Diagnostic accuracy studies:** • Reference standard: ultrasound, venography, MRI, CT scan, VTE event during 3 months or more follow-up **Test and treat RCTs:** Comparator: • Laboratory tests for D-dimer
Outcomes and prioritisation	**Diagnostic accuracy studies:** • Diagnostic accuracy metrics: Sensitivity/specificity, Positive and negative likelihood ratios **Test and treat RCTs:** • All-cause mortality • VTE-related mortality • Recurrence of VTE • Length of hospital stay • Quality of life o Generic and disease-specific measures will be reported o Overall score will be reported (data on subscales will not be reported) • Post-thrombotic syndrome • Adverse events o Total serious adverse events (as defined by the European medicines agency) will be reported if data is available. o Major bleeding (as defined by International Society on Thrombosis and Haemostasis) o Clinically relevant non-major bleeding (as defined by International Society on Thrombosis and Haemostasis)

	○ Intracranial haemorrhage ○ Liver injury
Eligibility criteria – study design	• Prospective diagnostic accuracy studies • Test and treat RCTs
Other inclusion exclusion criteria	• English language papers included only. • Diagnostic accuracy studies that do not report sufficient information to allow a 2*2 table (TP, FP, TN, FN) to be constructed will be excluded • Diagnostic accuracy studies where performance of index test depends of the result of the reference test (or vice versa) will be excluded. • Studies with the purpose of establishing optimal D-dimer thresholds • Retrospective studies • Studies using different reference standards across participants • Case-controlled studies
Proposed sensitivity/sub-group analysis	• Analysis will be stratified by pre-test probability (e.g. in groups categorised by Well's score) where data is available. • People with cancer. • People who have restricted movement. • People with leg trauma • People with chronic infection / HIV • People with previous VTE • People with delayed clinical presentation (7 days or more) • People with obesity III (a BMI of 40 kg/m^2 or more). • People who have stage 3 to 5 chronic kidney disease.

Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See Appendix B

Information sources – databases and dates	• Sources to be searched
	  o Clinical searches - Medline, Medline in Process, PubMed, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA.
	  o Economic searches - Medline, Medline in Process, PubMed, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied.
	• Supplementary search techniques
	  o None identified
	• Limits
	  o Studies reported in English
	  o Study design RCT, SR and Observational filter will be applied (as agreed)
	  o Animal studies will be excluded from the search results
	  o Conference abstracts will be excluded from the search results
	  o Date limit from August 2011

Identify if an update	This is an update of guideline CG144, however this is a new question for this update.

Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10087
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C of the evidence review
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or I (economic evidence tables) of the evidence review (where relevant).
Data items – define all variables to be collected	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or I (economic evidence tables) of the evidence review (where relevant).
Methods for assessing bias at outcome/study level	See appendix B
Criteria for quantitative synthesis (where suitable)	See appendix B
Methods for analysis – combining studies and exploring (in)consistency	See appendix B
Meta-bias assessment – publication bias, selective reporting bias	See appendix B
Assessment of confidence in cumulative evidence	See appendix B

Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NICE Guidelines Updates Team and chaired by Susan Bewley in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guidelines Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods section of the evidence review.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
PROSPERO registration number	N/A

Review protocol for the diagnostic accuracy of age-adjusted D-dimer tests in suspected PE

Field (based on PRISMA-P	Content
Review question	In people with suspected PE, what is the diagnostic accuracy of age-adjusted D-dimer tests compared with D-dimer tests without age adjustment?
Type of review question	Diagnostic
Objective of the review	The surveillance review highlighted that many false positive results were obtained with D-dimer tests, especially in older people. It has been suggested that use of age-adjusted D-dimer may be more appropriate, and lead to fewer false-positives. Therefore guidance is required on this.
Eligibility criteria – population	Adults (18+ years) with clinically suspected PE
Eligibility criteria – intervention(s)/ index test(s)	**Diagnostic accuracy studies:** **Index tests** • Age-adjusted D-dimer test 'Age-adjusted' means that the threshold for a positive test is dependent on the age of the patient • D-dimer test (without age adjustment – fixed test threshold) **Test and Treat RCTs:** **Intervention:** • Age-adjusted D-dimer test 'Age-adjusted' means that the threshold for a positive test is dependent on the age of the patient

Eligibility criteria – comparator(s)/control or reference (gold) standard	**For diagnostic accuracy studies:** • Reference standard: CT scan, MRI scan, VQ scan, pulmonary angiography, VTE event during 3 months or more follow-up **Test and treat RCTs:** **Comparator:** • D-dimer test (without age adjustment – fixed test threshold)
Outcomes and prioritisation	**For diagnostic accuracy studies:** • Diagnostic accuracy metrics: Sensitivity/specificity, Positive and negative likelihood ratios **For test and treat RCTs:** • All-cause mortality • VTE-related mortality • Recurrence of VTE • Length of hospital stay • Quality of life o Generic and disease-specific measures will be reported o Overall score will be reported (data on subscales will not be reported) • CTEPH • Adverse events o Total serious adverse events (as defined by the European medicines agency) will be reported if data is available. o Major bleeding (as defined by International Society on Thrombosis and Haemostasis) o Clinically relevant non-major bleeding (as defined by International Society on Thrombosis and Haemostasis) o Intracranial haemorrhage o Liver injury
Eligibility criteria – study design	• Prospective diagnostic accuracy studies[a] • Test and treat RCTs

[a] Note that a post-hoc protocol deviation was made to also include retrospective studies that directly compared age-adjusted and non-age adjusted D-dimer tests. For details, see methods.

Other inclusion exclusion criteria	• English language papers included only. • Diagnostic accuracy studies that do not report sufficient information to allow a 2*2 table (TP, FP, TN, FN) to be constructed will be excluded • Diagnostic accuracy studies where performance of index test depends of the result of the reference test (or vice versa) will be excluded. • Studies with the purpose of establishing optimal D-dimer thresholds • Retrospective studies • Studies using different reference standards across participants • Case-controlled studies
Proposed sensitivity/sub-group analysis, or meta-regression	• Analysis will be stratified by pre-test probability (e.g. in groups categorised by Well's score) where data is available. • People with cancer. • People who have restricted movement. • People with chronic infection / HIV • People with previous VTE • People with delayed clinical presentation (7 days or more) • People with obesity III (a BMI of 40 kg/m^2 or more). • People who have stage 3 to 5 chronic kidney disease.
Selection process – duplicate screening/selection/ analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued

	until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See appendix B

Information sources – databases and dates	• Sources to be searched
	  o Clinical searches - Medline, Medline in Process, PubMed, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA.
	  o Economic searches - Medline, Medline in Process, PubMed, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied.
	• Supplementary search techniques
	  o None identified
	• Limits
	  o Studies reported in English
	  o Study design RCT, SR and Observational filter will be applied (as agreed)
	  o Animal studies will be excluded from the search results
	  o Conference abstracts will be excluded from the search results

Identify if an update	This is a new question for the update of the guideline, therefore no previous search has been undertaken for this question.
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10087
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C of the evidence review

Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or I (economic evidence tables) of the evidence review (where relevant).
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or I (economic evidence tables) of the evidence review (where relevant).
Methods for assessing bias at outcome/study level	See appendix B
Criteria for quantitative synthesis (where suitable)	See appendix B
Methods for analysis – combining studies and exploring (in)consistency	See appendix B
Meta-bias assessment – publication bias, selective reporting bias	See appendix B
Assessment of confidence in cumulative evidence	See appendix B
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NICE Guidelines Updates Team and chaired by Susan Bewley in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guidelines Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-

	effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods section of the evidence review.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
PROSPERO registration number	N/A

Review protocol for the diagnostic accuracy of point-of-care D-dimer tests in suspected PE

Field (based on PRISMA-P	Content
Review question	In people with clinically suspected PE, what is the diagnostic accuracy of point-of-care D-dimer tests compared with laboratory tests to identify PE?
Type of review question	Diagnostic
Objective of the review	This was raised by the GP reference panel during the scoping process. There is lack of clarity over whether point of care testing for PE is clinically useful. Therefore this area was prioritised for update.
Eligibility criteria – population	Adults (18+ years) with clinically suspected PE
Eligibility criteria – intervention(s)/ index test(s)	**Diagnostic accuracy studies:** **Index tests:** • Point of care D-dimer test (including qualitative, semi quantitative and quantitative tests - these categories of tests will be reported and analysed separately) 'Point of care' is defined as testing at or near the place and time of patient contact (for example, in an emergency department or GP surgery) • Laboratory tests for D-dimer **Test and Treat RCTs:** **Intervention:** • Point of care D-dimer test (including qualitative, semi quantitative and quantitative tests - these categories of tests will be reported and analysed separately)
Eligibility criteria –	**Diagnostic accuracy studies:**

comparator(s)/ control or reference (gold) standard	Reference standard: CT scan, MRI scan, VQ scan, pulmonary angiography, 3 months or more follow-up **Test and treat RCTs:** Comparator: • Laboratory tests for D-dimer

Outcomes and prioritisation	**Diagnostic accuracy studies:**
	• Diagnostic accuracy metrics: Sensitivity/specificity, Positive and negative likelihood ratios
	
	Test and treat RCTs:
	
	• All-cause mortality
	• VTE-related mortality
	• Recurrence of VTE
	• Length of hospital stay
	• Quality of life
	  ○ Generic and disease-specific measures will be reported
	  ○ Overall score will be reported (data on subscales will not be reported)
	• CTEPH
	• Adverse events
	  ○ Total serious adverse events (as defined by the European medicines agency) will be reported if data is available.
	  ○ Major bleeding (as defined by International Society on Thrombosis and Haemostasis)
	  ○ Clinically relevant non-major bleeding (as defined by International Society on Thrombosis and Haemostasis)
	  ○ Intracranial haemorrhage
	  ○ Liver injury

Eligibility criteria – study design	• Prospective diagnostic accuracy studies • Test and treat RCTs
Other inclusion exclusion criteria	• English language papers included only.

	• Diagnostic accuracy studies that do not report sufficient information to allow a 2*2 table (TP, FP, TN, FN) to be constructed will be excluded • Diagnostic accuracy studies where performance of index test depends of the result of the reference test (or vice versa) will be excluded. • Studies with the purpose of establishing optimal D-dimer thresholds • Retrospective studies • Studies using different reference standards across participants • Case-controlled studies
Proposed sensitivity/sub-group analysis	• Analysis will be stratified by pre-test probability (e.g. in groups categorised by Well's score) where data is available. • People with cancer. • People who have restricted movement. • People with chronic infection / HIV • People with previous VTE • People with delayed clinical presentation (7 days or more) • People with obesity III (a BMI of 40 kg/m^2 or more). • People who have stage 3 to 5 chronic kidney disease.
Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer.

	This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See appendix B

Information sources – databases and dates	• Sources to be searched
	  o Clinical searches - Medline, Medline in Process, PubMed, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA.
	  o Economic searches - Medline, Medline in Process, PubMed, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied.
	• Supplementary search techniques
	  o None identified
	• Limits
	  o Studies reported in English
	  o Study design RCT, SR and Observational filter will be applied (as agreed)
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Identify if an update	This is a new question for the update of this guideline, therefore no date limit for searches.
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10087
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C of the evidence review
Data collection process –	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or I

forms/duplicate	(economic evidence tables) of the evidence review (where relevant).
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or I (economic evidence tables) of the evidence review (where relevant).
Methods for assessing bias at outcome/study level	See appendix B
Criteria for quantitative synthesis (where suitable)	See appendix B
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Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NICE Guidelines Updates Team and chaired by Susan Bewley in line with section 3 of Developing NICE guidelines: the manual.

	Staff from the NICE Guidelines Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods section of the evidence review.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
PROSPERO registration number	N/A

Appendix B – Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being ‘includes’ or ‘excludes’ during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstract can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstract (or 1,000 records, if that is a greater number) were always screened.
- After this point, screening was only terminated if a pre-specified threshold was met for a number of abstracts being screened without a single new include being identified. This threshold was set according to the expected proportion of includes in the review (with reviews with a lower proportion of includes needing a higher number of papers without an identified study to justify termination) and was always a minimum of 250.
- A random 10% sample of the studies remaining in the database were additionally screened, to check if a substantial number of relevant studies were not being correctly classified by the algorithm, with the full database being screened if concerns were identified.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search.

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All included studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.

- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline (for example, some of the factors in the protocol only).
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, and were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 14. When systematic reviews were used as a source of primary data, and unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 14: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Diagnostic test accuracy evidence

In this guideline, diagnostic test accuracy (DTA) data are classified as any data in which a feature – be it a symptom, a risk factor, a test result or the output of some algorithm that combines many such features – is observed in some people who have the condition of interest at the time of the test and some people who do not. Such data either explicitly provide, or can be manipulated to generate, a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not).

The 'raw' 2x2 data can be summarised in a variety of ways. Those that were used for decision making in this guideline are as follows:

- **Positive likelihood ratios** describe how many times more likely positive features are in people with the condition compared to people without the condition. Values greater than 1 indicate that a positive result makes the condition more likely.
  - LR^{+} = (TP/[TP+FN])/(FP/[FP+TN])
- **Negative likelihood ratios** describe how many times less likely negative features are in people with the condition compared to people without the condition. Values less than 1 indicate that a negative result makes the condition less likely.
  - LR^{-} = (FN/[TP+FN])/(TN/[FP+TN])
- **Sensitivity** is the probability that the feature will be positive in a person with the condition.
  - sensitivity = TP/(TP+FN)
- **Specificity** is the probability that the feature will be negative in a person without the condition.
  - specificity = TN/(FP+TN)

Interpretation of diagnostic accuracy measures

Clinical decision thresholds were chosen by the committee to correspond to the likelihood ratio above (for positive likelihood ratios) or below (for negative likelihood ratios) which a diagnostic test was accurate enough to be recommended. The following schema, adapted from the suggestions of Jaeschke et al. (1994), was used inform these discussions.

Table 15: Interpretation of likelihood ratios

Value of likelihood ratio	Interpretation
LR ≤ 0.1	**Very large** decrease in probability of disease
0.1 < LR ≤ 0.2	**Large** decrease in probability of disease
0.2 < LR ≤ 0.5	**Moderate** decrease in probability of disease
0.5 < LR ≤ 1.0	**Slight** decrease in probability of disease
1.0 < LR < 2.0	**Slight** increase in probability of disease
2.0 ≤ LR < 5.0	**Moderate** increase in probability of disease
5.0 ≤ LR < 10.0	**Large** increase in probability of disease
LR ≥ 10.0	**Very large** increase in probability of disease

The schema above has the effect of setting a minimal important difference for positive likelihoods ratio at 2, and a corresponding minimal important difference for negative likelihood ratios at 0.5. Likelihood ratios (whether positive or negative) falling between these thresholds were judged to indicate no meaningful change in the probability of disease.

Quality assessment

Individual studies were quality assessed using the QUADAS-2 tool, which contains four domains: patient selection, index test, reference standard, and flow and timing. Each individual study was classified into one of the following two groups:

- Low risk of bias – Evidence of non-serious bias in zero or one domain.
- Moderate risk of bias – Evidence of non-serious bias in two domains only, or serious bias in one domain only.
- High risk of bias – Evidence of bias in at least three domains, or of serious bias in at least two domains.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, index features and/or reference standard in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, index feature and/or reference standard.
- Partially indirect – Important deviations from the protocol in one of the population, index feature and/or reference standard.
- Indirect – Important deviations from the protocol in at least two of the population, index feature and/or reference standard.

Methods for combining diagnostic test accuracy evidence

Meta-analysis of diagnostic test accuracy data was conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

Where applicable, diagnostic syntheses were stratified by:

- Presenting symptomatology (features shared by all participants in the study, but not all people who could be considered for a diagnosis in clinical practice).
- The reference standard used for true diagnosis.

Where five or more studies were available for all included strata, a bivariate model was fitted using the `mada` package in R v3.4.0, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. Where sufficient data were not available (2-4 studies), separate independent pooling was performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using Microsoft Excel. This approach is conservative as it is likely to somewhat underestimate test accuracy, due to failing to account for the correlation and trade-off between sensitivity and specificity (see Deeks 2010).

Random-effects models (der Simonian and Laird) were fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Modified GRADE for diagnostic test accuracy evidence

GRADE has not been developed for use with diagnostic studies; therefore a modified approach was applied using the GRADE framework. GRADE assessments were only undertaken for positive and negative likelihood ratios, as the MIDs used to assess imprecision were based on these outcomes, but results for sensitivity and specificity are also presented alongside those data.

Cross-sectional and cohort studies (retrospective and prospective cohort studies) were initially rated as high-quality evidence if well conducted, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness) as detailed in Table 16 below. All retrospective cohort studies were judged to be at moderate or high risk of bias.

Table 16: Rationale for downgrading quality of evidence for diagnostic questions

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.

GRADE criteria	Reasons for downgrading quality
Imprecision	If the 95% confidence interval for positive or negative likelihood ratios crossed the decision threshold for recommending a test the outcome was downgraded 1 level. If the 95% confidence interval crossed 1 (the likelihood ratio corresponding to no diagnostic utility), the outcome was downgraded 1 level. If the 95% confidence interval crossed 1 and the decision threshold for recommending a test the outcome was downgraded 2 levels as suffering from very serious imprecision. For information on how decision thresholds were determined, see the section on interpretation of diagnostic accuracy measures. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if either of the following conditions were met:

- Data showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

Evidence statements were written for positive and negative likelihood ratios and indicate the magnitude of effect on the probability of having a PE or DVT (based on the categories in Table 15) associated with a positive test result or a negative test result with a quality rating for each finding. Additionally, evidence statements using sensitivity and specificity data were written when deemed necessary by the committee to summarise discussions.

Appendix C – Literature search strategies

A single systematic search was conducted for all of the questions within this evidence review on 1st May 2018 and re run on 4th April 2019. The following databases were searched Medline, Medline in Process, Medline e pub Ahead of print, Embase, (all via the Ovid platform), Cochrane Database of Systematic Reviews, CENTRAL and DARE (all via the Wiley platform). Date limits were applied to the date of the previous guideline for the deep vein thrombosis terms. Sensitive McMaster University Health Information Research Unit diagnosis and NICE inhouse RCT filters were attached were appropriate.

The Medline strategy is presented below. This was translated for other databases.

1	Venous Thrombosis/
2	(phlegmasia adj2 dolens).tw.
3	(thrombo* adj2 (vein* or venous)).tw.
4	(venous adj stasis).tw.
5	dvt.tw.
6	or/1-5
7	Venous Thromboembolism/ or Embolism, paradoxical/
8	vte.tw.
9	exp pulmonary embolism/
10	((pulmonary or lung) adj4 (embol* or thromboembo* or microembol*)).tw.
11	(pulmonary adj infarction).tw.
12	or/7-11
13	Fibrin Fibrinogen Degradation Products/
14	((fibrin* or fibrogen) adj4 (product* or fragment* or label*)).tw.
15	fdp.tw.
16	("d dimer*" or "d-dimer*").tw.
17	((wells or Geneva or clinical) adj score*).tw.
18	or/13-17
19	(201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018*).ed.
20	6 and 18 and 19
21	12 and 18
22	20 or 21
23	(sensitiv: or diagnos:).mp. or di.fs.
24	Randomized Controlled Trial.pt.
25	Controlled Clinical Trial.pt
26	Clinical Trial.pt.
27	exp Clinical Trials as Topic/
28	Placebos/
29	Random Allocation/
30	Double-Blind Method/
31	Single-Blind Method/
32	Cross-Over Studies/
33	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
34	(random$ adj3 allocat$).tw.
35	placebo$.tw.
36	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
37	(crossover$ or (cross adj over$)).tw.
38	or/24-37
39	animals/ not humans/

40 38 not 39
41 23 or 40
42 22 and 41
43 animals/ not humans/
44 42 not 43
45 limit 44 to english language

Searches to identify economic evidence were run on 3rd May 2018 in Medline, Medline in Process, Econlit and Embase (all va the Ovid platform), NHS EED and the Health Technology Database (via the Wiley platform. NICE inhouse economic evaluation and Quality of Life filters were attached to lines 1 to 22 of the core strategy (lines 1 to 22 of the Medline version shown above) in the Medline and Embase databases. A single search for economic evidence covering all questions was re run on 9th April 2019.The Medline version of the filters is displayed below.

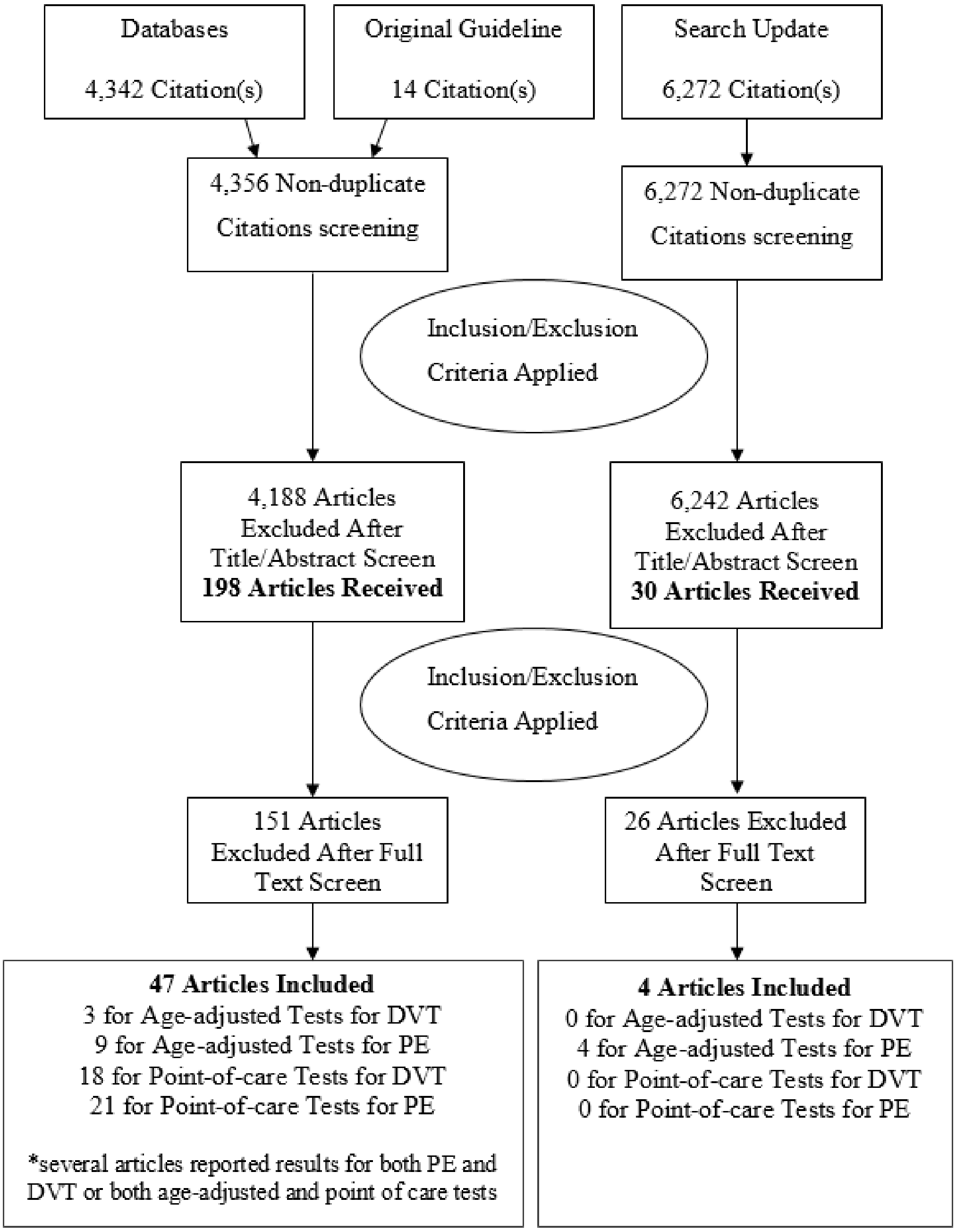
Economic evaluations

1 Economics/
2 exp "Costs and Cost Analysis"/
3 Economics, Dental/
4 exp Economics, Hospital/
5 exp Economics, Medical/
6 Economics, Nursing/
7 Economics, Pharmaceutical/
8 Budgets/
9 exp Models, Economic/
10 Markov Chains/
11 Monte Carlo Method/
12 Decision Trees/
13 econom$.tw.
14 cba.tw.
15 cea.tw.
16 cua.tw.
17 markov$.tw.
18 (monte adj carlo).tw.
19 (decision adj3 (tree$ or analys$)).tw.
20 (cost or costs or costing$ or costly or costed).tw.
21 (price$ or pricing$).tw.
22 budget$.tw.
23 expenditure$.tw.
24 (value adj3 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25

Quality of Life

1 "Quality of Life"/
2 quality of life.tw.
3 "Value of Life"/
4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly$ or qald$ or qale$ or qtime$).tw.
7 disability adjusted life.tw.
8 daly$.tw.
9 Health Status Indicators/ (22343)
10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

Appendix D – Clinical evidence study selection



Appendix E – Clinical evidence tables

Deep vein thrombosis

Age-adjusted D-dimer

Author (year)	Title	Study details	Quality assessment
Gomez-Jabalera (2017)	Age-adjusted D-dimer for the diagnosis of deep vein thrombosis	Study type • Prospective cohort study Study details • Study location Spain • Study setting single hospital primary care referrals • Study dates November 2015 - May 2016 Inclusion criteria • Suspected DVT • Outpatient/primary care patients Must have had previous examination by Primary Care Physician Exclusion criteria • Previous VTE Suspected prior DVT • Anticoagulation therapy • Extended duration of symptoms >1 months and suspicion of PE or final diagnosis of thrombophlebitis • Suspected PE • Well score high probability wells score (>3)	Patient selection • Low risk of bias Index test • Low risk of bias Reference standard • Low risk of bias Interpreted blind to index test results Flow and timing • Unclear risk of bias Unclear timing of reference standard in relation to index test Overall risk of bias • Low Unclear timing of reference standard in relation to admission however low risk of bias from other areas. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Sample characteristics • Sample size 138 • % female 60.5% female • Mean age (SD) 71.6 years • % pre-test probability Well score low = 69.6% intermediate = 21% High = 9.4% Index test (s) • Laboratory D-dimer Hemos IL-500 • Age-adjusted D-dimer tested several formulas: Age x 10 ug/L Age x 15 ug/L age x 20 ug/L Age x 25 ug/L Age x 30 ug/L We reported data for age x 10 ug/L Reference standard (s) • Ultrasonography Following the analysis, experienced personnel performed a whole leg compression ultrasonography of the symptomatic leg by a B mode and pulsed Doppler in the common femoral vein, the popliteal vein, calf veins and great and small saphenous veins. The sonographic scanner used was a linear array at 5–7.5MHz (SonoSite M-Turbo ultrasound).20 The DVT diagnosis was established if one or more deep veins in the leg were not completely compressible or there were not any phasic flow signs with respiratory movements of calf compression. Additional comments • 2 x 2 table	

Author (year)	Title	Study details	Quality assessment
		Was taken directly from Gomez-Jabalera (2017)	
Oude (2015)	Clinical evaluation of eight different D-dimer tests for the exclusion of deep venous thrombosis in primary care patients	Study type • Prospective cohort study Study details • Study location The Netherlands • Study dates "Over a period of 23 months" Inclusion criteria • Suspected DVT • Outpatient/primary care patients Exclusion criteria • Age <18 • Anticoagulation therapy with vitamin K antagonists and/or LMWH. Sample characteristics • Sample size 290 • % female 60.3% • Mean age (SD) 56.6 (18.1-87.9) years Index test (s) • Laboratory D-dimer Vidas (also reported innovance [on both CA-1500 and BCS systems separately), ACL-TOP, Tina-quant and Liatest but these were not extracted for this review)	Patient selection • Low risk of bias Index test • Low risk of bias Reference standard • Low risk of bias interpreted blind to D-dimer results Flow and timing • Unclear risk of bias Unclear timing of reference and index tests Overall risk of bias • Low Unclear timing of reference standard however all low-risk in all other respects. Directness • Directly applicable Although participants with distal DVT (N=15) were excluded from analysis.

Author (year)	Title	Study details	Quality assessment
		• Age-adjusted D-dimer Quantitative lab-based test: Vidas (also reported innovance [on both CA-1500 and BCS systems separately), ACL-TOP, Tina-quant and Liatest but these were not extracted for this review) Quantitative POINT-OF-CARE: pathfast (AQT90 also reported but was not extracted for this review) • Point-of-care D-dimer Quantitative: Pathfast (also reported AQT90 but was not extracted for this review) Qualitative test: Simplify Reference standard (s) • Ultrasonography Real time B-mode compression ultrasonography with a 9 mHz lineararray sonographic scanner Additional comments • 2 x 2 table Was taken directly from Oude Elferink 2015	
Prochaska (2017)	Age-related diagnostic value of D-dimer testing and the role of inflammation in patients with suspected deep vein thrombosis	Study type • Prospective cohort study Study details • Study location Germany • Study setting Department of Angiology • Study dates 2013 - 2015 • Loss to follow-up 56/500 • Sources of funding German Federal Ministry of Education and Research and the Centre for Translational Vascular Biology of	Patient selection • Low risk of bias Index test • Low risk of bias Fifty six participants (11.2%) had an inconclusive d-dimer test. This was not considered to introduce bias. Reference standard • Low risk of bias Flow and timing • Unclear risk of bias Unclear timing of reference standard

Author (year)	Title	Study details	Quality assessment
		the University Medical Center Mainz Inclusion criteria • Suspected DVT Clinical suspicion of acute DVT • Age ≥ 18 years Exclusion criteria • None reported Sample characteristics • Sample size 500 • % female 55.6 • Mean age (SD) Median age 60.0 (interquartile range [IQR] 45.0, 72.0) • % pre-test probability Low-to-moderate (Wells score 0–2): 84.4 High (Wells score >2): 15.6 • % people with cancer 17.0 Index test (s) • Laboratory D-dimer Innovance from 04/2013 to 07/2014 and HemosIL HS from 08/2014 to the end of study. Cut-off: 0.5 mg/L fibrinogen equivalent unit (FEU) • Age-adjusted D-dimer age-dependent threshold applied to patients over 60 years (age/100mg/L)	following admission Overall risk of bias • Moderate Unclear timing and over 10% of participants received and unclear reference standard result and were consequentially removed from analysis. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Reference standard (s) • Ultrasound Compression duplex ultrasound Subgroup analyses • People with cancer • People with previous VTE Suspected recurrent DVT • Provoked versus unprovoked Additional comments • 2 x 2 table Was taken from Proschaska (2017) and online supplementary material.	

Point-of-care D-dimer

Author (year)	Title	Study details	Quality assessment
Baker (2010)	Comparison of a point of care device against current laboratory methodology using citrated and EDTA samples for the determination of D-dimers in the exclusion of proximal deep vein thrombosis	Study type • Prospective cohort study Study details • Study location UK • Study setting Approached from DVT diagnosis service at Oxford Haemophilia and Thrombosis Centre • Study dates Not reported Inclusion criteria • None reported	Patient selection • Unclear risk of bias Patients were approached in a DVT diagnosis clinic but no inclusion/exclusion criteria was reported. Index test • Unclear risk of bias No information regarding whether D-dimers were interpreted independent of each other and without knowledge of reference standard result Reference standard • Unclear risk of bias Unclear whether reference standard

Author (year)	Title	Study details	Quality assessment
		Exclusion criteria • None reported Sample characteristics • Sample size 112 • % female 42% female • Mean age (SD) 62 years • % pre-test probability 17% <2 Wells score 81.2% >2 Well score PTP not completed for 2 participants. Index test (s) • Laboratory D-dimer STA-R Liatest D-dimer • Point-of-care D-dimer Biosite Triage, using an ELFA based D-dimer assay Reference standard (s) • Ultrasonography	was interpreted without knowledge of index test result Flow and timing • Unclear risk of bias Unclear timing of reference standard and index tests Overall risk of bias • High Unclear timing, participant selection and blinding. Directness • Directly applicable
Dempfle (2006)	Sensitivity and specificity of a quantitative point of care D-dimer assay using heparinized whole blood, in patients with clinically suspected deep vein thrombosis.	Study type • Prospective cohort study Study details • Study location Germany, Switzerland and The Netherlands • Study setting Multicentre across 19 sites in three countries • Study dates not reported	Patient selection • Low risk of bias Although participants with "unclear" CUS were excluded from analysis. Index test • Low risk of bias Reference standard • Low risk of bias Ultrasonograher did not know D-dimer

Author (year)	Title	Study details	Quality assessment
		Inclusion criteria • Suspected DVT "Clinically suspected acute DVT" Exclusion criteria • Pregnancy • Age Under 18 • Previous VTE Prior DVT in same leg • Anticoagulation therapy if treated with unfractionated or LMW heparin for more than 24h, or vitamin K antagonists before attempted inclusion • Hospitalisation For more than 72h at time of inclusion • Recent surgery within 30 days • Extended duration of symptoms Symptoms must be "acute". Excluded if duration is unclear or more than seven days. • Trauma requiring medical attention Sample characteristics • Sample size 637; 560 used in the analysis (77 excluded) • % female 61.3% female • Mean age (SD) 57.7 (SD 17.2) years Index test (s) • Laboratory D-dimer VIDAS (also reported tinaquant but was not extracted for this review) • Point-of-care D-dimer	results Flow and timing • Unclear risk of bias Unclear timing of reference standard in relation to index test Overall risk of bias • Low Unclear timing of reference standard however was blinded Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Cardiac D-dimer (Roche) Reference standard (s) • Ultrasonography Diagnosis determined by venous duplex sonography, including CUS and colour Doppler visualization of the veins of the symptomatic leg. According to the study protocol, the minimal requirement for B-mode ultrasonography was a high resolution real time scanner equipped with a 5 Mhz electronically focused linear-array transducer. Ultrasonography devices with better specifications could be used. The single criterion indicating the presence of venous thrombosis was the failure to fully compress the venous lumen, despite firm compression with the transducer probe. The following sites were examined: i) the common femoral vein at the inguinal ligament in supine position, ii) the popliteal vein at the popliteal fossa, down to the point of the trifurcation in the prone position. In case of anatomical abnormalities of the trifurcation of the anterior and posterior tibial and peroneal vein, the thrombus should involve the most upper vein junction. In case of a negative ultrasound this was to be documented by pictures of non-compressed and fully compressed veins at the popliteal fossa (popliteal vein) and inguinal ligament Additional comments • 2 x 2 table Was taken directly from Dempfle 2006	
Di Nisio (2006)	Combined use of clinical pretest probability and D-dimer test in cancer patients with clinically	Study type • Prospective cohort study	Patient selection • Low risk of bias

Author (year)	Title	Study details	Quality assessment
	suspected deep venous thrombosis.	Study details • Study location The Netherlands • Study setting Referrals to the thrombosis unit of the Academic Medical Center, Amsterdam. • Study dates November 1995 - December 2004 Inclusion criteria • Suspected DVT Exclusion criteria • None reported Sample characteristics • Sample size 2,066 • % people with cancer 11% Index test (s) • Point-of-care D-dimer SimpliRED Reference standard (s) • Ultrasonography In cases of negative CUS, serial testing was performed 1 week later and if still negative, the person was followed-up for 3 months for VTE occurrence. Subgroup analyses • People with cancer	Index test • Low risk of bias Technologists who performed index tests were blind to the patient's clinical status and results of objective testing. Reference standard • Low risk of bias Reference test was interpreted blind to the results of the D-dimer results Flow and timing • Unclear risk of bias Unclear timing of reference standard relative to index test Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Additional comments • 2 x 2 table Was taken directly from Di Nisio 2006	
Neale (2004)	Evaluation of the Simplify D-dimer assay as a screening test for the diagnosis of deep vein thrombosis in an emergency department.	Study type • Prospective cohort study Study details • Study location Wales • Study setting Single hospital • Study dates April 2001 - January 2003 • Sources of funding none Inclusion criteria • Suspected DVT Presenting in the emergency department with clinical features suspicious of DVT. Exclusion criteria • Pregnancy • Age Under 18 years • inadequate reference standard unable to perform reference standard due to technical difficulties or previous reaction to contrast. • Recent surgery Underwent surgery or experienced trauma within 6 weeks of study • Underlying malignancy	Patient selection • Low risk of bias Index test • Low risk of bias Were interpreted blind to results of Venography (if conducted prior) however unclear as to whether D-dimer results were interpreted blind to other D-dimer results Reference standard • Low risk of bias Interpreted without knowledge of results of index tests Flow and timing • Unclear risk of bias unclear timing of index tests and reference standards following admission to hospital. Overall risk of bias • Low Unclear timing of reference standard however it was conducted blind to knowledge of D-dimer result Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Sample characteristics • Sample size 187 • % female 54% female Index test (s) • Laboratory D-dimer Auto-dimer: Latex-agglutination test • Point-of-care D-dimer SimpliRED (also reported Simplify) Reference standard (s) • Venography contrast venography Additional comments • 2 x 2 table Was taken directly from Neale (2004)	
Oude (2015)	Clinical evaluation of eight different D-dimer tests for the exclusion of deep venous thrombosis in primary care patients	Study type • Prospective cohort study Study details • Study location The Netherlands • Study dates "Over a period of 23 months" Inclusion criteria • Suspected DVT • Outpatient/primary care patients Exclusion criteria • Age	Patient selection • Low risk of bias Index test • Low risk of bias Reference standard • Low risk of bias interpreted blind to D-dimer results Flow and timing • Unclear risk of bias Unclear timing of reference and index tests

Author (year)	Title	Study details	Quality assessment
		<18 • Anticoagulation therapy with vitamin K antagonists and/or LMWH. Sample characteristics • Sample size 290 • % female 60.3% • Mean age (SD) 56.6 (18.1-87.9) years Index test (s) • Laboratory D-dimer Vidas (also reported innovance [on both CA-1500 and BCS systems separately), ACL-TOP, Tina-quant and Liatest but these were not extracted for this review) • Age-adjusted D-dimer Quantitative lab-based test: Vidas (also reported innovance [on both CA-1500 and BCS systems separately), ACL-TOP, Tina-quant and Liatest but these were not extracted for this review) Quantitative POINT-OF-CARE: pathfast (AQT90 also reported but was not extracted for this review) • Point-of-care D-dimer Quantitative: Pathfast (also reported AQT90 but was not extracted for this review) Qualitative test: Simplify Reference standard (s) • Ultrasonography Real time B-mode compression ultrasonography with a 9 mHz linear array sonographic scanner Additional comments • 2 x 2 table	Overall risk of bias • Low Unclear timing of reference standard however all low-risk in all other respects. Directness • Partially applicable Participants with proximal dvt were excluded from analysis.

Author (year)	Title	Study details	Quality assessment
		Was taken directly from Oude 2015	
Subramaniam (2006)	Importance of pretest probability score and D-dimer assay before sonography for lower limb deep venous thrombosis.	Study type • Prospective cohort study Study details • Study location New Zealand • Study setting Referrals to an emergency department of a tertiary hospital • Study dates October 2001 - May 2003 Inclusion criteria • Suspected DVT Suspected lower-limb DVT Exclusion criteria • Anticoagulation therapy • Failure to perform index test prior to reference standard • inadequate reference standard Sample characteristics • Sample size 312 • % female 62.5% female • Mean age (SD) 55.8 years • % pre-test probability 48.4% unlikely modified wells criteria. • % people with previous VTE	Patient selection • Low risk of bias Index test • Low risk of bias Reference standard • Unclear risk of bias Unclear whether reference standard was interpreted blind to index test result Flow and timing • Unclear risk of bias Unclear timing of tests Overall risk of bias • Moderate Lack of clarity regarding blinding and timing of reference standard Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		12.8% previous VTE Index test (s) • Point-of-care D-dimer Simplify D-dimer Reference standard (s) • Ultrasonography Diagnosis of DVT made using duplex compression (acuson Sequoia 512 sonographic imaging system). The common femoral vein, superficial femoral vein, popliteal vein, and trifurcation, and all three deep calf vein sets were examined. Additional comments • 2 x 2 table Was taken directly from Subramaniam 2006	
Subramaniam (2006)	Does an immunochromatographic D-dimer exclude acute lower limb deep venous thrombosis?	Study type • Prospective cohort study Study details • Study location New Zealand • Study setting Presented on their own to emergency department • Study dates May 2002 - April 2004 • Sources of funding Funded by Department of Radiology research fund. No funds received from manufacturer of Simplify Inclusion criteria • Suspected DVT	Patient selection • Low risk of bias Index test • Low risk of bias Reference standard • Low risk of bias Flow and timing • Unclear risk of bias Unclear timing however D-dimer performed prior to reference standard (likely immediately prior)

Author (year)	Title	Study details	Quality assessment
		suspected lower limb DVT Exclusion criteria • Previous VTE prior lower limb DVT • Anticoagulation therapy • Failure to perform index test prior to reference standard • inadequate reference standard Sample characteristics • Sample size 453 • % female 64.9% female • Mean age (SD) 55.8 years • % pre-test probability 61.8% unlikely DVT on Hamilton score • % people with previous VTE 0% previous lower limb DVT Index test (s) • Point-of-care D-dimer Simplify Reference standard (s) • Ultrasonography Duplex compression carried out by experienced ultra-sonographers and senior radiology registrars (third- and fourth- year) under the supervision of consultant radiologists. Interpreted blind to D-dimer results.	Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Additional comments • 2 x 2 table Was taken directly from Subramaniam 2006	

Laboratory based D-dimer

Systematic review

Author (year)	Title	Study details	New column
Goodacre (2006)	Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis.	Study type • Systematic review Study details • Dates searched MEDLINE (1966 to April 2004), EMBASE (1980 to April 2004), CINAHL (1982 to April 2004), Web of Science (1970 to April 2004), BIOSIS (1985 to April 2004), Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, Database of Reviews of Effectiveness, NHS Economic Evaluations Database, Health Technology Assessment database, and the ACP Journal Club (all 1991 to April 2004). • Databases searched MEDLINE, EMBASE, CINAHL, Web of Science, BIOSIS, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, Database of Reviews of Effectiveness, NHS Economic Evaluations Database, Health Technology Assessment database, and the ACP Journal Club.	Study eligibility criteria • Low risk of bias Identification and selection of studies • Low risk of bias Data collection and study appraisal • Low risk of bias [Info] Based only on blinding procedures and whether application of reference standard was dependent on results of other tests. Other factors (timing and flow, participant selection) were not considered. However, the authors justified this decision as most criteria on available checklists relate to quality of reporting, rather than validity, and those that do relate to validity may not be supported by empirical evidence. Furthermore, using checklists with multiple criteria to assess quality may prove difficult to interpret, particularly as it may not be appropriate to combine criteria into a

Author (year)	Title	Study details	New column
		• Sources of funding Commissioned by the HTA programme as project number 02.03.01 Study inclusion criteria • Language English, Spanish, French or Italian Study exclusion criteria • Prognostic studies • Case-control studies • Studies with <10 participants • Suspected PE Outcome measures • Diagnostic accuracy data 2x2 table Was taken from data supplied by Goodacre (2006)	composite score. Synthesis and findings • Low risk of bias Overall quality • High Applicability as a source of data • Fully applicable

Primary studies

Author (year)	Title	Study details	Quality assessment
Anoop (2009)	Evaluation of an immunoturbidimetric D-dimer assay and pretest probability score for suspected venous thromboembolism in a district hospital setting.	Study type • Prospective cohort study Study details • Study location UK • Study setting Medium sized hospital • Study dates December 1, 2007 to March 31, 2008 Inclusion criteria • Suspected VTE	Patient selection • Low risk of bias Index test • High risk of bias D-dimer technique was changed prior to study to an unvalidated measure and this lack of validation was reason for all patients undergoing imaging Reference standard • High risk of bias Physician was unblinded

Author (year)	Title	Study details	Quality assessment
		Exclusion criteria • Inconclusive reference standard • Other evaluations D-dimer level not quantifiable due to specimen error; Wells' chart unavailable or illegible; modality other than CTPA used as confirmatory test • Intensive care unit patients Sample characteristics • Sample size 197 participants overall, 91 with suspected PE. • % female 66% female • Mean age (SD) Median 61 years (range: 19-96 years) • % pre-test probability 20.9% low; 79.1% intermediate Index test (s) • Laboratory D-dimer MDA autodimer T3103 Cut-off: 0.50 µg FEU/ml Reference standard (s) • Ultrasound Compression ultrasound (HDI 5000) of common and superficial femoral veins, popliteal vein trifurcation and all three deep calf vein sets • Pulmonary angiography 64-slice 0.625mm thickness CTPA (GE lightSpeed VCT) with Niopam 300 contrast, 74ml at 3 ml/s Additional comments • 2 x 2 table was taken directly from Anoop (2009)	Flow and timing • Low risk of bias Overall risk of bias • Moderate Radiologist was unblinded to D-dimer results. In addition, the D-dimer assay was unvalidated at point of study. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
Baker (2010)	Comparison of a point of care device against current laboratory methodology using citrated and EDTA samples for the determination of D-dimers in the exclusion of proximal deep vein thrombosis	Study type • Prospective cohort study Study details • Study location UK • Study setting Approached from DVT diagnosis service at Oxford Haemophilia and Thrombosis Centre • Study dates Not reported Inclusion criteria • None reported Exclusion criteria • None reported Sample characteristics • Sample size 112 • % female 42% female • Mean age (SD) 62 years • % pre-test probability 17% <2 Wells score 81.2% >2 Well score PTP not completed for 2 participants. Index test (s) • Laboratory D-dimer STA-R Liatest D-dimer • Point-of-care D-dimer Biosite Triage, using an ELFA based D-dimer assay	Patient selection • Unclear risk of bias Patients were approacted in a DVT diagnosis clinic but no inclusion/exclusion criteria was reported. Index test • Unclear risk of bias No information regarding whether D-dimers were interpreted independent of each other and without knowledge of reference standard result Reference standard • Unclear risk of bias Unclear whether reference standard was intereted without knowledge of index test result Flow and timing • Unclear risk of bias Unclear timing of reference standard and index tests Overall risk of bias • High Unclear timing, participant selection and blinding. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Reference standard (s) • Ultrasonography	
Boeer (2009)	Comparison of six D-dimer assays for the detection of clinically suspected deep venous thrombosis of the lower extremities	Study type • Prospective cohort study Study details • Study location Germany • Study setting Single hospital • Study dates not reported Inclusion criteria • Suspected DVT Ambulatory patients suspected of DVT • Age 16 years or older Exclusion criteria • Anticoagulation therapy • Hospitalisation 24h before the onset of symptoms • Recent surgery Sample characteristics • Sample size 79 • % female 50.6% female • Mean age (SD) 61 years (range 22 - 95)	Patient selection • Low risk of bias Index test • Unclear risk of bias Unclear whether D-dimer tests were reported without knowledge of other D-dimer tests and/or reference standard. Reference standard • Unclear risk of bias Unclear whether reference standard was interpreted without knowledge of the index test results. In addition, it is not clear whether all participants received the same reference standard due to limited reporting. Flow and timing • Unclear risk of bias Unclear timing of index tests and reference standard Overall risk of bias • Moderate Lack of clarity regarding timing and blinding of reference standard and the multiple index tests performed. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Index test (s) • Laboratory D-dimer Extracted: Tinaquant (evaluated on Architect c8000 system) Also reported but not extracted: Auto Dimer (evaluated on Architect c8000 system) Quantia D-dimer (evaluated on Architect c8000 system) D-Dimer HS(evaluated on ACL-TOP system) Innovance (evaluated on BCS system) D-Dimer plus (evaluated on BCS system) Reference standard (s) • Ultrasonography Limited data on the procedure and protocol for performing reference standard. Additional comments • 2 x 2 table Was taken directly from Boeer 2009	
Dempfle (2006)	Sensitivity and specificity of a quantitative point of care D-dimer assay using heparinized whole blood, in patients with clinically suspected deep vein thrombosis.	Study type • Prospective cohort study Study details • Study location Germany, Switzerland and The Netherlands • Study setting Multicentre across 19 sites in three countries • Study dates not reported Inclusion criteria • Suspected DVT "Clinically suspected acute DVT"	Patient selection • Low risk of bias Although participants with "unclear" CUS were excluded from analysis. Index test • Low risk of bias Reference standard • Low risk of bias Ultrasonograher did not know D-dimer results Flow and timing • Unclear risk of bias Unclear timing of reference standard in

Author (year)	Title	Study details	Quality assessment
		Exclusion criteria • Pregnancy Under 18 • Age Under 18 • Previous VTE Prior DVT in same leg • Anticoagulation therapy if treated with unfractionated or LMW heparin for more than 24h, or vitamin K antagonists before attempted inclusion • Hospitalisation For more than 72h at time of inclusion • Recent surgery within 30 days • Extended duration of symptoms Symptoms must be "acute". Excluded if duration is unclear or more than seven days. • Trauma requiring medical attention Sample characteristics • Sample size 637; 560 used in the analysis (77 excluded) • % female 61.3% female • Mean age (SD) 57.7 (SD 17.2) years Index test (s) • Laboratory D-dimer VIDAS (also reported tinaquant but was not extracted for this review) • Point-of-care D-dimer Cardiac D-dimer (Roche) Reference standard (s) • Ultrasonography	relation to index test Overall risk of bias • Low Unclear timing of reference standard however was blinded Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Diagnosis determined by venous duplex sonography, including CUS and colour Doppler visualization of the veins of the symptomatic leg. According to the study protocol, the minimal requirement for B-mode ultrasonography was a high resolution real time scanner equipped with a 5 Mhz electronically focused linear-array transducer. Ultrasonography devices with better specifications could be used. The single criterion indicating the presence of venous thrombosis was the failure to fully compress the venous lumen, despite firm compression with the transducer probe. The following sites were examined: i) the common femoral vein at the inguinal ligament in supine position, ii) the popliteal vein at the popliteal fossa, down to the point of the trifurcation in the prone position. In case of anatomical abnormalities of the trifurcation of the anterior and posterior tibial and peroneal vein, the thrombus should involve the most upper vein junction. In case of a negative ultrasound this was to be documented by pictures of non-compressed and fully compressed veins at the popliteal fossa (popliteal vein) and inguinal ligament Additional comments • 2 x 2 table Was taken directly from Dempfle 2006	
Diamond (2005)	Use of D-dimer to aid in excluding deep venous thrombosis in ambulatory patients.	Study type • Prospective cohort study Study details • Study location USA • Study setting Emergency department of hospital • Study dates	Patient selection • Low risk of bias Index test • Low risk of bias Reference standard • Unclear risk of bias

Author (year)	Title	Study details	Quality assessment
		September 1, 2002 - April 30, 2003 Inclusion criteria • Suspected DVT People with suspected DVT seen in emergency department Sample characteristics • Sample size 148 • % female 49.5% • Mean age (SD) 57.2 • % people with previous VTE 12.8% previous DVT Index test (s) • Laboratory D-dimer Tinaquant Reference standard (s) • Venous duplex imaging Examinations were performed using the ATL HDI 5000 scanner (Philips Medical Systems, Andover, MA). The common femoral, deep femoral, femoral, popliteal, posterior tibial, peroneal, gastrocnemius, and soleus veins were scanned in the transverse and longitudinal plane. Duplex criteria for a diagnosis of acute DVT included visualization of thrombus on B-mode, lack of venous compressibility, and the absence of doppler flow signals distal to the site of suspected thrombosis. Additional comments • 2 x 2 table	Unclear whether reference standard was interpreted without knowledge of results of index test. Flow and timing • Unclear risk of bias Unclear timing of reference standard in relation to index test. Overall risk of bias • Moderate Lack of clarify regarding blinding and timing of the reference standard. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Was taken directly from Diamond 2005	
Gomez-Jabalera (2017)	Age-adjusted D-dimer for the diagnosis of deep vein thrombosis	Study type • Prospective cohort study Study details • Study location Spain • Study setting single hospital primary care referrals • Study dates November 2015 - May 2016 Inclusion criteria • Suspected DVT • Outpatient/primary care patients Must have had previous examination by Primary Care Physician Exclusion criteria • Previous VTE Suspected prior DVT • Anticoagulation therapy • Extended duration of symptoms >1 months and suspicion of PE or final diagnosis of thrombophlebitis • Suspected PE • Well score high probability wells score (>3) Sample characteristics • Sample size 138 • % female 60.5% female	Patient selection • Low risk of bias Index test • Low risk of bias Reference standard • Low risk of bias Interpreted blind to index test results Flow and timing • Unclear risk of bias Unclear timing of reference standard in relation to index test Overall risk of bias • Low Unclear timing of reference standard in relation to admission however low risk of bias from other areas. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Mean age (SD) 71.6 years • % pre-test probability Well score low = 69.6% intermediate = 21% High = 9.4% Index test (s) • Laboratory D-dimer Hemos IL-500 • Age-adjusted D-dimer tested several formulas: Age x 10 ug/L Age x 15 ug/L age x 20 ug/L Age x 25 ug/L Age x 30 ug/L We reported data for age x 10 ug/L Reference standard (s) • Ultrasonography Following the analysis, experienced personnel performed a whole leg compression ultrasonography of the symptomatic leg by a B mode and pulsed Doppler in the common femoral vein, the popliteal vein, calf veins and great and small saphenous veins. The sonographic scanner used was a linear array at 5–7.5MHz (SonoSite M-Turbo ultrasound).20 The DVT diagnosis was established if one or more deep veins in the leg were not completely compressible or there were not any phasic flow signs with respiratory movements of calf compression. Additional comments • 2 x 2 table Was taken directly from Gomez-Jabalera (2017)	
Ilkhanipour (2004)	Combining clinical risk with D-dimer testing to	Study type • Prospective cohort study	Patient selection • Low risk of bias

Author (year)	Title	Study details	Quality assessment
	rule out deep vein thrombosis.	Study details • Study location USA • Study setting two sites, a university hospital and a community teaching hospital • Study dates June 2000 -February 2002 Inclusion criteria • Suspected DVT suspected lower extremity acute DVT • Age 18 years or older Exclusion criteria • Extended duration of symptoms >1 month Sample characteristics • Sample size 365 • % female 65% female • Mean age (SD) 54 years • % pre-test probability 35% low risk 43% intermediate risk 22% high risk Index test (s) • Laboratory D-dimer Quantitative ELISA assay with a previously established threshold value of 500 ug/L or greater for a positive result	Index test • Low risk of bias Reference standard • Low risk of bias Physicians were blinded to results of the D-dimer test Flow and timing • Unclear risk of bias Unclear timing of reference standard in relation to index tests Overall risk of bias • Low Low although lack of clarity as to when reference standard was completed Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Reference standard (s) • Ultrasonography All patients underwent duplex ultrasound examination of the symptomatic leg by experienced vascular technologists who were blinded to the results of the clinical assessment and ELISA D-dimer values. Sonography was performed using a 128 XP scanner (Acuson, Mountain View, CA) with a 5-MHz linear array probe. Additional comments • 2 x 2 table Was taken directly from Ilkhanipour 2004	
Kong (2016)	Plasma Level of D-dimer is an Independent Diagnostic Biomarker for Deep Venous Thrombosis in Patients with Ischemic Stroke	Study type • Prospective cohort study Study details • Study location China • Study setting • Study dates July 2013 to December 2014 Inclusion criteria • Suspected DVT Ischemic stroke patients suspected of DVT, admitted within 15 days of stroke onset Exclusion criteria • DVT patients with isolated calf DVT, superficial thrombosis, or symptoms of simultaneous upper and lower extremity (LE) clot; or patients who had a DVT attack within the past 3 months	Patient selection • Low risk of bias Index test • Low risk of bias Unclear whether D-dimer was interpreted blind however a quantitative test was used. Reference standard • Unclear risk of bias Unclear whether reference standard was interpreted blind Flow and timing • Unclear risk of bias Unclear timing of reference standard in relation to index test Overall risk of bias • Moderate

Author (year)	Title	Study details	Quality assessment
		• Anticoagulation therapy patients who had a previous history of indeterminate duplex scanner received therapeutic anticoagulation treatment, • Recent surgery previous surgical operation or trauma during the preceding 2 months • other severe oedema, seriously infections at study enrolment, and autoimmune diseases with/without immunosuppressive therapy Sample characteristics • Sample size 255, all ischemic stroke patients • % female With DVT: 68 Without DVT: 61 • Mean age (SD) With DVT 45.2% female Without DVT: 62.5% female Index test (s) • Laboratory D-dimer INNOVANCE (SYSMEX CA-7000 System) with a detection limit of 0.05mg/L Reference standard (s) • Ultrasonography Colour Doppler Ultrasonography (CDUS) was performed in all the included patients to assess the incidence of DVT. Further, real-time B-mode ultrasonography (with compression) was performed with a 7.5-MHz (higher frequency) or a 5.0-MHz transducer. Additional comments • 2 x 2 table	Unclear whether index test or reference standard was interpreted blind, unclear timing of reference standard in relation to index test Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Was taken directly from Kong (2016)	
Luxembourg (2012)	Performance of five D-dimer assays for the exclusion of symptomatic distal leg vein thrombosis	Study type • Prospective cohort study Study details • Study location Germany • Study setting Division of Angiology, University Hospital • Study dates Inclusion criteria • Suspected DVT symptoms suggestive of acute DVT • Age 18 years + • Outpatient/primary care patients outpatients Exclusion criteria • Written informed consent could not be obtained • Anticoagulation therapy received continuous anticoagulation at the onset of symptoms Sample characteristics • Sample size 216 • % female 57% female • Mean age (SD) 51 years • % pre-test probability 46% low 38% intermediated 17% high	Patient selection • Low risk of bias Index test • Low risk of bias All DD measurements were carried out by technicians blinded to the results of the clinical pretest probability and cCUS of the legs. Reference standard • Low risk of bias physicians were aware of PTP but unaware of D-dimer results Flow and timing • Low risk of bias Venous blood samples were collected in 3.2% trisodium citrate syringes prior to cCUS. Samples were immediately centrifuged for 15 minutes at 2,500 x g and were either assayed within 2 hours (h) apart from blood collection (Vidas-DD, Liatest-DD) or frozen in aliquots at –24 ± 2°C for up to 24 months until assay performance Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• % people with cancer 17% Index test (s) • Laboratory D-dimer Vidas (N=215), also reported Liatest (N=216), HemosIL (N=191), HemosIL-DDHS (N=189), Innovance on BCS system (n =195) but these were not reported for this review Reference standard (s) • Ultrasonography complete CUS (cCUS) of the symptomatic leg(s) which means that the femoral, popliteal, tibial, fibular as well as calf muscle veins (gastrocnemius and soleal muscular veins) were examined by moving the transducer distally from the groin to the ankle level. Additional comments • 2 x 2 table was taken directly from Luxembourg 2012	
Michiels (2016)	Safe Exclusion of Deep Vein Thrombosis by a Rapid Sensitive ELISA D-dimer and Compression Ultrasonography in 1330 Outpatients With Suspected DVT	Study type • Prospective cohort study Study details • Study location The Netherlands • Study setting Primary care- Medical diagnostic centre • Study dates 2000 - 2005 Inclusion criteria • Suspected DVT	Patient selection • Low risk of bias Index test • Low risk of bias Reference standard • Unclear risk of bias Unclear whether reference standard was interpreted without knowledge of index test

Author (year)	Title	Study details	Quality assessment
		• Outpatient/primary care patients Exclusion criteria • None reported Sample characteristics • Sample size 1330 Index test (s) • Laboratory D-dimer VIDAS ELISA D-dimer assay Reference standard (s) • Ultrasonography All participants underwent both d-dimer and CUS Positive CUS = DVT positive Negative CUS and <500 D-dimer = DVT negative CUS and >500 D-dimer = repeat CUS after 5-7 days. Additional comments • 2 x 2 table Was taken directly from Michiels 2016	Flow and timing • Unclear risk of bias Unclear timing for conducting of reference standard and index test Overall risk of bias • Moderate Lack of clarity regarding timing and blinding procedures for the conducting of the reference standard Directness • Directly applicable
Neale (2004)	Evaluation of the Simplify D-dimer assay as a screening test for the diagnosis of deep vein thrombosis in an emergency department.	Study type • Prospective cohort study Study details • Study location Wales • Study setting Single hospital • Study dates April 2001 - January 2003 • Sources of funding	Patient selection • Low risk of bias Index test • Low risk of bias Were interpreted blind to results of Venography (if conducted prior) however unclear as to whether D-dimer results were interpreted blind to other D-dimer results

Author (year)	Title	Study details	Quality assessment
		none Inclusion criteria • Suspected DVT Presenting in the emergency department with clinical features suspicious of DVT. Exclusion criteria • Pregnancy • Age Under 18 years • inadequate reference standard unable to perform reference standard due to technical difficulties or previous reaction to contrast. • Recent surgery Underwent surgery or experienced trauma within 6 weeks of study • Underlying malignancy Sample characteristics • Sample size 187 • % female 54% female Index test (s) • Laboratory D-dimer Auto-dimer: Latex-agglutination test • Point-of-care D-dimer SimpliRED (also reported Simplify) Reference standard (s) • Venography contrast venography	Reference standard • Low risk of bias Interpreted without knowledge of results of index tests Flow and timing • Unclear risk of bias unclear timing of index tests and reference standards following admission to hospital. Overall risk of bias • Low Unclear timing of reference standard however it was conducted blind to knowledge of D-dimer result Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Additional comments • 2 x 2 table Was taken directly from Neale (2004)	
Oude (2015)	Clinical evaluation of eight different D-dimer tests for the exclusion of deep venous thrombosis in primary care patients	Study type • Prospective cohort study Study details • Study location The Netherlands • Study dates "Over a period of 23 months" Inclusion criteria • Suspected DVT • Outpatient/primary care patients Exclusion criteria • Age <18 • Anticoagulation therapy with vitamin K antagonists and/or LMWH. Sample characteristics • Sample size 290 • % female 60.3% • Mean age (SD) 56.6 (18.1-87.9) years Index test (s) • Laboratory D-dimer Vidas (also reported innovance [on both CA-1500 and BCS systems separately), ACL-TOP, Tina-quant and	Patient selection • Low risk of bias Index test • Low risk of bias Reference standard • Low risk of bias interpreted blind to D-dimer results Flow and timing • Unclear risk of bias Unclear timing of reference and index tests Overall risk of bias • Low Unclear timing of reference standard however all low-risk in all other respects. Directness • Partially applicable Participants with proximal DVT were excluded from analysis.

Author (year)	Title	Study details	Quality assessment
		Liatest but these were not extracted for this review) • Age-adjusted D-dimer Quantitative lab-based test: Vidas (also reported innovance [on both CA-1500 and BCS systems separately), ACL-TOP, Tina-quant and Liatest but these were not extracted for this review) Quantitative POINT-OF-CARE: pathfast (AQT90 also reported but was not extracted for this review) • Point-of-care D-dimer Quantitative: Pathfast (also reported AQT90 but was not extracted for this review) Qualitative test: Simplify Reference standard (s) • Ultrasonography Real time B-mode compression ultrasonography with a 9 mHz linear array sonographic scanner Additional comments • 2 x 2 table Was taken directly from Oude 2015	
Prochaska (2017)	Age-related diagnostic value of D-dimer testing and the role of inflammation in patients with suspected deep vein thrombosis	Study type • Prospective cohort study Study details • Study location Germany • Study setting Department of Angiology • Study dates 2013 - 2015 • Loss to follow-up 56/500 • Sources of funding German Federal Ministry of Education and Research	Patient selection • Low risk of bias Index test • Low risk of bias Fifty six participants (11.2%) had an inconclusive d-dimer test. This was not considered to introduce bias. Reference standard • Low risk of bias Flow and timing • Unclear risk of bias

Author (year)	Title	Study details	Quality assessment
		and the Center for Translational Vascular Biology of the University Medical Center Mainz Inclusion criteria • Suspected DVT Clinical suspicion of acute DVT • Age ≥ 18 years Exclusion criteria • None reported Sample characteristics • Sample size 500 • % female 55.6 • Mean age (SD) Median age 60.0 (interquartile range [IQR] 45.0, 72.0) • % pre-test probability Low-to-moderate (Wells score 0–2): 84.4 High (Wells score >2): 15.6 • % people with cancer 17.0 Index test (s) • Laboratory D-dimer Innovance from 04/2013 to 07/2014 and HemosIL HS from 08/2014 to the end of study. Cut-off: 0.5 mg/L fibrinogen equivalent unit (FEU) • Age-adjusted D-dimer age-dependent threshold applied to patients over 60 years (age/100mg/L)	Unclear timing of reference standard following admission Overall risk of bias • Moderate Unclear timing and over 10% of participants received and unclear reference standard result and were consequentially removed from analysis. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Reference standard (s) • Ultrasound Compression duplex ultrasound Subgroup analyses • People with cancer • People with previous VTE Suspected recurrent DVT • Provoked versus unprovoked Additional comments • 2 x 2 table Was taken from Proschaska (2017) and online supplementary material.	
Yamada (2015)	Occurrence of Deep Vein Thrombosis among Hospitalized Non-Surgical Japanese Patients	Study type • Prospective cohort study Study details • Study location Japan • Study setting Mie University Hospital and Niigata University Medical and Dental Hospital • Study dates April 2006 to April 2008 Inclusion criteria • Age 20 years or older • Suspected VTE hospitalised, bed-ridden for at least 24h and moderate-high risk factors for VTE.	Patient selection • Low risk of bias Index test • High risk of bias unclear whether D-dimer was interpreted blind to other tests. 97 participants did not undergo D-dimer testing. Reference standard • Unclear risk of bias Unclear whether reference standard was interpreted without knowledge of index test results. Flow and timing • High risk of bias 27 days mean time between referral and ultrasonography with variance

Author (year)	Title	Study details	Quality assessment
		Exclusion criteria • Previous VTE diagnosed VTE, prior VTE or symptoms or findings of VTE at admission • Recent surgery surgery or trauma within past 3 months Sample characteristics • Sample size 525 • % female 44.4% female • Mean age (SD) 64 (SD 14) years • % people with cancer 18.3% Index test (s) • Laboratory D-dimer latex photometric immunoassay (LPIA) at a cut-off point of 1.0 µg/mL Reference standard (s) • Ultrasonography Venous ultrasonography: Aplio (Toshiba Medical Systems Corporation) and SSD-5500 (Hitachi Aloka Medical, Ltd.) diagnostic ultrasound systems	(median 12 days), meaning that patients different in time to reference standard Overall risk of bias • High Unclear whether tests were interpreted blind. There was a wide range in the time from referral to performing of the reference standard. Directness • Partially applicable Participants were suspected of VTE generally, rather than specifically DVT and were hospitalised patients bed-ridden for 24h

Pulmonary embolism

Age-adjusted D-dimer

Author (year)	Title	Study details	Quality assessment
Dutton (2018)	Can the use of an age-adjusted D-dimer cut-off value help in our diagnosis of suspected pulmonary embolism?	Study type • Retrospective cohort study Study details • Study location UK • Study setting District general hospital • Study dates April 2016 – March 2017 • Loss to follow-up 0 • Sources of funding not reported Inclusion criteria • Suspected PE Clinically suspected PE that underwent investigation with imaging (CTPA or V/Q scan) • Over 50 years old Exclusion criteria • High PTP • uncompleted scans • No D-dimer assay performed. Sample characteristics • Sample size 329 • % female with PE: 49.3%	Patient selection • High risk of bias Only patients with CT pulmonary angiography and recorded D-dimer laboratory values were included Index test • Low risk of bias Reference standard • Low risk of bias Flow and timing • Unclear risk of bias The interval between D-dimer and CT pulmonary angiography was not reported, unclear when D-dimer was conducted Overall risk of bias • High Retrospective study where only patients with imaging and recorded D-dimer laboratory values were included. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Without PE: 54.6% • Median age (IQR) With PE: 71 (64-82) Without PE: 71 (63-79) Index test (s) • standard and age-adjusted D-dimer Age adjusted: age x 10 Reference standard (s) • Imaging using CTPA or V/Q scan Additional comments • 2 x 2 table was taken directly from Dutton (2018)	
Flores (2016a)	Can the tandem measurement of age adjusted D-dimer and tissue plasminogen activator improve the clinical utility of a conventional D-dimer in the pulmonary embolism diagnosis?	Associated studies • Flores (2016b) Clinical usefulness and safety of an age-adjusted D-dimer cut-off levels to exclude pulmonary embolism: a retrospective analysis. Internal & Emergency Medicine; 11 (1):69-75. Study type • Prospective cohort study Study details • Study location Spain • Study setting Emergency department • Study dates 2008 - 2010 • Loss to follow-up 23/385	Patient selection • Low risk of bias Consecutive sample Index test • Low risk of bias The technician performing the analysis was unaware of the final diagnosis for each patient Reference standard • Low risk of bias It was not reported whether reference standard was interpreted without knowledge of D-dimer Flow and timing • High risk of bias

Author (year)	Title	Study details	Quality assessment
		• Sources of funding Research Foundation of Hospital Principe de Asturias Inclusion criteria • Suspected PE Clinically suspected PE Exclusion criteria • Pregnancy • Age Younger than 18 years • Medications Patients already on therapeutic anticoagulation • Logistic reasons For example, unavailability of MDCT, V/Q lung scanning or contrast pulmonary angiography Sample characteristics • Sample size 362 • % female 46 • Mean age (SD) People with PE: 65 (18) People without PE: 63 (15) • % pre-test probability Wells score People with PE Low: 21.4 Moderate: 54.1 High: 24.5 People without PE Low: 53.8 Moderate: 43.5 High: 2.6 • % people with cancer People with PE: 7 People without PE: 6.1 • % people with previous VTE People with PE: 13.1 People without PE: 9.5 Index test (s) • Laboratory D-dimer VIDAS; Cut-off: 500 ng/mL	Plasma samples were obtained at enrolment but D-dimer was measured at the end of study, and the results for the PE diagnosis were analysed retrospectively Overall risk of bias • High It was unclear whether reference standard was interpreted without knowledge of D-dimer results. Plasma samples were obtained at enrolment but D-dimer was measured at the end of study Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Age-adjusted D-dimer VIDAS; Cut-off: patient's age x 10 ng/mL Reference standard (s) • Composite reference standard Multidetector computed tomography (MDCT) or ventilation–perfusion (V/Q) lung scanning (in the presence of allergy to intravenous contrast agents or renal insufficiency) was done on all patients. A lower-limb venous compression ultrasonography (US) was done when MDCT or V/Q lung scanning showed no definite results for the diagnosis of PE, and a contrast pulmonary angiography was performed only in patients with inconclusive non-invasive workup. PE was ruled out if: a negative result on MDCT along with a low or moderate clinical pretest probability (PTP) according to Wells score; or normal V/Q lung scanning was found; or normal contrast pulmonary angiography; or low clinical PTP according to Wells score and V/Q lug scanning inconclusive with lower-limb US negative for DVT. Patients with PE ruled out did not receive anticoagulation, and were followed up over a three-month period. PE was confirmed if: a MDCT showing thrombi; or a high probability V/Q lung scanning and high clinical PTP; or inconclusive (low or moderate) V/Q lung scanning and moderate/high clinical PTP with DVT thrombosis shown by venous compression US of lower limbs; or a contrast pulmonary angiography showing thrombi; or presence of pulmonary emboli at necropsy Additional comments • 2 x 2 table was taken directly from Flores (2016)	

Author (year)	Title	Study details	Quality assessment
Gupta (2014)	Assessing 2 D-dimer age-adjustment strategies to optimize computed tomographic use in ED evaluation of pulmonary embolism	Study type • Retrospective cohort study Study details • Study location US • Study setting Emergency department • Study dates 2011 - 2013 • Loss to follow-up 0 • Sources of funding The National Library of Medicine and the National Institute of Biomedical Imaging and Bioengineering Inclusion criteria • Suspected PE With recorded D-dimer laboratory values and CT pulmonary angiography Exclusion criteria • None reported Sample characteristics • Sample size 1055 • % female 69.1 • Mean age (SD) 52.8 (range 18 to 96) • % pre-test probability Wells score: median 4.5 (range 0 to 12.5)	Patient selection • High risk of bias Only patients with CT pulmonary angiography and recorded D-dimer laboratory values were included Index test • Low risk of bias D-dimer was done before ordering a CT pulmonary angiography Reference standard • High risk of bias Physician ordered CT pulmonary angiography providing evidence-based decision support as to the appropriateness of CT pulmonary angiography for evaluation of PE which included D-dimer results and individual Wells score Flow and timing • Unclear risk of bias The interval between D-dimer and CT pulmonary angiography was not reported Overall risk of bias • High Only patients with CT pulmonary angiography and recorded D-dimer laboratory values were included. CT pulmonary angiography was interpreted with knowledge of D-dimer

Author (year)	Title	Study details	Quality assessment
		Index test (s) • Laboratory D-dimer STA-Liatest; Cut-off: 500 ng/mL • Age-adjusted D-dimer STA-Liatest; Cut-off: age in years × 10 ng/mL Reference standard (s) • Pulmonary angiography Computed tomography pulmonary angiography Additional comments • 2 x 2 table was taken directly from Gupta (2014)	results Directness • Directly applicable
Kozlowska (2017)	Age-adjusted plasma D-dimer levels in suspected acute pulmonary embolism: a retrospective, single-center study	Study type • Retrospective cohort study Study details • Study location Poland • Study setting Hospital • Study dates 2014 - 2016 • Loss to follow-up 0 • Sources of funding Not reported Inclusion criteria • Suspected PE With symptoms suggestive f acute PE lasting no longer than 14 days • Age >50 years	Patient selection • High risk of bias Retrospective study including people who had adequate quality of multislice computed tomography, thromboemboli visualised in at least segmental arteries, and full information on D-dimer testing method Index test • Unclear risk of bias It was not reported whether D-dimer was interpreted without knowledge of CT scan Reference standard • High risk of bias The results of CT scan were not verified by an independent radiologist

Author (year)	Title	Study details	Quality assessment
		• Diagnostic studies Adequate quality of multislice computed tomography, thromboemboli visualised in at least segmental arteries, and full information on D-dimer testing method Exclusion criteria • None reported Sample characteristics • Sample size 321 • % female 54.8 • Mean age (SD) 74.2 (range 51 to 101) Index test (s) • Laboratory D-dimer VIDAS; Cut-off: 500 ng/ml • Age-adjusted D-dimer VIDAS; Cut-off: patient's age (years) × 10 ng/ml, for patients above the age of 50 years Reference standard (s) • Composite reference standard Multislice computed tomography angiography; in one case of inconclusive findings, acute PE was confirmed by a lower-limb venous ultrasound Additional comments • 2 x 2 table was calculated taking data from Kozlowska (2017)	Flow and timing • Unclear risk of bias The interval between D-dimer and CT scan was not reported Overall risk of bias • High Retrospective study including people who had adequate quality of multislice computed tomography and D-dimer test. It was not reported whether D-dimer and CT scan interpretations were independent and blinded. The interval between D-dimer and CT scan was not reported Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
Kubak (2016)	Elevated D-dimer cut-off values for computed tomography pulmonary angiography-D-dimer correlates with location of embolism	Study type • Retrospective cohort study Study details • Study location Norway • Study setting Radiology department • Study dates 2012 • Loss to follow-up 0 • Sources of funding Not reported Inclusion criteria • Suspected PE Suspected acute PE referred to the department of radiology for CT pulmonary angiography Exclusion criteria • Inconclusive reference standard CT pulmonary angiography Sample characteristics • Sample size 822 • % female 53 • Mean age (SD) 64 (range 16 to 99) Index test (s) • Laboratory D-dimer HemosIL D-dimer HS; Cut-off: 0.5 mg/L	Patient selection • High risk of bias Retrospective study including patients referred to a radiology department for CT pulmonary angiography Index test • Unclear risk of bias It was not reported whether D-dimer was interpreted without knowledge of CT pulmonary angiography Reference standard • Unclear risk of bias It was not reported whether CT pulmonary angiography was interpreted without knowledge of D-dimer Flow and timing • Low risk of bias D-dimer were done within 48 hours prior to or after the CT pulmonary angiography examination Overall risk of bias • High Retrospective study including patients referred to a radiology department for CT pulmonary angiography. It was not reported whether D-dimer and CT pulmonary angiography interpretations were independent and blinded

Author (year)	Title	Study details	Quality assessment
		• Age-adjusted D-dimer HemosIL D-dimer HS; Cut-off: age/100 mg/L Reference standard (s) • Pulmonary angiography Computed tomography pulmonary angiography (CTPA) on multidetector CT scanners; patients received an age adapted 60–90 mL intravenous bolus of iomeron 350, iomeprol 350 mg Iodine per mL (Bracco Imaging) followed by a 35 mL chasing bolus of saline. Pregnant patients and patients with impaired kidney function were examined with a low dose protocol (80 kV) with a reduced age adapted contrast bolus of 35–45 mL followed by 35 mL of saline. Patients were categorized according to the CTPA result into four categories: no pulmonary embolism (category 0), peripheral pulmonary embolism (category I), pulmonary embolism in lobar arteries (category II) and central embolisms in the pulmonary trunk or pulmonary arteries (category III) Additional comments • 2 x 2 table was calculated taking data from Kubak (2016)	Directness • Directly applicable
Laruelle (2013)	D-dimer cut-off adjusted to age performs better for exclusion of pulmonary embolism in patients over 75 years	Study type • Retrospective cohort study Study details • Study location Belgium • Study setting Emergency department or hospital • Study dates 2010 - 2011	Patient selection • High risk of bias Retrospective study including people ≥75 years with available results of D-dimer measurement and pulmonary computed tomography or pulmonary scintigraphy Index test • Unclear risk of bias

Author (year)	Title	Study details	Quality assessment
		• Loss to follow-up 0 • Sources of funding Not reported Inclusion criteria • Suspected PE • Age ≥75 years • Diagnostic studies Results of D-dimer measurement and pulmonary computed tomography and pulmonary scintigraphy were available Sample characteristics • Sample size 165 • % female 59 • Mean age (SD) 83 (range 75 to 102) • % pre-test probability Geneva score Low: 24 Intermediate: 70 High: 6 Index test (s) • Laboratory D-dimer Innovance; Cut-off: 0.5 µg/ml • Age-adjusted D-dimer Innovance; Cut-off: age in years multiplied by 0.01 µg/ml/year Reference standard (s) • Composite reference standard Final diagnosis of PE was based on pulmonary computed tomography (PC) and pulmonary scintigraphy (PS). PE was considered as excluded in	It was not reported whether D-dimer was interpreted without knowledge of reference standard Reference standard • Unclear risk of bias It was not reported whether reference standard was interpreted without knowledge of D-dimer Flow and timing • Unclear risk of bias The interval between D-dimer and reference standard was not reported Overall risk of bias • High Retrospective study including people ≥75 years with available results of D-dimer and reference standard. It was not reported whether D-dimer and reference standard interpretations were independent and blinded. The interval between D-dimer and reference standard was not reported Directness • Partially applicable Only people ≥75 years were included

Author (year)	Title	Study details	Quality assessment
		case of normal imaging on PC or PS. Four cases of unclear imaging on PS were found. These cases had low clinical probability and a negative D-dimer test (based on the CDC) and were considered by the clinicians as not having PE Additional comments • 2 x 2 table was taken directly from Laruelle (2013)	
Lim (2018)	Age-adjusted cut-off using the IL D-dimer HS assay to exclude pulmonary embolism in patients presenting to emergency.	Study type • Retrospective cohort study Study details • Study location Austrailia • Study setting Hospital Emergency department • Study dates January 2013 – January 2014 • Sources of funding Not reported Inclusion criteria • Suspected PE Clinically suspected PE evaluated in the emergency department • Age >18 years Exclusion criteria • Medications Full-dose anticoagulation before being evaluated in the emergency department for clinically suspected PE • Previous VTE	Patient selection • High risk of bias Retrospective study including people who underwent D-dimer and pulmonary CT angiography Index test • Low risk of bias Reference standard • Unclear risk of bias Retrospective study therefore it is likely that imaging was performed unblinded. Flow and timing • Low risk of bias Overall risk of bias • Moderate Retrospective study including people who underwent D-dimer and pulmonary CT angiography.

Author (year)	Title	Study details	Quality assessment
		• Sample size • Pregnancy • imaging performed >48 hours after initial D-dimer Sample characteristics • Sample size 176 • % female 45.7% • Mean age (SD) 58.5 (16.8) Index test (s) • Laboratory D-dimer Cut-off: normal <230 ng/mL • Age-adjusted D-dimer Cut-off: age x 5 ng/mL Reference standard (s) • Pulmonary angiography PE was ruled out or confirmed on the basis of a negative or positive CT angiography. Additional comments • 2 x 2 table was calculated taking data from Lim (2018)	Directness • Directly applicable
Parks (2018)	Investigation of age-adjusted D-dimer using an uncommon assay	Study type • Retrospective cohort study Study details • Study location USA • Study setting	Patient selection • High risk of bias Retrospective study only including people who underwent both a D-dimer and CTPA.

Author (year)	Title	Study details	Quality assessment
		Christiana Care Health System, containing 3 EDs. • Study dates January 2012 – July 2017 • Sources of funding Christiana Care Value Institute support Inclusion criteria • Suspected PE Clinically suspected PE evaluated in the emergency department • Age >18 years Exclusion criteria • evaluated by V/Q scan Sample characteristics • Sample size 4845 • % female 66.3 • Mean age (SD) 52.2 Index test (s) • Laboratory D-dimer Hemosil D-Dimer HS automated latex enhanced immunoassay; Cut-off: normal <230 ng/mL • Age-adjusted D-dimer Hemosil D-Dimer HS automated latex enhanced immunoassay; Cut-off: age x 5 ng/mL (another age-adjusted formula was described and presented by the study, to avoid double counting, the formula (age x 5ng/mL) was extracted as this is more common in the literature.	Index test • Unclear risk of bias It was not reported whether D-dimer was interpreted without knowledge of pulmonary CT angiography Reference standard • Unclear risk of bias Unclear whether CTPA was interpreted without knowledge of D-dimer. Flow and timing • Unclear risk of bias The interval between D-dimer and CT scan was not reported Overall risk of bias • High Retrospective study including people who underwent D-dimer and pulmonary CT angiography. It was not reported whether D-dimer and pulmonary CT angiography interpretations were independent and blinded. The interval between D-dimer and pulmonary CT angiography was not reported Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Reference standard (s) • Pulmonary angiography PE was ruled out or confirmed on the basis of a negative or positive CTPA, as evidenced by diagnosis discharge codes ICD-9 or 10. Additional comments • 2 x 2 table was calculated taking data from Parks (2018)	
Polo (2014)	A higher D-dimer threshold safely rules-out pulmonary embolism in very elderly emergency department patients	Study type • Retrospective cohort study Study details • Study location Italy • Study setting Emergency department • Study dates 2010 - 2012 • Loss to follow-up 11/492 • Sources of funding Not reported Inclusion criteria • Suspected PE Clinically suspected PE evaluated in the emergency department • Age >18 years Exclusion criteria • Medications Full-dose anticoagulation before being evaluated in the	Patient selection • High risk of bias Retrospective study including people who underwent D-dimer and pulmonary CT angiography Index test • Unclear risk of bias It was not reported whether D-dimer was interpreted without knowledge of pulmonary CT angiography Reference standard • Unclear risk of bias It was not reported whether pulmonary CT angiography was interpreted without knowledge of D-dimer Flow and timing • Unclear risk of bias The interval between D-dimer and CT scan was not reported Overall risk of bias • High

Author (year)	Title	Study details	Quality assessment
		emergency department for clinically suspected PE Sample characteristics • Sample size 481 • % female 63.4 • Mean age (SD) 73.0 (16.1) Index test (s) • Laboratory D-dimer Innovance; Cut-off: normal <490 ng/mL • Age-adjusted D-dimer Innovance; Cut-off: age x 10 ng/mL Reference standard (s) • Pulmonary angiography PE was ruled out or confirmed on the basis of a negative or positive CT angiography, that is the absence or presence of a filling defect in one or more pulmonary arteries up to sub-segmental arteries Additional comments • 2 x 2 table was calculated taking data from Polo (2014)	Retrospective study including people who underwent D-dimer and pulmonary CT angiography. It was not reported whether D-dimer and pulmonary CT angiography interpretations were independent and blinded. The interval between D-dimer and pulmonary CT angiography was not reported Directness • Directly applicable
Sharp (2016)	An Age-Adjusted D-dimer Threshold for Emergency Department Patients With Suspected Pulmonary Embolus: Accuracy and Clinical Implications	Study type • Retrospective cohort study Study details • Study location US • Study setting Emergency department	Patient selection • High risk of bias Retrospective study including people who received a D-dimer test with a possible PE Index test • Unclear risk of bias

Author (year)	Title	Study details	Quality assessment
		• Study dates 2008 - 2013 • Loss to follow-up 0 • Sources of funding The Kaiser Permanente Southern California Care Improvement Research Team Inclusion criteria • Suspected PE Possible PE not DVT; therefore only patients presenting with a chief complaint related to a possible pulmonary embolism, such as chest pain or dyspnoea • Age >50 years • Diagnostic studies D-dimer test Exclusion criteria • Previous VTE PE diagnosis in the previous 90 days • Other evaluations Ultrasonographic imaging evaluation for deep venous thrombosis Sample characteristics • Sample size 31094 • % female 61.0 • Mean age (SD) 65.0 (10.9) • % people with cancer 10.3	It was not reported whether D-dimer was interpreted without knowledge of reference standard Reference standard • Unclear risk of bias It was not reported whether reference standard was interpreted without knowledge of D-dimer Flow and timing • Unclear risk of bias The interval between D-dimer and reference standard was not reported Overall risk of bias • High Retrospective study including people who received a D-dimer test with a possible PE. It was not reported whether D-dimer and reference standard interpretations were independent and blinded. The interval between D-dimer and reference standard was not reported Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Index test (s) • Laboratory D-dimer Immunoturbidimetric assay; Cut-off: 500 ng/dL • Age-adjusted D-dimer Immunoturbidimetric assay; Cut-off: patient's age in years x 10 Reference standard (s) • Composite reference standard CT pulmonary angiography, ventilation-perfusion scan, pulmonary angiography, or chest magnetic resonance angiography or pulmonary embolism diagnosis within 30 days of the index emergency department encounter Additional comments • 2 x 2 table was taken directly from Sharp (2016)	
Senior (2019)	Age-adjusted D-dimer thresholds in the investigation of suspected pulmonary embolism: A retrospective evaluation in patients ages 50 and older using administrative data	Study type • Retrospective cohort study Study details • Study location Canada • Study setting four Eds in Calgary, Canada • Study dates July 2013 to January 2015 • Sources of funding none reported Inclusion criteria • age >50 years • presenting with triage complaint codes of chest pain, shortness of breath, or syncope, and who underwent	Patient selection • High risk of bias Retrospective study including people who received a D-dimer test as part of their medical work-up. Index test • Unclear risk of bias It was not reported whether D-dimer was interpreted without knowledge of CT scan. Reference standard • High risk of bias reference standard was a diagnosis at 30 days and therefore the sample include a large number of people who

Author (year)	Title	Study details	Quality assessment
		D-dimer testing. Exclusion criteria • pre-existing diagnosis of PE in 90 days prior to presentation. Sample characteristics • Sample size 6655 • % female 53.1% • Mean age (SD) 67.3 (11.7) Index test (s) • Laboratory D-dimer HemosIL HS 500; Cut-off: positive result ≥500 ng/mL • Age-adjusted D-dimer HemosIL; Cut-off: age x 10 ng/mL Reference standard (s) • 30 days diagnosis using imaging. Any diagnosis of PE made using CTPA or a V/Q scan within 30-days of presentation. Additional comments • 2 x 2 table was taken directly from Senior (2019).	did not undergo imaging. Flow and timing • High risk of bias all diagnoses had to be made either at initial presentation or during 30 days follow-up Overall risk of bias • High Retrospective study including people who received a D-dimer test as part of their medical work-up. Reference standard was diagnosis within 30 days and therefore a large number of participants never underwent Directness • Directly applicable
Sheele (2018)	A retrospective evaluation of the age-adjusted D-dimer versus the	Study type • Retrospective cohort study	Patient selection • High risk of bias Retrospective study including people who received a D-dimer test as part of

Author (year)	Title	Study details	Quality assessment
	conventional D-dimer for pulmonary embolism	Study details • Study location US • Study setting Emergency department • Study dates 2010 - 2014 • Loss to follow-up 203/3320 • Sources of funding The UHCMC Department of Emergency Medicine Inclusion criteria • None reported Exclusion criteria • None reported Sample characteristics • Sample size 3117 • % female Not reported • Mean age (SD) 65.9 (11.8) Index test (s) • Laboratory D-dimer D-dimer type was not reported; Cut-off: positive result ≥500 µg FEU/l • Age-adjusted D-dimer D-dimer type was not reported; Cut-off: age x 10 Reference standard (s) • CT scan	their medical work-up Index test • Unclear risk of bias It was not reported whether D-dimer was interpreted without knowledge of CT scan Reference standard • Unclear risk of bias It was not reported whether CT scan was interpreted without knowledge of D-dimer Flow and timing • Low risk of bias CT scan was done within 24 hours of D-dimer test result Overall risk of bias • High Retrospective study including people who received a D-dimer test as part of their medical work-up. It was not reported whether D-dimer and CT scan interpretations were independent and blinded Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		CT pulmonary embolism study. A radiology report stating no pulmonary embolism to the level of the segmental pulmonary arteries was considered negative for pulmonary embolism. Any pulmonary embolism reported on CT, including those in subsegmental arteries, was considered positive for pulmonary embolism. If the radiologist was unable to clearly evaluate the anatomy down to the segmental pulmonary arteries, the study was categorized as indeterminate for pulmonary embolism Additional comments • 2 x 2 table was taken directly from Sheele (2018). Sensitivity and specificity were calculated by Sheele (2018) assuming that participants without a CT scan (referred as 'No CT') did not have PE. We calculated sensitivity and specificity using data of PE confirmation by CT scan	
Woller (2014)	Assessment of the safety and efficiency of using an age-adjusted D-dimer threshold to exclude suspected pulmonary embolism	Study type • Retrospective cohort study Study details • Study location US • Study setting Emergency department • Study dates Not reported • Loss to follow-up 0 • Sources of funding Intermountain Research & Medical Foundation	Patient selection • High risk of bias Retrospective study including people with pretest probability of PE unlikely and aged >50 years Index test • Unclear risk of bias It was not reported whether D-dimer was interpreted without knowledge of CT pulmonary angiography Reference standard • Unclear risk of bias It was not reported whether CT pulmonary angiography was

Author (year)	Title	Study details	Quality assessment
		Inclusion criteria • Suspected PE and low revised Geneva score (RGS) defined as an RGS ≤10 (pretest probability of PE unlikely) • Age >50 years Exclusion criteria • None reported Sample characteristics • Sample size 923 • % female 61.3 • Mean age (SD) 67 (11.5) • % people with cancer 5.0 • % people with previous VTE 12.8 Index test (s) • Laboratory D-dimer Stago latex agglutination; Cut-off: <500 ng/mL • Age-adjusted D-dimer Stago latex agglutination; Cut-off: patient age x 10 ng/mL Reference standard (s) • Pulmonary angiography CT pulmonary angiography interpreted by an in-house board-certified radiologist	interpreted without knowledge of D-dimer Flow and timing • Unclear risk of bias The interval between D-dimer and CT pulmonary angiography was not reported Overall risk of bias • High Retrospective study including people with pretest probability of PE unlikely and aged >50 years. It was not reported whether D-dimer and CT pulmonary angiography interpretations were independent and blinded. The interval between D-dimer and CT pulmonary angiography was not reported Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Additional comments • 2 x 2 table was calculated taking data from Woller (2014)	

Point of care D-dimer

Author (year)	Title	Study details	Quality assessment
Ginsberg (1995)	Application of a novel and rapid whole blood assay for D-dimer in patients with clinically suspected pulmonary embolism	Study type • Prospective cohort study Study details • Study location Canada • Study setting Hospital • Study dates 1992 - 1993 • Loss to follow-up 0 • Sources of funding Agen Inc. supplied the D-dimer reagents Inclusion criteria • Suspected PE Clinically suspected PE Exclusion criteria • None reported Sample characteristics • Sample size 86	Patient selection • Low risk of bias Consecutive sample Index test • Low risk of bias The nurses performing and interpreting the D-dimer assays, were unaware of the results of the diagnostic tests for PE Reference standard • Low risk of bias Lung scans, venography, and pulmonary angiography was avoided by having the tests interpreted by physicians who were unaware of the results of the D-dimer assay Flow and timing • Low risk of bias Blood (to measure D-dimer) was taken at the time of referral or within 24 hours of the initiation of heparin. Reference standard was done within 24 hours of presentation or confirmed

Author (year)	Title	Study details	Quality assessment
		• % female 59.3 • Mean age (SD) 51 (range 17 to 90) Index test (s) • Point-of-care D-dimer SimpliRED assay; Cut-off: positive test if any agglutination was observed; negative test if no agglutination was observed Reference standard (s) • Composite reference standard PE positive When one of the following occurred: a) positive pulmonary angiography, or b) high probability lung scan, or c) non-high probability lung scan and either abnormal impedance plethysmography (IPG) (either at presentation or upon serial testing and confirmed by venography) or symptomatic venous thromboembolic event, verified by objecting test, within three months of presentation PE negative When one of the following occurred: a) normal perfusion lung scan or b) normal pulmonary angiography or c) non-high probability lung scan and normal serial IPG and absence of symptomatic venous thromboembolism within three months of follow-up Additional comments • 2 x 2 table was taken directly from Ginsberg (1995)	at 3-month follow-up Overall risk of bias • Low Directness • Directly applicable
Ginsberg (1998)	Sensitivity and specificity of a rapid whole-blood assay for D-dimer in the	Study type • Prospective cohort study	Patient selection • Low risk of bias Consecutive sample

Author (year)	Title	Study details	Quality assessment
	diagnosis of pulmonary embolism	Study details • Study location Canada • Study setting Hospital • Study dates 1993 - 1996 • Loss to follow-up 73/1250 • Sources of funding Medical Research Council of Canada; Heart and Stroke Foundation of Canada; Heart and Stroke Foundation of Ontario Inclusion criteria • Suspected PE Clinically suspected acute pulmonary embolism • Age 18 years and older Exclusion criteria • Medications Treatment with anticoagulants for 72 hours or more • Expected survival Less than 3 months • Contraindications Contraindication to contrast media • Suspected upper-extremity DVT • No symptoms within 48 hours of presentation • Geographic inaccessibility Sample characteristics • Sample size 1177 • % female 59	Index test • Low risk of bias The results of the D-dimer assay were not disclosed to caregivers and were obtained independently of the pretest probability assessment and results of other diagnostic tests Reference standard • Unclear risk of bias It was not reported whether reference standard was interpreted without knowledge of D-dimer Flow and timing • Low risk of bias Blood (to measure D-dimer) was taken at the time of referral. Reference standard was done within 24 hours of presentation or confirmed at 3-month follow-up Overall risk of bias • Low Although it was not reported whether reference standard was interpreted without knowledge of D-dimer, it seems that index test and reference standard were independent (see note about index test) Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Mean age (SD) 53.4 (range 20 to 94) • % pre-test probability Low: 60 Moderate: 32 High: 8 Index test (s) • Point-of-care D-dimer SimpliRED; Cut-off: normal if absence of erythrocyte agglutination; abnormal if presence of erythrocyte agglutination Reference standard (s) • Composite reference standard Patients were classified as positive if one or more of the following occurred: positive pulmonary angiogram; positive compression ultrasonogram (at any time) or positive contrast venogram; high-probability perfusion lung scan plus moderate or high pretest probability; or symptomatic, objectively confirmed venous thromboembolism during the 3-month follow-up. All other patients were classified as negative Additional comments • 2 x 2 table was taken directly from Ginsberg (1998)	
Gosselin (2012)	Evaluation of the Stratus CS Acute Care D-dimer assay (DDMR) using the Stratus CS STAT Fluorometric Analyzer: a prospective multisite study for exclusion of pulmonary embolism and deep vein thrombosis	Study type • Prospective cohort study Study details • Study location US and Germany • Study setting Emergency department • Study dates	Patient selection • Low risk of bias Consecutive sample Index test • Unclear risk of bias It was not reported whether D-dimer was interpreted without knowledge of

Author (year)	Title	Study details	Quality assessment
		Not reported • Loss to follow-up 62/1074 • Sources of funding Not reported Inclusion criteria • Suspected DVT Patients presenting to the emergency department with suspicion of DVT • Suspected PE Patients presenting to the emergency department with suspicion of PE • No prior history of VTE • Medications Patients who were not on oral vitamin K antagonist or heparin treatment • Diagnostic studies Patients who had objective radiographic studies for diagnosing VTE • Consent Patients who consented to participation Exclusion criteria • Diagnostic workup could not be initiated within 24 h Patients who did not have imaging studies within 24 hours of emergency department presentation or patients whose symptoms subsided over 48 hours • Pregnancy • Age <18 years • Medications Those currently on anticoagulant therapy • Previous VTE • Blood sample Those whose blood was not collected within 12 hours	reference standard Reference standard • Low risk of bias All emergency department and radiology physicians were blinded to D-dimer results Flow and timing • Low risk of bias Reference standard was done within 24 hours of presentation. After enrolment and completion of reference standard, blood was obtained to measure D-dimer Overall risk of bias • Moderate It was not reported whether D-dimer was interpreted without knowledge of reference standard Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		of imaging studies • Prisoners • Consent Patients who refused consent Sample characteristics • Sample size 1012 • % female 59.5 • Mean age (SD) Median age from 52 to 70 (range 18 to 94) • % pre-test probability Wells pre-test probability scores For people with PE Low: 60.2 Moderate: 34.7 High: 5.1 For people with DVT Unlikely: 60.4 Likely: 39.6 Index test (s) • Point-of-care D-dimer Stratus R CS Acute Care TM; heparin or citrate plasma blood samples; Cut-off: 450 mg/L FEU Reference standard (s) • Composite reference standard Spiral computerised tomography pulmonary angiograms (CTA), ventilation-perfusion scans (VQ), or contrast pulmonary angiogram for PE, and compression ultrasound (CUS) or venography for DVT. In addition of filling defects noted on CT or angiograms, only high probability VQ scans were considered positive for PE Additional comments • 2 x 2 table	

Author (year)	Title	Study details	Quality assessment
		was calculated taking data from Gosselin (2012)	
Kline (2001)	Diagnostic accuracy of a bedside D-dimer assay and alveolar dead-space measurement for rapid exclusion of pulmonary embolism: a multicenter study	Study type • Prospective cohort study Study details • Study location US • Study setting Emergency department • Study dates 1998 - 1999 • Loss to follow-up 21/401 • Sources of funding The Established Investigator Award from the Emergency Medicine Foundation; an educational grant from the Novametrix Corp.; D-dimer assays were provided free from the Agen Corp. Inclusion criteria • Suspected PE When the emergency department physician had suspected PE enough to order a pulmonary vascular imaging study • Age >18 • Who were not transferred from another medical care facility Exclusion criteria • Circulatory shock Clinical signs (systolic blood pressure <90 mm Hg, base deficit <-4 mEq/L) • Inability to breathe room air	Patient selection • Low risk of bias Consecutive sample Index test • Low risk of bias D-dimer measurement was completed at the bedside prior to the completion of pulmonary vascular imaging Reference standard • Low risk of bias Radiographic examinations used for the reference standard were interpreted by radiologists who were unaware of study results Flow and timing • Low risk of bias D-dimer was completed at the bedside prior to the completion of reference standard Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		and maintain pulse oximetry reading of at least 90% • Inability to cooperate with volumetric capnometry measurement and D-dimer collection Sample characteristics • Sample size 380 • % female 70.2 • Mean age (SD) People with PE: 55.6 (16.9) People without PE: 49.2 (16.2) • % people with cancer 15.5 • % people with previous VTE 23.9 Index test (s) • Point-of-care D-dimer SimpliRED; Cut-off: strong-positive and weak-positive agglutination were considered abnormal Reference standard (s) • Composite reference standard All subjects underwent at least 1 pulmonary vascular imaging procedure, either a ventilation-perfusion scintillation lung scan (V/Q scan) or a contrast-enhanced helical computed tomography (CT) scan of the chest. The V/Q read as either normal or high probability were considered diagnostic for the absence or presence of PE, respectively. Subjects with non-diagnostic V/Q scans and higher suspicion for PE, including all subjects with intermediate probability V/Q scans, underwent bilateral lower-extremity venous duplex ultrasonography. A subject with a non-	

Author (year)	Title	Study details	Quality assessment
		diagnostic V/Q scan and sonographic evidence of deep venous thrombosis was diagnosed with PE. Subjects with non-diagnostic V/Q scans, no deep venous thrombosis, but with a high clinical probability of PE underwent pulmonary angiography. Results of the angiography were considered diagnostic. Contrast-enhanced helical CT scans of the chest were performed. Subjects with no evidence of PE on their scans underwent additional testing if the clinical suspicion for PE remained high. Subjects were considered to be free of PE when, at 6-month follow-up, the subject reported the same or better state of health and had no interval diagnosis of PE or DVT. For subjects who died during the 6-month follow-up period, PE was diagnosed if death occurred during the hospitalisation attendant to the time of study entry in a subject without a normal V/Q scan or normal pulmonary angiogram result; subjects were deemed as negative for PE if autopsy results were negative for PE or if death occurred more than 3 months after study entry in a subject with a known end-stage disease and with no autopsy performed Additional comments • 2 x 2 table was taken directly from Kline (2001)	
Lucassen (2015)	Qualitative point-of-care D-dimer testing compared with quantitative D-dimer testing in excluding pulmonary embolism in primary care	Study type • Prospective cohort study Post-hoc analysis Study details • Study location Netherlands • Study setting Primary care	Patient selection • Low risk of bias Consecutive sample Index test • Low risk of bias GP performed the POINT-OF-CARE Simplify D-dimer test before referring the patient to secondary care for

Author (year)	Title	Study details	Quality assessment
		• Study dates Not reported • Loss to follow-up None but there were missing values for POINT-OF-CARE D-dimer results (n=16 patients) and for quantitative D-dimer results (n=197 patients). Both of these missing values were imputed for the analysis • Sources of funding Dutch Heart Foundation Inclusion criteria • Suspected PE By GP • Age ≥18 years Exclusion criteria • None reported Sample characteristics • Sample size 598 • % female 71 • Mean age (SD) 48 • % people with cancer 3 • % people with previous VTE 15 Index test (s) • Laboratory D-dimer Either ELISA or latex assay; Cut-off: not reported • Point-of-care D-dimer	reference testing Reference standard • High risk of bias GPs were asked to document the final diagnosis of every patient during the 3 months follow-up Flow and timing • Unclear risk of bias The interval between D-dimer and reference standard was not reported Overall risk of bias • High Final PE diagnosis was recorded by the GP who also performed the POINT-OF-CARE D-dimer. The interval between D-dimer and reference standard was not reported Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Simplify Clearview; Cut-off: positive >80 ng mL-1 Reference standard (s) • Composite reference standard Composite reference standard of spiral CT scanning, ventilation- perfusion scanning, pulmonary angiography, leg ultrasonography, and clinical probability assessment in combination with D-dimer testing as performed in routine secondary care at the participating hospital. During 3 months of follow-up, GPs were asked to document the possible occurrence of venous thromboembolism Additional comments • 2 x 2 table was taken directly from Lucassen (2015)	
Subedi (2009)	Use of SimpliRED D-dimer assay and computerised tomography in the diagnosis of acute pulmonary embolism	Study type • Prospective cohort study Study details • Study location UK • Study setting Radiology department • Study dates Not reported • Loss to follow-up 1/48 • Sources of funding Not reported Inclusion criteria • Suspected PE Patients who were referred to the radiology department	Patient selection • Low risk of bias Consecutive sample Index test • Unclear risk of bias It was not reported whether D-dimer was interpreted without knowledge of CT pulmonary angiography Reference standard • Low risk of bias The radiologist, who was blinded to the results of the D-dimer assay, reported the CT pulmonary angiography results

Author (year)	Title	Study details	Quality assessment
		for investigation of suspected acute pulmonary embolism Exclusion criteria • None reported Sample characteristics • Sample size 47 • % female 61.7 • Mean age (SD) Not reported Index test (s) • Point-of-care D-dimer SimpliRED; Cut-off: positive; negative Reference standard (s) • Pulmonary angiography CT pulmonary angiography reported by radiologist as positive or negative for PE Additional comments • 2 x 2 table was taken directly from Subedi (2009)	Flow and timing • Low risk of bias D-dimer and CT pulmonary angiography were done in the radiologist department when the patient attended for the CT pulmonary angiography Overall risk of bias • Moderate It was not reported whether D-dimer was interpreted without knowledge of CT pulmonary angiography Directness • Directly applicable

Laboratory based D-dimer

Author (year)	Title	Study details	Quality assessment
Anoop (2009)	Evaluation of an immunoturbidimetric D-dimer assay	Study type • Prospective cohort study	Patient selection • Low risk of bias

Author (year)	Title	Study details	Quality assessment
	and pretest probability score for suspected venous thromboembolism in a district hospital setting.	Study details • Study location UK • Study setting Medium sized hospital • Study dates December 1, 2007 to March 31, 2008 Inclusion criteria • Suspected VTE Exclusion criteria • Inconclusive reference standard • Other evaluations D-dimer level not quantifiable due to specimen error; Wells' chart unavailable or illegible; modality other than CTPA used as confirmatory test • Intensive care unit patients Sample characteristics • Sample size 197 participants overall, 91 with suspected PE. • % female 66% female • Mean age (SD) Median 61 years (range: 19-96 years) • % pre-test probability 20.9% low; 79.1% intermediate Index test (s) • Laboratory D-dimer MDA autodimer T3103 Cut-off: 0.50 µg FEU/ml	Index test • High risk of bias D-dimer technique was changed prior to study to an unvalidated measure and this lack of validation was reason for all patients undergoing imaging Reference standard • High risk of bias Physician was unblinded Flow and timing • Low risk of bias Overall risk of bias • Moderate Radiologist was unblinded to D-dimer results. In addition, the D-dimer assay was unvalidated at point of study. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Reference standard (s) • Pulmonary angiography 64-slice 0.625mm thickness CTPA (GE lightSpeed VCT) with Niopam 300 contrast, 74ml at 3 ml/s Additional comments • 2 x 2 table was taken directly from Anoop (2009)	
Arnautovic-Torlak (2014)	Values of D-dimer test in the diagnostics of pulmonary embolism	Study type • Prospective cohort study Study details • Study location Bosnia and Herzegovina • Study setting Hospital • Study dates 2012 - 2013 • Loss to follow-up 0 • Sources of funding No specific funding was received for this study Inclusion criteria • Suspected PE Symptoms indicating probable presence of pulmonary thromboembolism Exclusion criteria • None reported Sample characteristics • Sample size	Patient selection • Low risk of bias Consecutive sample Index test • Unclear risk of bias It was not reported whether D-dimer was interpreted without knowledge of CT scan Reference standard • Unclear risk of bias It was not reported whether CT scan was interpreted without knowledge of D-dimer Flow and timing • Unclear risk of bias The interval between D-dimer and CT scan was not reported Overall risk of bias • High It was not reported whether D-dimer and CT scan interpretations were independent and blinded. The interval between D-dimer and CT scan was not reported

Author (year)	Title	Study details	Quality assessment
		80 • % female People with PE: 59.73 People without PE: 59.8 • Mean age (SD) 59.83 (16.40) Index test (s) • Laboratory D-dimer New method of immunoturbidimetry (BCSX System); Cut-off: >500 ng/L Reference standard (s) • CT scan The Ultravist 300 mg/ml pack iopromide radiological contrast agent was used Additional comments • 2 x 2 table was taken directly from Arnautović-Torlak (2014)	Directness • Directly applicable
Burkill (2002)	The use of a D-dimer assay in patients undergoing CT pulmonary angiography for suspected pulmonary embolus	Study type • Prospective cohort study Study details • Study location UK • Study setting CT unit • Study dates Not reported • Loss to follow-up 48/149 • Sources of funding	Patient selection • Low risk of bias Consecutive sample Index test • Unclear risk of bias It was not reported whether D-dimer was interpreted without knowledge of reference standard Reference standard • Unclear risk of bias It was not reported whether reference standard was interpreted without knowledge of D-dimer

Author (year)	Title	Study details	Quality assessment
		Not reported Inclusion criteria • Suspected PE Suspected acute pulmonary embolism Exclusion criteria • Previous VTE Prior history of thromboembolic disease • Contraindications Contraindication to intravenous contrast medium Sample characteristics • Sample size 101 • % female 54.4 • Mean age (SD) 58 Index test (s) • Laboratory D-dimer Semi-quantitative Accuclot TM; Cut-off: positive result ≥0.25 mg/l Reference standard (s) • CT scan High resolution CT • Pulmonary angiography CT pulmonary angiogram with 150 ml Omnipaque 300 contrast medium Additional comments • 2 x 2 table	Flow and timing • Unclear risk of bias The interval between D-dimer and reference standard was not reported Overall risk of bias • Moderate It was not reported whether D-dimer and reference standard interpretations were independent and blinded Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		was taken directly from Burkill (2002)	
de Moerloose (1996)	Contribution of a new, rapid, individual and quantitative automated D-dimer ELISA to exclude pulmonary embolism	Study type • Prospective cohort study Study details • Study location Switzerland • Study setting Emergency department • Study dates 1994 • Loss to follow-up 0 • Sources of funding Not reported Inclusion criteria • Suspected PE Patients with clinically suspected PE who were admitted to the emergency ward Exclusion criteria • None reported Sample characteristics • Sample size 195 • % female 56.4 • Mean age (SD) 60 (range 19 to 95)	Patient selection • Low risk of bias Consecutive sample Index test • Unclear risk of bias It was not reported whether D-dimer was interpreted without knowledge of reference standard Reference standard • Unclear risk of bias It was not reported whether reference standard was interpreted without knowledge of D-dimer Flow and timing • Unclear risk of bias The interval between D-dimer and reference standard was not reported Overall risk of bias • High It was not reported whether D-dimer and reference standard interpretations were independent and blinded. The interval between D-dimer and reference standard was not reported Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Index test (s) • Laboratory D-dimer VIDAS quantitative ELISA; Cut-off level: 500 ng/ml Reference standard (s) • Composite reference standard The diagnosis of PE was established either by a high probability scan or a positive pulmonary angiogram or a positive venous compression ultrasonography of the lower limbs Additional comments • 2 x 2 table was calculated taking data from de Moerloose (1996)	
de Monye (2002)	The performance of two rapid quantitative D-dimer assays in 287 patients with clinically suspected pulmonary embolism	Study type • Prospective cohort study Study details • Study location The Netherlands • Study setting Hospital • Study dates 1997 - 1998 • Loss to follow-up 153/440 • Sources of funding Dutch Health Insurance Council Inclusion criteria • Suspected PE	Patient selection • Low risk of bias Consecutive sample Index test • Low risk of bias Technicians were not aware of patient identity and diagnostic imaging results Reference standard • Low risk of bias D-dimer measurements were not made known to the interpreters of the diagnostic imaging tests Flow and timing • Low risk of bias Prior to or within 24 hours after the start of heparin therapy, blood samples were taken to measure D-dimers. The maximum time span

Author (year)	Title	Study details	Quality assessment
		Clinically suspected PE Exclusion criteria • Already undergone objective diagnostic examinations • Diagnostic workup could not be initiated within 24 h • Age Less than 18 years • Medications Use of oral anticoagulant drugs, use of heparin for more than 24h prior to inclusion in the study and the immediate need for thrombolytic therapy Sample characteristics • Sample size 287 • % female 58.7 • Mean age (SD) 50 (18) Index test (s) • Laboratory D-dimer Tinaquant R; Cut-off: 0.5 µg/ml Vidas R Cut-off: 500 ng/ml Note: also reported Tinaquant R; Cut-off: 0.5 µg/ml (excluded from review to avoid double-counting) Reference standard (s) • Composite reference standard All patients underwent lung perfusion scintigraphy. A normal perfusion scintigram excluded PE, and no further examinations were performed. Both	between reference standard examinations was 24 hours Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		ventilation scintigraphy and a spiral CT scan were performed following an abnormal perfusion result. Ventilation-perfusion results were classified either as high probability for pulmonary embolism (defined as one or more segmental perfusion defects with locally normal ventilation) or non-diagnostic. Pulmonary angiography was performed in patients with a nondiagnostic VQ-scan and in patients with a high-probability VQ-scan and a contradictory normal CT scan. The maximum time span between examinations was 24 h. The final diagnosis of PE was established by a high-probability VQ-scan with a concurrent abnormal CT scan or by an abnormal pulmonary angiogram. PE was excluded on the basis of a normal perfusion scan or a normal pulmonary angiogram. All patients underwent compression ultrasound of the leg veins to ascertain the presence of DVT Additional comments • 2 x 2 table was taken directly from de Monye (2002)	
Goldhaber (1993)	Quantitative plasma D-dimer levels among patients undergoing pulmonary angiography for suspected pulmonary embolism	Study type • Prospective cohort study Study details • Study location US • Study setting Hospital • Study dates 1990 - 1992 • Loss to follow-up 31/204	Patient selection • Low risk of bias Consecutive sample Index test • Low risk of bias Those performing the assay were blinded to angiography results. In addition, clinicians involved in the care of study patients were unaware of D-dimer levels

Author (year)	Title	Study details	Quality assessment
		• Sources of funding Abbott Laboratories, North Chicago, Ill; Sandra Bakalar Fund; and National Institutes of Health Clinical Research Center Inclusion criteria • All patients undergoing Diagnostic pulmonary arteriography for suspected PE Exclusion criteria • There were no exclusion criteria Sample characteristics • Sample size 173 • % female Abnormal pulmonary angiogram: 46.7 Normal pulmonary angiogram: 63.3 • Mean age (SD) Abnormal pulmonary angiogram: 57.6 (17.1) Normal pulmonary angiogram: 58.2 (16.6) • % people with cancer Abnormal pulmonary angiogram: 17.8 Normal pulmonary angiogram: 11.7 • % people with previous VTE Abnormal pulmonary angiogram: 8.9 Normal pulmonary angiogram: 10.2 • % people with previous PE Abnormal pulmonary angiogram: 17.8 Normal pulmonary angiogram: 11.7 Index test (s) • Laboratory D-dimer	Reference standard • Low risk of bias Angiograms were interpreted without knowledge of results of the D-dimer assay. In addition, clinicians involved in the care of study patients were unaware of D-dimer levels Flow and timing • Low risk of bias Blood (to measure D-dimer) was taken prior to angiography Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Asserachrom; Cut-off: 500 ng/mL Reference standard (s) • Pulmonary angiography Performed using a low-osmolar contrast agent Additional comments • 2 x 2 table was taken directly from Goldhaber (1993)	
Gupta (2009)	D-dimers and efficacy of clinical risk estimation algorithms: sensitivity in evaluation of acute pulmonary embolism	Study type • Prospective cohort study Study details • Study location US • Study setting Emergency department • Study dates 2007 - 2008 • Loss to follow-up 0 • Sources of funding Not reported Inclusion criteria • Suspected PE With PE suspected because the patient had acute onset of new or worsening dyspnoea or chest pain without another obvious cause Exclusion criteria • Pregnancy • Renal insufficiency	Patient selection • Low risk of bias Consecutive sample Index test • Unclear risk of bias It was not reported whether D-dimer was interpreted without knowledge of pulmonary CT angiography Reference standard • Unclear risk of bias It was not reported whether pulmonary CT angiography was interpreted without knowledge of D-dimer Flow and timing • Unclear risk of bias The interval between D-dimer and pulmonary CT angiography was not reported Overall risk of bias • High It was not reported whether D-dimer and pulmonary CT angiography interpretations were independent and blinded. The interval between

Author (year)	Title	Study details	Quality assessment
		• Refusing to undergo reference standard Patients who chose not to undergo pulmonary CT angiography Sample characteristics • Sample size 627 • % female 66.0 • Mean age (SD) 46.9 (range 15 to 94) • % pre-test probability Geneva score Low: 44.8 Intermediate: 52.6 High: 2.6% Index test (s) • Laboratory D-dimer Advanced D-dimer; Cut-off: 1.2 mg/L Reference standard (s) • Pulmonary angiography Performed with a 16 MDCT scanner; patients received 100 mL of iopamidol (Isovue 370, Bracco) Subgroup analyses • Pre-test probability Geneva score: low, intermediate, and high Additional comments • 2 x 2 table was taken directly from Gupta (2009)	D-dimer and pulmonary CT angiography was not reported Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
King (2008)	D-dimer assay to exclude pulmonary embolism in high-risk oncologic population: correlation with CT pulmonary angiography in an urgent care setting	Study type • Prospective cohort study Study details • Study location US • Study setting Urgent care centre of a tertiary care cancer centre • Study dates 2005 - 2006 • Loss to follow-up 13/214 • Sources of funding Not reported Inclusion criteria • Suspected PE Who were referred for CT pulmonary angiography Exclusion criteria • CT angiography without D-dimer Patients who did not have a D-dimer assay sample drawn within 24 hours before or after the CT pulmonary angiogram • Contraindications Patients with a known contrast agent allergy or poor intravenous access • Consent Patients unable to provide consent to the study • Unwilling to participate For a variety of reasons, including medical instability, inability to communicate, lack of financial compensation, or absence of a health care proxy or	Patient selection • High risk of bias All but one participant had cancer Index test • Low risk of bias The reader of the D-dimer assay was blinded to the CT pulmonary angiogram results and other clinical information Reference standard • Low risk of bias CT pulmonary angiograms were interpreted by radiologists who were blinded to the results of the D-dimer tests Flow and timing • Low risk of bias D-dimer was done within 24 hours of CT pulmonary angiography Overall risk of bias • Moderate Study was specific for people with cancer Directness • Partially applicable All participants but one had cancer

Author (year)	Title	Study details	Quality assessment
		other available representative Sample characteristics • Sample size 201 • % female 64 • Mean age (SD) Median age 61 years • % people with cancer 99 Index test (s) • Laboratory D-dimer STA Liatest; Cut-off: positive ≥0.21 µg/mL Reference standard (s) • CT scan 16-section multidetector CT scan of the chest or the chest, abdomen, and pelvis; contrast agent varied: - 100-150 mL of iohexol (Omnipaque 300) or - 100-150 mL Omnipaque 300 and 80-120 mL saline bolus or - 40 mL of saline then 80 mL iohexol (Omnipaque 350) and finally 80 mL of saline or - 40 mL of saline then 150 mL of Omnipaque 300 and finally 80 mL of saline Results were designated as positive, negative, or equivocal Additional comments • 2 x 2 table was taken directly from King (2008)	

Author (year)	Title	Study details	Quality assessment
Lichey (1991)	Fibrin degradation product D-dimer in the diagnosis of pulmonary embolism	Study type • Prospective cohort study Study details • Study location Germany • Study setting Four Berlin hospitals Inclusion criteria • Suspected VTE Any patient presenting in ER with dyspnea and/or chest pain were considered. Exclusion criteria • Acute myocardial infarction • Other evaluations participant found to have bronchial asthma, pneumothorax, or hyperventilation-syndrome, which could be clearly diagnosed by physical examination, ECG and chest X-ray. Sample characteristics • Sample size 73 participants • % female 53% female • Mean age (SD) 59.2 years Index test (s) • Laboratory D-dimer quantitative enzyme-immunoassay (ELISA D-dimer)	Patient selection • High risk of bias Unclear patient recruitment period. D-dimer was taken at time of imaging. It is therefore likely that only people with symptoms indicating a likely PE were included. Index test • Low risk of bias Reference standard • Unclear risk of bias Unclear whether reference standard was interpreted blind to D-dimer results. Flow and timing • Low risk of bias Overall risk of bias • High unclear whether reference standard was interpreted blind and selection for imaging being based on clinical presentation alone Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Note: Also reported a D-dimer test by latex agglutination assay; Cut-off: 1000 ng/mL (excluded from analysis to avoid double-counting) Reference standard (s) • Composite reference standard In each of these patients an ECG and a two-view chest X-ray were performed. The patients were submitted to an additional four-view lung perfusion scan with technetium-99M-laveled macroaggregated albumin. If lung scans were negative we refrained from performing further diagnostic procedures for pulmonary embolism. In case of a positive lung scan, with segmental or larger lung scan perfusion defects, or an indecisive lung scan, in which scintigraphic defects match abnormalities on the chest X-ray, contract venography and arterial blood gas analysis were performed. No Venography was performed if immediate pulmonary angiography was necessary or indecisive lung scans were obtained in combination with low clinical probability for pulmonary embolism. A selective pulmonary angiography was performed within 24h after admission in 24 patients having no contraindication for thrombolytic or long-term anticoagulant therapy. Pulmonary angiography was also performed when contraindication for anticoagulant therapy existed or if surgical therapy was contemplated (as in venous interruption), but a diagnosis of pulmonary embolism could not be established sufficiently without angiography (indecisive or indeterminate lung scan), Additional comments • 2 x 2 table	

Author (year)	Title	Study details	Quality assessment
		was taken directly from Lichey (1991)	
Nilsson (2002)	A comparison of spiral computed tomography and latex agglutination D-dimer assay in acute pulmonary embolism using pulmonary arteriography as gold standard	Study type • Prospective cohort study Study details • Study location Sweden • Study setting Emergency department • Study dates 1999 - 2001 • Loss to follow-up 55/139 • Sources of funding Stockholm City Expo-95 and Amersham Health AB, Lidingo, Sweden Inclusion criteria • Suspected PE Symptoms or signs of acute PE possible to investigate during the daytime • Age 18 to 79 years Exclusion criteria • Pregnancy • Medications Metformin, ongoing anticoagulation therapy • Previous adverse reactions to contrast media • Renal insufficiency Serum-creatinin >150 umol/l • Previous VTE 2 or more previous events	Patient selection • Low risk of bias Consecutive sample Index test • Unclear risk of bias It was not reported whether D-dimer was interpreted without knowledge of reference standard Reference standard • Low risk of bias Interpretations of reference standard were carried out by chest radiologists or vascular radiologists, blinded to all other data Flow and timing • Low risk of bias Blood samples (to measure D-dimer) were taken on arrival to the emergency room. Reference standard was done within 24 hours from admission and within 12 hours each other in people receiving both spiral CT of the pulmonary arteries and pulmonary arteriography Overall risk of bias • Low Although, it was not reported whether D-dimer was interpreted without knowledge of reference standard, D-dimer might have likely happened before reference standard was done Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Severe malnutrition or cachexia • Expected survival Less than 3 months • Advanced psychiatric disorder • Thrombocytopenia TPK <70 X 10 9/l • Hepatitis • HIV infection • Acute myocardial infarction • Unstable hemodynamics Sample characteristics • Sample size 84 • % female PE: 42 No PE: 60 • Mean age (SD) PE: 59.0 (14) No PE: 49.5 (15) Index test (s) • Laboratory D-dimer Tinaquant R; Cut-off: 0.5 mg/l Reference standard (s) • Pulmonary angiography A standard dose of 40 ml Visipaque, 320 mg I/ml or Iomeron 350 mg I/ml was injected during 2 s. The diagnostic criterion was an intraluminal filling defect or an occlusion with a concave border at the end of the contrast medium column, indicating a trailing edge of an embolus Additional comments • 2 x 2 table	

Author (year)	Title	Study details	Quality assessment
		was taken directly from Nilsson (2002)	
Pappas (1993)	The application of a rapid D-dimer test in suspected pulmonary embolus	Study type • Prospective cohort study Study details • Study location USA • Study setting Single hospital • Study dates not reported • Sources of funding none reported Inclusion criteria • Suspected PE referred for lung scans Exclusion criteria • None reported Sample characteristics • Sample size 169 participants (149 analysed for VQ alone, 20 analysed for VQ and PA) • % female not reported • Mean age (SD) not reported Index test (s) • Laboratory D-dimer D-di test (a negative result was recorded only if no	Patient selection • Unclear risk of bias Limited reporting of baseline characteristics of participants Index test • Low risk of bias Reference standard • High risk of bias Unclear whether reference standard was interpreted blind to D-dimer result. Unclear reasoning for why 20 participants also underwent PA. Flow and timing • Low risk of bias Overall risk of bias • High Unclear whether reference standard was interpreted blind. Limited reporting of participant characteristics. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		record of agglutination [approx. 250 ng/mL]) Reference standard (s) • VQ scan 133 xenon gas and technetium Tc99m aggregated albumin. 20 patients also underwent PA Additional comments • 2 x 2 table Was taken directly from Pappas (1993)	
Quinn (1994)	Pulmonary embolism in patients with intermediate probability lung scans: diagnosis with Doppler venous US and D-dimer measurement	Study type • Prospective cohort study Study details • Study location Austrailia • Study setting Single hospital • Study dates October 1991 - October 1992 Inclusion criteria • Suspected PE intermediate probability Exclusion criteria • did not complete all reference standards • DVT Sample characteristics • Sample size 131 enrolled; 36 underwent required reference standard for inclusion in analysis	Patient selection • High risk of bias Only participants that underwent all reference standards were included in the analysis however it is unclear why excluded participants did not undergo these Index test • Low risk of bias Reference standard • Unclear risk of bias See patient selection. Unclear whether the decision for participant to undergo all reference standards was based on other scans or D-dimer results. Unclear whether reference standard was interpreted blind to D-dimer results Flow and timing • Low risk of bias Overall risk of bias • High Unclear whether reference standard was done blinded to D-dimer tests, unclear rationale for participants not undergoing all reference

Author (year)	Title	Study details	Quality assessment
		• % female not reported • Mean age (SD) not reported Index test (s) • Laboratory D-dimer Dimertest II ELISA stripwell kit. Taken within 24h of V-P scan Reference standard (s) • Composite reference standard Only included in analysis if underwent PA, V-P scan, doppler venous compression and D-dimer tests all performed within 24 hours Additional comments • 2 x 2 table was taken directly from Quinn (1994)	standards (therefore excluded from study) Directness • Directly applicable
Quinn (1999)	D-dimers in the diagnosis of pulmonary embolism	Study type • Prospective cohort study Study details • Study location USA • Study setting Single hospital • Study dates August 1, 1994 - June 30, 1995 Inclusion criteria • Suspected PE	Patient selection • High risk of bias Only included participants undergoing pulmonary angiography Index test • Low risk of bias Reference standard • Unclear risk of bias Unclear whether reference standard was interpreted blind to D-dimer results

Author (year)	Title	Study details	Quality assessment
		Exclusion criteria • Previous VTE history or suspicion of chronic PE (progressive dyspnea over months, physical exam suggestive of right ventricular failure) Sample characteristics • Sample size 103 • % female 44% female • Mean age (SD) 59 years Index test (s) • Laboratory D-dimer Asserachrom ELISA D-dimer test Note: Study also reported outcomes of 5 latex agglutination assays (excluded from this review to avoid double-counting) Reference standard (s) • Pulmonary angiography Additional comments • 2 x 2 table Was taken directly from Quinn (1999)	Flow and timing • Low risk of bias Overall risk of bias • High Unclear whether reference standard was interpreted blind to D-dimer results. Patients were only included if they were undergoing pulmonary angiography, unclear what tests were done to determine need for imaging. Directness • Directly applicable
Taman (2016)	Reliability of D-dimer test results in deciding the necessity of performing CTA in high risk	Study type • Prospective cohort study Study details • Study location Egypt	Patient selection • Low risk of bias Consecutive sample Index test • Unclear risk of bias

Author (year)	Title	Study details	Quality assessment
	population to establish the diagnosis of PE	• Study setting Oncology, Cardiology and Surgery Departments • Study dates 2014 - 2015 • Loss to follow-up 0 • Sources of funding Not reported Inclusion criteria • Suspected PE Clinical probability of pulmonary embolism; referral based on clinical examination with symptoms and signs suggestive of pulmonary embolism and/or history of DVT or PE Exclusion criteria • CT angiography without D-dimer High risk cases who performed CT Angiography but did not perform D-dimer test for whom the referring clinician assumed false positive D-dimer because of repeated catheterization and hemodynamic instability • Allergy Patients with history of contrast medium allergy • Renal failure • CT angiography contraindicated Intravenous line inaccessibility for whom CT angiography was contraindicated Sample characteristics • Sample size 98 • % female 43.9	It was not reported whether D-dimer was interpreted without knowledge of pulmonary angiography Reference standard • Unclear risk of bias It was not reported whether pulmonary angiography was interpreted without knowledge of D-dimer Flow and timing • Unclear risk of bias The interval between D-dimer and pulmonary angiography was not reported Overall risk of bias • High It was not reported whether D-dimer and pulmonary angiography interpretations were independent and blinded. The interval between D-dimer and pulmonary angiography was not reported Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Mean age (SD) 50 (range 17 to 88) • % people with cancer 39.8 Index test (s) • Laboratory D-dimer STA Liatest; Cut-off: normal value <0.5 ug/ml; positive test ≥0.5 ug/ml Reference standard (s) • Pulmonary angiography Multidetector pulmonary CT angiography. Patients were injected with 100 mL of iopamidol diluted with saline chaser dose to 120 mL total volume at a rate of 3 mL/s using automated bolus-triggering technique. Imaging began 20s after initiation of contrast infusion Additional comments • 2 x 2 table was taken directly from Taman (2016)	
Youssf (2014)	Diagnostic accuracy of D-dimer assay in suspected pulmonary embolism patients	Study type • Prospective cohort study Study details • Study location Egypt • Study setting Intensive care unit • Study dates 2010 - 2011 • Loss to follow-up	Patient selection • Low risk of bias Consecutive sample Index test • Unclear risk of bias It was not reported whether D-dimer was interpreted without knowledge of pulmonary angiography Reference standard • Unclear risk of bias

Author (year)	Title	Study details	Quality assessment
		0 • Sources of funding Not reported Inclusion criteria • Suspected PE 1. Clinical history and symptoms suggestive of PE 2. Clinical examination and signs that raise the suspicion of PE Exclusion criteria • Renal insufficiency • Refusing to undergo reference standard CT pulmonary angiogram • Hypersensitivity to intravenous contrast Sample characteristics • Sample size 30 • % female 40 • Mean age (SD) 49.1 (10.1) Index test (s) • Laboratory D-dimer ELFA technique (Enzyme Linked Fluorescent Assay); Cut-off: positive ≥500 ng/ml; negative <500 ng/ml Reference standard (s) • Pulmonary angiography Pulmonary CT angiography	It was not reported whether pulmonary angiography was interpreted without knowledge of D-dimer Flow and timing • Unclear risk of bias The interval between D-dimer and pulmonary angiography was not reported Overall risk of bias • High It was not reported whether D-dimer and pulmonary angiography interpretations were independent and blinded. The interval between D-dimer and pulmonary angiography was not reported Directness • Directly applicable

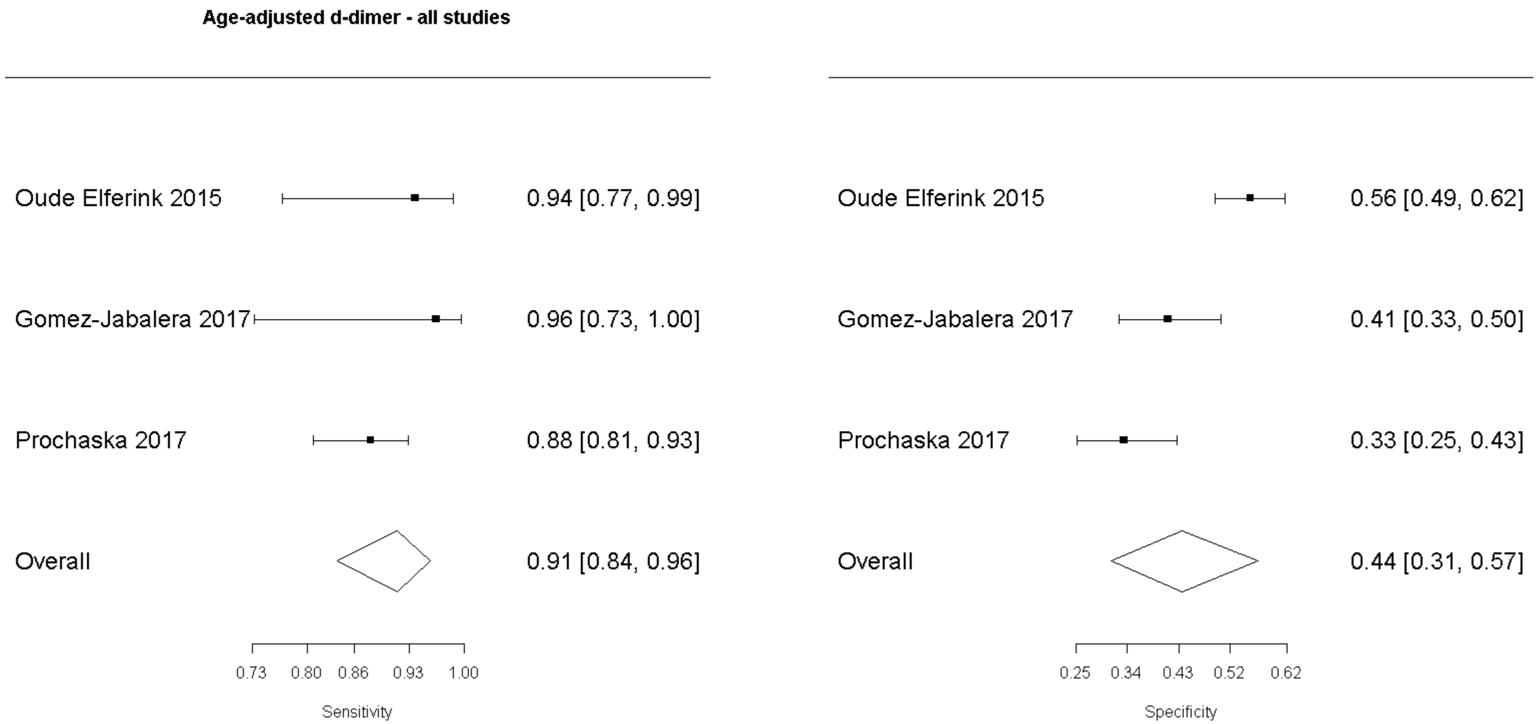
Author (year)	Title	Study details	Quality assessment
		Subgroup analyses • Pre-test probability Clinical probability by Revised Geneva Score: low, intermediate, high Additional comments • 2 x 2 table was taken directly from Youssf (2014)	

Appendix F – Forest plots

Age-adjusted vs unadjusted D-dimer test for deep vein thrombosis

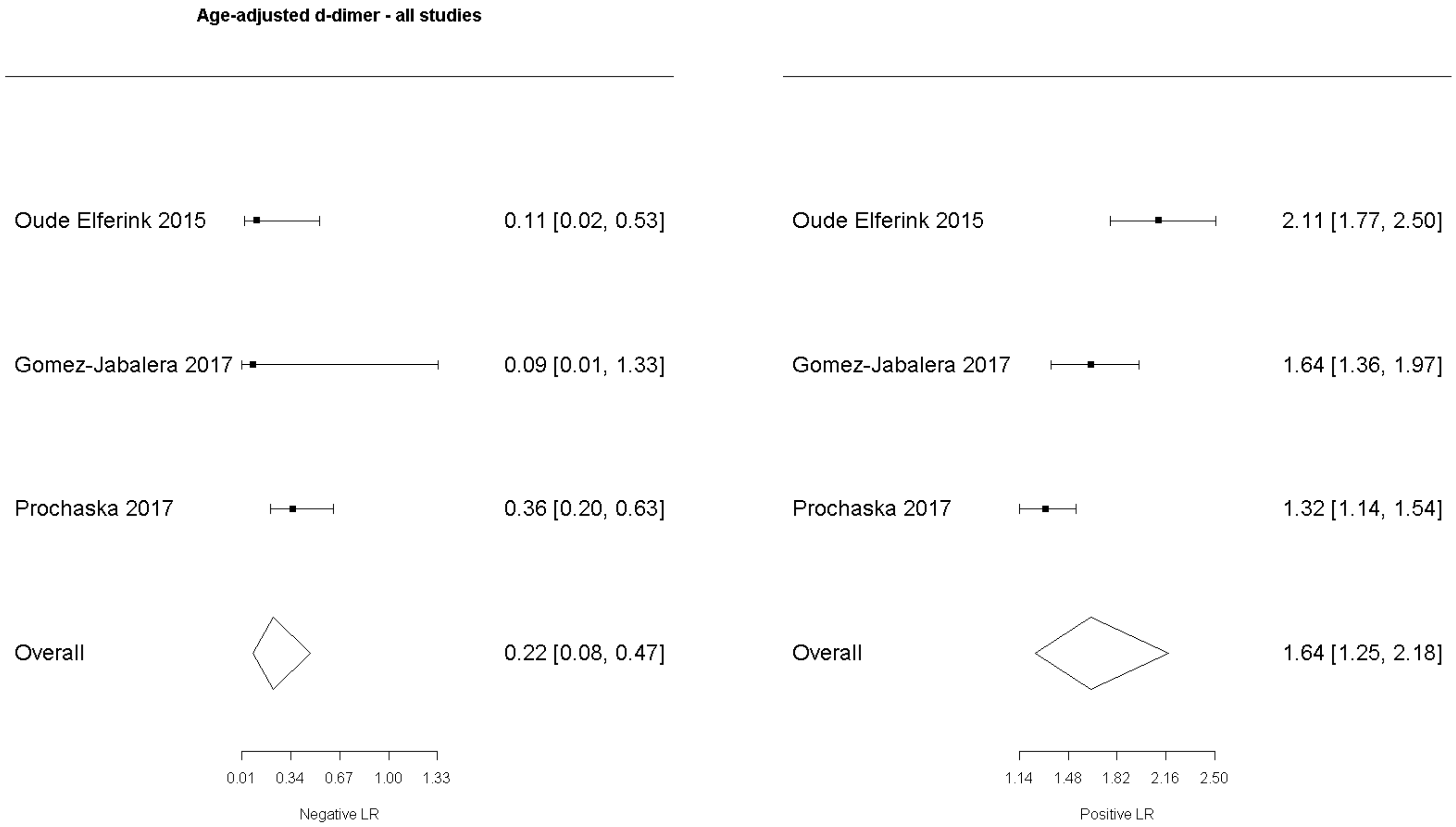
(See above for the corresponding evidence statements for this section.)

Figure 1: Sensitivity and specificity for age-adjusted D-dimer tests for deep vein thrombosis



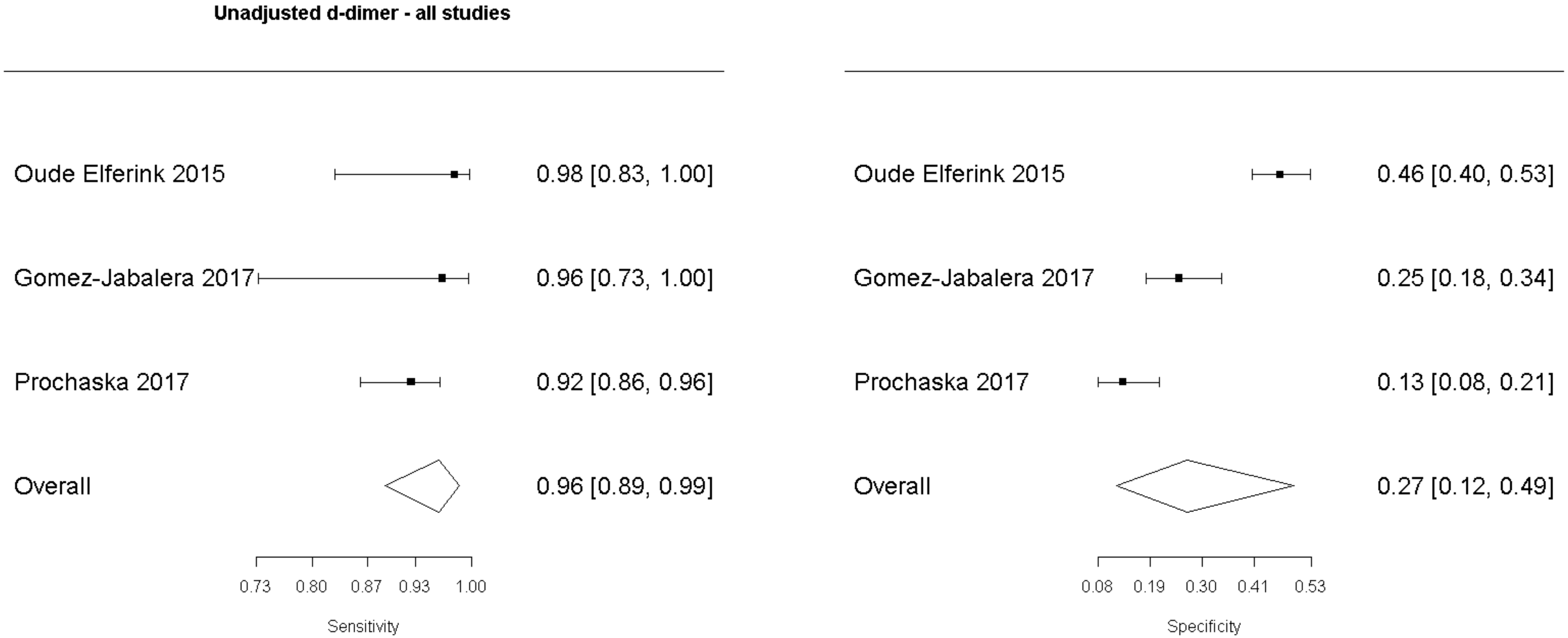
I^2 (sensitivity)=0.0%, I^2 (specificity)=88.1%

Figure 2: Likelihood ratios for age-adjusted D-dimer tests for deep vein thrombosis



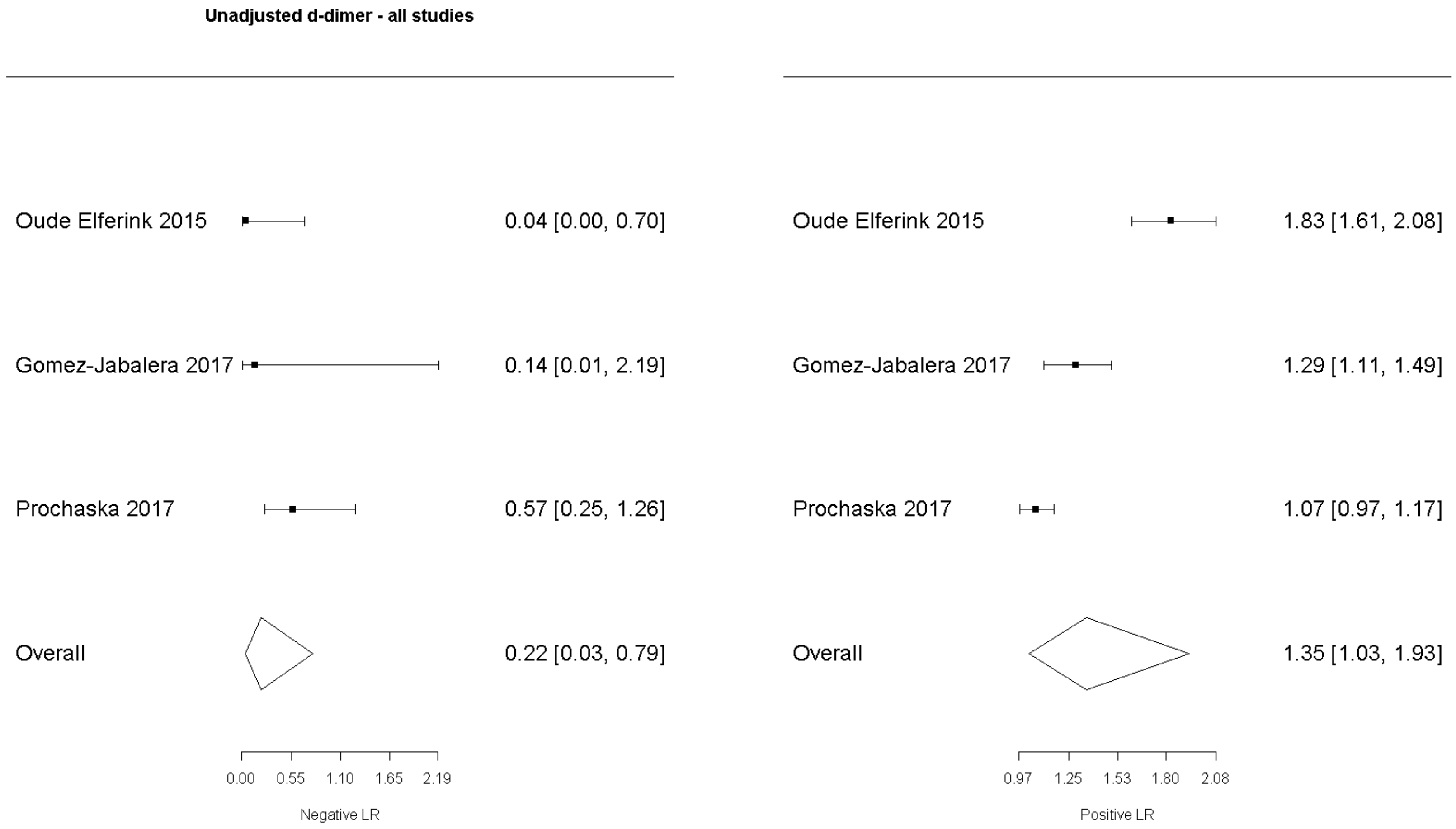
I^2 (Negative LR)=31.6%, I^2 (Positive LR)=89.1%

Figure 3: Sensitivity and specificity for non-age-adjusted D-dimer tests for deep vein thrombosis



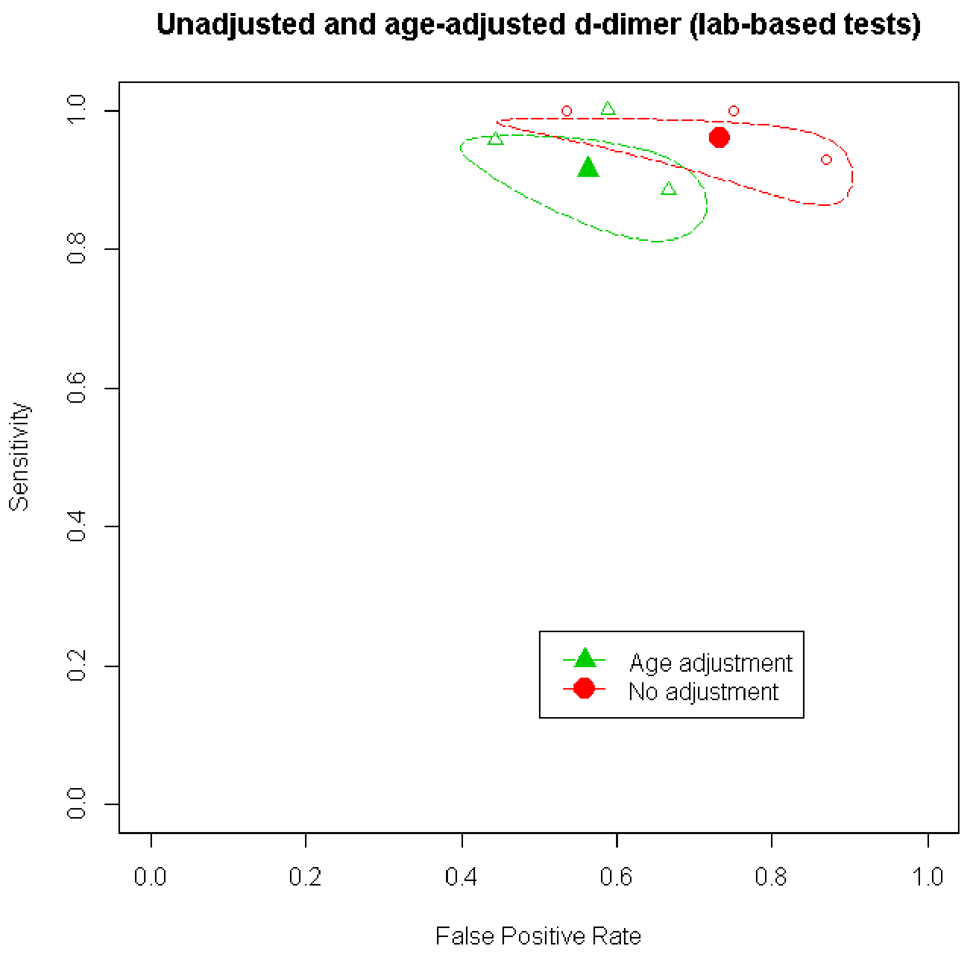
I^2 (Sensitivity)= 0.0% , I^2 (Specificity)= 95.2%

Figure 4: Likelihood ratios for non-age-adjusted D-dimer tests for deep vein thrombosis



I^2 (Negative LR)= 0.0% , I^2 (Positive LR)= 94.5%

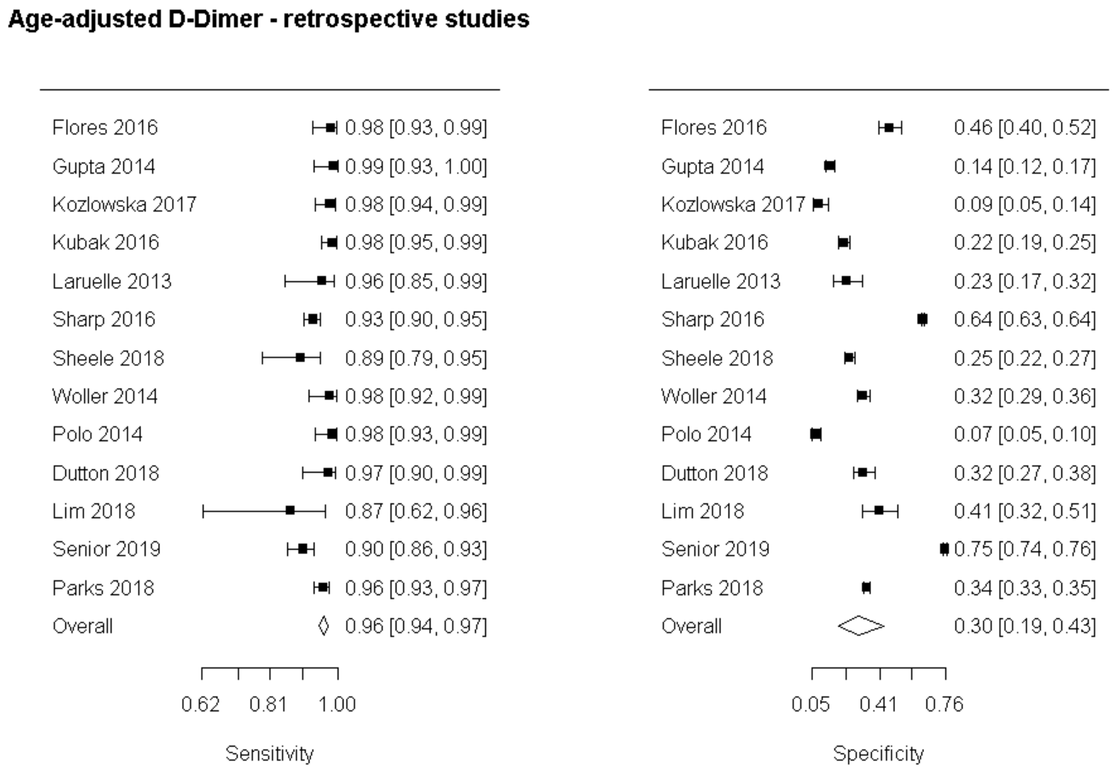
Figure 5: Sensitivity and specificity for age-adjusted and unadjusted D-dimer tests for deep vein thrombosis.



Age-adjusted vs unadjusted D-dimer test for pulmonary embolism

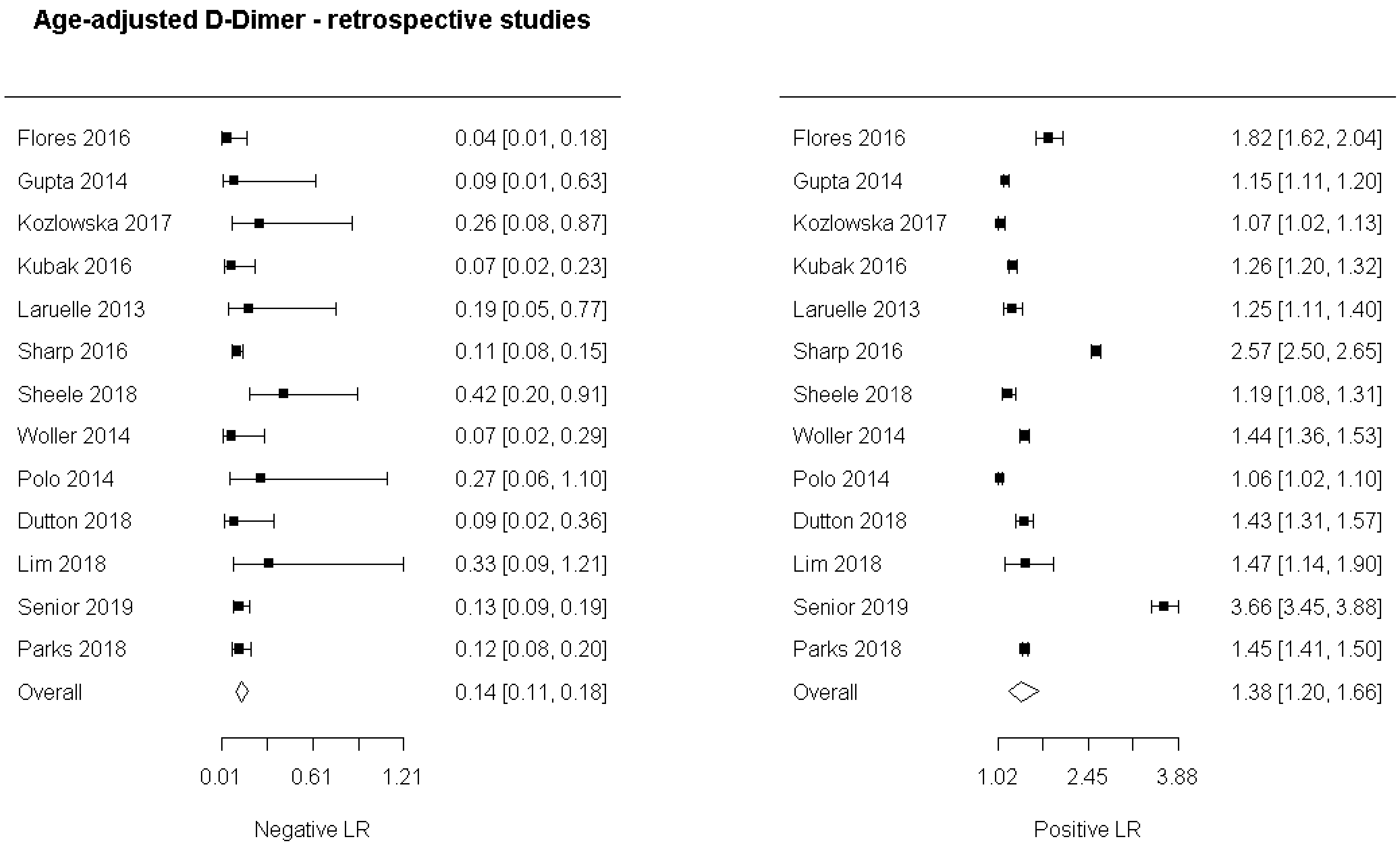
(See above for the corresponding evidence statements for this section.)

Figure 6: Sensitivity and specificity for age-adjusted D-dimer tests for pulmonary embolism (retrospective studies)



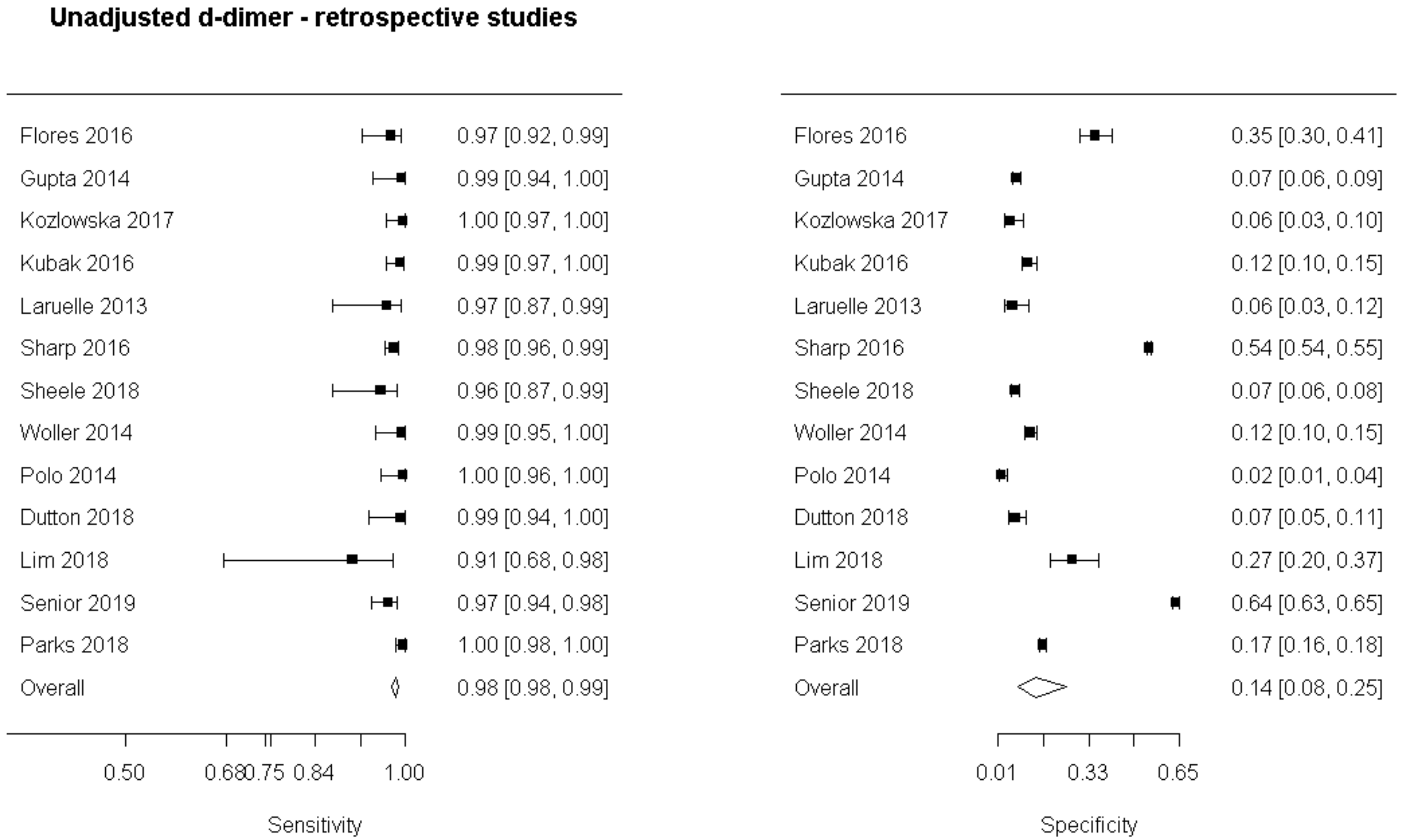
I^2 (sensitivity)=62.9%, I^2 (specificity)= 99.7%

Figure 7: Likelihood ratios for age-adjusted D-dimer tests for pulmonary embolism (retrospective studies)



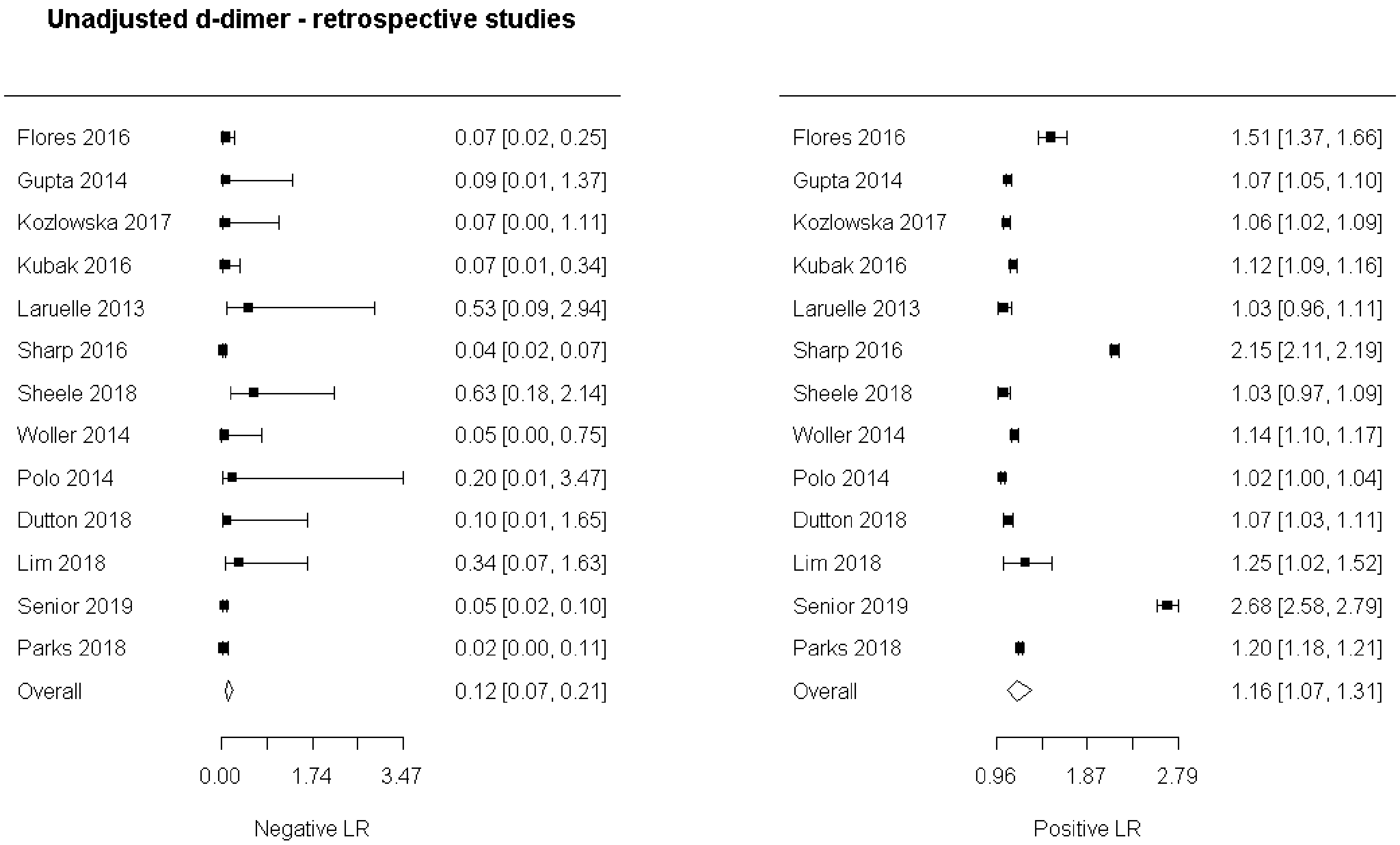
I2 (negative LR)=38.6%, I2 (positive LR)=99.6%

Figure 8: Sensitivity and specificity for non-age-adjusted D-dimer tests for pulmonary embolism (retrospective studies)



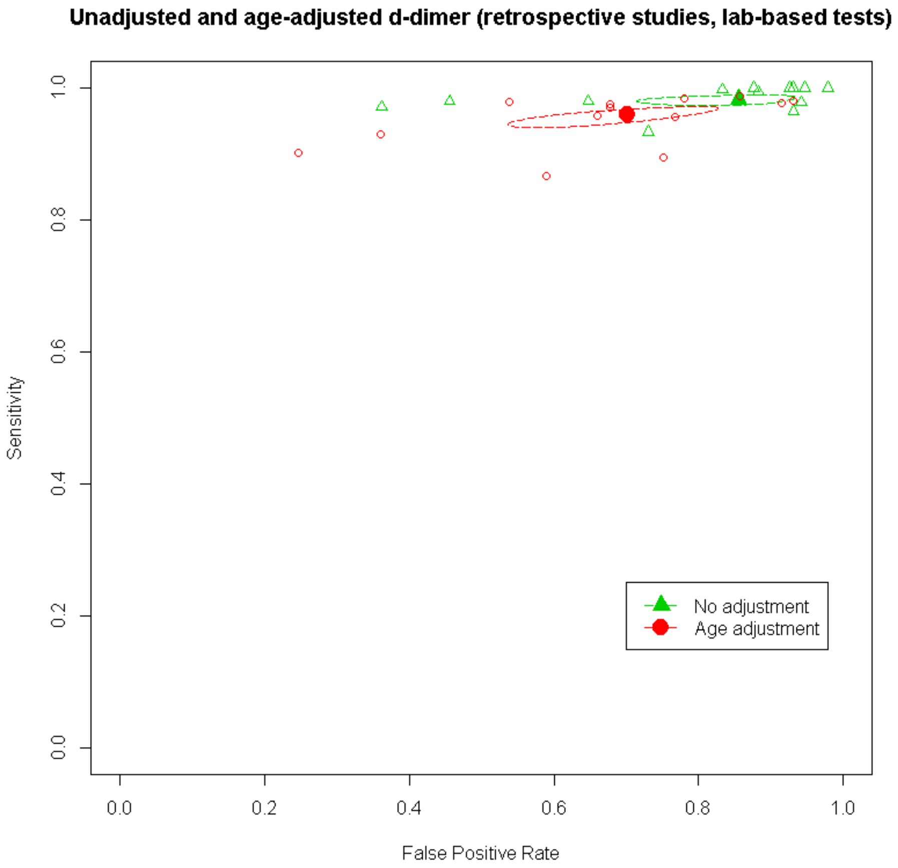
I^2 (sensitivity)=11.1%, I^2 (specificity)=99.7%

Figure 9: Likelihood ratios for non-age-adjusted D-dimer tests for pulmonary embolism (retrospective studies)



I^2 (Negative LR)=41.7%, I^2 (Positive LR)=99.8%

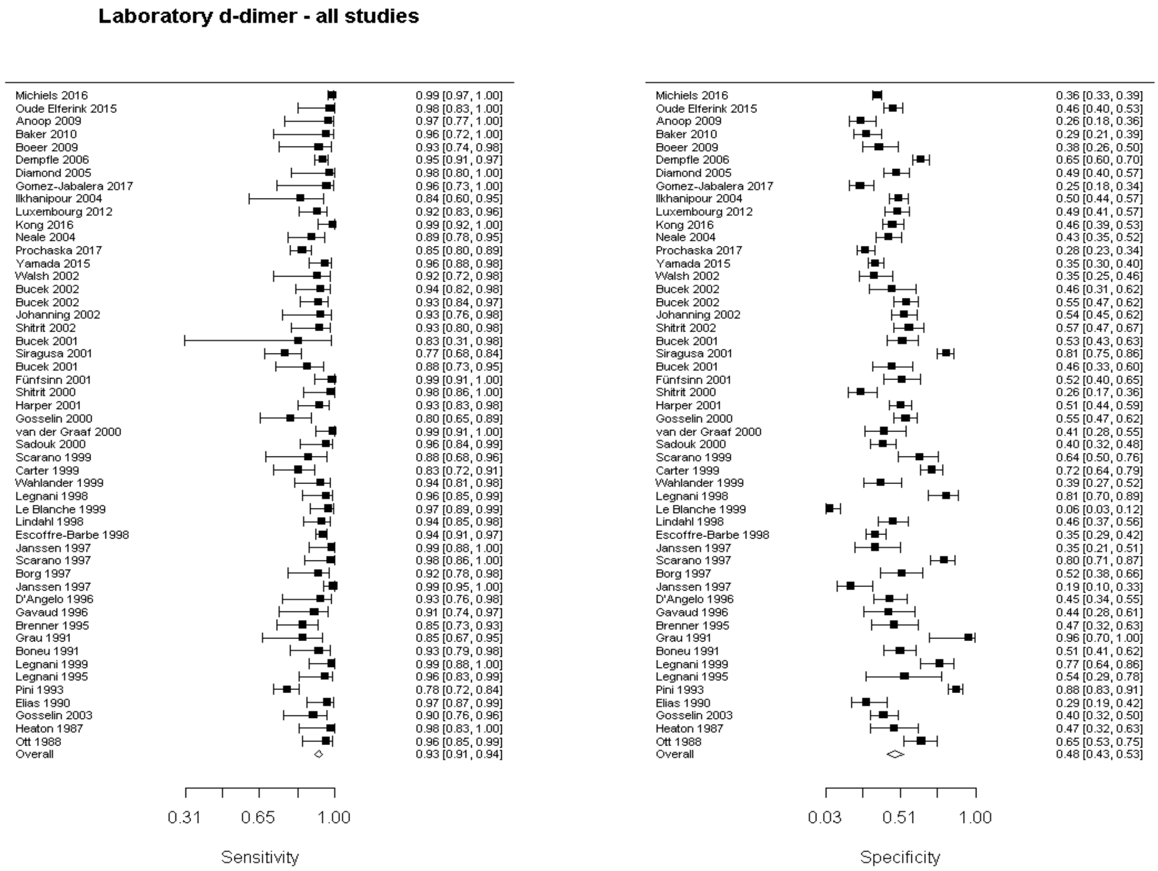
Figure 10: Sensitivity and specificity for age adjusted vs non-age-adjusted D-dimer tests for pulmonary embolism



Laboratory and point-of care D-dimer test for deep vein thrombosis

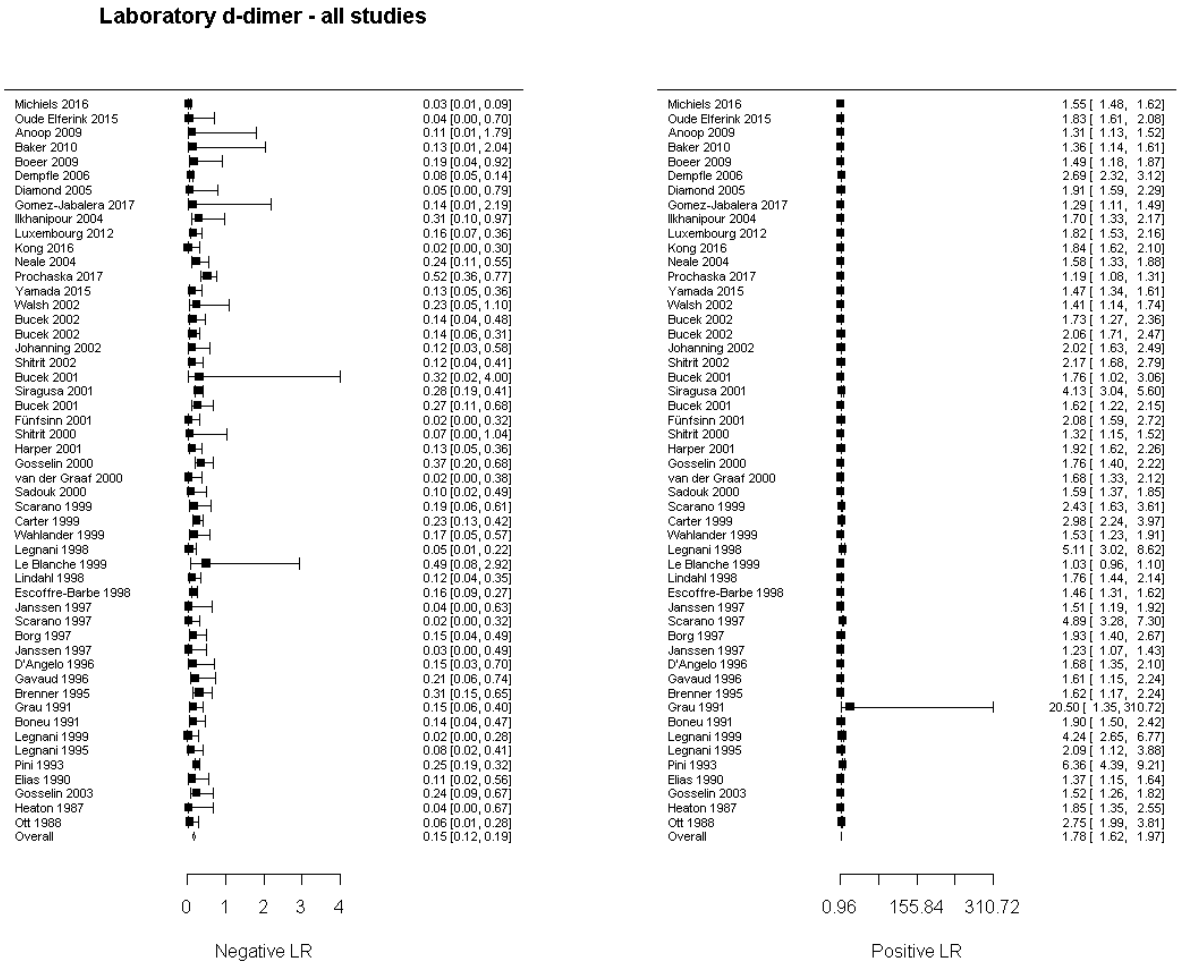
(See above for the corresponding evidence statements for this section.)

Figure 11: Sensitivity and specificity for laboratory-based D-dimer tests for deep vein thrombosis – All studies



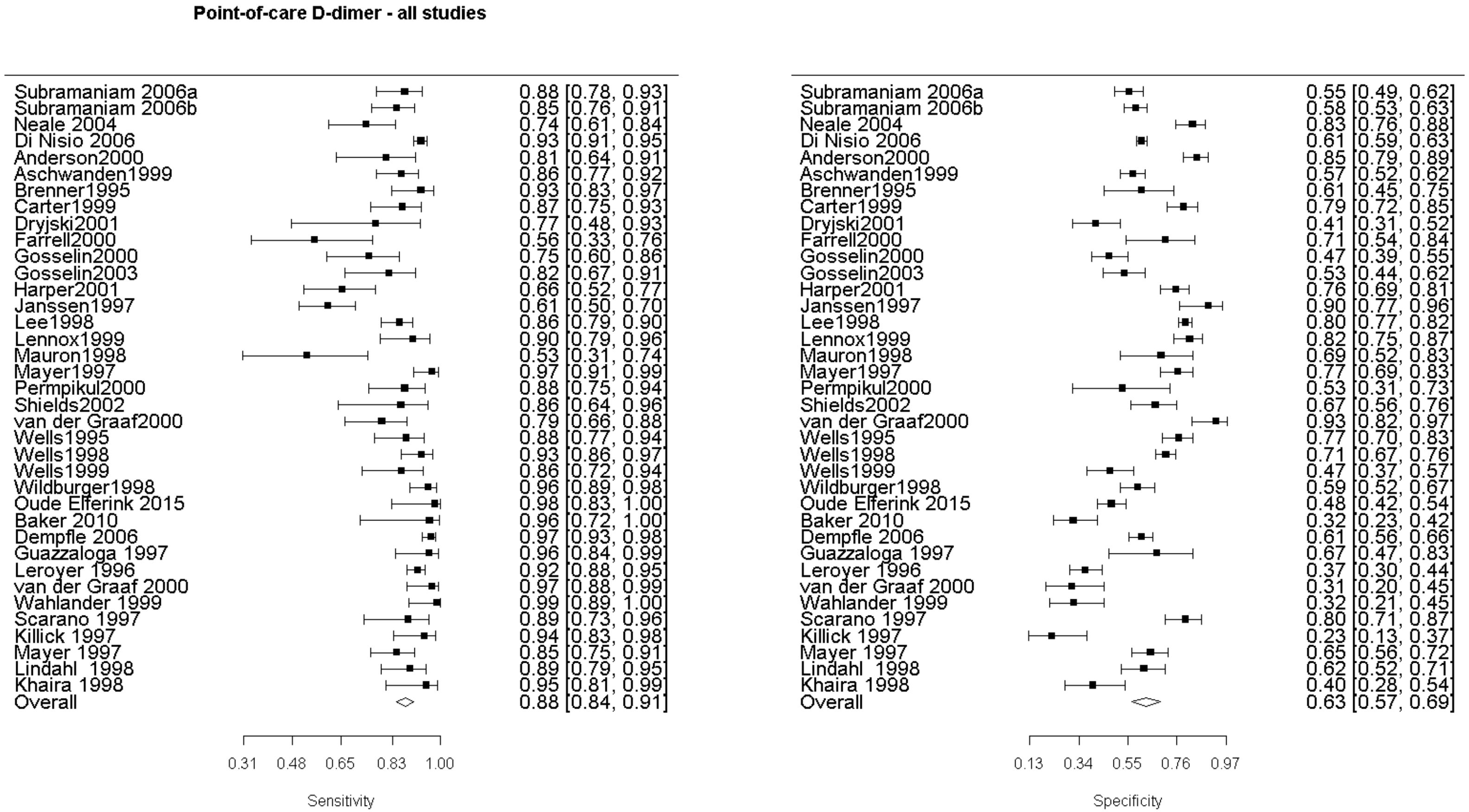
I^2 (sensitivity)=62.6%, I^2 (specificity)=91.8%

Figure 12: Likelihood ratios for laboratory based D-dimer tests for deep vein thrombosis – All studies



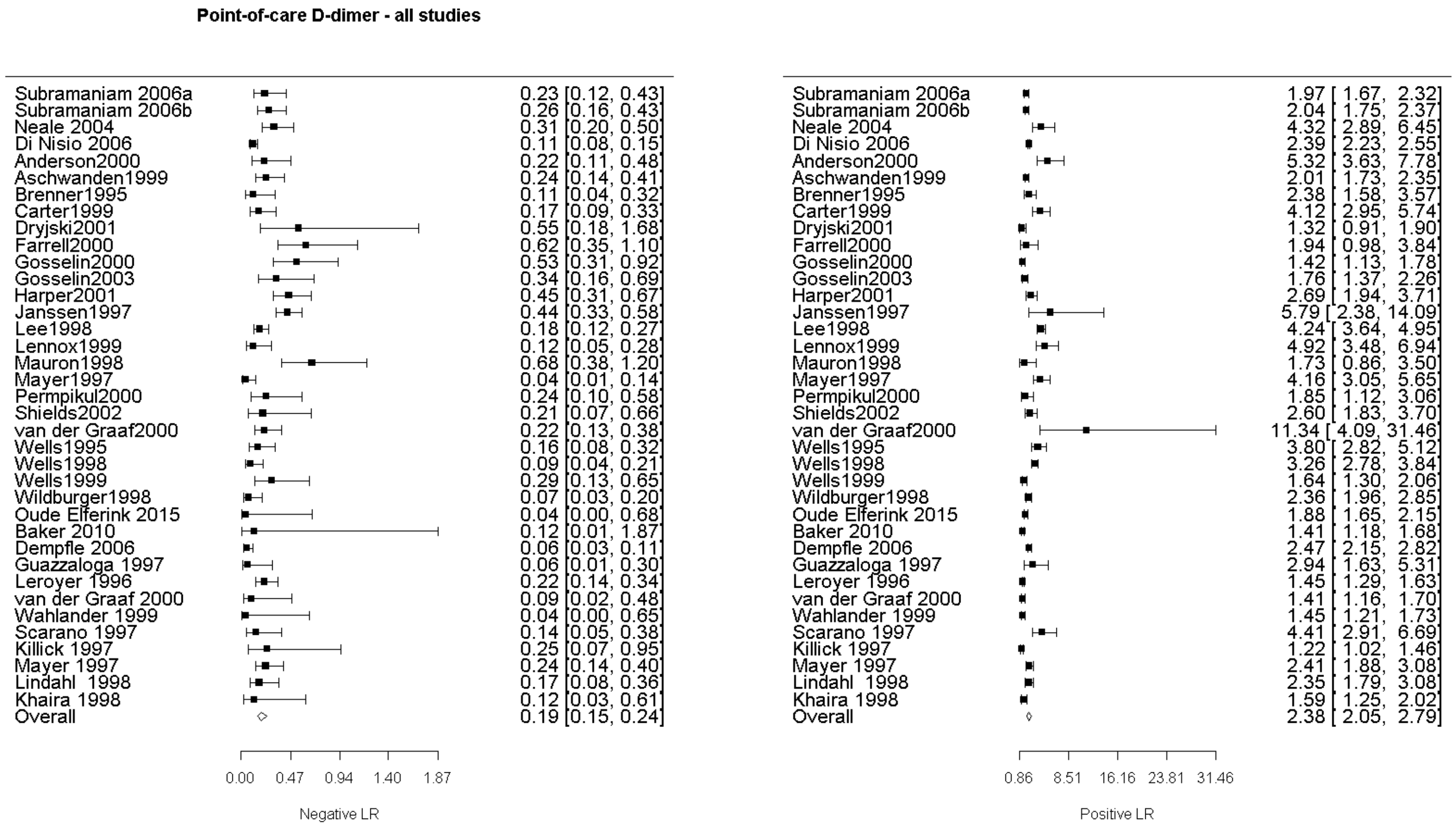
I^2 (Negative LR)= 47.4%, I^2 (Positive LR)= 91.2%

Figure 13: Sensitivity and specificity for Point-of-care D-dimer tests for deep vein thrombosis – all studies



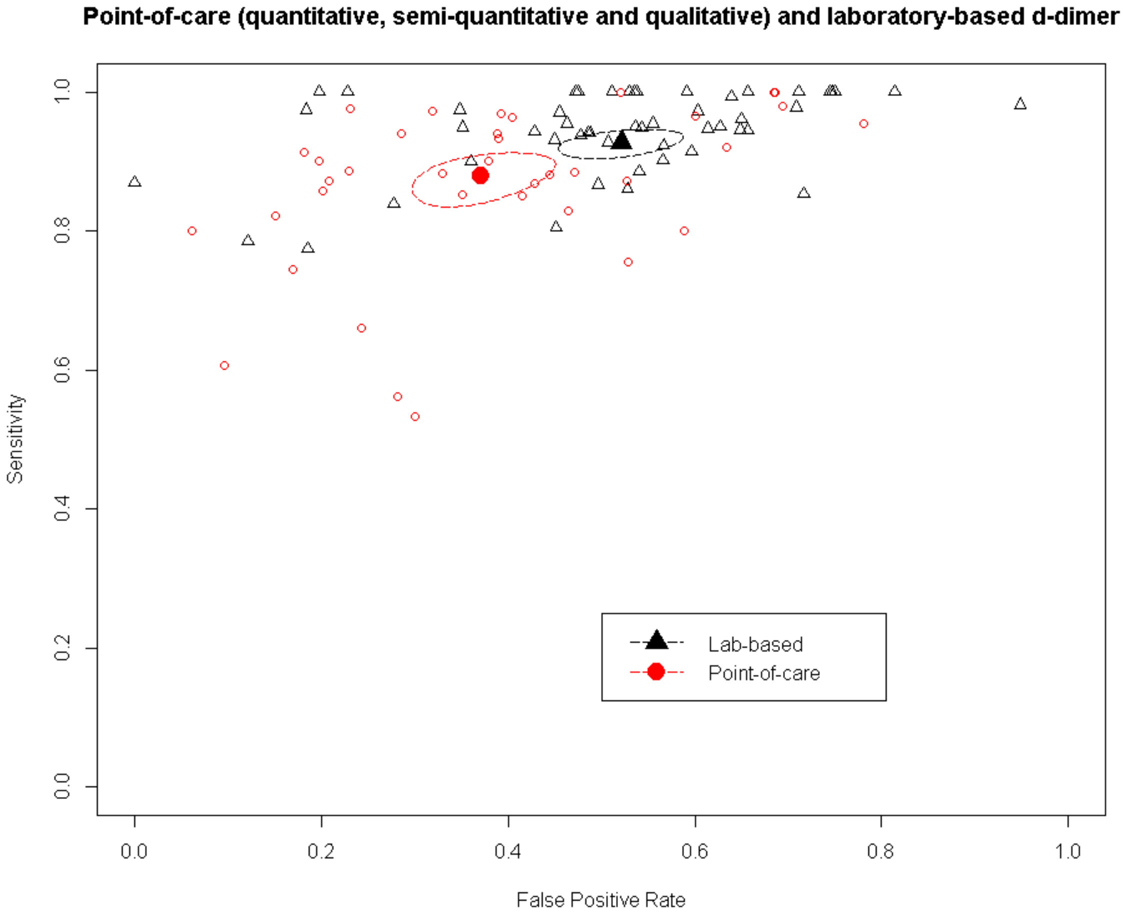
I^2 (sensitivity)=81.9%, I^2 (specificity)=92.8%

Figure 14: Likelihood ratios for point-of-care D-dimer tests for deep vein thrombosis – all studies



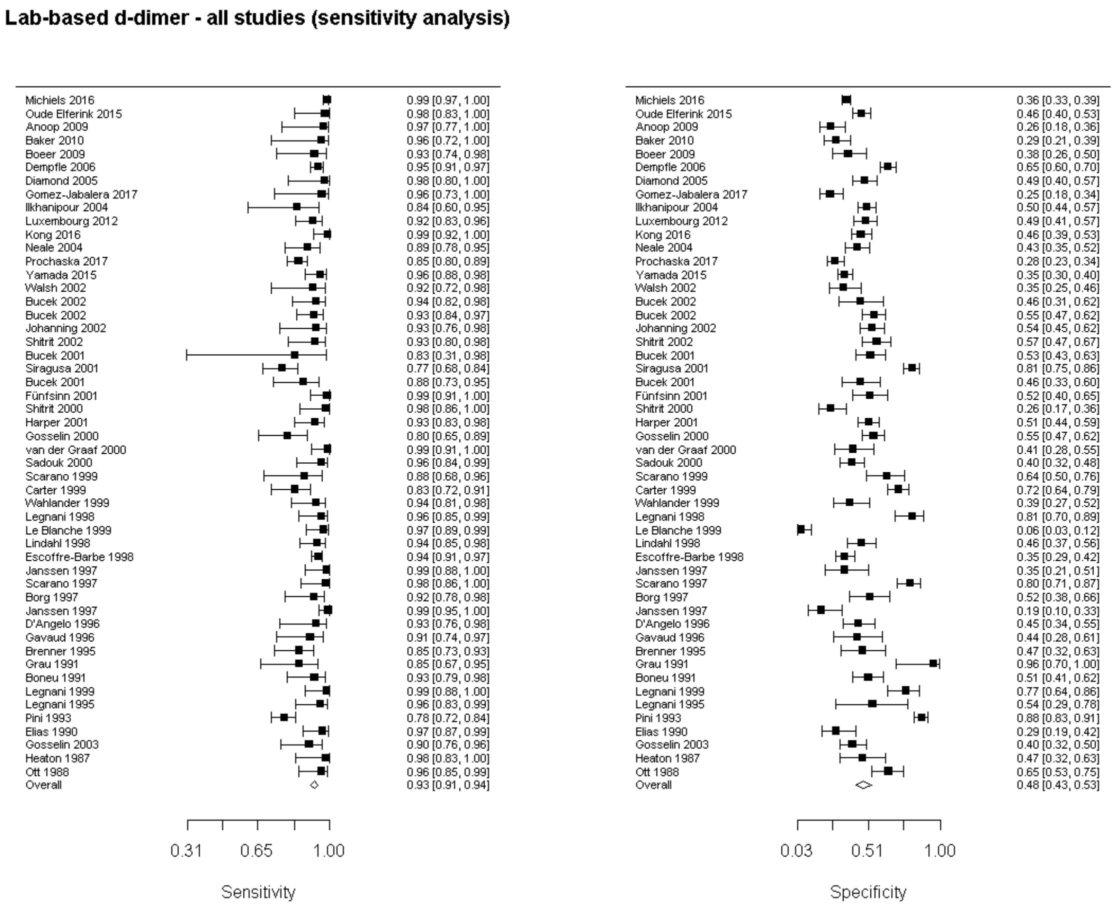
I^2 (Negative LR)=79.1%, I^2 (Positive LR)=89.9%

Figure 15: Sensitivity and specificity for laboratory-based and point-of-care based D-dimer tests for deep vein thrombosis.



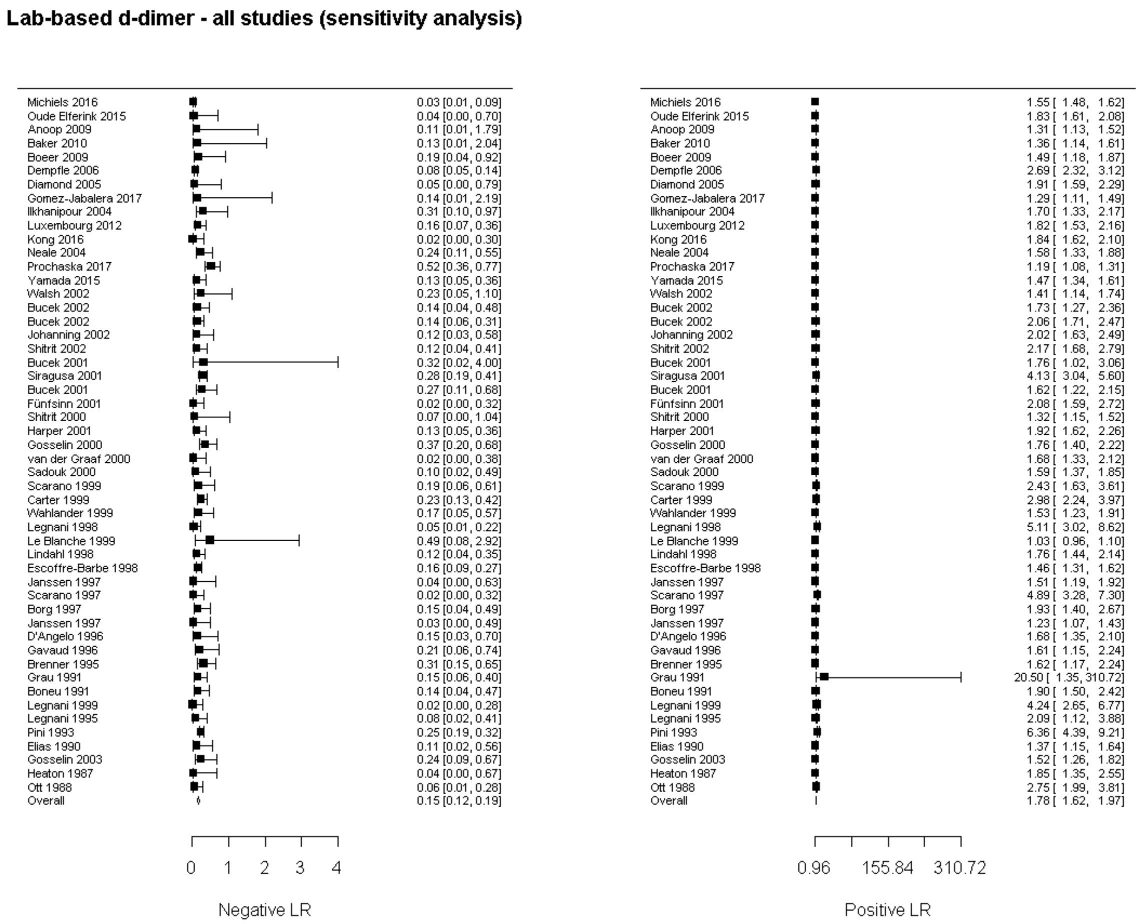
Sensitivity analysis: Laboratory and point-of-care D-dimer tests for deep vein thrombosis, excluding high risk of bias studies

Figure 16: Sensitivity and specificity for laboratory based D-dimer tests for deep vein thrombosis – all studies (sensitivity analysis)



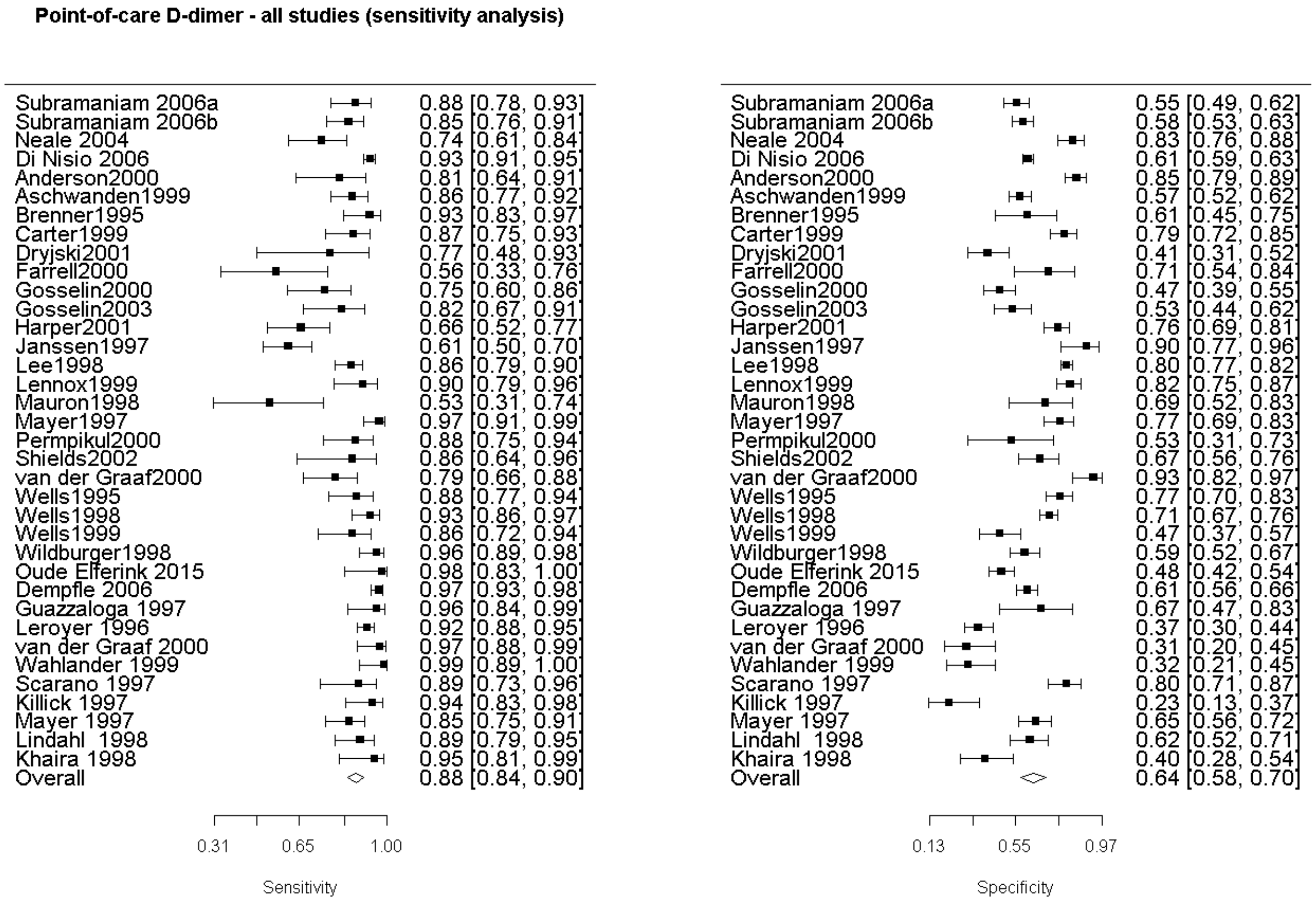
I^2 (sensitivity)=63.9%, I^2 (specificity)=92.1%

Figure 17: Likelihood ratios for laboratory-based D-dimer tests for deep vein thrombosis – all studies (sensitivity analysis)



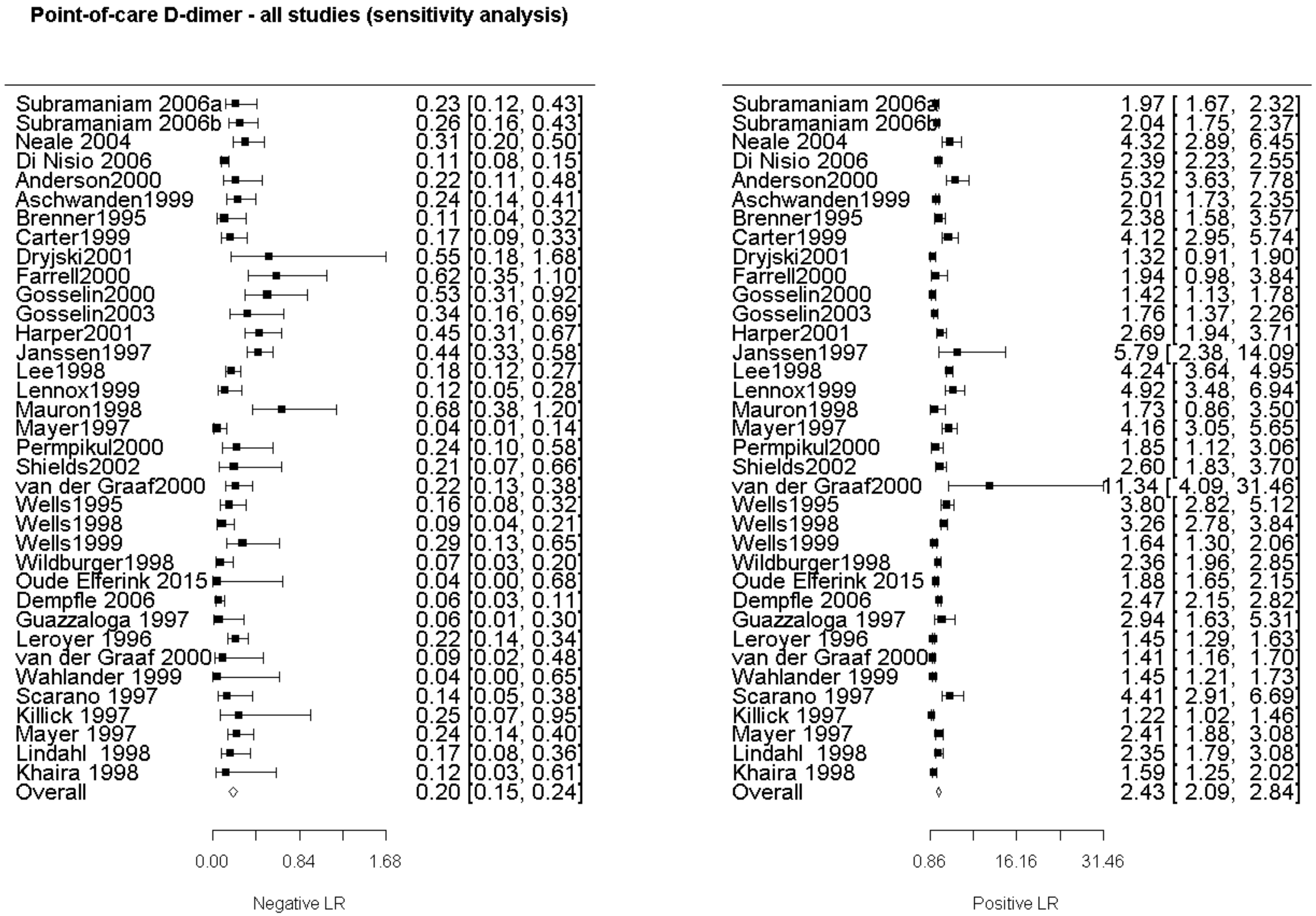
I^2 (Negative LR)=49.8%, I^2 (Positive LR)=91.9%

Figure 18: Sensitivity and specificity for point-of-care based D-dimer tests for deep vein thrombosis – all studies (sensitivity analysis)



I^2 (sensitivity)=82.1%, I^2 (specificity)=92.0%

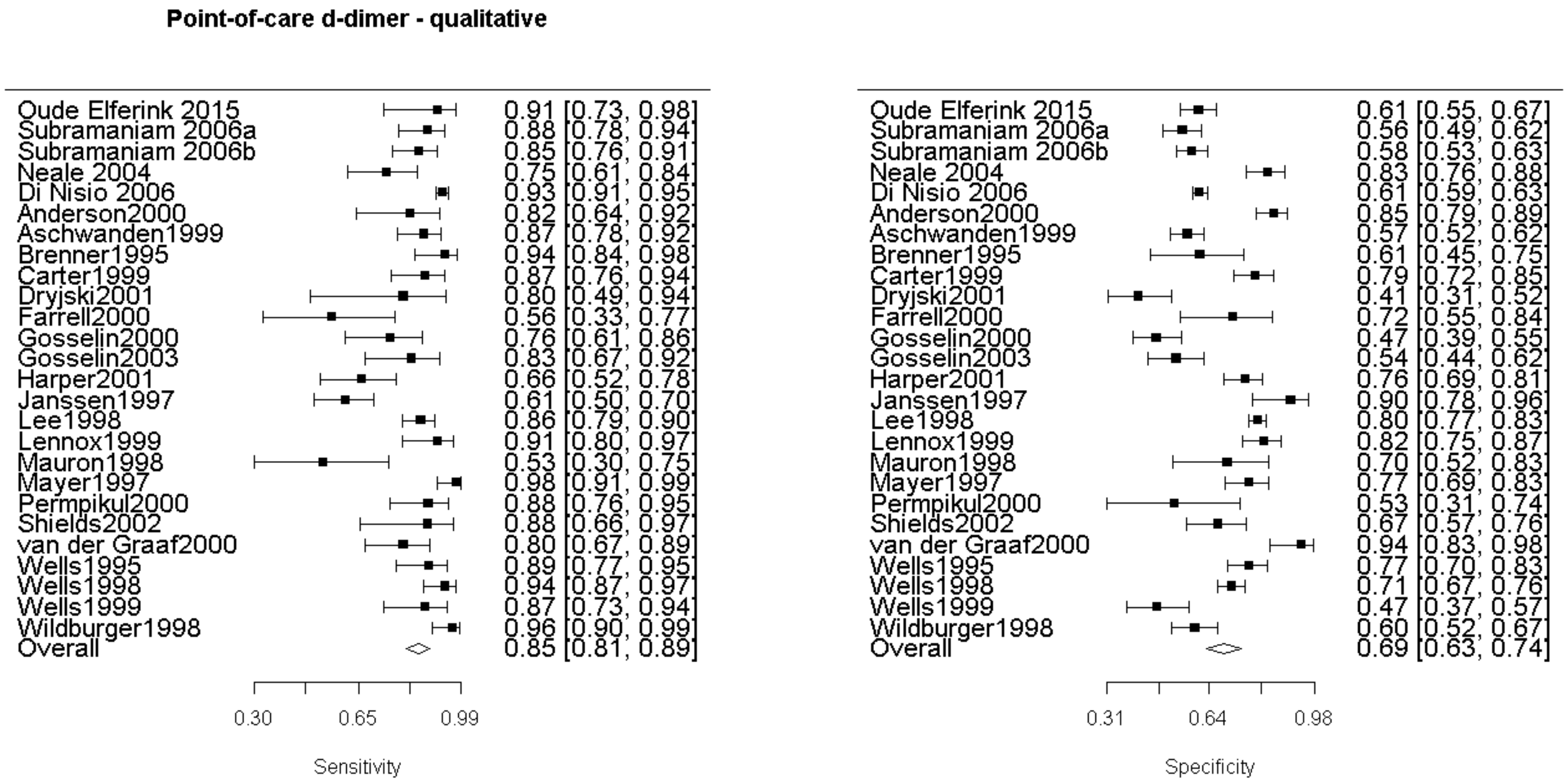
Figure 19: Likelihood ratios for point-of-care based D-dimer tests for deep vein thrombosis – all studies (sensitivity analysis)



I^2 (Negative LR)=0.0%, I^2 (Positive LR)=85.0%

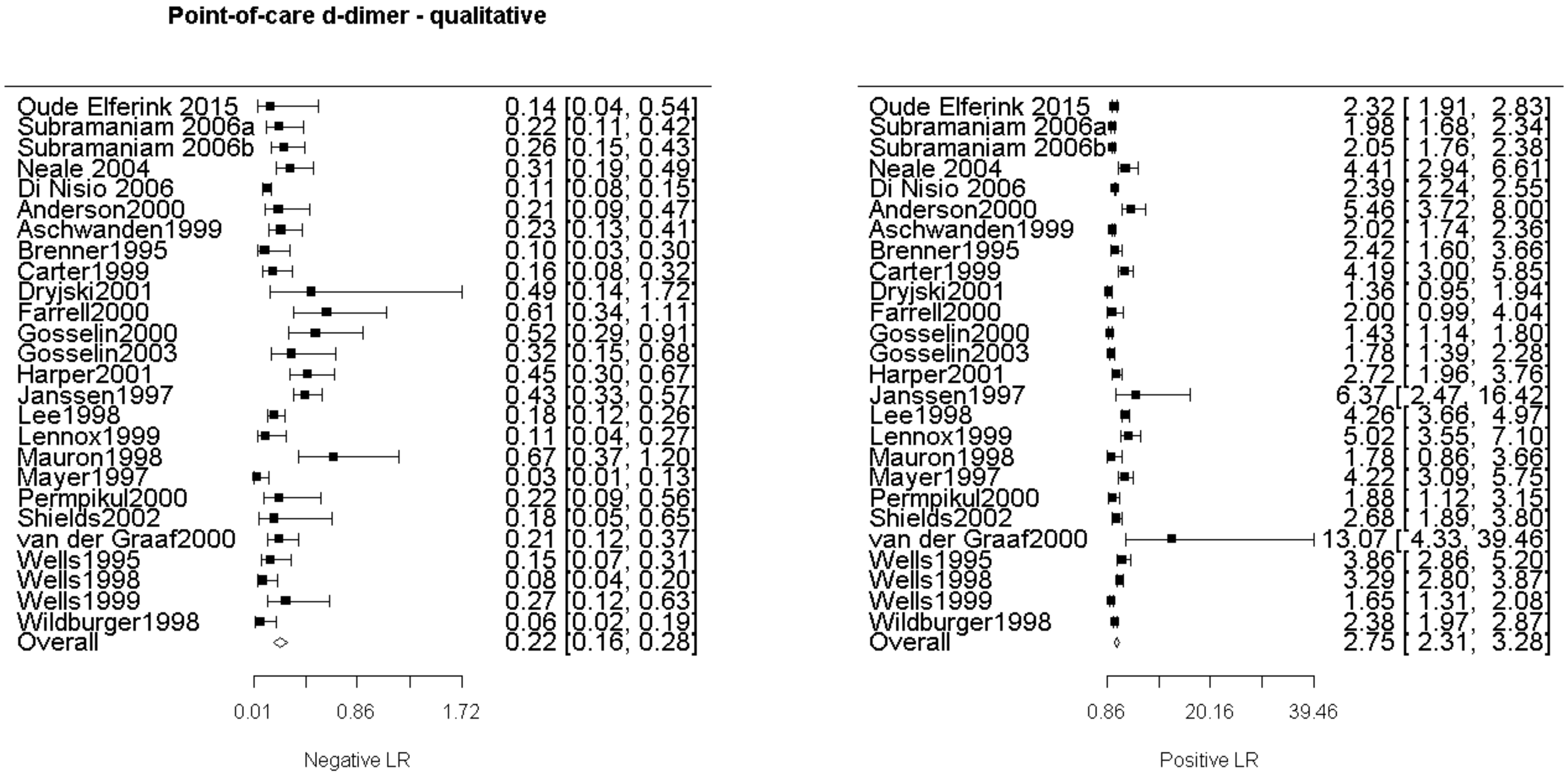
Subgroup analysis: Point-of-care D-dimer tests for deep vein thrombosis, separating qualitative, quantitative and semi-quantitative test

Figure 20: Sensitivity and specificity for Point-of-care D-dimer tests for deep vein thrombosis – qualitative



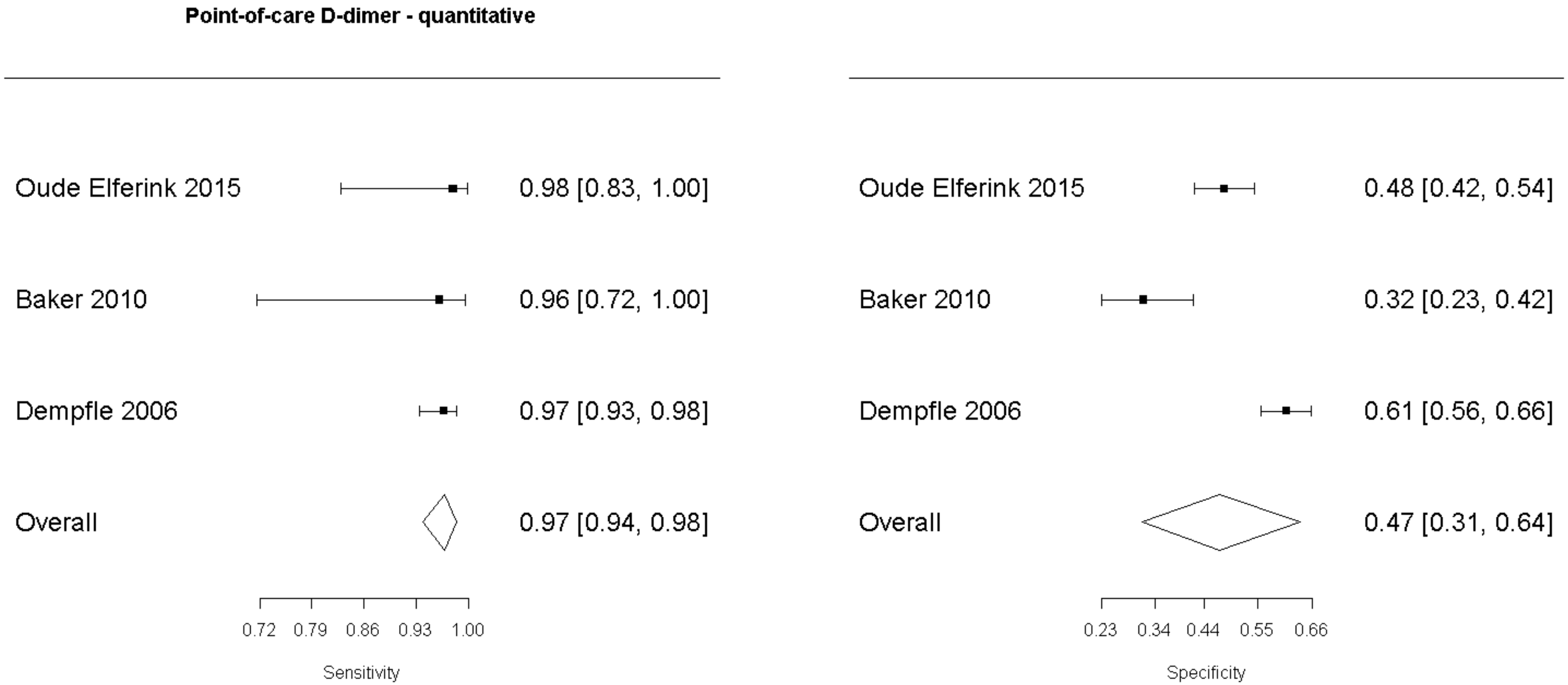
I^2 (sensitivity)=80.2%, I^2 (specificity)=91.9%

Figure 21: Likelihood ratios for point-of-care D-dimer tests for deep vein thrombosis – qualitative



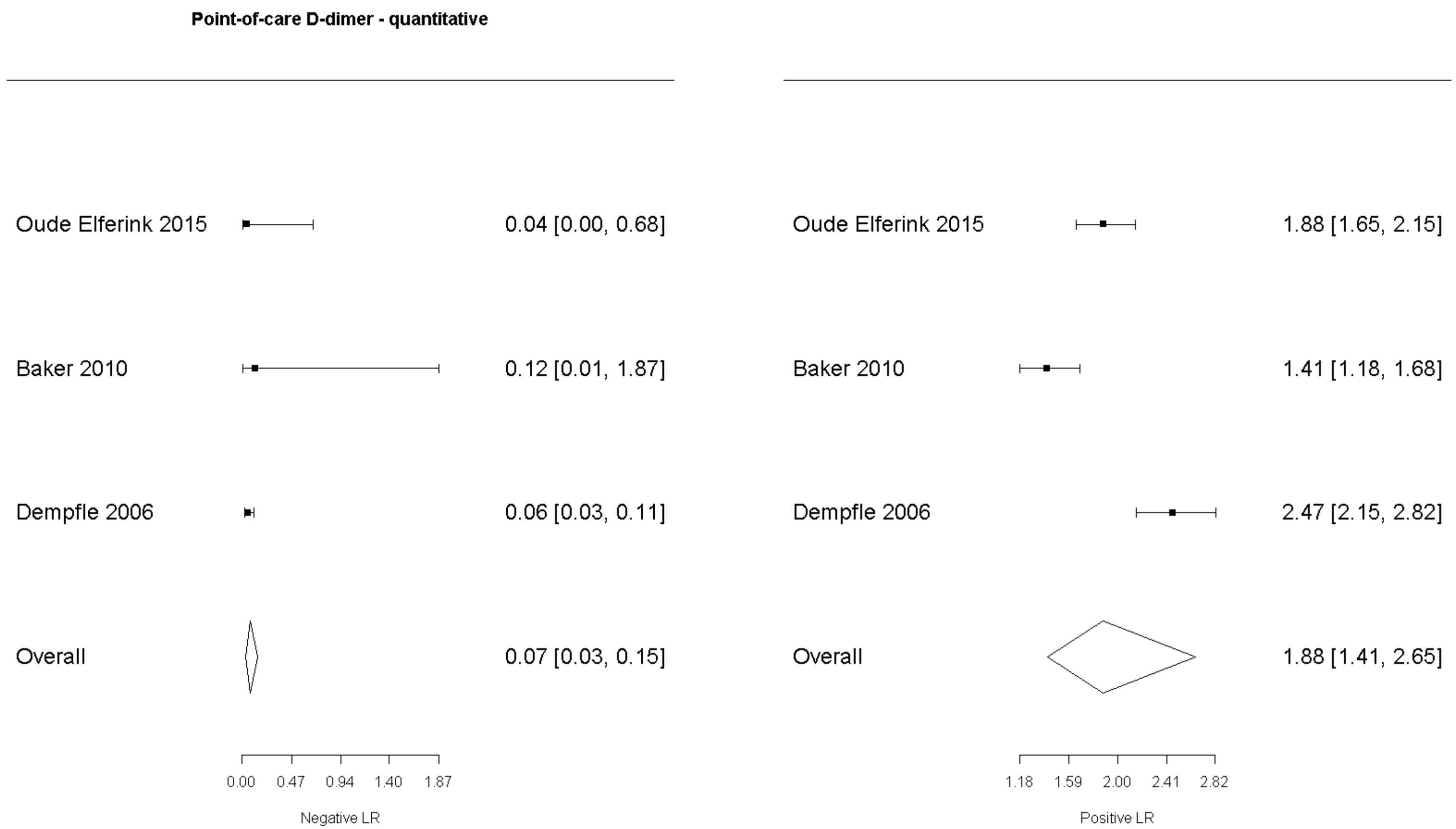
I^2 (Negative LR)=77.4%, I^2 (Positive LR)=88.5%

Figure 22: Sensitivity and specificity for Point-of-care D-dimer tests for deep vein thrombosis – quantitative



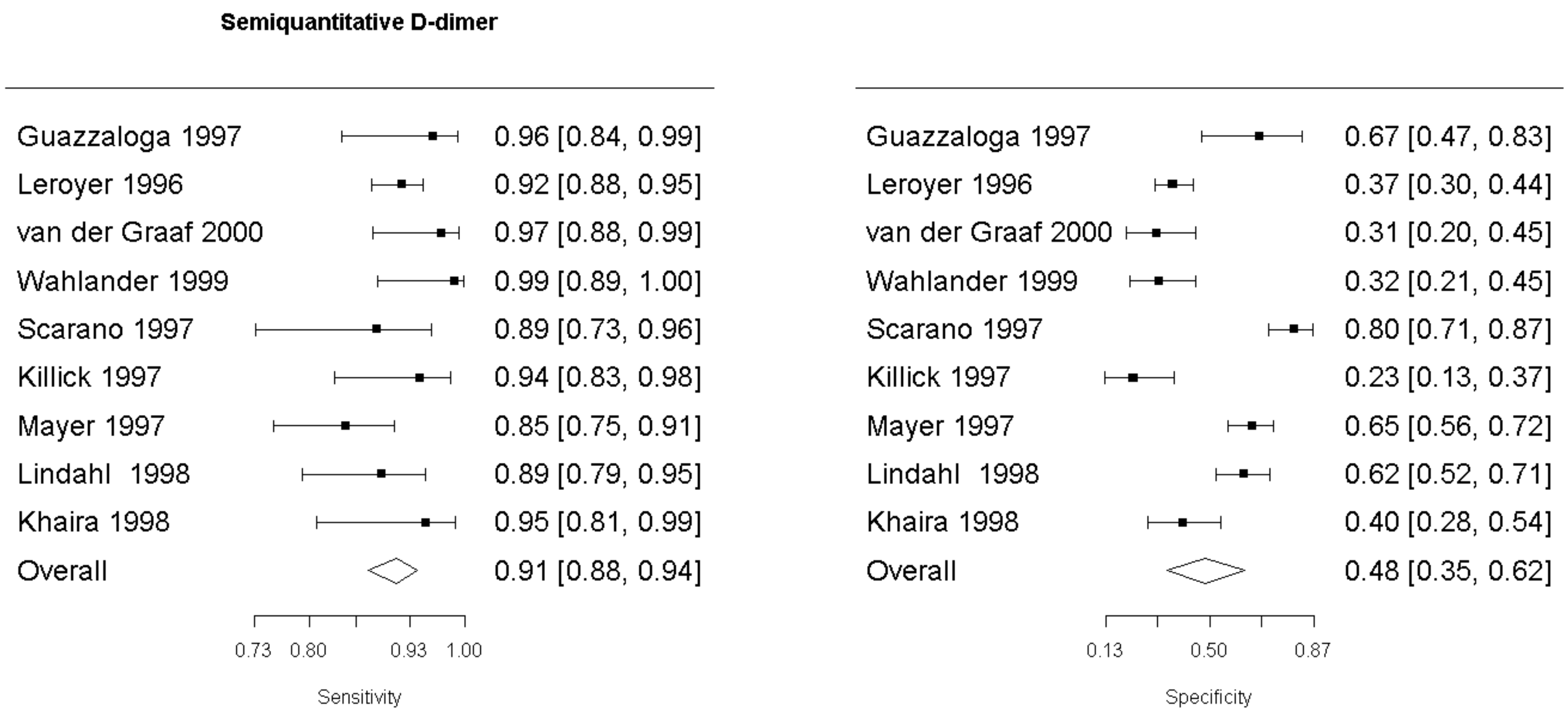
I^2 (sensitivity)=0%
I^2 (specificity)=92.3%

Figure 23: Likelihood ratios for point-of-care D-dimer tests for deep vein thrombosis – quantitative



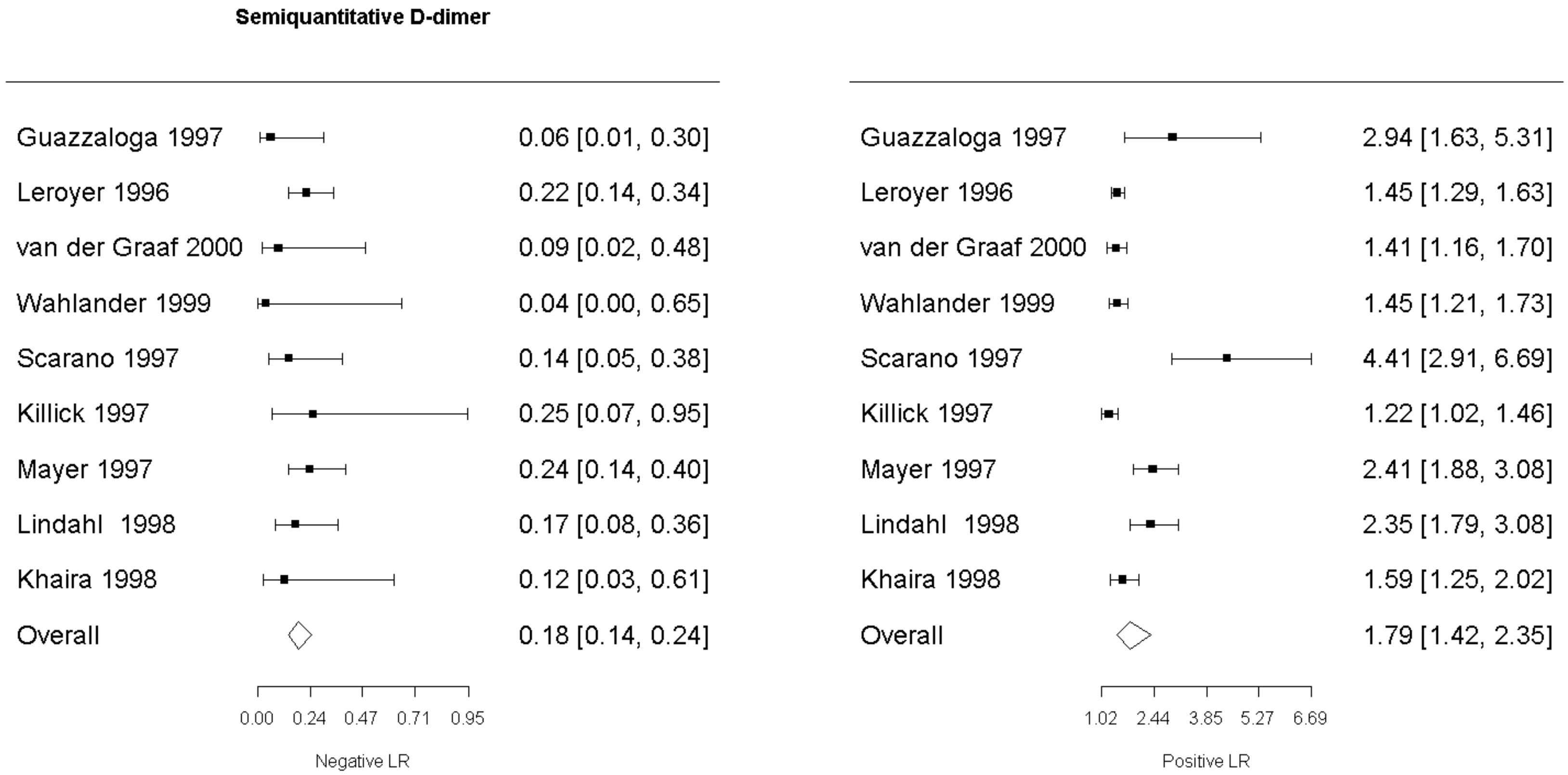
I^2 (Negative LR)=0%
I^2 (Positive LR)=92.0%

Figure 24: Sensitivity and specificity for Semiquantitative D-dimer tests for deep vein thrombosis – Instant IA and Nycocard



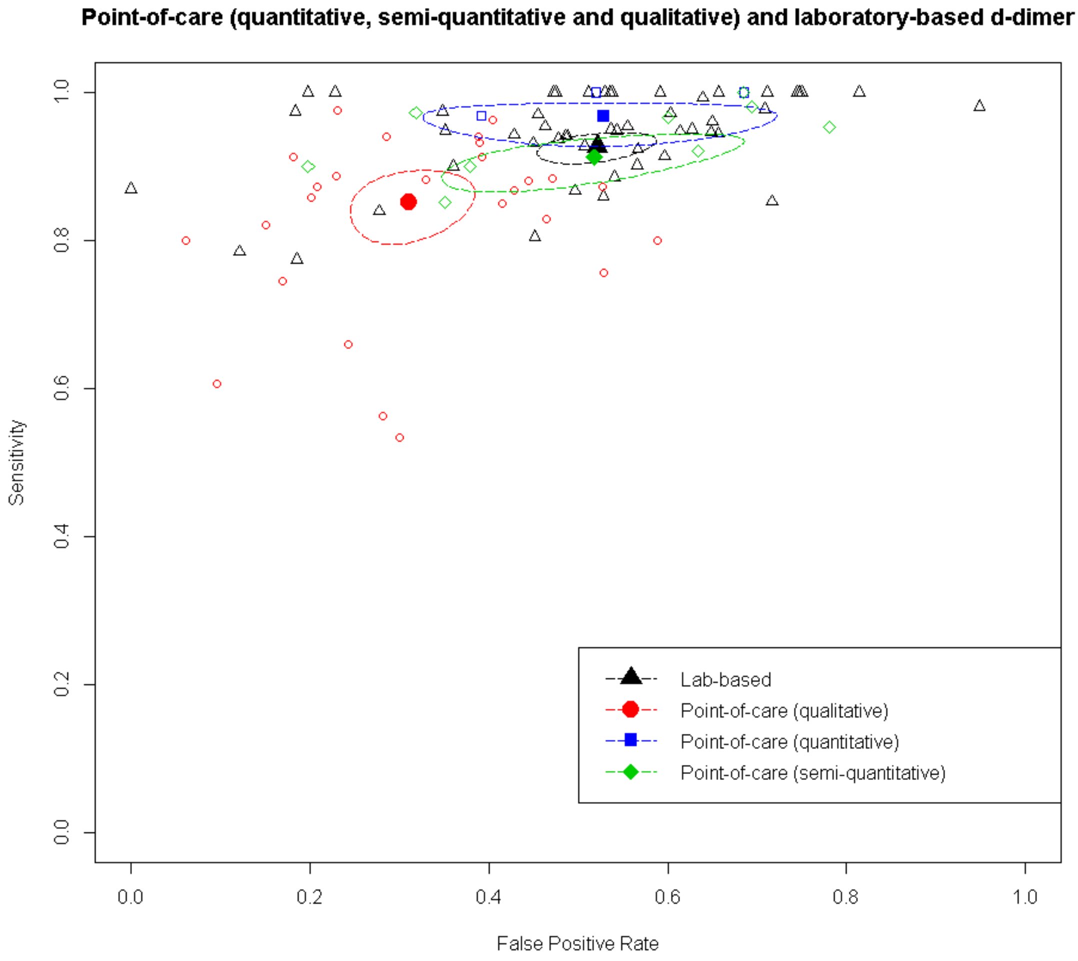
I^2 (sensitivity)=30.9%
I^2 (specificity)=91.1%

Figure 25: Likelihood ratios for Semiquantitative D-dimer tests for deep vein thrombosis – Instant IA and Nycocard



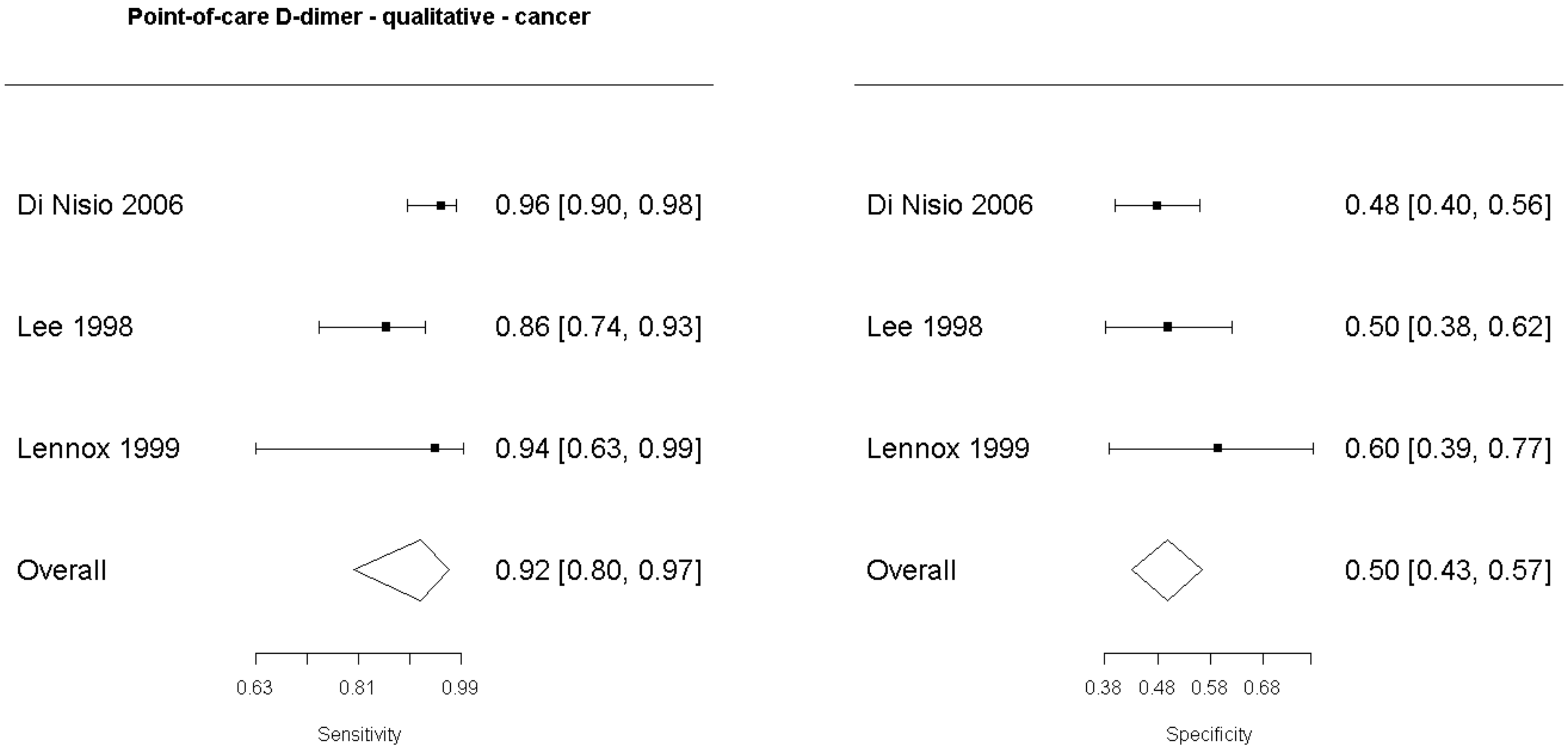
I^2 (Negative LR)=0.0%, I^2 (Positive LR)=87.0%

Figure 26: Sensitivity and specificity for laboratory-based and point-of-care based D-dimer tests for deep vein thrombosis. Qualitative, quantitative and semi-quantitative point-of-care tests shown separately



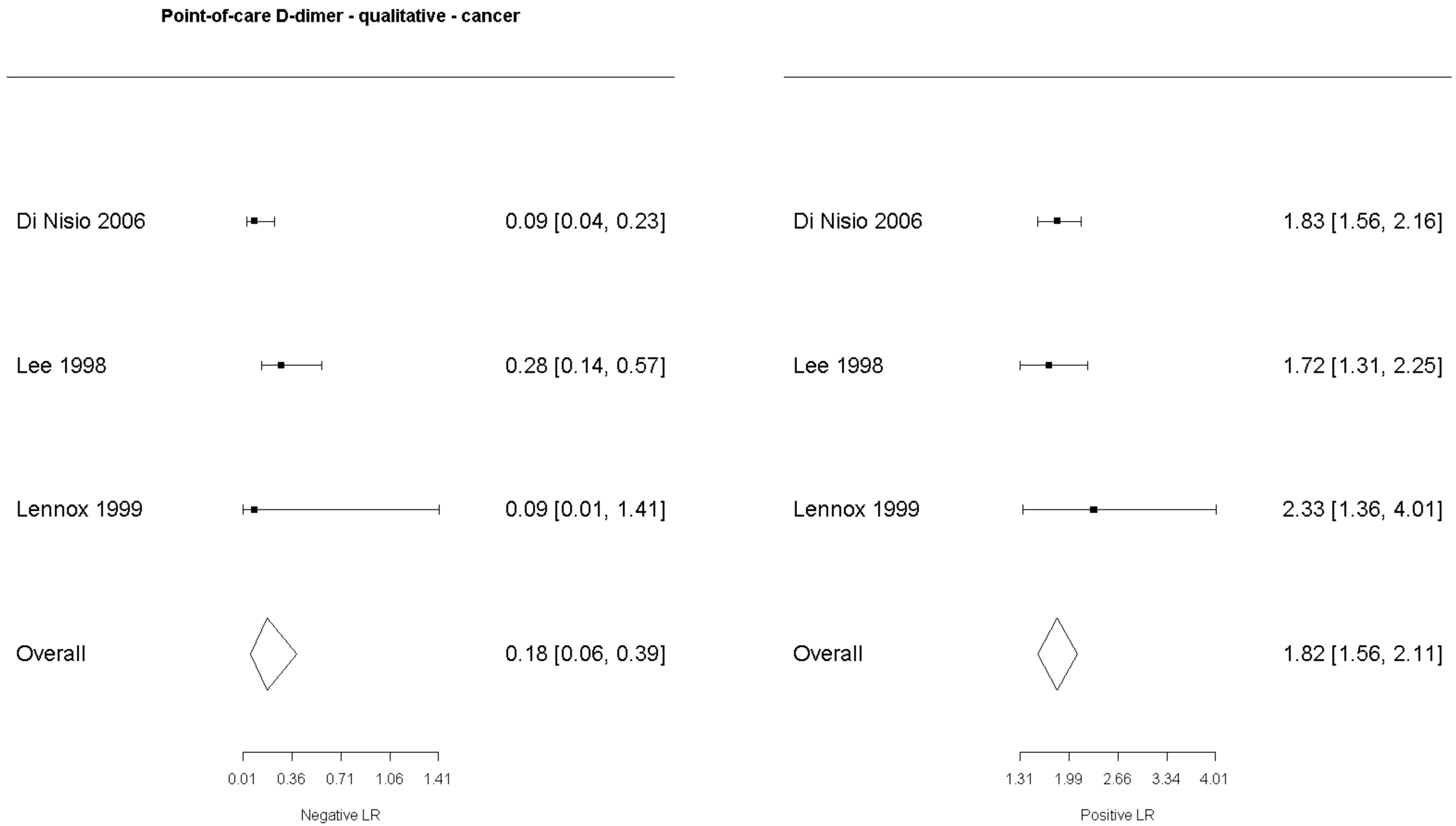
Subgroup analysis: Qualitative point-of-care D-dimer tests for deep vein thrombosis, participants with cancer

Figure 27: Sensitivity and specificity for Point-of-care D-dimer tests for deep vein thrombosis – qualitative (Cancer subgroup only)



I^2 (sensitivity)=52.1%, I^2 (specificity)=0.0%

Figure 28: Likelihood ratios for point-of-care based D-dimer tests for deep vein thrombosis – qualitative (Cancer subgroup only)



I^2 (Negative LR)=46.6%, I^2 (Positive LR)=0%

Sensitivity analysis: Laboratory and point-of-care D-dimer tests for deep vein thrombosis, excluding studies without direct comparisons

Figure 29: Sensitivity and specificity for laboratory-based and qualitative point-of-care D-dimer tests for deep vein thrombosis – all studies with a direct comparison (sensitivity analysis)

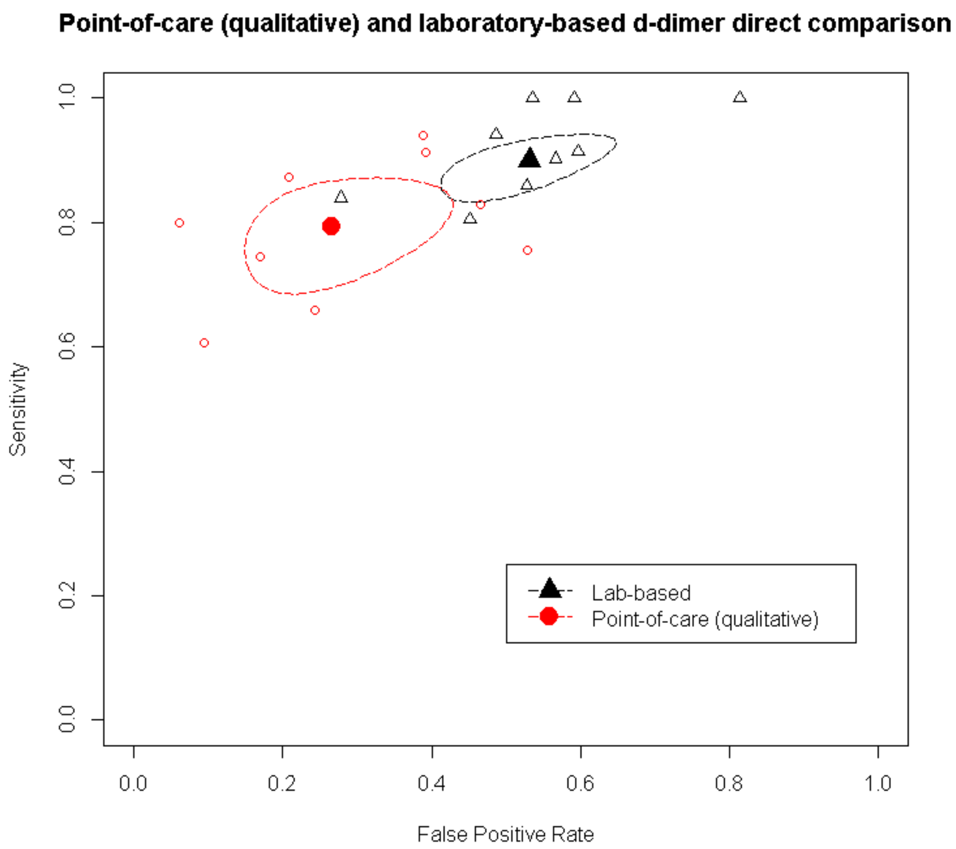


Figure 30: Sensitivity and specificity for laboratory-based and quantitative point-of-care D-dimer tests for deep vein thrombosis – all studies with a direct comparison (sensitivity analysis)

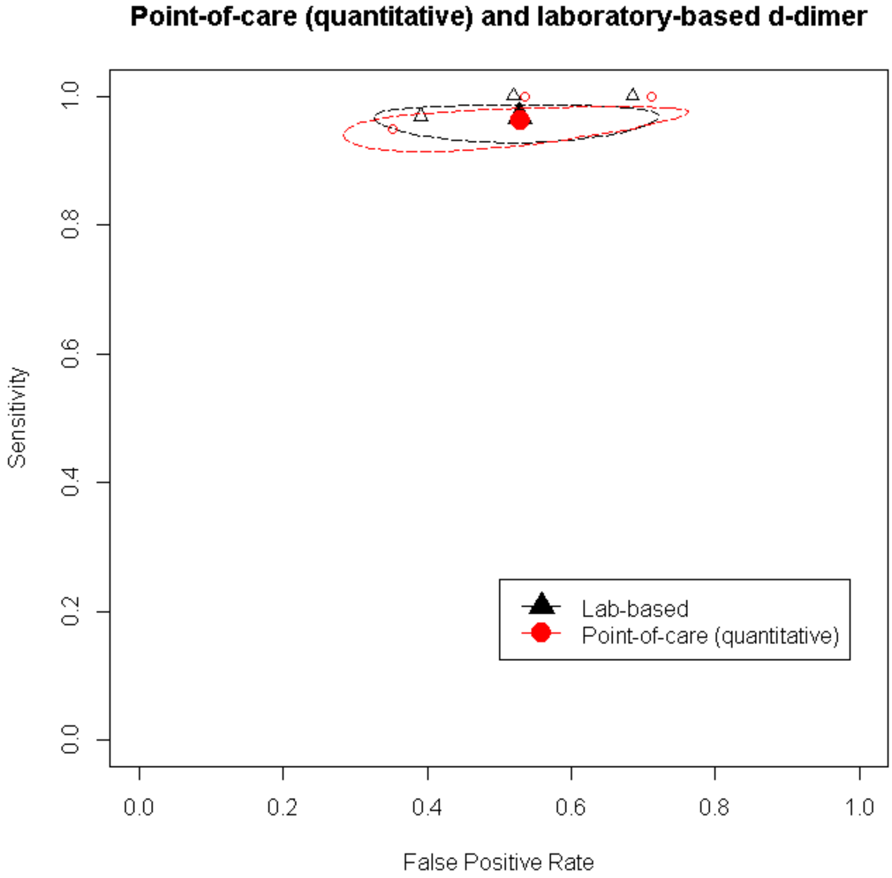
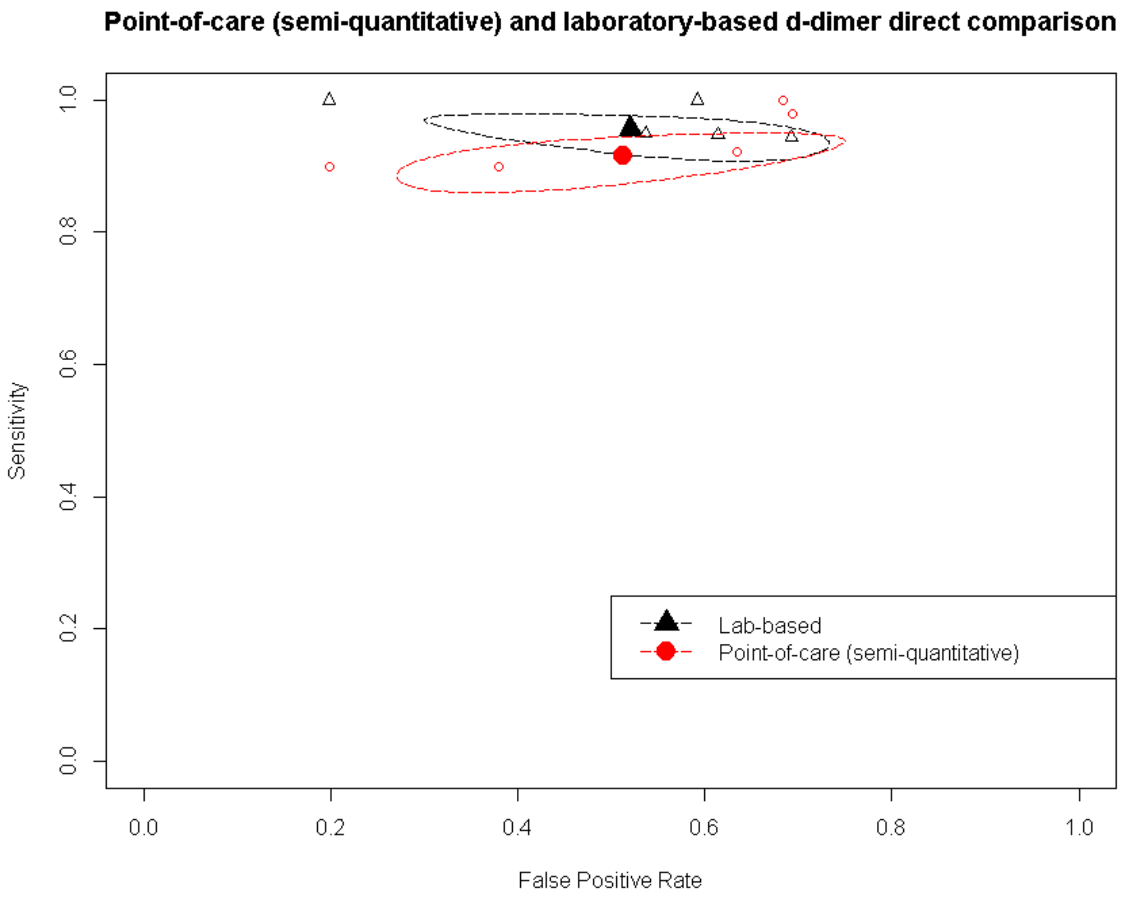
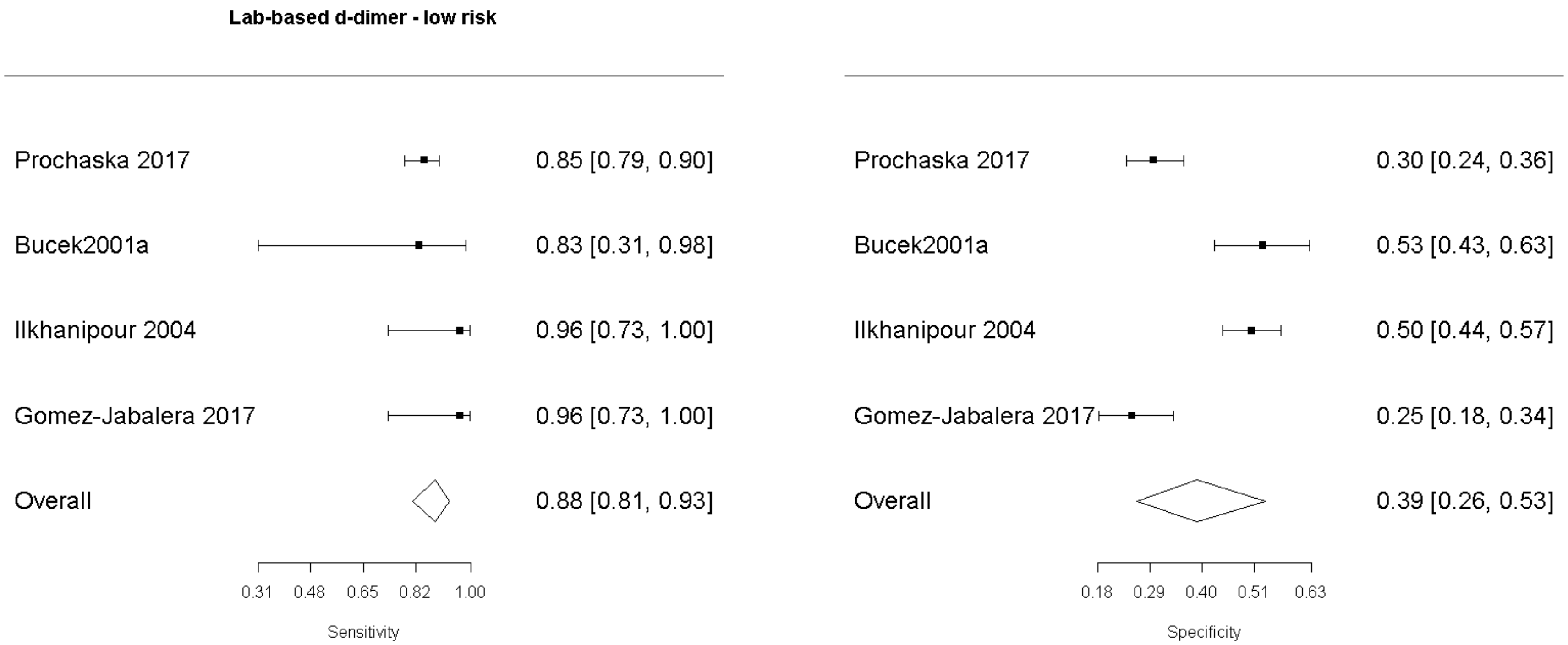


Figure 31: Sensitivity and specificity for laboratory-based and semi-quantitative point-of-care D-dimer tests for deep vein thrombosis – all studies with a direct comparison (sensitivity analysis)



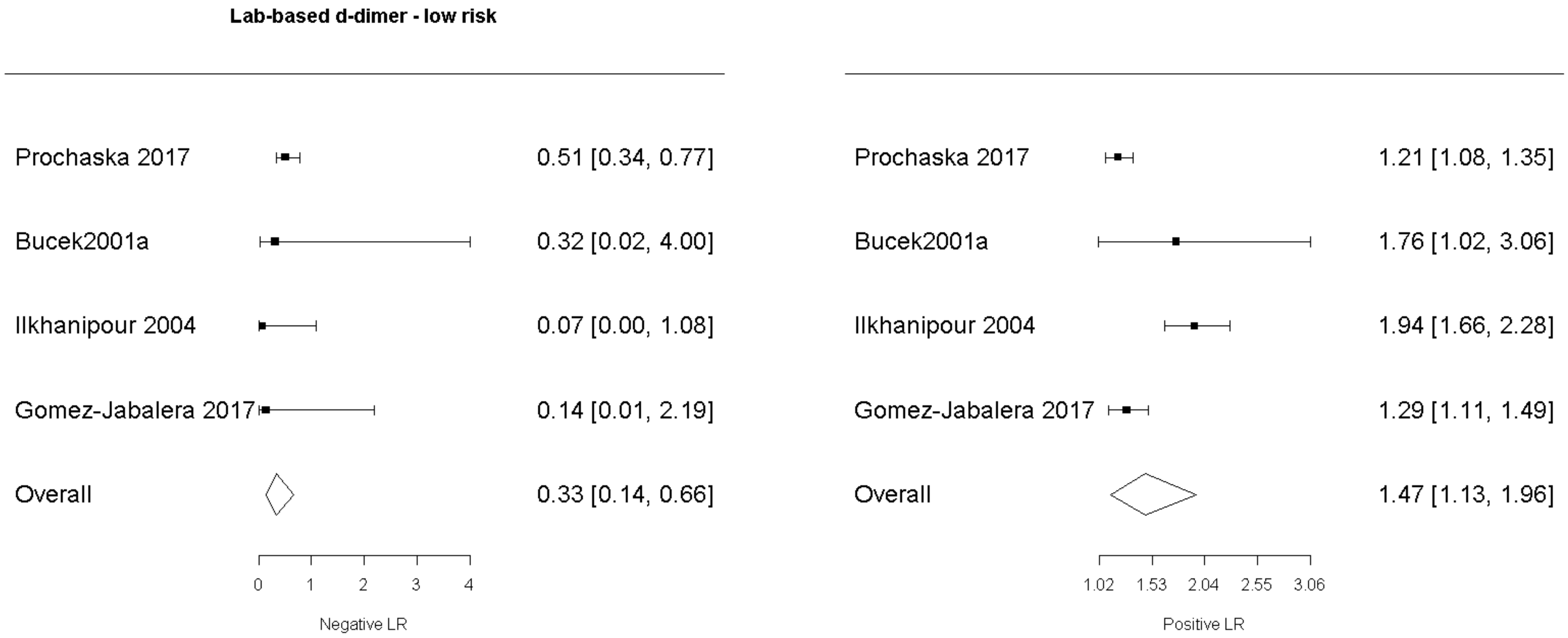
Subgroup analysis: Laboratory and point-of-care D-dimer tests for deep vein thrombosis, separating low/intermediate and high pre-test-probability participants

Figure 32: Sensitivity and specificity for laboratory based D-dimer tests for deep vein thrombosis – Low/moderate pretest probability only (according to 3-level Wells score)



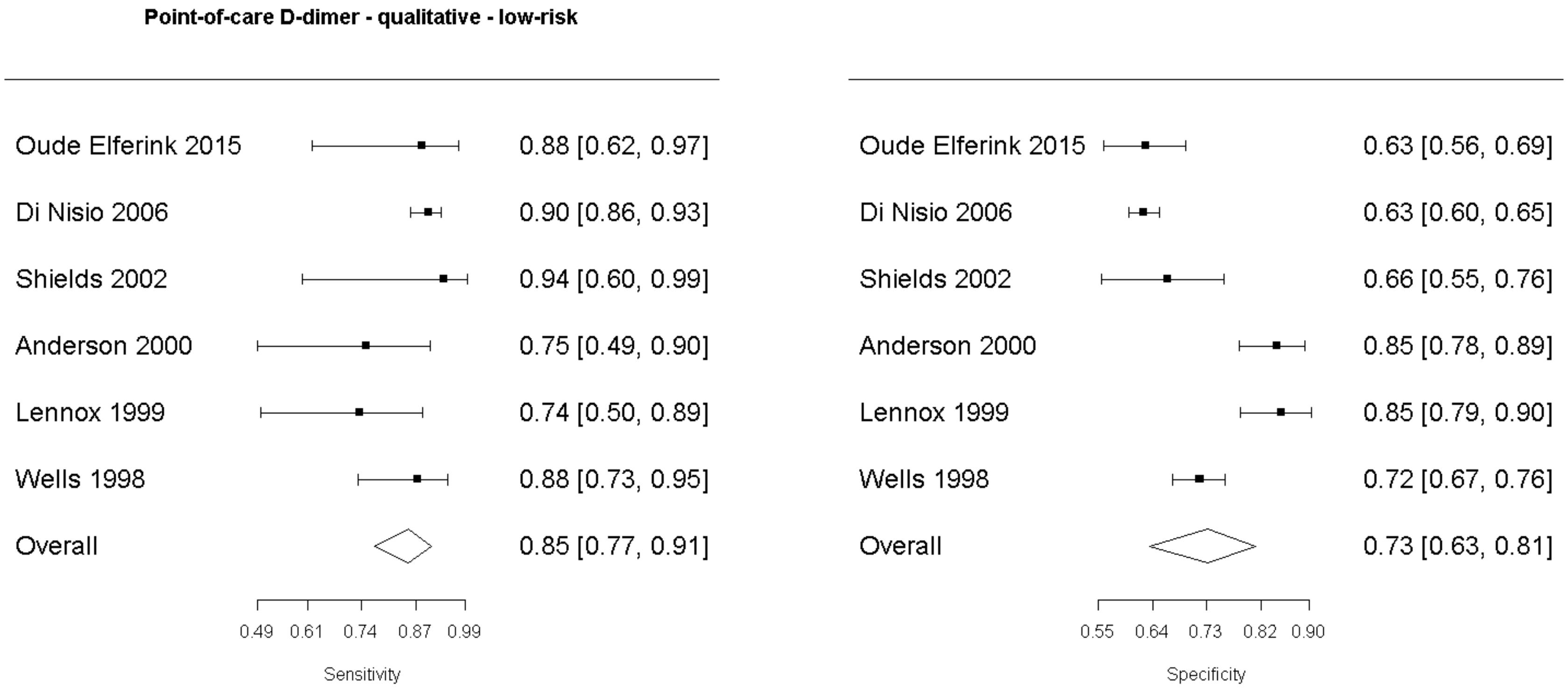
I^2 (sensitivity)=0.0%
I^2 (specificity)=93.1%

Figure 33: Likelihood ratios for laboratory based D-dimer tests for deep vein thrombosis – Low/moderate pretest probability only (according to 3-level Wells score)



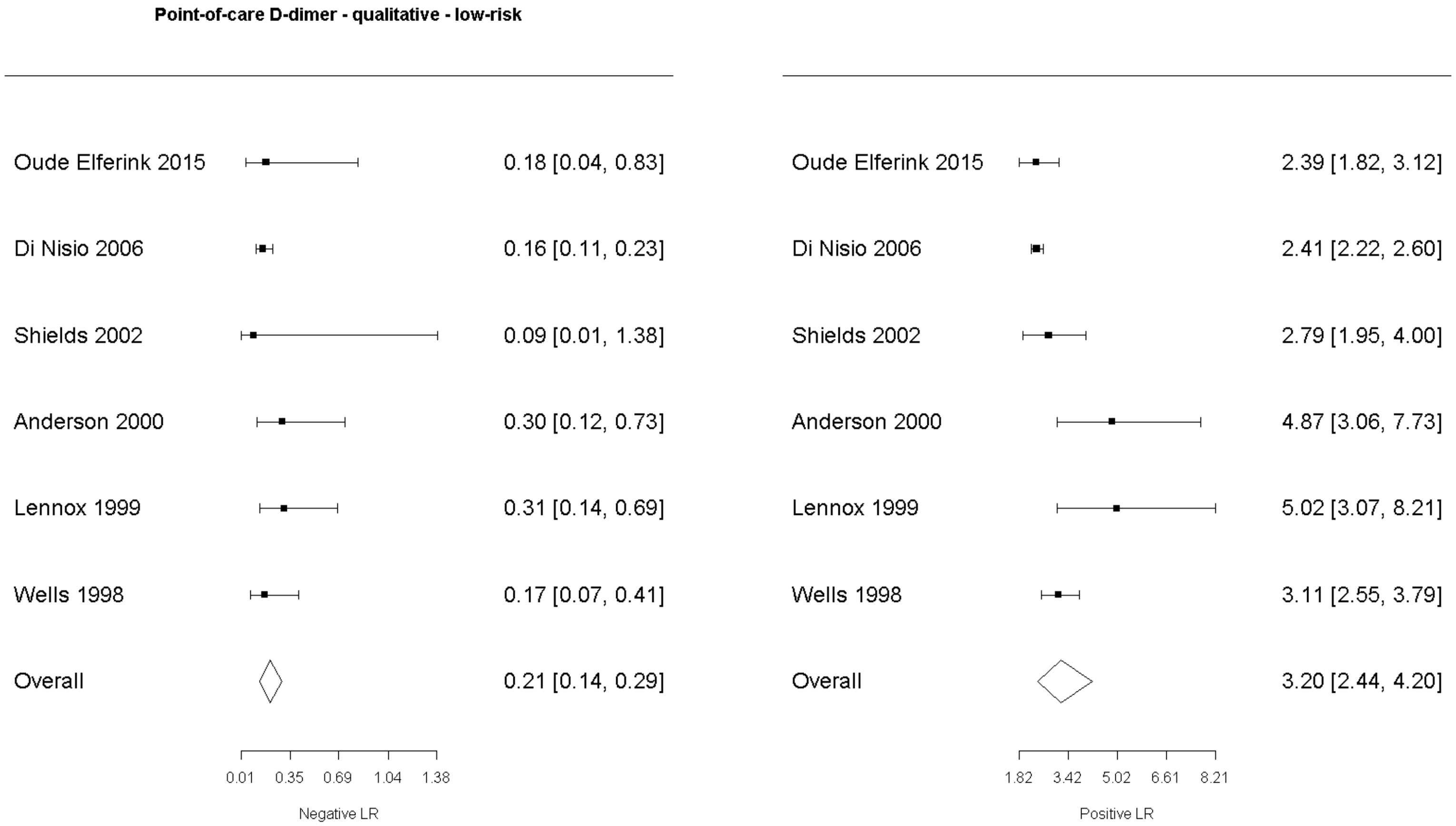
I^2 (Negative LR)=0.0%
I^2 (Positive LR)=42.6%

Figure 34: Sensitivity and specificity for Point-of-care D-dimer tests for deep vein thrombosis – qualitative: Low/moderate pretest probability only (according to 3-level Wells score)



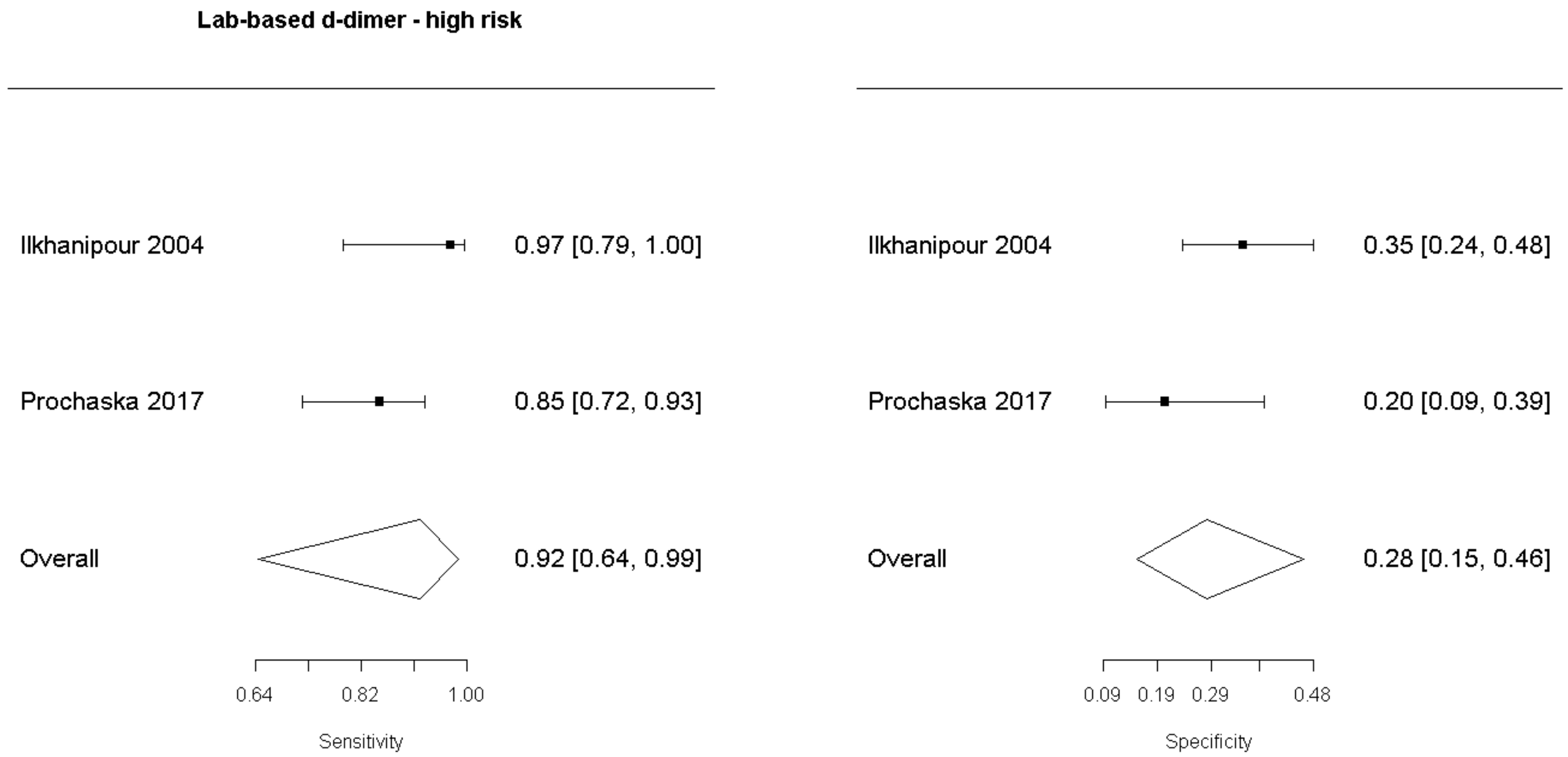
I^2 (sensitivity)=5.4%
I^2 (specificity)=91.7%

Figure 35: Likelihood ratios for point-of-care D-dimer tests for deep vein thrombosis – qualitative: Low/moderate pretest probability only (according to 3-level Wells score)



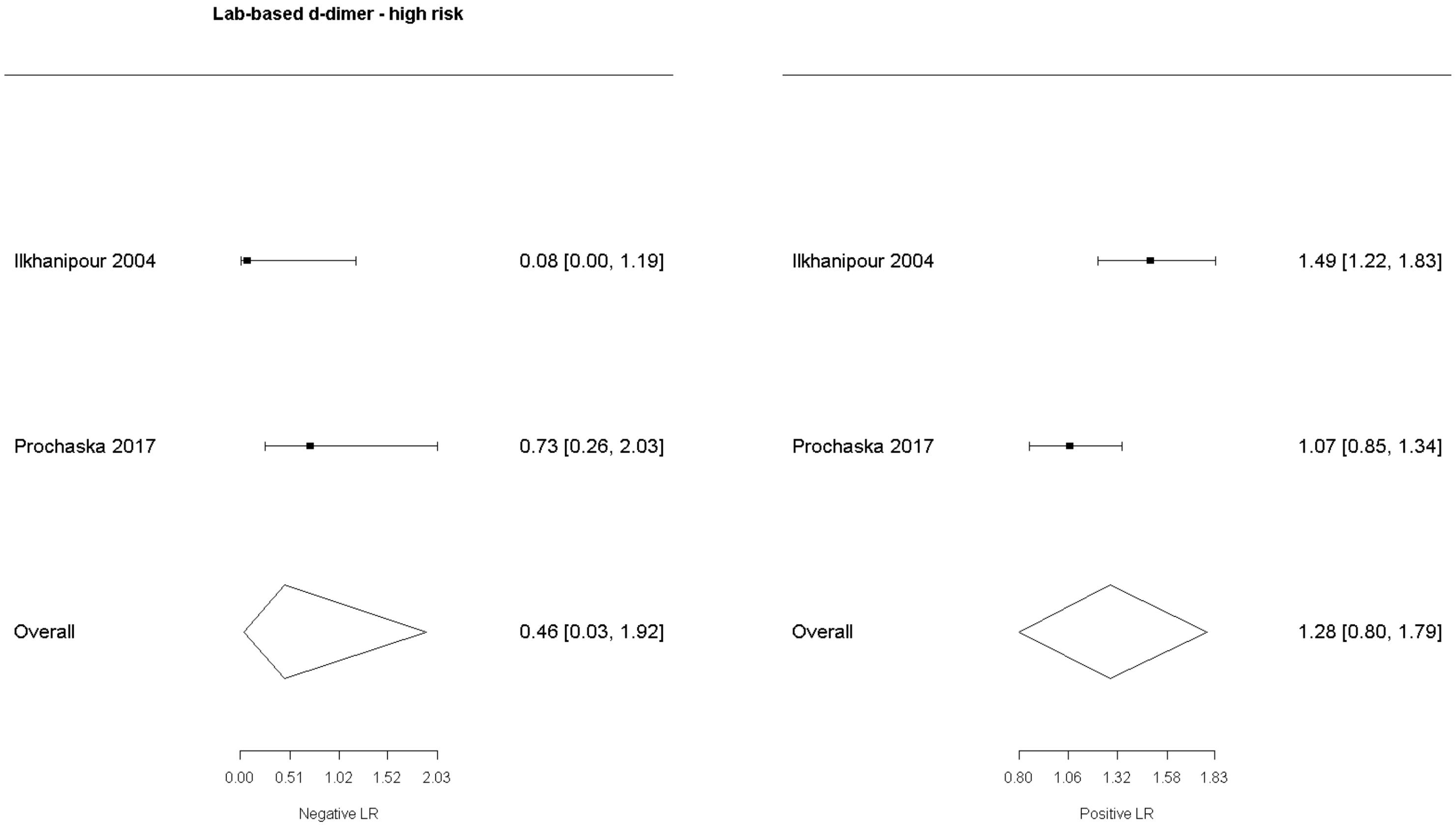
I^2 (Negative LR)=0.0%
I^2 (Positive LR)=78.3%

Figure 36: Sensitivity and specificity for laboratory based D-dimer tests for deep vein thrombosis – High pretest probability only (according to 3-level Wells score)



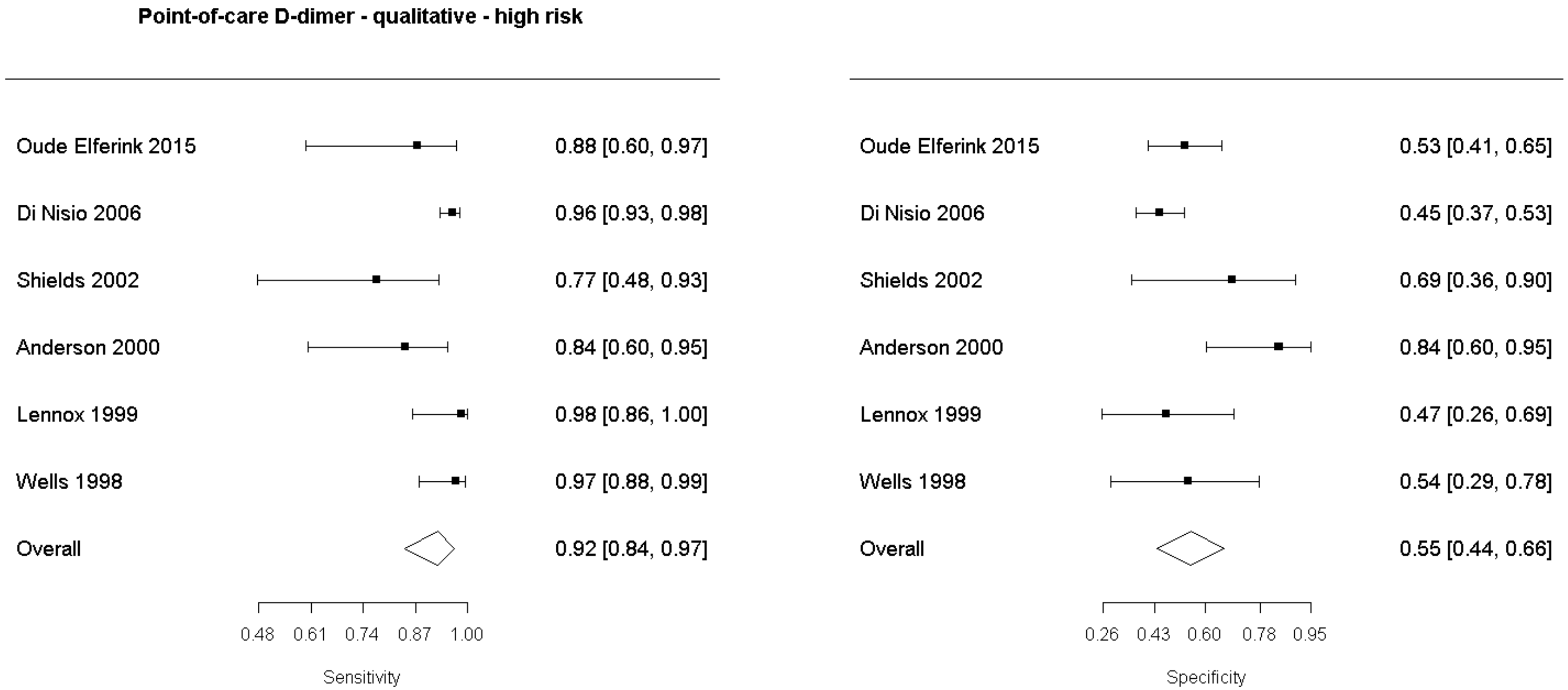
I^2 (sensitivity)=30.0%
I^2 (specificity)=50.0%

Figure 37: Likelihood ratios for laboratory-based D-dimer tests for deep vein thrombosis – High pretest probability only (according to 3-level Wells score)



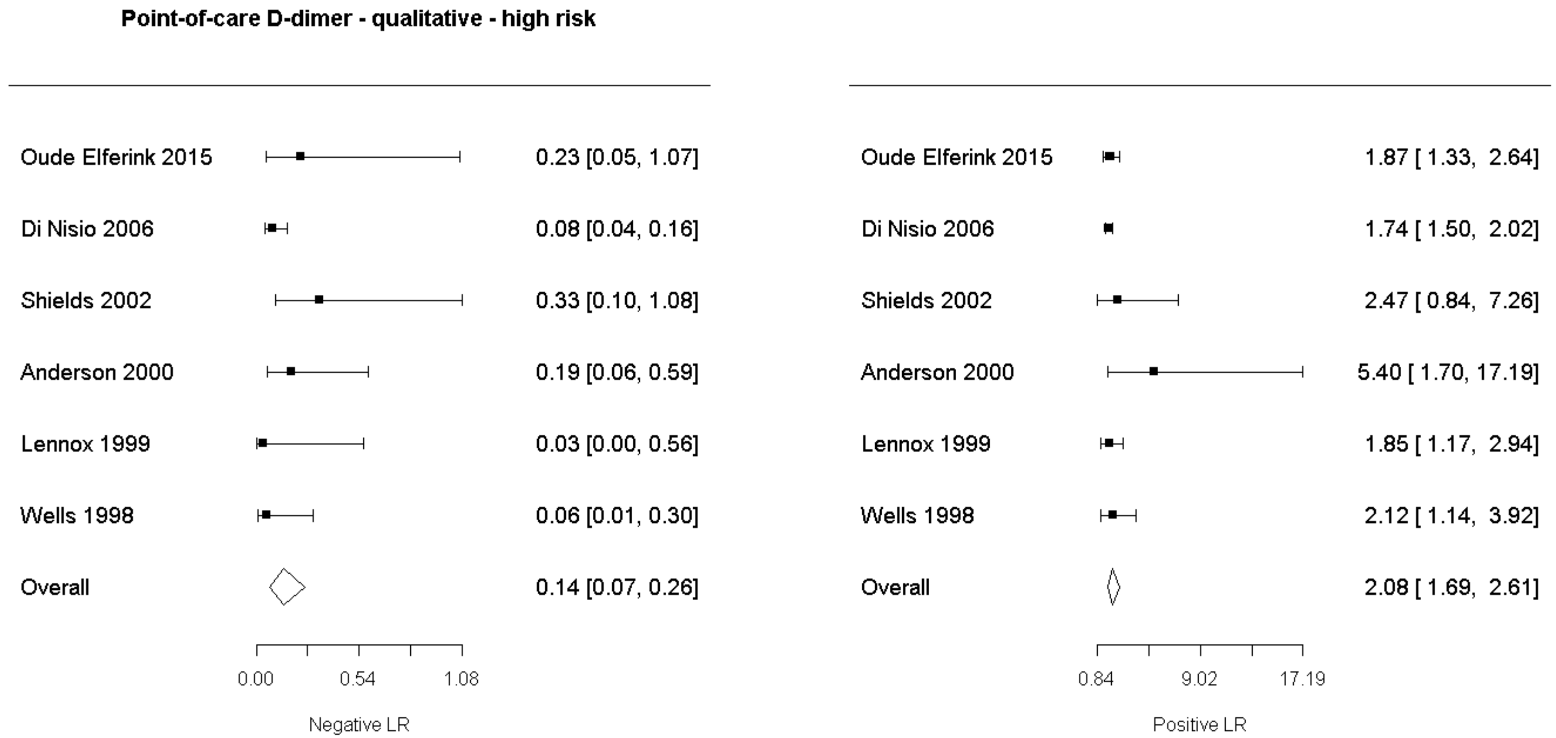
I^2 (Negative LR)=55.3%
I^2 (Positive LR)=79.1%

Figure 38: Sensitivity and specificity for Point-of-care D-dimer tests for deep vein thrombosis – qualitative: High pretest probability only (according to 3-level Wells score)



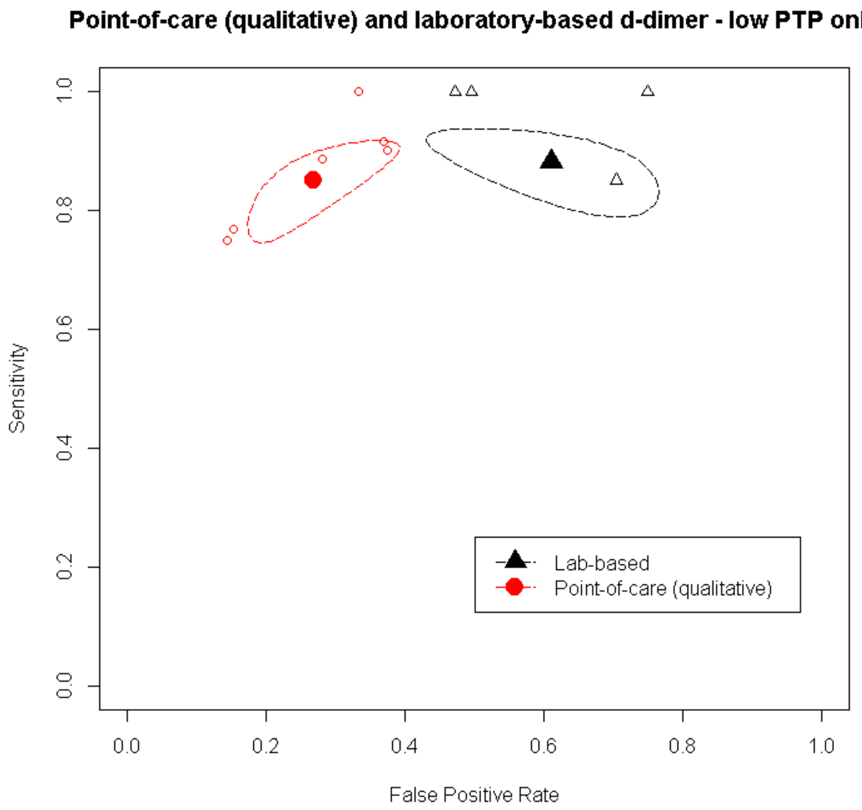
I^2 (sensitivity)=52.4%
I^2 (specificity)=54.7%

Figure 39: Likelihood ratios for point-of-care D-dimer tests for deep vein thrombosis – qualitative: High pretest probability only (according to 3-level Wells score)



I^2 (Negative LR)=12.9%
I^2 (Positive LR)=15.1%

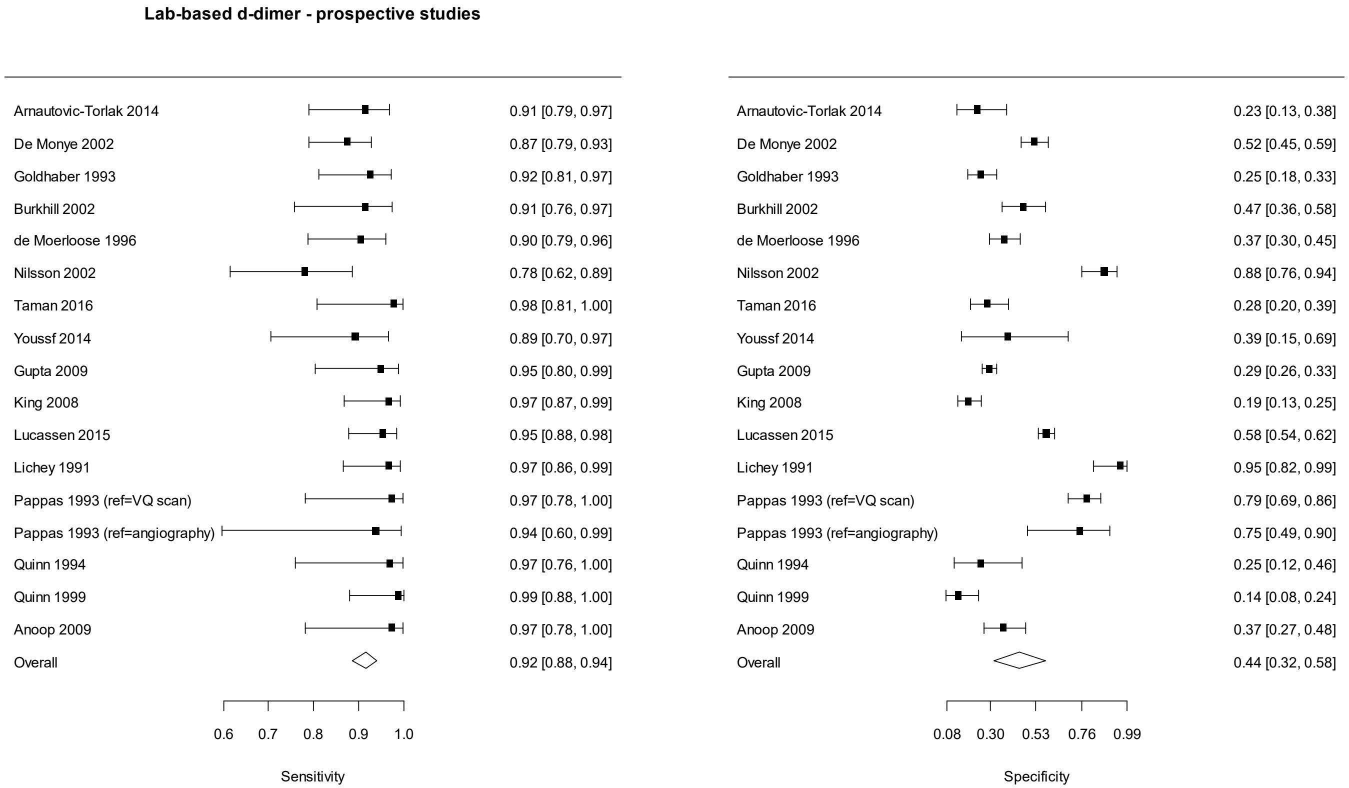
Figure 40: Sensitivity and specificity for laboratory-based and point-of-care D-dimer tests for deep vein thrombosis – low pre-test probability only



Laboratory and point-of care D-dimer test for pulmonary embolism

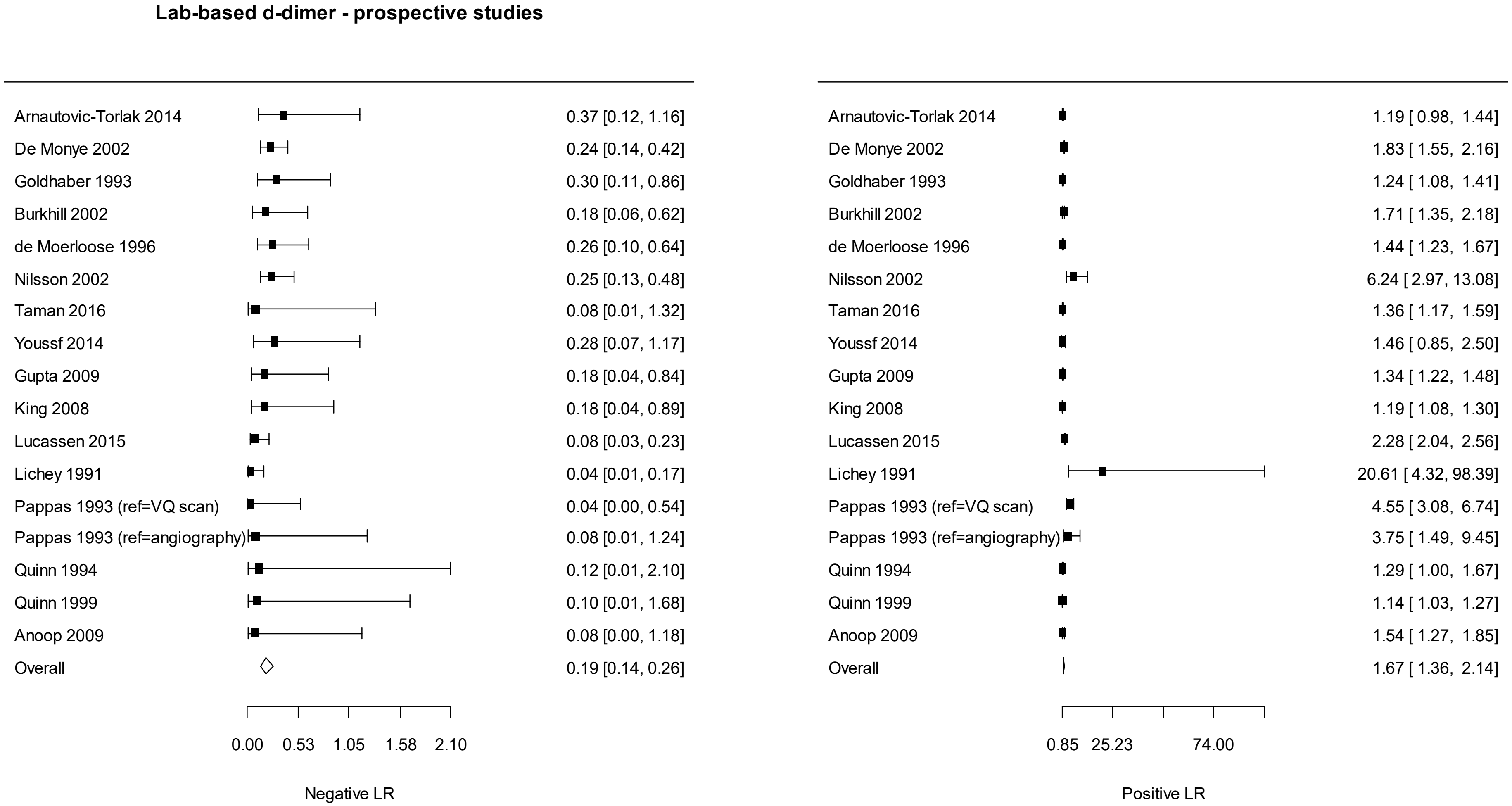
(See [above]() for the corresponding evidence statements for this section.)

Figure 41: Sensitivity and specificity for laboratory-based D-dimer tests for pulmonary embolism (prospective studies)



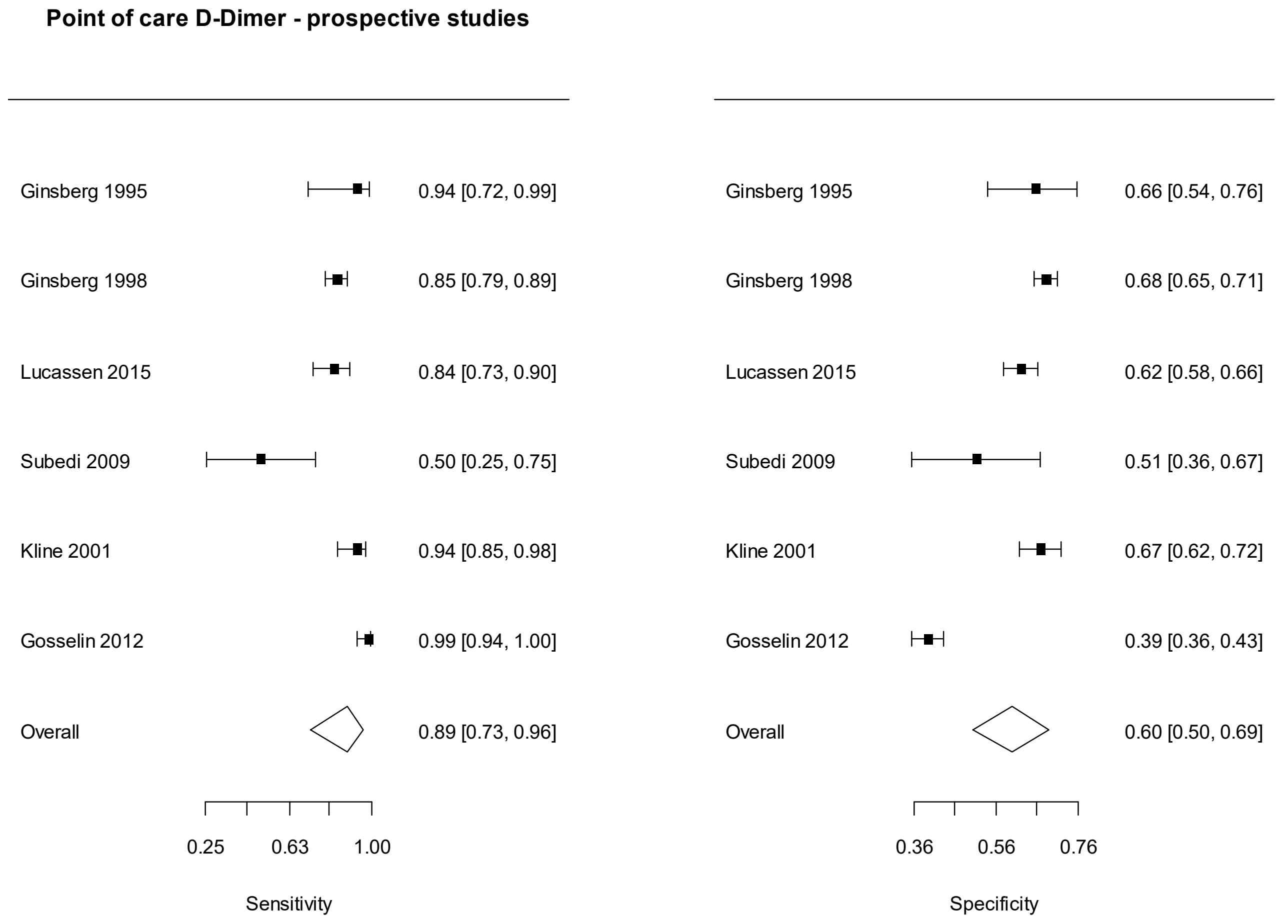
I^2 (sensitivity)=15.5%, I^2 (specificity)=94.2

Figure 42: Likelihood ratios for laboratory-based D-dimer tests for pulmonary embolism (prospective studies)



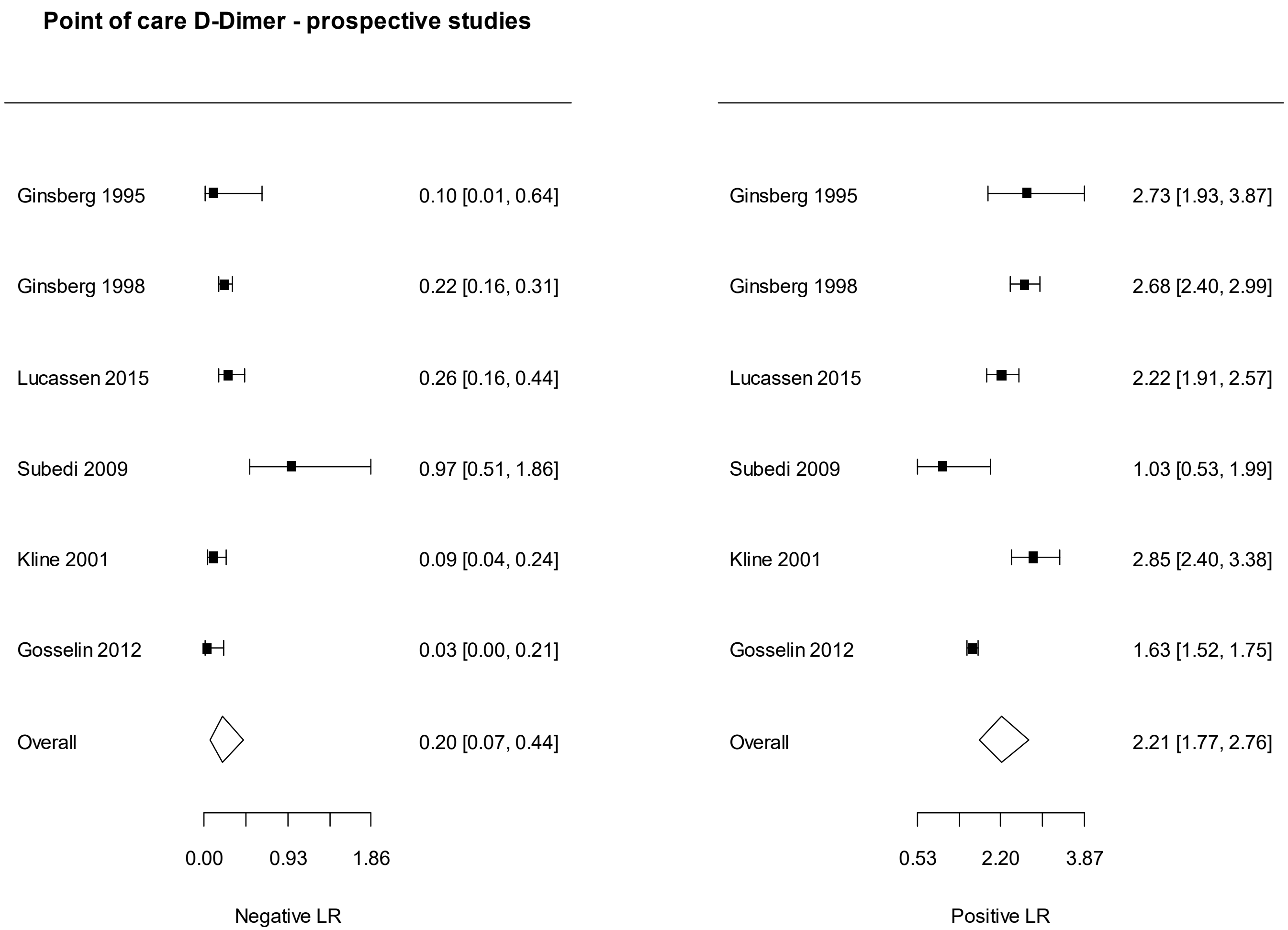
I^2 (negative LR)=0.0%, I^2 (positive LR)=91.5%

Figure 43: Sensitivity and specificity for point-of-care D-dimer tests for pulmonary embolism (prospective studies)



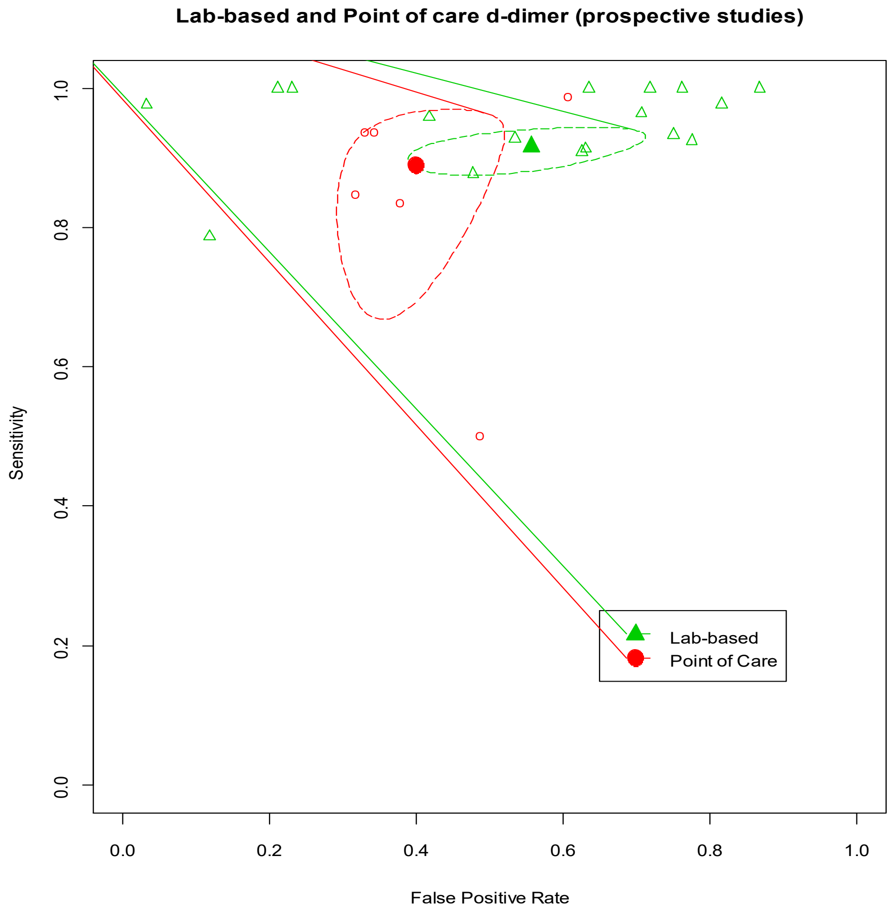
I^2 (sensitivity)=75.9%, I^2 (specificity)=96.4%

Figure 44: Likelihood ratios for point-of-care D-dimer tests for pulmonary embolism (prospective studies



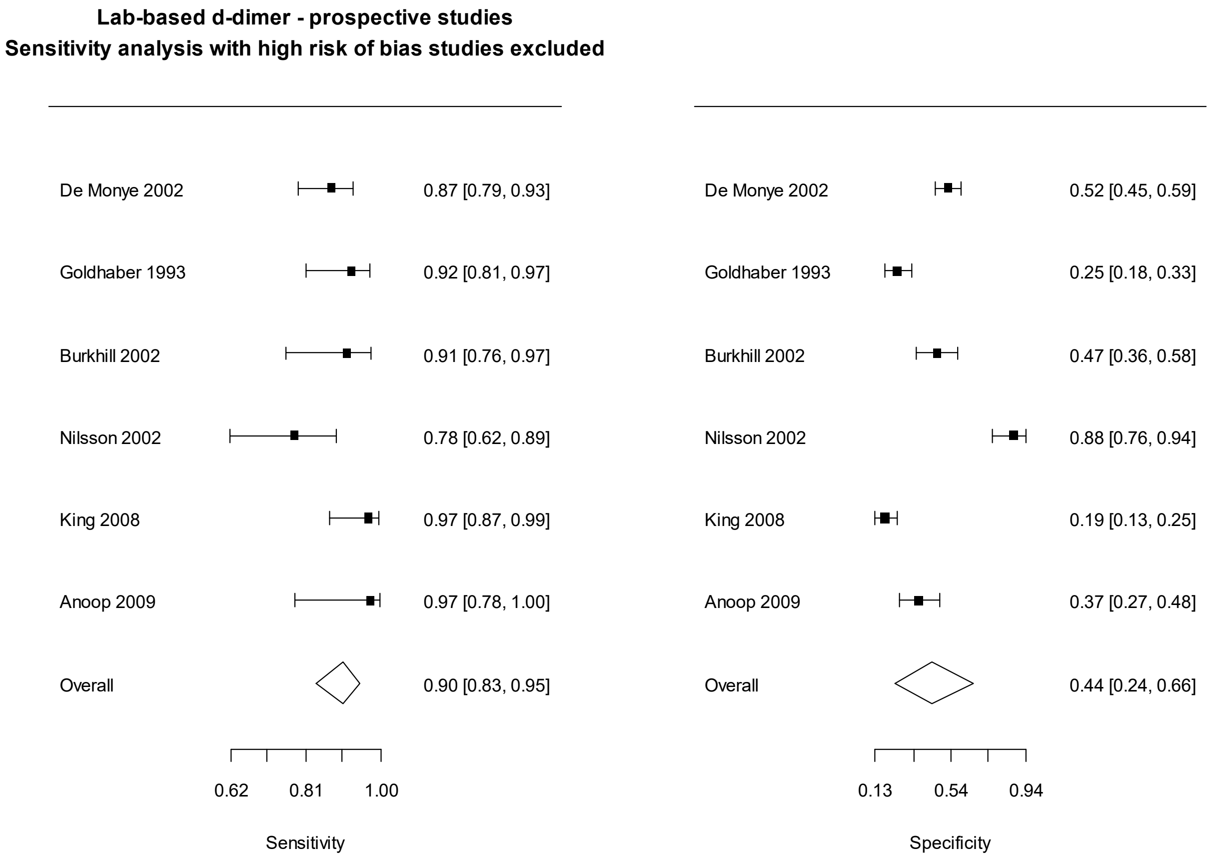
I^2 (negative LR) =81.4%, I^2 (positive LR) =94.2%

Figure 45: Sensitivity and specificity for laboratory-based and point-of-care based



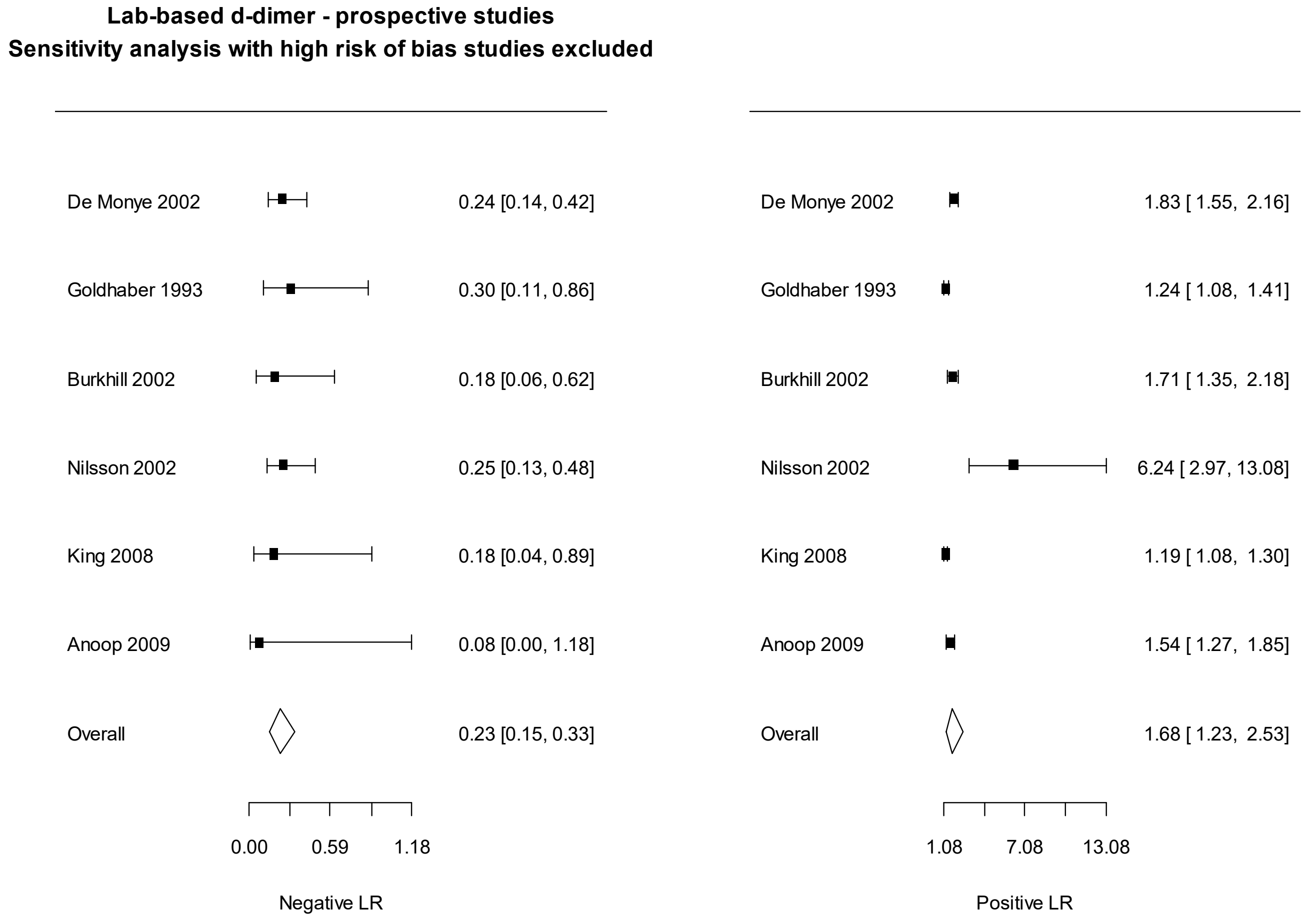
Sensitivity analysis excluding high risk-of-bias studies: Laboratory and point-of care D-dimer test for pulmonary embolism

Figure 46: Sensitivity and specificity for laboratory-based D-dimer tests for pulmonary embolism (prospective studies). Sensitivity analysis excluding high risk-of-bias studies.



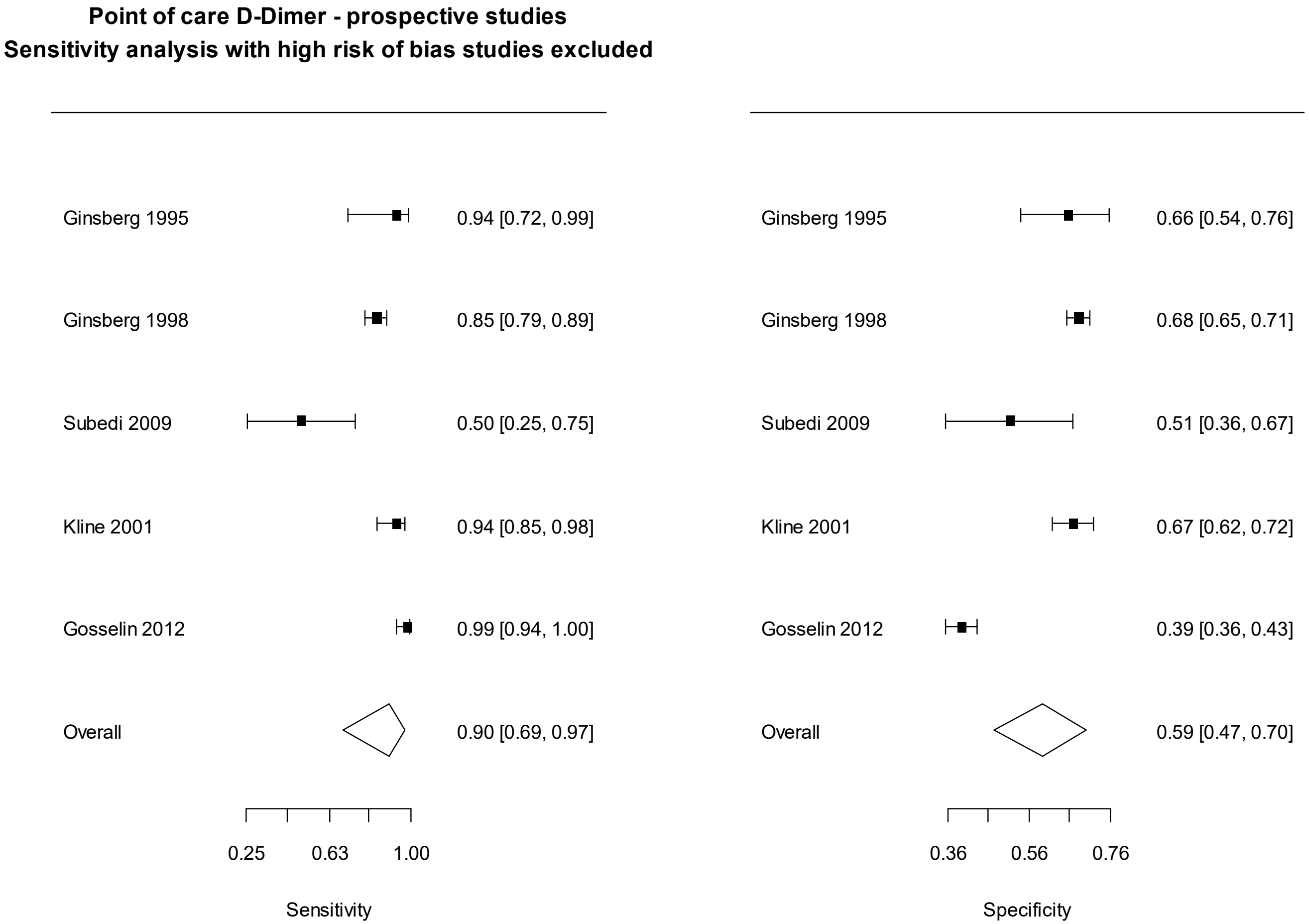
I^2 (sensitivity)=41.1%, I^2 (specificity)=94.0%

Figure 47: Likelihood ratios for laboratory-based D-dimer tests for pulmonary embolism (prospective studies). Sensitivity analysis excluding high risk-of-bias studies



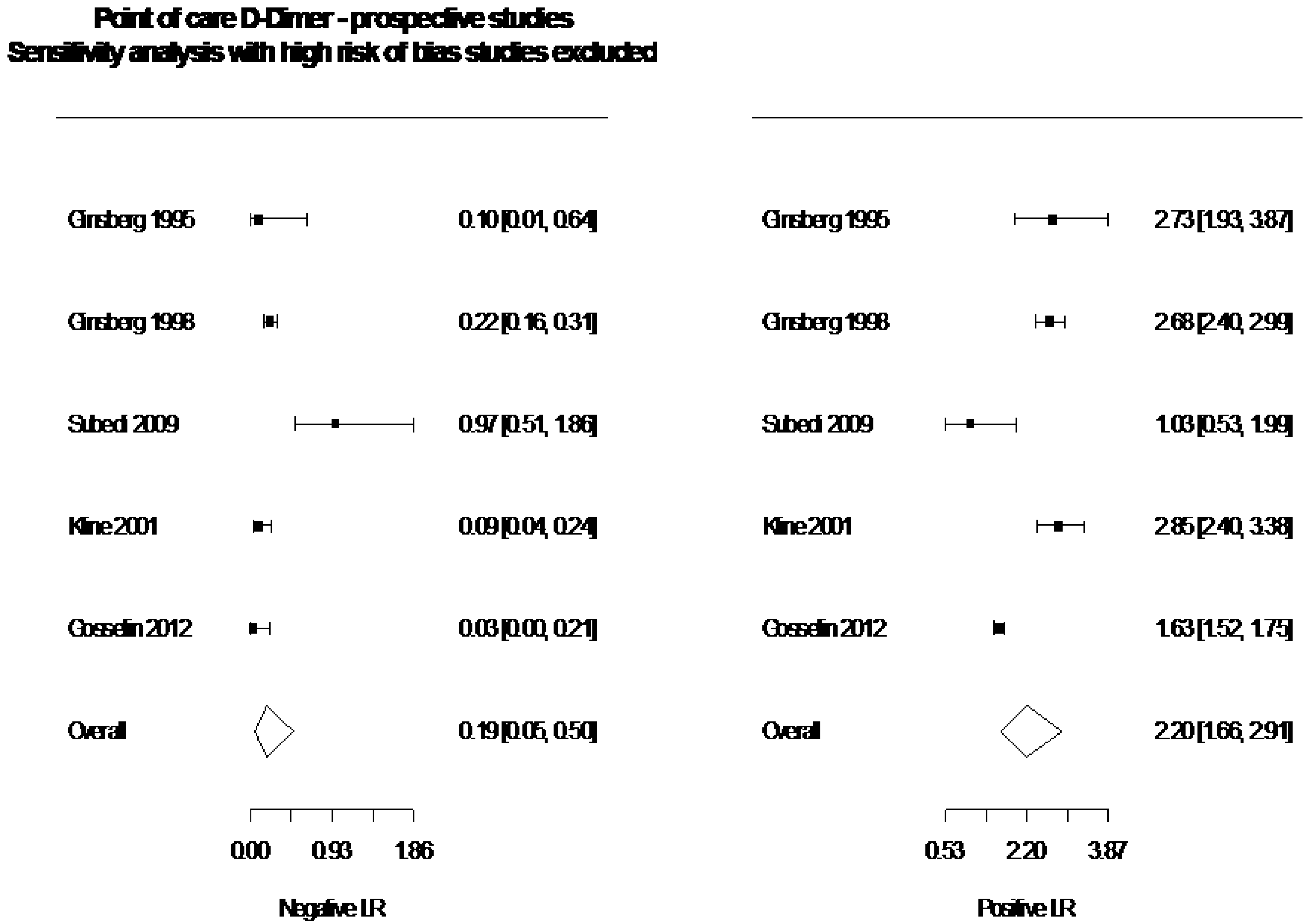
I^2 (Negative LR)=0.0%, I^2 (Positive LR)=88.8%

Figure 48: Sensitivity and specificity for point-of-care D-dimer tests for pulmonary embolism (prospective studies). Sensitivity analysis excluding high risk-of-bias studies.



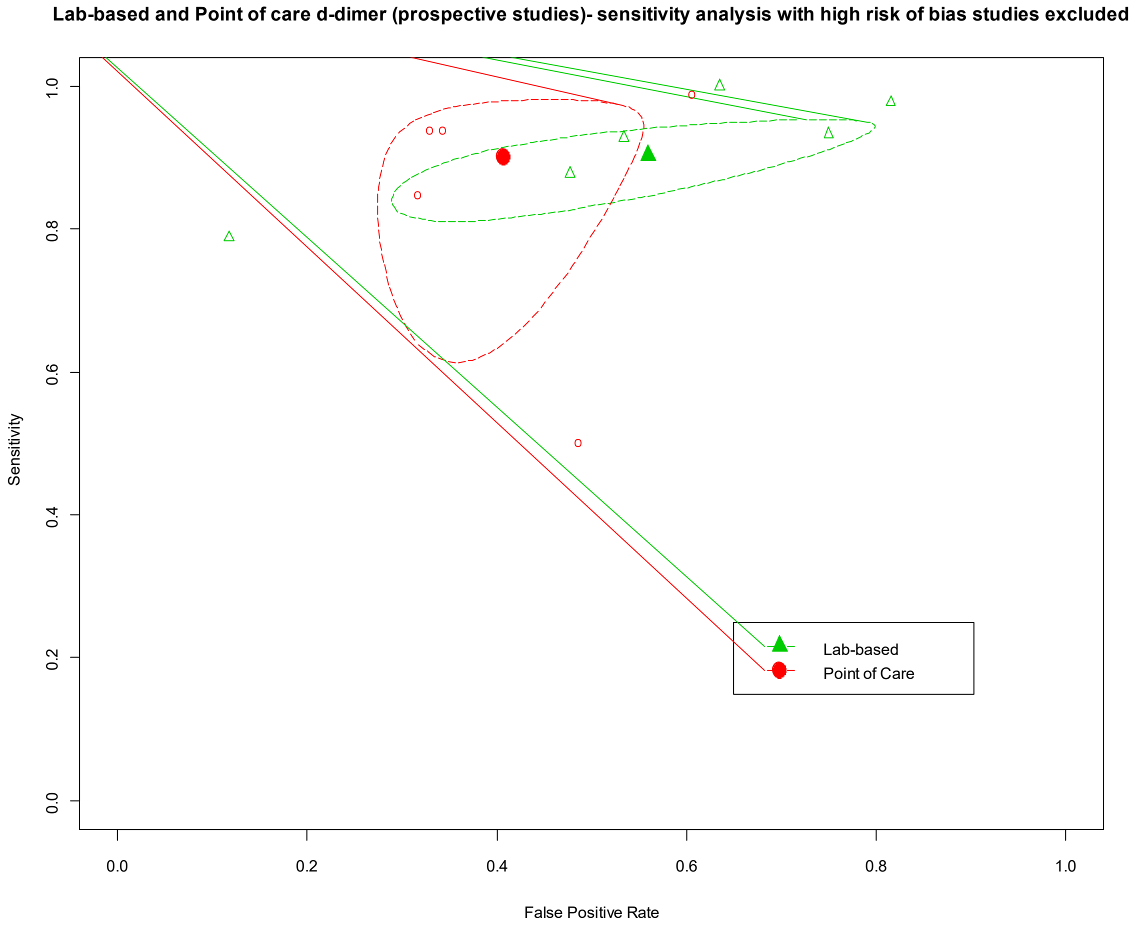
I^2 (sensitivity)=80.6%, I^2 (specificity)=97.1%

Figure 49: Likelihood ratios for point-of-care D-dimer tests for pulmonary embolism (prospective studies)



I^2 (Negative LR)=85.1%, I^2 (Positive LR)=95.3%

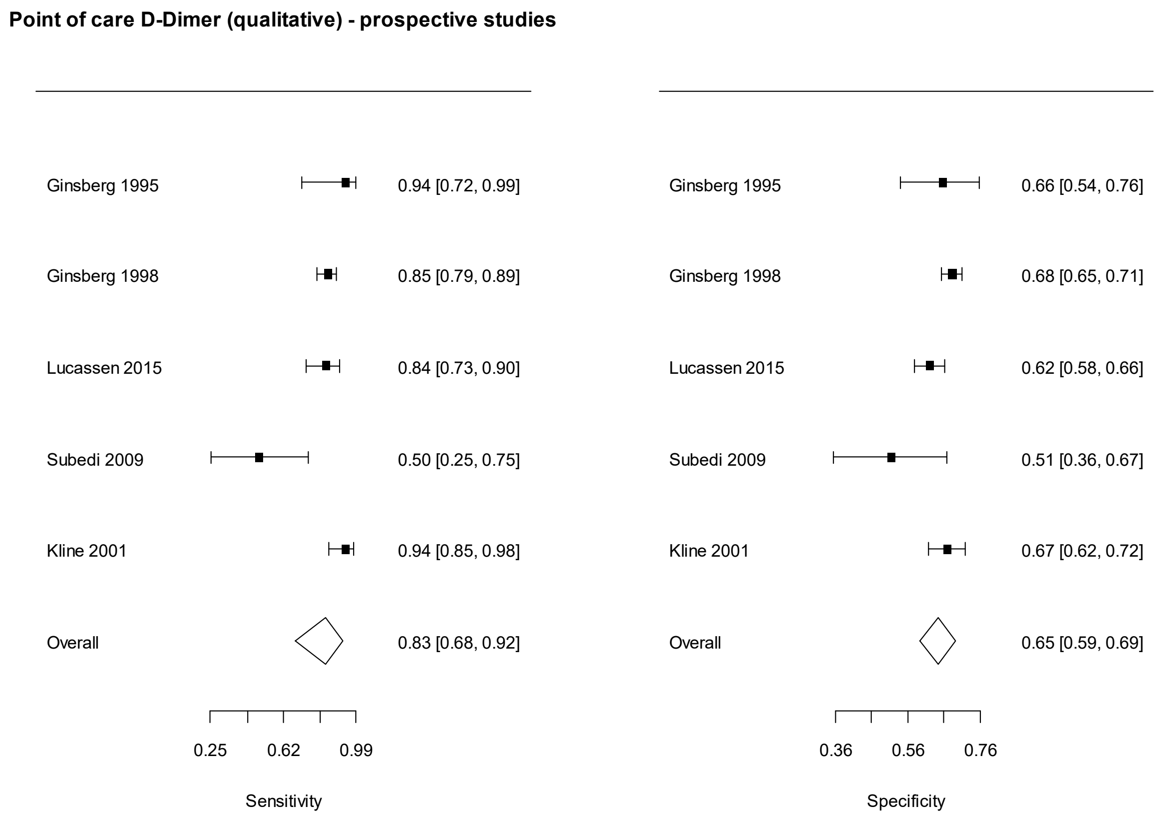
Figure 50: Sensitivity and specificity for laboratory-based and point-of-care based D-dimer tests for pulmonary embolism. Sensitivity analysis excluding high risk-of-bias studies



Subgroup analysis: point-of care D-dimer tests for pulmonary embolism, separating qualitative and quantitative studies

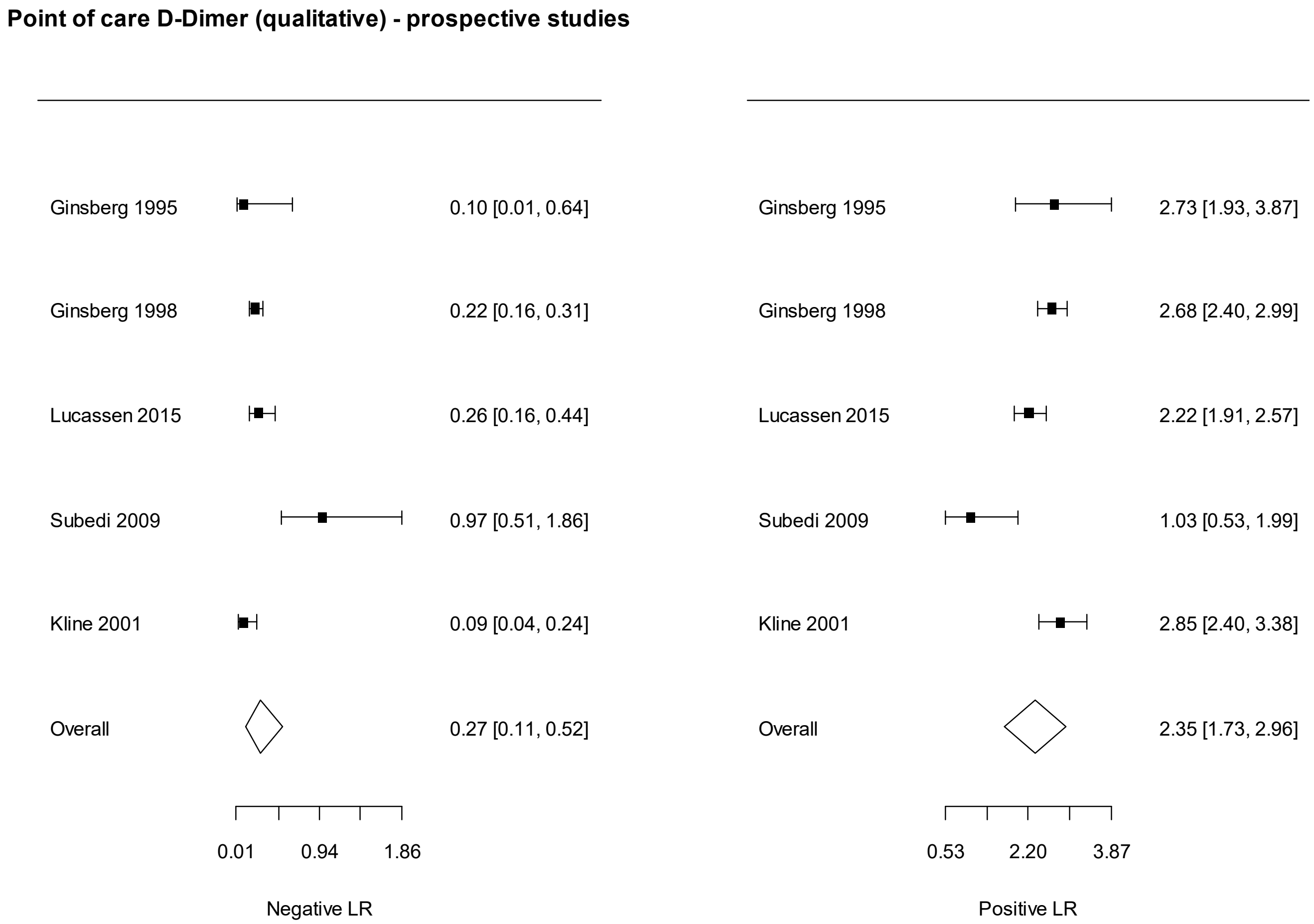
Note that there are no forest plots showing quantitative point-of-care tests, as these were reported by a single study.

Figure 51: Sensitivity and specificity for point-of-care D-dimer tests (qualitative only) for pulmonary embolism (prospective studies



I^2 (sensitivity)=70.3%, I^2 (specificity)=55.8%

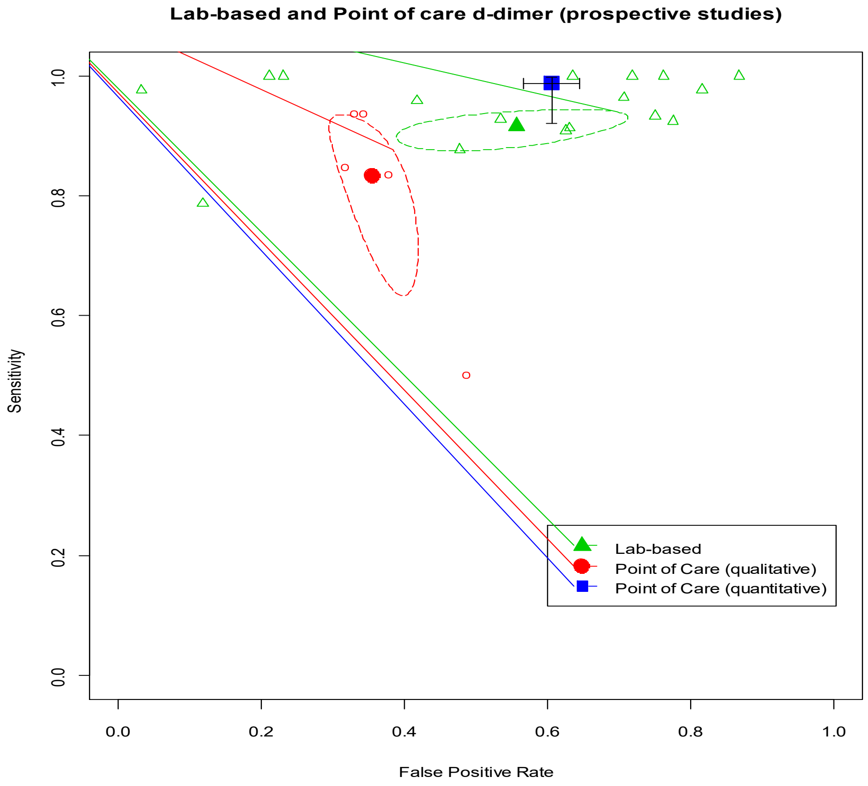
Figure 52: Likelihood ratios for point-of-care D-dimer tests (qualitative only) for pulmonary embolism (prospective studies



I^2 (Negative LR)=81.9%, I^2 (Positive LR)=69.7%

Figure 53: Subgroup analysis: sensitivity and specificity for laboratory-based and point-of-care based D-dimer tests for pulmonary embolism. Qualitative and quantitative point-of-care tests shown separately

Note that a single study reported a point-of-care quantitative test, and this plotted as a single blue square with confidence intervals indicated by error bars. 95% confidence intervals for lab-based and qualitative point-of-care tests are shown by dotted ellipses.



Appendix G – GRADE profiles

Age-adjusted vs unadjusted D-dimer tests for deep vein thrombosis

See above for the corresponding evidence statements for this section.

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Main analysis: Age-adjusted D-dimer (Figure 1 and Figure 2)										
3	Prospective diagnostic accuracy	620	0.91 (0.84, 0.96)	0.44 (0.31, 0.57)	LR+ 1.64 (1.25, 2.18)	Serious[4]	Not serious	Not serious[10]	Serious[5]	Low
					LR- 0.22 (0.08, 0.47)	Serious[4]	Not serious	Not serious[10]	Not serious	Moderate
Main analysis: Unadjusted D-dimer (Figure 3 and Figure 4)										
3	Prospective diagnostic accuracy	620	0.96 (0.89, 0.99)	0.27 (0.12, 0.49)	LR+ 1.35 (1.03, 1.93)	Serious[4]	Not serious	Not serious[10]	Not serious	Moderate
					LR- 0.22 (0.03, 0.79)	Serious[4]	Not serious	Not serious[10]	Serious[5]	Low
Subgroup analysis: Age-adjusted D-dimer (low risk only: according to 3-level Well's score)										
Gomez-Jabalera 2017	Prospective diagnostic accuracy	96	0.90 (0.33, 0.99)	0.39 (0.30, 0.50)	LR+ 1.48 (1.06, 2.07)	Serious[4]	Not serious	N/A	Serious[5]	Low
					LR- 0.26 (0.02, 3.6)	Serious[4]	Not serious	N/A	Very serious[8]	Very low
Subgroup analysis: unadjusted D-dimer (low risk only: according to 3-level Well's score)										
Gomez-Jabalera 2017	Prospective diagnostic accuracy	96	0.90 (0.33, 0.99)	0.24 (0.17, 0.34)	LR+ 1.19 (0.87, 1.63)	Serious[4]	Not serious	N/A	Very serious[8]	Very low
					LR- 0.41 (0.03, 5.87)	Serious[4]	Not serious	N/A	Very serious[8]	Very low
Subgroup analysis: Age-adjusted D-dimer (Moderate risk only: according to 3-level Well's score)										
Gomez-Jabalera 2017	Prospective diagnostic accuracy	29	0.95 (0.55, 0.99)	0.50 (0.30, 0.70)	LR+ 1.90 (1.21, 2.98)	Serious[4]	Not serious	N/A	Serious[5]	Low
					LR- 0.10 (0.01, 1.54)	Serious[4]	Not serious	N/A	Very serious[8]	Very low
Subgroup analysis: unadjusted D-dimer (Moderate risk only: according to 3-level Well's score)										
Gomez-Jabalera 2017	Prospective diagnostic accuracy	29	0.95 (0.53, 0.99)	0.31 (0.15, 0.53)	LR+ 1.38 (0.99, 1.89)	Serious[4]	Not serious	N/A	Serious[5]	Low
					LR- 0.16 (0.01, 2.59)	Serious[4]	Not serious	N/A	Very serious[8]	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

1. >33.3% of weighted data from studies at high risk of bias (Majority of studies were retrospective)
2. i-squared >33.3%
3. i-squared >66.7%
4. >33.3% of weighted data from studies at moderate or high risk of bias
5. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (1, 2) or (0.5,1)
6. i-squared >66.7%
7. >33.3% of weighted data from studies at high risk of bias
8. 95% confidence interval for likelihood ratio crosses both ends of a defined MID interval – (1, 2) or (0.5,1)
9. >33.3% of weighted data from studies were only partially applicable.
10. Although I^2 was greater than the specified limit, the committee were concerned with the relative difference between age-adjusted and unadjusted tests and this relative difference was homogenous between studies.

Age-adjusted vs unadjusted D-dimer tests for pulmonary embolism

See above for the corresponding evidence statements for this section.

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Age-adjusted D-dimer (Figure 6 and Figure 7)										
13	Retrospective diagnostic accuracy	48,324	0.96 (0.94, 0.97)	0.30 (0.19, 0.43)	LR+ 1.38 (1.20, 1.66)	Very serious[1]	Not serious	Not serious[2]	Not serious	Low
					LR- 0.14 (0.11, 0.18)	Very serious[1]	Not serious	Not serious[2]	Not serious	Low
Unadjusted D-dimer (Figure 8 and Figure 9)										
13	Retrospective diagnostic accuracy	48,379	0.98 (0.98, 0.99)	0.14 (0.08, 0.25)	LR+ 1.16 (1.07, 1.31)	Very serious[1]	Not serious	Not serious[2]	Not serious	Low
					LR- 0.12 (0.07, 0.21)	Very serious[1]	Not serious	Not serious[2]	Not serious	Low

1. >33.3% of weighted data from studies at high risk of bias (Majority of studies were retrospective)
2. Although I^2 was greater than the specified limits, the committee were concerned with the relative difference between age-adjusted and unadjusted tests and this relative difference was homogenous between studies and so the test was not downgraded for inconsistency.

Laboratory-based and point-of-care D-dimer tests for deep vein thrombosis

See above for the corresponding evidence statements for this section.

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Main analysis: laboratory-based D-dimer test (Figure 11 and Figure 12)										
53	Prospective diagnostic accuracy	10163	0.93 (0.91,0.94)	0.48 (0.43, 0.53)	LR+ 1.78 (1.62, 1.97)	Serious[4]	Not serious	Very serious[6]	Not serious	Very low
					LR- 0.16 (0.14, 0.19)	Serious[4]	Not serious	Serious[2]	Not serious	Low
Main analysis: point-of-care D-dimer test (qualitative, quantitative and semiquantitative) (Figure 13 and Figure 14)										
37	Prospective diagnostic accuracy	9811	0.88 (0.84,0.91)	0.63 (0.57, 0.69)	LR+ 2.38 (2.05, 2.79)	Not serious	Not serious	Very serious[6]	Not serious	Low
					LR- 0.19 (0.15, 0.24)	Not serious	Not serious	Very serious[6]	Not serious	Low
Age-adjusted quantitative point-of-care D-dimer test										
Oude 2015	Prospective diagnostic accuracy	275	0.98 (0.74, 0.99)	0.48 (0.42, 0.54)	LR+ 1.88 (1.65, 2.15)	Not serious	Not serious	N/A	Serious[5]	Moderate
					LR- 0.04 (0.00, 0.68)	Not serious	Not serious	N/A	Serious[5]	Moderate
Non age-adjusted quantitative point-of-care D-dimer test										
Oude 2015	Prospective diagnostic accuracy	275	0.98 (0.74, 0.99)	0.48 (0.42, 0.54)	LR+ 1.88 (1.65, 2.15)	Not serious	Not serious	N/A	Serious[5]	Moderate
					LR- 0.04 (0.00, 0.68)	Not serious	Not serious	N/A	Serious[5]	Moderate
Sensitivity analysis: laboratory-based D-dimer test excluding high risk of bias studies (Figure 16 and Figure 17)										
51	Prospective diagnostic accuracy	9,559	0.93 (0.91,0.94)	0.48 (0.43, 0.53)	LR+ 1.78 (1.62, 1.97)	Serious[4]	Not serious	Very serious[6]	Not serious	Very low
					LR- 0.15 (0.12, 0.19)	Serious[4]	Not serious	Serious[2]	Not serious	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Sensitivity analysis: point-of-care D-dimer test excluding high risk of bias studies (qualitative, quantitative and semiquantitative) (Figure 18 and Figure 19)										
36	Prospective diagnostic accuracy	9710	0.88 (0.84,0.90)	0.64 (0.58, 0.70)	LR+ 2.43 (2.09, 2.84)	Not serious	Not serious	Very serious[6]	Not serious	Low
					LR- 0.20 (0.15, 0.24)	Not serious	Not serious	Very serious[6]	Not serious	Low
Subgroup analysis: point-of-care D-dimer test (qualitative) (Figure 20 and Figure 21)										
26	Prospective diagnostic accuracy	7791	0.85 (0.81, 0.89)	0.69 (0.63, 0.74)	LR+ 2.75 (2.31, 3.28)	Serious[4]	Not serious	Very serious[6]	Not serious	Very low
					LR- 0.22 (0.16. 0.28)	Serious[4]	Not serious	Very serious[6]	Not serious	Very low
Subgroup analysis: point-of-care D-dimer test (quantitative) (Figure 22 and Figure 23)										
3	Prospective diagnostic accuracy	936	0.97 (0.94, 0.98)	0.47 (0.31, 0.64)	LR+ 1.88 (1.41, 2.65)	Not serious	Not serious	Very serious[6]	Serious[5]	Low
					LR- 0.07 (0.03, 0.15)	Not serious	Not serious	Not serious	Not serious	High
Subgroup analysis: Point-of-care D-dimer test (semiquantitative) (Figure 24 and Figure 25)										
9	Prospective diagnostic accuracy	1359	0.91 (0.88, 0.95)	0.48 (0.35, 0.62)	LR+ 1.79 (1.42, 2.35)	Not serious	Not serious	Very serious[6]	Serious[5]	Very Low
					LR- 0.18 (0.14, 0.24)	Not serious	Not serious	Not serious	Not serious	High
Subgroup analysis: point-of care-D-dimer test (Qualitative - Cancer subgroup only) (Figure 27 and Figure 28)										
3	Prospective diagnostic accuracy	384	0.92 (0.80, 0.97)	0.50 (0.43, 0.57)	LR+ 1.82 (1.56, 2.11)	Serious[4]	Not serious	Not serious	Serious[5]	Low
					LR- 0.15 (0.06, 0.39)	Serious[4]	Not serious	Serious[2]	Not serious	Low
Subgroup analysis: laboratory-based D-dimer test (low-moderate pretest probability only: according to 3-level Well's score) (Figure 32 and Figure 33)										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
4	Prospective diagnostic accuracy	855	0.88 (0.81, 0.93)	0.39 (0.26, 0.53)	LR+ 1.47 (1.13, 1.96)	Serious[4]	Not serious	Serious[2]	Not serious	Low
					LR- 0.33 (0.14, 0.66)	Serious[4]	Not serious	Not serious	Serious[5]	Low
Subgroup analysis: point-of-care D-dimer test (Qualitative- low/moderate pretest probability only: according to 3-level Well's score) (Figure 34 and Figure 35)										
6	Prospective diagnostic accuracy	2739	0.85 (0.77, 0.91)	0.73 (0.65, 0.81)	LR+ 3.20 (2.44, 4.20)	Serious[4]	Not serious	Very serious[8]	Not serious	Very low
					LR- 0.21 (0.14, 0.29)	Serious[4]	Not serious	Not serious	Not serious	Moderate
Subgroup analysis: laboratory-based D-dimer test (high pretest probability only: according to 3-level Well's score) (Figure 36 and Figure 37)										
2	Prospective diagnostic accuracy	142	0.92 (0.64, 0.99)	0.28 (0.15, 0.46)	LR+ 1.28 (0.80, 1.79)	Serious[4]	Not serious	Very serious[6]	Very serious[8]	Very low
					LR- 0.46 (0.03, 1.92)	Serious[4]	Not serious	Serious[2]	Very serious[8]	Very low
Subgroup analysis: point-of-care D-dimer test (Qualitative- high pretest probability only: according to 3-level Well's score) (Figure 38 and Figure 39)										
6	Prospective diagnostic accuracy	614	0.92 (0.84, 0.97)	0.55 (0.44, 0.66)	LR+ 2.08 (1.69, 2.61)	Serious[4]	Not serious	Not serious	Serious[5]	Low
					LR- 0.14 (0.07. 0.26)	Serious[4]	Not serious	Not serious	Not serious	Moderate

1. >33.3% of weighted data from studies at high risk of bias (Majority of studies were retrospective)
2. i-squared >33.3%
3. i-squared >66.7%
4. >33.3% of weighted data from studies at moderate or high risk of bias
5. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (1, 2) or (0.5,1)
6. i-squared >66.7%
7. >33.3% of weighted data from studies at high risk of bias
8. 95% confidence interval for likelihood ratio crosses both ends of a defined MID interval – (1, 2) or (0.5,1)
9. >33.3% of weighted data from studies were only partially applicable.

Laboratory-based and point-of-care D-dimer tests for pulmonary embolism

See above for the corresponding evidence statements for this section.

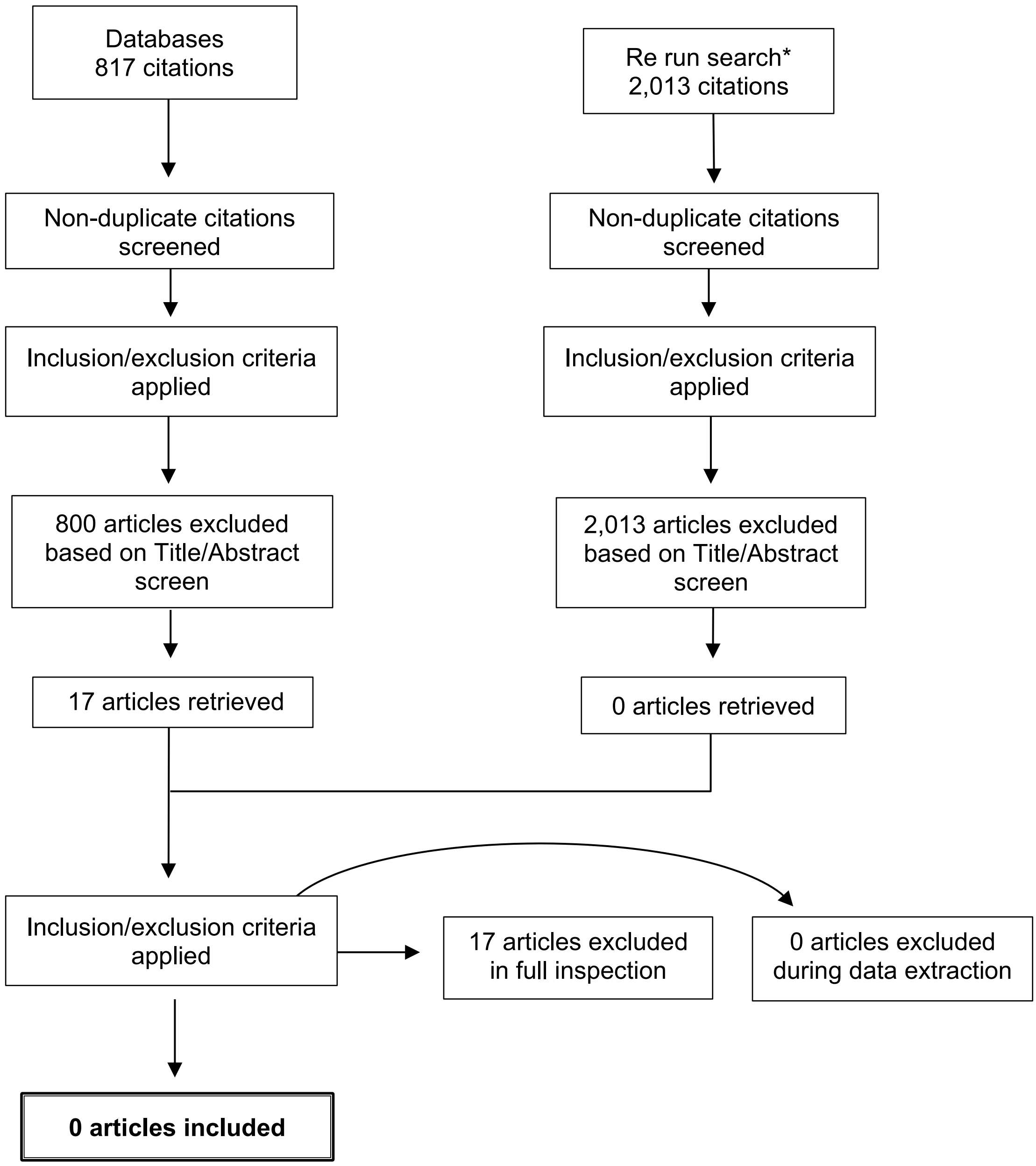
No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Main analysis: Laboratory-based D-dimer test (Figure 41 and Figure 42)										
19	Prospective diagnostic accuracy	2819	0.92 (0.88,0.94)	0.44 (0.32, 0.58)	LR+ 1.67 (1.36, 2.14)	Very serious[4]	Not serious	Very serious[3]	Serious[2]	Very low
					LR- 0.19 (0.14, 0.26)	Very serious[4]	Not serious	Not serious	Not serious	Low
Main analysis: Point-of-care D-dimer test (Figure 43 and Figure 44)										
6	Prospective diagnostic accuracy	2976	0.89 (0.73, 0.96)	0.60 (0.50, 0.69)	LR+ 2.21 (1.77, 2.76)	Serious[1]	Not serious	Very serious[3]	Serious[2]	Very low
					LR- 0.20 (0.07. 0.44)	Serious[1]	Not serious	Very serious[3]	Not serious	Very low
Sensitivity analysis excluding high risk-of-bias studies: Laboratory-based D-dimer test (Figure 46 and Figure 47)										
6	Prospective diagnostic accuracy	937	0.90 (0.83, 0.95)	0.44 (0.24, 0.66)	LR+ 1.68 (1.23, 2.53)	Serious[1]	Not serious	Very serious[3]	Serious[2]	Very low
					LR- 0.23 (0.15, 0.33)	Serious[1]	Not serious	Not serious	Not serious	Moderate
Sensitivity analysis excluding high risk-of-bias studies: point-of-care D-dimer test (Figure 48 and Figure 49)										
5	Prospective diagnostic accuracy	2378	0.90 (0.69, 0.97)	0.59 (0.47, 0.70)	LR+ 2.20 (1.66, 2.91)	Serious[1]	Not serious	Very serious[3]	Serious[2]	Very low
					LR_ 0.19 (0.05, 0.50)	Serious[1]	Not serious	Very serious[3]	Not serious	Very low
Subgroup analysis: Point of care D-dimer test (qualitative) (Figure 51 and Figure 52)										
5	Prospective diagnostic accuracy	2288	0.83 (0.68, 0.92)	0.65 (0.59, 0.69)	LR+ 2.35 (1.73, 2.96)	Serious[1]	Not serious	Very serious[3]	Serious[2]	Very low
					LR- 0.27 (0.11. 0.52)	Serious[1]	Not serious	Very serious[3]	Serious[2]	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Subgroup analysis: Point of care D-dimer test (quantitative)										
Gosselin 2012	Prospective diagnostic accuracy	1177	0.99 (0.92, 1.00)	0.40 (0.36, 0.43)	LR+ 1.63 (1.53, 1.75)	Serious[1]	Not serious	N/A	Not serious	Moderate
					LR- 0.03 (0.00, 0.21)	Serious[1]	Not serious	N/A	Not serious	Moderate
Subgroup analysis: laboratory-based D-dimer test (low pretest probability only: according to 3-level Well's score)										
Gupta (2009)	Prospective diagnostic accuracy	281	0.93 (0.42, 0.97)	0.25 (0.20, 0.31)	LR+ 1.24 (1.00, 1.54)	Very serious[4]	Not serious	N/A	Serious[2]	Very low
					LR- 0.28 (0.02, 4.1)	Very serious[4]	Not serious	N/A	Very serious[5]	Very low
Subgroup analysis: point of care D-dimer test (low pretest probability only: according to 3-level Well's score)										
Ginsberg 1998	Prospective diagnostic accuracy	703	0.79 (0.59, 0.91)	0.76 (0.73, 0.79)	LR+ 3.30 (2.58, 4.21)	Not serious	Not serious	N/A	Not serious	High
					LR- 0.27 (0.13, 0.60)	Not serious	Not serious	N/A	Serious[2]	Moderate
Subgroup analysis: laboratory-based D-dimer test (moderate pretest probability only: according to 3-level Well's score)										
Gupta (2009)	Prospective diagnostic accuracy	330	0.97 (0.68, 1.00)	0.33 (0.28, 0.38)	LR+ 1.45 (1.30, 1.62)	Very serious[4]	Not serious	N/A	Not serious	Low
					LR- 0.08 (0.01, 1.30)	Very serious[4]	Not serious	N/A	Very serious[5]	Very low
Subgroup analysis: point of care D-dimer test (moderate pretest probability only: according to 3-level Well's score)										
Ginsberg 1998	Prospective diagnostic accuracy	382	0.80 (0.71, 0.87)	0.52 (0.46, 0.57)	LR+ 1.66 (1.42, 1.93)	Not serious	Not serious	N/A	Not serious	High
					LR- 0.38 (0.26, 0.58)	Not serious	Not serious	N/A	Serious[2]	Moderate
Subgroup analysis: laboratory-based D-dimer test (high pretest probability only: according to 3-level Well's score)										
Gupta (2009)		16	0.80 (0.31, 0.97)	0.36 (0.41, 0.66)	LR+ 1.26 (0.67, 2.35)	Very serious[4]	Not serious	N/A	Very serious[5]	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
	Prospective diagnostic accuracy				LR- 0.55 (0.08, 3.75)	Very serious[4]	Not serious	N/A	Very serious[5]	Very low
Subgroup analysis: Point of care D-dimer test (high pretest probability only: according to 3-level Well's score)										
Ginsberg 1998	Prospective diagnostic accuracy	92	0.93 (0.84, 0.97)	0.45 (0.25, 0.66)	LR+ 1.69 (1.13, 2.53)	Not serious	Not serious	N/A	Serious[2]	Moderate
					LR- 0.15 (0.06, 0.41)	Not serious	Not serious	N/A	Not serious	High

1. >33.3% of weighted data from studies at moderate or high risk of bias
2. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (1, 2) or (0.5,1)
3. i-squared >66.7%
4. >33.3% of weighted data from studies at high risk of bias
5. 95% confidence interval for likelihood ratio crosses both ends of a defined MID interval – (1, 2) or (0.5,1)

Appendix H – Economic evidence study selection



**Combined search for all questions in the guideline*

Appendix I – Economic model

Background

This appendix describes the economic modelling for point-of-care versus laboratory D-dimer testing in both patients with suspected DVT and suspected PE.

For review questions on point-of-care versus laboratory D-dimer testing, the committee indicated that, alongside testing accuracy data, recommendation making would be facilitated by information on absolute numbers of patients with each testing outcome (i.e. true positives, false negatives, true negatives, and false positives), as well as estimates of costs involved in the testing process. To provide this information, a simple cost-consequences analysis was developed, comparing outcomes for point-of-care and laboratory D-dimer tests in people with suspected DVT and people with suspected PE.

A full cost-utility analysis was felt to be inappropriate for these review questions, as cost effectiveness is likely to be heavily dependent on the long-term health outcomes and costs associated with false negative results (patients who have a VTE, but are incorrectly diagnosed). Since randomised evidence of sufficient quality on the consequences of an intentionally untreated VTE is unlikely to exist, such an analysis would not be feasible without substantial speculation on the downstream outcomes for these patients.

Methods

Population

People with suspected VTE (DVT or PE), who have an unlikely two-level Wells score.

Comparators

The model compares point-of-care D-dimer with laboratory D-dimer, for populations with suspected DVT and PE separately.

For patients with suspected DVT, data were also available on quantitative, semi-quantitative, and qualitative point-of-care tests separately, so sub-analyses were also conducted for each of these compared to laboratory D-dimer. For suspected PE, no data were available for semi-quantitative point-of-care tests but separate sub-analyses were conducted for quantitative and qualitative tests.

Perspective, time horizon, and discount rate

This evaluation is conducted from the perspective of the NHS/PSS. The time horizon only considers short-term costs and outcomes (<48 hours). As the time horizon is less than a year, no discounting of costs or health outcomes is applied.

Model structure

The model takes the form of a simple decision tree, which calculates the numbers of true positive, false negative, true negative, and false positive test results for a cohort of 1,000 patients, based on the underlying prevalence of VTE, and the diagnostic accuracy of tests. This structure is shown in Figure 54.

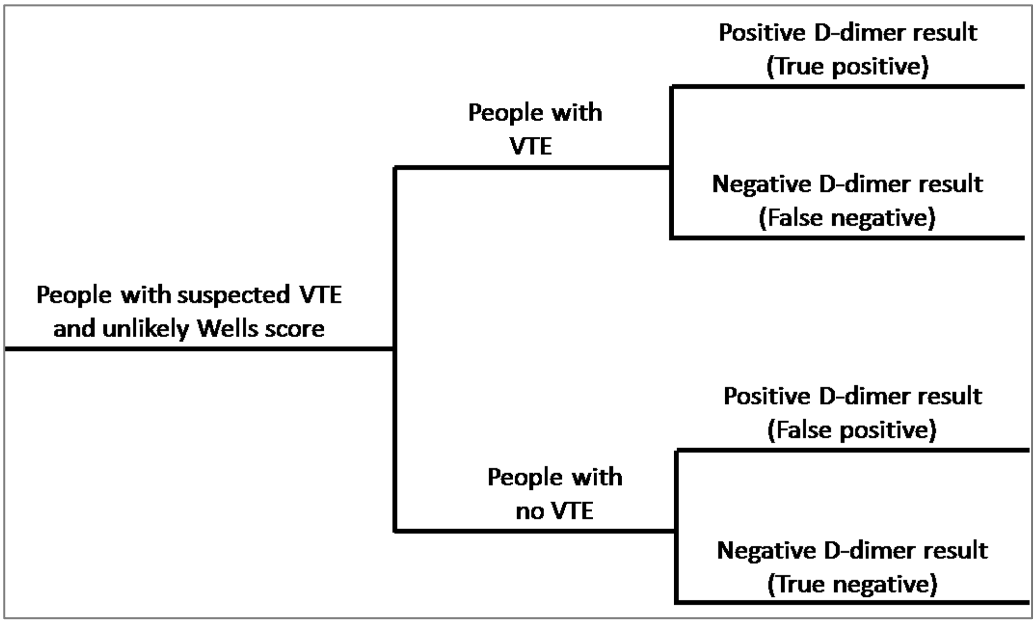


Figure 54 – Decision tree structure

Model inputs

Probabilities

Probability inputs (relating to prevalence of VTE and test accuracies) are shown in Table 17.

The prevalence of DVT in patients with an unlikely Wells score (≤1) was calculated from Geersing et al. (2014), a meta-analysis of Wells score outcomes in outpatients with suspected DVT. To do this, the prevalence of DVT reported for each Wells score (ranging from -2 to 1) was weighted by the number of patients in the analysis with that score. This provided a prevalence of 8.3%.

The prevalence of PE in patients with an unlikely Wells score (≤4) was calculated based on a study that reported an overall prevalence of PE (12.3%) among 941 consecutive patients with suspected PE (Goekoop et al., 2007) and data on the accuracy of the two-level Wells score for PE. This was achieved by calculating the proportion of test results which are false negatives and true negatives and, from this, the proportion of all negative results which are false negatives. This provided a prevalence of 5.7%.

Sensitivities and specificities of D-dimer tests were taken directly from the results of the clinical review.

Table 17 – Probability input parameters

Parameter	Point estimate (95% CIs)	Distribution in PSA	Source
Suspected DVT			
Prevalence of DVT in people with Wells score of -2	3.5% (2.3% to 4.7%)	Beta	Geersing (2014)
Prevalence of DVT in people with Wells score of -1	5.4% (4.2% to 6.6%)	Beta	Geersing (2014)
Prevalence of DVT in people with Wells score of 0	8.1% (6.9% to 9.3%)	Beta	Geersing (2014)
Prevalence of DVT in people with Wells score of 1	13.3% (11.8% to 14.8%)	Beta	Geersing (2014)
Overall prevalence of DVT in people with unlikely Wells score	8.3%	-	Calculated
Sensitivity of point-of-care test - combined	88.0% (84.0% to 91.0%)	Beta	Clinical evidence review
Specificity of point-of-care test - combined	63.0% (57.0% to 69.0%)	Beta	Clinical evidence review
Sensitivity of point-of-care test - quantitative	97.0% (94.0% to 98.0%)	Beta	Clinical evidence review
Specificity of point-of-care test - quantitative	47.0% (31.0% to 64.0%)	Beta	Clinical evidence review
Sensitivity of point-of-care test – semi-quantitative	91.0% (88.0% to 95.0%)	Beta	Clinical evidence review
Specificity of point-of-care test – semi-quantitative	48.0% (35.0% to 62.0%)	Beta	Clinical evidence review

Parameter	Point estimate (95% CIs)	Distribution in PSA	Source
Sensitivity of point-of-care test - qualitative	85.0% (81.0% to 89.0%)	Beta	Clinical evidence review
Specificity of point-of-care test - qualitative	69.0% (63.0% to 74.0%)	Beta	Clinical evidence review
Sensitivity of laboratory test	92.0% (91.0% to 94.0%)	Beta	Clinical evidence review
Specificity of laboratory test	47.0% (42.0% to 52.0%)	Beta	Clinical evidence review
Suspected PE			
Prevalence of PE in people with suspected PE	12.3% (10.2% to 14.5%)		Goekoop (2007)
Sensitivity of Wells PE score	65.0% (59.0% to 72.0%)	Beta	Posadas-Martínez (2014)
Specificity of Wells PE score	81.0% (77.0% to 85.0%)	Beta	Posadas-Martínez (2014)
Overall prevalence of PE in people with unlikely Wells score	5.7%	-	Calculated
Sensitivity of point-of-care test - combined	89.0% (73.0% to 96.0%)	Beta	Clinical evidence review
Specificity of point-of-care test - combined	60.0% (50.0% to 69.0%)	Beta	Clinical evidence review
Sensitivity of point-of-care test - quantitative	99.0% (92.0% to 100.0%)	Beta	Clinical evidence review
Specificity of point-of-care test - quantitative	40.0% (36.0% to 43.0%)	Beta	Clinical evidence review
Sensitivity of point-of-care test – qualitative	83.0% (68.0% to 92.0%)	Beta	Clinical evidence review
Specificity of point-of-care test – qualitative	65.0% (59.0% to 69.0%)	Beta	Clinical evidence review
Sensitivity of lab test	92.0% (88.0% to 94.0%)	Beta	Clinical evidence review
Specificity of lab test	44.0% (32.0% to 58.0%)	Beta	Clinical evidence review

Costs

All costs used in the model are shown in Table 18. Costs of point-of-care tests were taken from the NHS Supply Chain Catalogue. A simple mean of these costs was used in the model base case. For sub-analyses by type of point-of-care test, individual tests were classified according to whether they were quantitative or qualitative, and a mean of each category was taken. None of the included tests could be identified as semi-quantitative, so the overall mean of all tests was used as a proxy.

Costs of laboratory D-dimer tests could not be identified in the literature or from standard NHS costing sources, since these values tend to vary regionally depending on the local laboratory service used. Therefore, costs were obtained from the committee, and a mean was taken of these values.

The model also considered costs of further testing for VTE. Patients with suspected DVT who had a positive D-dimer test result (either true positive or false positive) incurred the cost of a vascular ultrasound scan (NHS Reference Costs 2017/18). For people with suspected PE who had a positive D-dimer test, the committee indicated that around 80% would receive a computed tomography pulmonary angiogram (CTPA), and 20% would receive a lung ventilation or perfusion scan (unit costs both taken from NHS Reference Costs 2017/18).

The committee indicated that one of the key advantages of point-of-care testing is that it provides a much quicker result in settings where laboratory testing is not available on-site (typically around 30 minutes compared to around 24 hours). Therefore, a scenario analysis was conducted in order to capture the additional costs associated with laboratory testing in a primary care setting. The assumption was made that all patients would incur the cost of a GP visit (PSSRU Unit Costs of Health and Social Care, 2018), regardless of the type of test. Additionally, all patients tested with laboratory D-dimer incurred the cost of a single dose of low-molecular-weight heparin as interim treatment while awaiting results (NHS Drug Tariff, November 2019) whereas for point-of-care testing, it was assumed only patients with a positive D-dimer result would receive interim treatment while awaiting ultrasound. Finally, for the laboratory D-dimer strategy, it was assumed an additional 10 minutes of GP (general medical services) time would be required for positive test results in order to arrange further testing (PSSRU Unit Costs of Health and Social Care, 2018). This cost was not applied to patients undergoing point-of-care testing, as the assumption was made that arrangements for further tests would be made within a single visit.

Table 18 – Cost input parameters

Parameter	Point estimate (95% CIs)	Distribution in PSA	Source
Costs of D-dimer tests			
Alere Triage (5 pack) - quantitative	£29.22	-	NHS Supply Chain Catalogue
Alere Triage (25 pack) - quantitative	£12.63	-	NHS Supply Chain Catalogue
Roche Cobas (2 pack) - quantitative	£27.37	-	NHS Supply Chain Catalogue
Roche Cobas (10 pack) - quantitative	£9.44	-	NHS Supply Chain Catalogue
Ciga Suresign (10 pack) - qualitative	£8.81	-	NHS Supply Chain Catalogue
Siemens dil pak (5 pack) - qualitative	£6.48	-	NHS Supply Chain Catalogue
Chirus StatusFirst (20 pack) - qualitative	£10.04	-	NHS Supply Chain Catalogue
Mean point-of-care test cost - all	£14.86 (£7.91 to £21.80)	Gamma	Calculated
Mean point-of-care test cost - quantitative	£19.67 (£9.79 to £29.54)	Gamma	Calculated
Mean point-of-care test cost - qualitative	£8.44 (£6.40 to £10.49)	Gamma	Calculated
Cost of laboratory test	£6.79 (£2.44 to £11.13)	Gamma	Committee assumption

Parameter	Point estimate (95% CIs)	Distribution in PSA	Source
Costs of imaging for patients with a positive D-dimer result			
Computed tomography pulmonary angiogram (CTPA)	£106.12	-	NHS Reference Costs 2017/18 - Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over
Lung ventilation or perfusion (V/Q) scan	£311.07	-	NHS Reference Costs 2017/18- Lung Ventilation or Perfusion Scan, 19 years and over
Proportion of patients who receive a lung V/Q scan versus CTPA	20%/80%	-	Committee assumption
Weighted average cost (CTPA and V/Q scan)	£147.11	-	Calculated
Vascular ultrasound scan	£66.36	-	NHS Reference Costs 2017/18 - Vascular ultrasound scan
Primary care costs			
Initial GP visit	£37.00	-	PSSRU Unit Costs of Health and Social Care 2018
GP time to arrange imaging for positive result (laboratory D-dimer)	£25.00	-	PSSRU Unit Costs of Health and Social Care 2018 - 10 minutes of GP GMS activity
Interim LMWH dose (laboratory D-dimer)	£8.79	-	NHS Drug Tariff November 2019 - Enoxaparin sodium 120mg/0.8ml solution for injection pre-filled syringe

PSA = probabilistic sensitivity analysis

Uncertainty

Uncertainty in model results was explored via probabilistic sensitivity analysis. Model input parameters were assigned probability distributions reflecting uncertainty surrounding point estimates, defined by standard error/confidence intervals and type of parameter. A random value was drawn from each of these distributions for 1,000 iterations and, for each of these, model results were recorded for each testing strategy. This process allowed uncertainty in results to be expressed as 95% credible intervals.

The particular distribution assigned to each type of model parameter was chosen to reflect the nature of the data. Probabilities were parameterised using a beta distribution, as these values must lie between 0 and 1. Unit costs were given a gamma distribution, as these values are bound at 0, but theoretically have no upper limit.

Results

People with suspected deep vein thrombosis

Testing outcomes for people with suspected DVT comparing all types of point-of-care test to laboratory testing are shown in Table 19. These results show that, overall, point-of care testing results in a small increase in false negative results (4 per 1,000 people) and a large reduction in false positive results (138 per 1,000). Both of these results are statistically significant at the 5% level (95% credible intervals for incremental results do not cross 0). For qualitative point-of-care tests alone, this difference widens further; point-of-care testing produces 7 more false negative results and 193 fewer false positive results than laboratory testing. For semi-quantitative point-of-care tests alone, there is no statistically significant difference in the number of false negative of false positive results compared to laboratory testing. Quantitative point-of-care testing is the only strategy that produces a statistically significant reduction in false negative results compared to laboratory testing but also results in a non-statistically significant increase in false positive results (9 per 1,000 people).

Table 19 – Testing outcomes for people with suspected deep vein thrombosis

	Absolute results					Incremental results versus laboratory D-dimer			
Testing outcomes	Overall POC	Quantitative POC	Semi-quantitative POC	Qualitative POC	Lab test[(a)]	Overall POC (95% CrIs)	Quantitative POC (95% CrIs)	Semi-quantitative POC (95% CrIs)	Qualitative POC (95% CrIs)
True positive	73	81	76	71	77	-4 (-7 to -1)	3 (1 to 5)	-2 (-5 to 1)	-7 (-11 to -3)
False negative	10	2	7	12	6	4 (1 to 7)	-3 (-5 to -1)	2 (-1 to 5)	7 (3 to 11)
True negative	578	431	440	633	440	138 (66 to 207)	-9 (-163 to 151)	0 (-131 to 131)	193 (122 to 260)
False positive	339	486	477	284	477	-138 (-207 to -66)	9 (-151 to 163)	0 (-131 to 131)	-193 (-260 to -122)

(a) Testing outcomes sum to >1000 due to rounding

Cost outcomes for people with suspected DVT are shown in Table 20. Point-of-care D-dimer tests are more expensive than laboratory tests. When all types of point-of-care tests (overall POC) are included in the analysis, the higher D-dimer testing costs are offset by the reduction in false positive results, which reduces the cost of further imaging tests. Excluding primary care costs, the total costs of the point-of-care testing and laboratory testing strategies are similar (£42,225 versus £43,556). When primary care costs are included, this results in overall cost savings for the point-of-care strategy.

In contrast, the results for quantitative point-of-care testing show that when primary care costs are excluded, the point-of-care testing and laboratory testing strategies have similar imaging costs because they produce similar numbers of false positive results but the point-of-care strategy is more expensive due to the higher acquisition cost of point-of-care D-dimer tests. However, when taking primary care costs into account, the point-of-care testing reduces the amount of GP time and the need for interim anticoagulation and becomes cost saving (although there is a high degree of uncertainty around this result).

Table 20 – Cost outcomes for people with suspected deep vein thrombosis

	Absolute results					Incremental results versus laboratory D-dimer			
Cost category	**Overall POC**	**Quantitative POC**	**Semi-quantitative POC**	**Qualitative POC**	**Lab test**	**Overall POC (95% CrIs)**	**Quantitative POC (95% CrIs)**	**Semi-quantitative POC (95% CrIs)**	**Qualitative POC (95% CrIs)**
D-dimer test	£14,856	£19,665	£14,856	£8,443	£6,785	£8,071 (£32 to £16,868)	£12,880 (£3,264 to £24,565)	£8,071 (£120 to £16,790)	£1,658 (-£3,807 to £5,969)
Imaging	£27,369	£37,600	£36,661	£23,553	£36,771	-£9,402 (-£14,152 to -£4,580)	£829 (-£9,764 to £11,057)	-£110 (-£8,744 to £8,593)	-£13,218 (-£17,715 to -£8,519)
Total without primary care costs	**£42,225**	**£57,265**	**£51,516**	**£31,997**	**£43,556**	**-£1,331 (-£10,777 to £8,721)**	**£13,709 (-£864 to £29,418)**	**£7,960 (-£3,772 to £20,140)**	**-£11,559 (-£18,596 to -£5,085)**
Primary care costs	£40,625	£41,981	£41,856	£40,120	£59,460	-£18,835 (-£20,064 to -£17,594)	-£17,480 (-£19,209 to -£15,746)	-£17,604 (-£19,181 to -£16,027)	-£19,340 (-£20,552 to -£18,102)
Total with primary care costs	**£82,850**	**£99,246**	**£93,372**	**£72,117**	**£103,016**	**-£20,166 (-£30,296 to -£9,527)**	**-£3,770 (-£19,706 to £12,951)**	**-£9,644 (-£22,402 to £3,627)**	**-£30,900 (-£38,712 to -£23,489)**

People with suspected pulmonary embolism

Test outcomes for patients with suspected PE are shown in Table 21. These results show that overall, using a point-of-care test results in 2 more false negative results but 151 fewer false positive results per 1,000 patients, although neither of these results is statistically significant at the 5% level. If test accuracy data for only quantitative point-of-care tests is used, this results in 4 fewer false negatives and 38 more false positives compared to laboratory testing (also not statistically significant).

Table 21 – Testing outcomes for people with suspected pulmonary embolism

Testing outcomes	Absolute results				Incremental results – POC versus laboratory (95% CrIs)		
	Overall POC	Quantitative POC[(a)]	Qualitative POC	Lab test[(a)]	Overall POC	Quantitative POC	Qualitative POC
True positive	51	57	47	53	-2 (-10 to 4)	4 (0 to 7)	-5 (-13 to 1)
False negative	6	1	10	5	2 (-4 to 10)	-4 (-7 to 0)	5 (-1 to 13)
True negative	566	377	613	415	151 (-6 to 296)	-38 (-168 to 90)	198 (66 to 326)
False positive	377	566	330	528	-151 (-296 to 6)	38 (-90 to 168)	-198 (-326 to -66)

(a) *Testing outcomes sum to >1000 due to rounding*

Cost outcomes for people with suspected PE are shown in Table 22. These results indicate that despite a higher acquisition cost for point-of-care tests, the reduction in false positive results means that the overall point-of care testing strategy is less costly than laboratory testing (£77,819 versus £92,193) but there is a high degree of uncertainty around this result. When primary care costs are included in the analysis, this further increases the difference in total costs between the two strategies and there is greater certainty that the overall point-of-care testing strategy is cost saving.

In the analysis of quantitative point-of-care tests only, results show that when primary care costs are excluded, the point-of-care testing strategy is more costly than laboratory testing because of the higher acquisition cost of the tests and the higher number of false positives results requiring further imaging. However, when primary care costs are included, the total costs between the point-of-care testing and laboratory testing strategies is similar.

Table 22 – Cost outcomes for people with suspected pulmonary embolism

Cost category	Absolute results				Incremental results – POC versus laboratory (95% CrIs)		
	Overall POC	Quantitative POC	Qualitative POC	Lab test	Overall POC	Quantitative POC	Qualitative POC
D-dimer test	£14,856	£19,665	£8,443	£6,785	£8,071 (£266 to £16,879)	£12,880 (£2,965 to £24,471)	£1,658 (-£3,717 to £5,839)
Imaging	£62,963	£91,544	£55,523	£85,408	-£22,445 (-£43,820 to £710)	£6,137 (-£12,722 to £25,262)	-£29,884 (-£48,691 to -£10,514)
Total without primary care costs	**£77,819**	**£111,209**	**£63,967**	**£92,193**	**-£14,374 (-£37,279 to £10,115)**	**£19,017 (-£2,189 to £41,566)**	**-£28,226 (-£47,727 to -£8,115)**
Primary care costs	£40,762	£42,470	£40,318	£60,113	-£19,351 (-£22,360 to -£16,052)	-£17,643 (-£20,665 to -£14,520)	-£19,795 (-£22,729 to -£16,714)

Cost category	Absolute results				Incremental results – POC versus laboratory (95% CrIs)		
	Overall POC	Quantitative POC	Qualitative POC	Lab test	Overall POC	Quantitative POC	Qualitative POC
Total with primary care costs	£118,581	£153,679	£104,284	£152,305	-£33,725 (-£59,124 to -£6,331)	£1,374 (-£22,667 to £26,316)	-£48,021 (-£70,243 to -£25,043)

Discussion

For people with suspected DVT and suspected PE, the cost-consequences analysis shows that overall point-of-care D-dimer testing produces substantially fewer false positive results compared to laboratory testing, at the expense of a small absolute increase in the number of false negative results. If the detrimental effects of these two events were weighted equally, point-of-care testing would be the superior strategy, considering that it also results in substantial cost savings in a primary care setting. However, this is unlikely to be the case; false negative test results cause a delay in diagnosis and treatment of people with a VTE, which could result in serious detrimental health effects (including death) and substantial downstream costs, for example if a person with an untreated DVT develops a PE and requires emergency medical care. Contrastingly, false positive results mean that patients without a VTE would undergo unnecessary imaging. While this produces additional costs, patient anxiety, and (in the case of PE testing) exposure to radiation, these outcomes are clearly not as serious as those of a false negative result.

A full cost-utility analysis would quantify all downstream cost and QALYs for each testing outcome in order to explicitly weigh up the trade-off between sensitivity and specificity in point-of-care tests. However, as previously discussed, conducting such an analysis would be impractical, as high-quality evidence on the costs and outcomes for patients with a false negative D-dimer test result is unlikely to exist. Therefore, the weighting of the trade-off between false negatives and false positives must fall to the experience of the committee, to be considered alongside cost outcomes.

In discussing the results of the diagnostic test accuracy evidence review, the committee prioritised sensitivity over specificity because they were concerned with the potential for any test to increase false negative rates and noted that quantitative point-of-care tests had higher sensitivity (but lower specificity) compared to qualitative and semi-quantitative point-of-care tests. The cost-consequences analysis shows how this trade-off between sensitivity and specificity translates into expected numbers of false negative and false positive results for different types of point-of-care tests versus laboratory testing. Point-of-care D-dimer tests are more expensive than laboratory testing. For both suspected DVT and suspected PE, quantitative point-of-care tests also produce more false positive results than laboratory testing, which means more people will receive further imaging tests and incur more costs. Therefore, where laboratory testing is immediately available, the small reduction in false negative results associated with quantitative point-of-care testing may not outweigh the additional testing costs due to the increase in false positive results. However, in primary care settings where laboratory facilities are often not immediately available, point-of-care tests can provide more rapid results and reduce the need for additional GP time and unnecessary interim anticoagulation treatment while awaiting D-dimer test results. When these cost offsets in primary care are taken into account, the difference in total costs between quantitative point-of-care testing and laboratory testing is much reduced. In the case of suspected DVT, the analysis suggests that using quantitative point-of-care testing where laboratory facilities are not immediately available may even be cost saving but this finding was associated with a high degree of uncertainty.

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Appendix J - Excluded studies

Clinical studies (main search)

Author (year)	Title	Reason for exclusion
Abcarian (2004)	Role of a quantitative D-dimer assay in determining the need for CT angiography of acute pulmonary embolism	• Not a relevant study design (retrospective study)
Adams (2014)	Clinical utility of an age-adjusted D-dimer in the diagnosis of venous thromboembolism	• Conference abstract
Alexander (2016)	A systematic review of biomarkers for the prediction of thromboembolism in lung cancer - Results, practical issues and proposed strategies for future risk prediction models	• Not possible to calculate a 2x2 table from data presented in the study
Antovic (2012)	Comparison of five point-of-care D-dimer assays with the standard laboratory method	• Reference standard was not done to all participants
Bai (2017)	Clinical application of the Innovance D-dimer assay in the diagnosis of acute pulmonary thromboembolism	• Study looking for optimal thresholds
Bounameaux (1991)	Measurement of D-dimer in plasma as diagnostic aid in suspected pulmonary embolism	• Participants received different reference standards
Broen (2016)	Predicting the need for further thrombosis diagnostics in suspected DVT is increased by using age adjusted D-dimer values	• Participants received different reference standards Patients with elevated D-dimer received a second ultrasound a week after a first negative ultrasound (negative D-dimer participants received one ultrasound).
Brotman (2003)	Limitations of D-dimer testing in unselected inpatients with suspected venous thromboembolism	• Data was not reported separately for DVT and PE
Brown (2002)	The accuracy of the enzyme-linked immunosorbent assay D-dimer test in the diagnosis of pulmonary embolism: a meta-analysis	• More recent systematic review included that covers the same topic
Brown (2003)	Turbidimetric D-dimer test in the diagnosis of pulmonary embolism: a metaanalysis	• Systematic review used as a source of individual studies
Bucek (2001)	Results of a new rapid d-dimer assay (cardiac d-dimer) in the diagnosis of deep vein thrombosis	• Study contained within systematic review
Chunilal (2002)	The sensitivity and specificity of a red blood cell agglutination D-dimer assay for venous thromboembolism when performed on venous blood	• Data was not reported separately for DVT and PE

Author (year)	Title	Reason for exclusion
Cini (2014)	D-dimer use for deep venous thrombosis exclusion in elderly patients: a comparative analysis of three different approaches to establish cut-off values for an assay with results expressed in D-dimer units	• Reference standard repeated in a selective sample
Courtney (2010)	Prospective diagnostic accuracy assessment of the HemosIL HS D-dimer to exclude pulmonary embolism in emergency department patients	• Data was not reported separately for DVT and PE
Crawford (2016)	D-dimer test for excluding the diagnosis of pulmonary embolism	• Systematic review used as a source of individual studies
Crop (2014)	Influence of C-reactive protein levels and age on the value of D-dimer in diagnosing pulmonary embolism	• Reference standard was not done to all participants
Dempfle (2001)	Multicentre evaluation of a new point-of-care test for the quantitative determination of D-dimer	• Not possible to calculate a 2x2 table from data presented in the study
Der (2010)	Accuracy of D-Dimers to Rule Out Venous Thromboembolism Events across Age Categories	• Not possible to calculate a 2x2 table from data presented in the study Not possible to get a 2 x 2 table specifically for DVT
Di Nisio (2007)	Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review	• Not possible to identify relevant individual studies in the systematic review
Duet (1998)	A new quantitative D-dimer assay appropriate in emergency: reliability of the assay for pulmonary embolism exclusion diagnosis	• Participants received different reference standards
Eng (2009)	Exclusion of acute pulmonary embolism: computed tomography pulmonary angiogram or D-dimer?	• Not a relevant study design (retrospective study)
Farm (2018)	Age-adjusted D-dimer cut-off leads to more efficient diagnosis of venous thromboembolism in the emergency department: a comparison of four assays	• Reference standard was not done to all participants
Farrell (2000)	A negative SimpliRED D-dimer assay result does not exclude the diagnosis of deep vein thrombosis or pulmonary embolus in emergency department patients	• At-risk of VTE but without suspected VTE
Firdous (2013)	Comparison of non-invasive diagnostic tests to multi-detector CT pulmonary angiography for the diagnosis of pulmonary embolism	• Participants with Wells score <2 were excluded
Froehling (2004)	Sensitivity and specificity of the semiquantitative latex agglutination D-dimer assay for the diagnosis of acute pulmonary	• Not a relevant study design (retrospective study)

Author (year)	Title	Reason for exclusion
	embolism as defined by computed tomographic angiography	
Froehling (2007)	Evaluation of a quantitative D-dimer latex immunoassay for acute pulmonary embolism diagnosed by computed tomographic angiography	• Not a relevant study design (retrospective study)
Fuchs (2016)	Age-Adjusted Cutoff D-Dimer Level to Rule Out Acute Pulmonary Embolism: A Validation Cohort Study	• Study does not contain any relevant index tests Participants were only imaged if D-dimer level was >500ug/L
Fukuda (2007)	A rapid and quantitative D-Dimer assay in whole blood and plasma on the point-of-care PATHFAST analyzer.	• Study looking for optimal thresholds
Geersing (2009)	Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic meta-analysis	• Systematic review used as a source of individual studies
Gerotziafas (2016)	Rapid detection of D-Dimers with mLabs whole blood method for venous thromboembolism exclusion. Comparison with Vidas D-Dimers assay	• Data was not reported separately for DVT and PE
Ghanima (2007)	Validation of a new D-dimer microparticle enzyme immunoassay (AxSYM D-Dimer) in patients with suspected pulmonary embolism (PE)	• Reference standard was not done to all participants
Ghys (2008)	Diagnostic accuracy of the Triage D-dimer test for exclusion of venous thromboembolism in outpatients	• Not a relevant study design (retrospective study)
Gosselin (2002)	Evaluation of a new automated quantitative d-dimer, Advanced D-Dimer, in patients suspected of venous thromboembolism	• Participants received different reference standards
Hajsadeghi (2012)	Accuracy of D-dimer: fibrinogen ratio to diagnose pulmonary thromboembolism in patients admitted to intensive care units	• Study looking for optimal thresholds
Han (2015)	The performance of age-adjusted D-dimer cut-off in Chinese outpatients with suspected venous thromboembolism	• Data was not reported separately for DVT and PE
Harrison (1993)	Plasma D-dimer: a useful tool for evaluating suspected pulmonary embolus.[Erratum appears in J Nucl Med 1993 Sep;34(9):1409]	• Reference standard was not done to all participants
Heit (1999)	Determinants of plasma fibrin D-dimer sensitivity for acute pulmonary embolism as defined by pulmonary angiography	• Study looking for optimal thresholds
Hogg (2005)	The emergency department utility of Simplify D-dimer to exclude pulmonary embolism in patients with pleuritic chest pain	• Reference standard was not done to all participants
Jaconelli (2015)	Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 2: Should we use an age adjusted D-dimer threshold in managing	• Systematic review used as a source of individual studies

Author (year)	Title	Reason for exclusion
	low risk patients with suspected pulmonary embolism?	
Johanning (2002)	D-dimer and calf circumference in the evaluation of outpatient deep venous thrombosis	• Study contained within systematic review
Kabrhel (2009)	Potential impact of adjusting the threshold of the quantitative D-dimer based on pretest probability of acute pulmonary embolism	• Participants received different reference standards
Keeling (1999)	D-dimer for the exclusion of venous thromboembolism: comparison of a new automated latex particle immunoassay (MDA D-dimer) with an established enzyme-linked fluorescent assay (VIDAS D-dimer)	• Participants received different reference standards
Kline (2006)	Prospective study of the diagnostic accuracy of the simplify D-dimer assay for pulmonary embolism in emergency department patients	• Reference standard was not done to all participants
Kollef (2000)	Predictive value of a rapid semiquantitative D-dimer assay in critically ill patients with suspected venous thromboembolic disease	• Data was not reported separately for DVT and PE
Legnani (2010)	Multicenter evaluation of a new quantitative highly sensitive D-dimer assay, the Hemosil D-dimer HS 500, in patients with clinically suspected venous thromboembolism	• Reference standard was not done to all participants
Legnani (2017)	Diagnostic Accuracy of a New d-Dimer Assay (Sclavo Auto d-Dimer) for Exclusion of Deep Vein Thrombosis in Symptomatic Outpatients	• Reference standard repeated in a selective sample
Lippi (2012)	Analytical performance of the new ACL AcuStar HemosIL D-Dimer	• Study looking for optimal thresholds
Ma (2016)	Competitive assessments of pulmonary embolism: Non-invasiveness versus the golden standard	• Review article but not a systematic review
Mac (2001)	Diagnostic accuracy of triage tests to exclude pulmonary embolism	• Participants received different reference standards
Masotti (2008)	Potential applicability of the D-dimer assay in elderly patients with suspected venous thromboembolism: importance of the sensitivity and specificity of the methods	• Review article but not a systematic review
Masuda (2015)	D-dimer screening for deep venous thrombosis in traumatic cervical spinal injuries	• Study looking for optimal thresholds
Matsuo (2016)	Evaluation of D-Dimer in Screening Deep Vein Thrombosis in Hospitalized Japanese Patients with Acute Medical Diseases/Episodes	• Does not contain a population of people with suspected DVT and/or PE
Meyer (1998)	Diagnostic value of two rapid and individual D-dimer assays in patients with clinically suspected pulmonary embolism: comparison with microplate enzyme-linked immunosorbent assay	• Participants received different reference standards

Author (year)	Title	Reason for exclusion
Michiels (2005)	Screening for deep vein thrombosis and pulmonary embolism in outpatients with suspected DVT or PE by the sequential use of clinical score: a sensitive quantitative D-dimer test and non-invasive diagnostic tools	• Review article but not a systematic review
Mohsin (2004)	Value of D-dimers assay in diagnosis of pulmonary embolism	• Does not contain a population of people with suspected DVT and/or PE Participants must be suspected of PE and have two of the following: Diagnosis of DVT Imaging suggestive of PE Predisposing factor(s) for DVT/PE
Mountain (2007)	The VIDAS D-dimer test for venous thromboembolism: a prospective surveillance study shows maintenance of sensitivity and specificity when used in normal clinical practice	• Data was not reported separately for DVT and PE
Mullier (2014)	Comparison of five D-dimer reagents and application of an age-adjusted cut-off for the diagnosis of venous thromboembolism in emergency department	• Data was not reported separately for DVT and PE
Nazerian (2017)	Diagnostic Performance of Wells Score Combined With Point-of-care Lung and Venous Ultrasound in Suspected Pulmonary Embolism	• Index test was not done to all participants
Ortiz (2017)	Age-Adjusted D-Dimer in the Prediction of Pulmonary Embolism: Does a Normal Age-Adjusted D-Dimer Rule Out PE?	• Data on age-adjusted without comparing to conventional D-dimer
Ota (2005)	Diagnosis of deep vein thrombosis by plasma-soluble fibrin or D-dimer	• Study looking for optimal thresholds
Palen (2005)	Performance characteristics of three quantitative D-dimer assays for outpatient evaluation of venous thromboembolism and its use in a clinical guideline for a group model HMO	• Reference standard repeated in a selective sample
Palen (2005)	Performance characteristics of three quantitative d-dimer assays for outpatient evaluation of venous thromboembolism and its use in a clinical guideline for a group model HMO	• Data was not reported separately for DVT and PE
Parent (2007)	Diagnostic value of D-dimer in patients with suspected pulmonary embolism: results from a multicentre outcome study	• Participants received different reference standards
Parikh (2015)	MDCT diagnosis of acute pulmonary embolism in the emergent setting	• Not a relevant study design (retrospective study)

Author (year)	Title	Reason for exclusion
Park (2011)	Evaluation of performance including influence by interfering substances of the Innovance D-dimer assay on the Sysmex coagulation analyzer	• Reference standard in study does not match that specified in protocol
Parry (2018)	International, multicenter evaluation of a new D-dimer assay for the exclusion of venous thromboembolism using standard and age-adjusted cut-offs	• Reference standard was not done to all participants
Pedraza (2018)	Comparison of the Accuracy of Emergency Department-Performed Point-of-Care-Ultrasound (POINT-OF-CAREUS) in the Diagnosis of Lower-Extremity Deep Vein Thrombosis	• Study does not contain any relevant index tests
Pernod (2017)	Validation of STA-Liatest D-Di assay for exclusion of pulmonary embolism according to the latest Clinical and Laboratory Standard Institute/Food and Drug Administration guideline. Results of a multicenter management study	• Reference standard was not done to all participants
Perrier (1997)	D-dimer testing for suspected pulmonary embolism in outpatients	• Reference standard was not done to all participants
Perveen (2013)	Point of care D-dimer testing in the emergency department: a bioequivalence study	• Data was not reported separately for DVT and PE
Ray (2006)	Referent d-dimer enzyme-linked immunosorbent assay testing is of limited value in the exclusion of thromboembolic disease: result of a practical study in an ED	• Reference standard was not done to all participants • Index test was not done to all participants
Reber (1995)	A new, semi-quantitative and individual ELISA for rapid measurement of plasma D-dimer in patients suspected of pulmonary embolism	• Participants received different reference standards
Reber (1999)	Performances of the fibrin monomer test for the exclusion of pulmonary embolism in symptomatic outpatients	• Reference standard was not done to all participants
Reber (2004)	A new rapid point-of-care D-dimer enzyme-linked immunosorbent assay (Stratus CS D-dimer) for the exclusion of venous thromboembolism	• Not a relevant study design (retrospective study) Point-of-care
Rectenwald (2005)	D-dimer, P-selectin, and microparticles: novel markers to predict deep venous thrombosis. A pilot study.	• Does not contain a population of people with suspected DVT and/or PE

Author (year)	Title	Reason for exclusion
Righini (2006)	Clinical usefulness of D-dimer testing in cancer patients with suspected pulmonary embolism	• Reference standard was not done to all participants
Righini (2014)	Age-adjusted D-dimer cut-off levels to rule out pulmonary embolism: the ADJUST-PE study.[Erratum appears in JAMA. 2014 Apr 23-30;311(16):1694]	• Reference standard was not done to all participants
Risch (2004)	The predictive characteristics of D-dimer testing in outpatients with suspected venous thromboembolism: a Bayesian approach	• Not possible to calculate a 2x2 table from data presented in the study Does not segment PE and DVT
Riva (2018)	Age-adjusted D-dimer to rule out deep vein thrombosis: findings from the PALLADIO algorithm	• Participants received different reference standards
Rodger (2001)	Steady-state end-tidal alveolar dead space fraction and D-dimer: bedside tests to exclude pulmonary embolism	• Participants received different reference standards
Rodger (2006)	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	• Reference standard was not done to all participants
Ruiz-Gimenez (2004)	Rapid D-dimer test combined a clinical model for deep vein thrombosis. Validation with ultrasonography and clinical follow-up in 383 patients.	• Reference standard repeated in a selective sample
Runyon (2008)	Comparison of the Simplify D-dimer assay performed at the bedside with a laboratory-based quantitative D-dimer assay for the diagnosis of pulmonary embolism in a low prevalence emergency department population	• Reference standard was not done to all participants
Sartori (2012)	The Wells rule and D-dimer for the diagnosis of isolated distal deep vein thrombosis	• Does not contain a population of people with suspected DVT and/or PE suspected isolated distal DVT only
Scarvelis (2008)	HemosIL D-dimer HS assay in the diagnosis of deep vein thrombosis and pulmonary embolism. Results of a multicenter management study	• Reference standard was not done to all participants
Schols (2018)	Point-of-care testing in primary care patients with acute cardiopulmonary symptoms: a systematic review	• Systematic review used as a

Author (year)	Title	Reason for exclusion
		source of individual studies
Schouten (2013)	Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis	• Systematic review without relevant studies
Schrecengost (2003)	Comparison of diagnostic accuracies in outpatients and hospitalized patients of D-dimer testing for the evaluation of suspected pulmonary embolism	• Reference standard was not done to all participants
Sen (2014)	Comparison of D-dimer point of care test (POINT-OF-CARET) against current laboratory test in patients with suspected venous thromboembolism (VTE) presenting to the emergency department (ED)	• Reference standard was not done to all participants
Signorelli (2017)	Evaluating the Potential of Routine Blood Tests to Identify the Risk of Deep Vein Thrombosis: A 1-Year Monocenter Cohort Study	• Not possible to calculate a 2x2 table from data presented in the study
Sohne (2005)	Diagnostic strategy using a modified clinical decision rule and D-dimer test to rule out pulmonary embolism in elderly in- and outpatients	• Participants received different reference standards Also excluded from original guideline
Song (2014)	Analytical and clinical performance of a new point of care LABGEOIB D-dimer test for diagnosis of venous thromboembolism	• Reference standard in study does not match that specified in protocol
Stein (2004)	D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review	• Systematic review • Systematic review used as a source of individual studies
Stender (2008)	Combined use of clinical pre-test probability and D-dimer test in the diagnosis of preoperative deep venous thrombosis in colorectal cancer patients	• Does not contain a population of people with suspected DVT and/or PE
Stevens (2005)	The use of a fixed high sensitivity to evaluate five D-dimer assays' ability to rule out deep venous thrombosis: a novel approach.	• Study looking for optimal thresholds
Takach (2016)	Questioning the use of an age-adjusted D-dimer threshold to exclude venous thromboembolism: analysis of individual patient data from two diagnostic studies	• Secondary publication of paper(s) not meeting inclusion criteria
Takach (2017)	Comparison of clinical probability-adjusted D-dimer and age-adjusted D-dimer interpretation to exclude venous thromboembolism	• Secondary publication of paper(s) not meeting inclusion criteria

Author (year)	Title	Reason for exclusion
Tan (2010)	Point-of-care D-dimer tests can contribute to patient management in outpatients with suspected venous thromboembolism, particularly those at low risk	• Review article but not a systematic review
Tardy (1998)	Evaluation of D-dimer ELISA test in elderly patients with suspected pulmonary embolism	• Reference standard was not done to all participants
Than (2009)	Comparison of high specificity with standard versions of a quantitative latex D-dimer test in the assessment of community pulmonary embolism: HaemosIL D-dimer HS and pulmonary embolism	• Reference standard was not done to all participants various difference reference standards were used
Toulon (2009)	Evaluation of a rapid qualitative immuno-chromatography D-dimer assay (Simplify D-dimer) for the exclusion of pulmonary embolism in symptomatic outpatients with a low and intermediate pretest probability. Comparison with two automated quantitative assays	• Not a relevant study design (retrospective study)
Toulon (2017)	Age-adjusted D-dimer cut-off levels in the diagnosis strategy of venous thromboembolism in patients with non-high pre-test probability. Clinical performance and health economic analysis	• Conference abstract
Toulon (2017)	Economic impact of introducing age-adjusted D-dimer cut-off levels in the diagnosis strategy of venous thromboembolism	• Conference abstract
Turkstra (1996)	Reliable rapid blood test for the exclusion of venous thromboembolism in symptomatic outpatients	• Data was not reported separately for DVT and PE
Valls (2015)	Performance of a diagnostic algorithm based on a prediction rule, D-dimer and CT-scan for pulmonary embolism in patients with previous venous thromboembolism: A systematic review and meta-analysis	• Systematic review used as a source of individual studies
van Beek (1993)	A comparative analysis of D-dimer assays in patients with clinically suspected pulmonary embolism	• Study looking for optimal thresholds
Van Der Velde (2007)	Feasibility and accuracy of a rapid 'point-of-care' D-dimer test performed with a capillary blood sample	• Reference standard in study does not match that specified in protocol
van Es (2012)	The combination of four different clinical decision rules and an age-adjusted D-dimer cut-off increases the number of patients in whom acute pulmonary embolism can safely be excluded	• Reference standard was not done to all participants

Author (year)	Title	Reason for exclusion
van Es (2012)	The accuracy of D-dimer testing in suspected pulmonary embolism varies with the Wells score	• Reference standard was not done to all participants
van Es (2016)	Wells Rule and d-Dimer Testing to Rule Out Pulmonary Embolism: A Systematic Review and Individual-Patient Data Meta-analysis	• Systematic review used as a source of individual studies
van Es (2017)	Is stand-alone D-dimer testing safe to rule out acute pulmonary embolism?	• Reference standard was not done to all participants • Systematic review without relevant studies
van Es (2017)	The original and simplified Wells rules and age-adjusted D-dimer testing to rule out pulmonary embolism: an individual patient data meta-analysis	• Systematic review used as a source of individual studies
Vandy (2013)	Soluble P-selectin for the diagnosis of lower extremity deep venous thrombosis	• Does not contain a population of people with suspected DVT and/or PE Contained mixed sample of diagnosed upper and lower extermity DVT
Veitl (1996)	Comparison of four rapid D-Dimer tests for diagnosis of pulmonary embolism	• Reference standard in study does not match that specified in protocol
Vermeer (2005)	Exclusion of venous thromboembolism: evaluation of D-Dimer PLUS for the quantitative determination of D-dimer	• Study looking for optimal thresholds
Wang (2011)	Predictive value of D-dimer test for recurrent venous thromboembolism at hospital discharge in patients with acute pulmonary embolism	• Does not contain a population of people with suspected DVT and/or PE Population was confirmed PE
Wells (2006)	Does this patient have deep vein thrombosis?	• Systematic review • Systematic review used as a source of individual studies
Wilson (2003)	Evaluation of an automated, latex-enhanced turbidimetric D-dimer test (advanced D-dimer) and usefulness in the exclusion of acute thromboembolic disease	• Study looking for optimal thresholds
Wilts (2016)	PO-29 - Age-adjusted D-dimer cut-off level increases the number of cancer patients in who pulmonary embolism can be safely	• Conference abstract

Author (year)	Title	Reason for exclusion
	excluded without CT-PA imaging: The ADJUST-PE cancer substudy	
Wilts (2017)	Performance of the age-adjusted cut-off for D-dimer in patients with cancer and suspected pulmonary embolism	• Reference standard was not done to all participants Subgroup analysis of the ADJUST-PE study (Righini 2014)
Yang (2017)	d-Dimer as a Screening Marker for Venous Thromboembolism After Surgery Among Patients Younger Than 50 With Lower Limb Fractures	• Does not contain a population of people with suspected DVT and/or PE

Clinical studies (search update)

Author (year)	Title	Reason for exclusion
Ackerly (2018)	Diagnostic utility of an age-specific cut-off for d-dimer for pulmonary embolism assessment when used with various pulmonary embolism risk scores.	- Diagnostic question: 2x2 table not possible
Aguilar (2018)	Validation of the STA-Liatest DDi assay for exclusion of proximal deep vein thrombosis according to the latest Clinical and Laboratory Standards Institute/Food and Drug Administration guideline: results of a multicenter management study.	- Diagnostic question: Not all participants given a D-dimer test went on to get imaging.
Alhassan (2018)	) Assessment of the current D-dimer cutoff point in pulmonary embolism workup at a single institution:	- Diagnostic question: retrospective cohort study
Barry (2009)	New automated chemiluminescent d-dimer immunoassay: analytical and clinical performance in patients suspected of vte.	- Abstract only
Contant (2017)	A new D-dimer concept for more specific detection of venous thromboembolism.	- Abstract only
Fronas (2018)	Safety of D-dimer testing as a stand-alone test for the exclusion of deep vein thrombosis as compared with other strategies.	- Diagnostic question: Not all participants given a D-dimer test went on to get imaging.
Gomez-Jabalera (2018)	Age-adjusted D-dimer for the diagnosis of deep vein thrombosis.	- Duplicate reference already contained in review
Jaconelli (2018)	Can an age-adjusted D-dimer level be adopted in managing venous thromboembolism in the emergency department? A retrospective cohort study.	- Diagnostic question: Not all participants given a D-dimer test went on to get imaging.
Kraaijpoel (2017)	Different D-dimer assays have similar performance using the age-adjusted threshold for the diagnosis of pulmonary embolism.	- Abstract only
Li (2019)	The Diagnostic Efficacy of Age-Adjusted D-Dimer Cutoff Value and Pretest Probability Scores for Deep Venous Thrombosis.	- Diagnostic question: Not all participants given a D-dimer test went on to get imaging.
Lozano-Polo (2018)	Diagnosis of pulmonary embolism in the elderly: adherence to guidelines and age-adjusted D-dimer concentration values.	- Abstract only
Merron (2018)	Age adjusted D-dimer in the Belfast Health and Social Care Trust: A retrospective study.	- Diagnostic question: 2x2 table not possible
Michiels (20160	Safe Exclusion of Deep Vein Thrombosis by a Rapid Sensitive ELISA D-dimer and Compression Ultrasonography in 1330 Outpatients With Suspected DVT.	- Duplicate reference already contained in review
Nagel (2019)	Age-dependent diagnostic accuracy of clinical scoring systems and D-dimer levels in the	- Diagnostic question: 2x2 table not possible

Author (year)	Title	Reason for exclusion
	diagnosis of pulmonary embolism with computed tomography pulmonary angiography (CTPA).	
Ortiz (2017)	Age-Adjusted D-Dimer in the Prediction of Pulmonary Embolism: Does a Normal Age-Adjusted D-Dimer Rule Out PE?.	- Diagnostic question: 2x2 table not possible
Parks (2018)	Investigation of age-adjusted D-dimer using an uncommon assay.	- Diagnostic question: 2x2 table not possible
Parry (2018)	International, multicenter evaluation of a new D-dimer assay for the exclusion of venous thromboembolism using standard and age-adjusted cut-offs.	- Diagnostic question: 2x2 table not possible
Planquette (2017)	Improved exclusion of the pulmonary embolism diagnosis in the emergency department using a new D-dimer-based assay.	- Abstract only
Reardon (2019)	Diagnostic Accuracy and Financial Implications of Age-Adjusted D-Dimer Strategies for the Diagnosis of Deep Venous Thrombosis in the Emergency Department.	- Diagnostic question: retrospective cohort study
Riva (2019)	Riva, N., Righini, M., Camporese, G. et al. (2019) Accuracy of age-adjusted D-dimer to rule out deep vein thrombosis in the elderly. Thrombosis Research 174: 148-150	- Diagnostic question: Not all participants given a D-dimer test went on to get imaging.
Rodger (2018)	"HERDOO2" clinical decision rule to guide duration of anticoagulation in women with unprovoked venous thromboembolism. Can I use any d-Dimer?.	- Diagnostic question: outcome(s) not of interest
Sharif (2018)	Comparison of the age-adjusted and clinical probability-adjusted D-dimer to exclude pulmonary embolism in the emergency department.	- Diagnostic question: Not all participants given a D-dimer test went on to get imaging.
Sheele (2018)	A retrospective evaluation of the age-adjusted D-dimer versus the conventional D-dimer for pulmonary embolism.	- Duplicate reference already contained in review
Takach (2017)	Comparison of clinical probability-adjusted D-dimer and age-adjusted D-dimer interpretation to exclude venous thromboembolism.	- Diagnostic question: 2x2 table not possible
Takach (2018)	Age-adjusted versus clinical probability-adjusted D-dimer to exclude pulmonary embolism	- Appears to have used data from a study already included in the evidence review.
Van der Pol (2017)	No added value of the age-adjusted D-dimer cut-off to the YEARS algorithm in patients with suspected pulmonary embolism.	- Diagnostic question: Not all participants given a D-dimer test went on to get imaging.

Economic studies

Short title	Title	Reason for exclusion
Bogavac-Stanojevic (2013)	Economic evaluation of different screening alternatives for patients with clinically suspected acute deep vein thrombosis	Does not evaluate the comparators of interest
Bounameaux (2001)	Diagnostic strategies for suspected pulmonary embolism among outpatients	Does not include a cost-utility analysis
Bounameaux (2003)	Diagnostic approaches to suspected deep vein thrombosis and pulmonary embolism	Does not evaluate the comparators of interest
Cate-Hoek (2009)	Cost-effectiveness of ruling out deep venous thrombosis in primary care versus care as usual	Does not evaluate the comparators of interest
Duriseti (2006)	Value of quantitative D-dimer assays in identifying pulmonary embolism: implications from a sequential decision model	Does not evaluate the comparators of interest
Duriseti (2010)	Cost-effectiveness of strategies for diagnosing pulmonary embolism among emergency department patients presenting with undifferentiated symptoms	Does not evaluate the comparators of interest
Erkens (2013)	Cost-effectiveness of ruling out pulmonary embolism in primary care using the Wells rule and D-dimer testing	Conference abstract
Freyburger (1998)	D-dimer strategy in thrombosis exclusion--a gold standard study in 100 patients suspected of deep venous thrombosis or pulmonary embolism: 8 DD methods compared	Does not include a cost-utility analysis
Gil-Rojas (2016)	Cost-effectiveness of D-dimer in the diagnosis of venous thromboembolism in Colombia	Conference abstract
Hendriksen (2013)	The cost-effectiveness of 'point of care' D-dimer tests to rule out deep venous thrombosis in primary care	Conference abstract
Hendriksen (2015)	The cost-effectiveness of point-of-care D-dimer tests compared with a laboratory test to rule out deep venous thrombosis in primary care	Very serious limitations
Marquardt (2015)	Point-of-care D-dimer testing in emergency departments	Review article
Prins (2009)	D-dimer and clinical decision rules revisited for the diagnosis of deep vein thrombosis	Does not evaluate the comparators of interest
Raymakers (2014)	Diagnostic strategies incorporating computed tomography angiography for pulmonary embolism: a systematic review of cost-effectiveness analyses	Review article
Righini (2007)	Influence of age on the cost-effectiveness of diagnostic strategies for suspected pulmonary embolism	Does not evaluate the comparators of interest
Toulon (2016)	Age-adjusted D-dimer cut-off levels to rule-out venous thromboembolism in patients	Conference abstract

Short title	Title	Reason for exclusion
	with non-high pre-test probability. Clinical performance and cost-effectiveness analysis	
Toulon (2017)	Age-adjusted D-dimer cut-off levels in the diagnosis strategy of venous thromboembolism in patients with non-high pre-test probability. Clinical performance and health economic analysis	Conference abstract

Appendix K – References

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Appendix L – Expert testimony

Section A:	
Name:	Dianne Kitchen
Role:	Lead Scientist for Point of care testing programmes
Institution/Organisation:	National External Quality Assessment Schemes for Blood Coagulation
Guideline title:	Venous thromboembolic diseases: diagnosis, management and thrombophilia testing
Guideline Committee:	Committee for the Venous thromboembolic diseases: diagnosis, management and thrombophilia testing update
Subject of expert testimony:	Point of care D-dimer tests for PE and DVT

Evidence gaps or uncertainties:

The committee were unclear about various aspects of D-dimer testing. In particular, there was uncertainty regarding how different types of tests (qualitative, semi-quantitative and quantitative) work and whether different brands of laboratory tests work differently and/or have differing levels of diagnostic test accuracy. Additionally, there was uncertainty regarding the level of current usage of the different types of point of care tests (quantitative, semi-quantitative and qualitative) within the UK.

The expert was asked in advance to prepare a presentation to address the following points:

- What are the differences in how qualitative, quantitative and semi-quantitative d-dimer tests are performed and interpreted?
- What special equipment is needed for each?
- What is the split between qualitative, quantitative and semi-quantitative tests in current practice?

The committee were able to ask additional questions on the day.

Section B

Summary testimony:

The invited expert gave a 15-20 minute presentation covering the nature of D-dimer tests and their use in clinical practice as part of the diagnosis of VTE.

The presentation provided the following information:

1. An overview of what a D-dimer is and their relevance to VTE. Thrombus formation leads to a process of fibrinolysis, which in turn creates D-dimer as a by-product. Thus, D-dimer naturally increases as a result of a thrombus and a negative D-dimer test can rule of VTE effectively as it is unlikely that a VTE is present in the absence of a clinically meaningful increase in D-dimer levels. However, D-dimer levels are also raised in a variety of other conditions (including cancer, disseminated intravascular coagulation, pregnancy, inflammation and infection).

2. To effectively exclude VTE, a standard cut-off value is needed and if a person's D-dimer levels are lower than it then VTE can safely be ruled out. Typically, both laboratory and point-of-care tests use threshold values supplied by the manufacturer.

3. Due to the dangers associated with undetected VTE, D-dimer tests aim for as close to 100% sensitivity as possible to ensure that very few cases of VTE are missed. This is at the expense of specificity and many people with positive D-dimer results do not actually have VTE. Further investigation of these false positives are a waste of time and resources and the process is stressful for patients, but missing VTE (false negatives) cases can be fatal.

4. The expert witness briefly described the methods underlying different types of D-dimer tests including: the manual latex agglutination slide test; enzyme linked immunosorbent assay (ELISA); immuno -filtration; whole blood agglutination; automated latex light scattering immunoassay and enzyme linked fluorescent assays.

5. The expert witness provided a list of tests currently in the UK National External Quality Assessment Schemes for Blood Coagulation (NEQAS BC) (as of October 2018), including a variety of laboratory tests and two point-of-care tests (Biosite Triage and Roche Cobas h232) and showed the committee pictures of the machines to highlight their relative sizes.

6. The expert witness outlined the difficulty in comparing the different types of tests, with different methods giving different results for the same samples. The difference in results should not be a problem providing method specific cut offs for VTE are used.

7. The coefficient of variance (CV%) is used to measure the precision of tests, with the CV for laboratory D-dimer tests being between 5-10% but CVs for between laboratories can be up to 30%.

8. 99% of UK laboratories that take part in the NEQAS BC use quantitative methods, with some historic use of semi-quantitative methods and none currently using qualitative methods.

9. An external quality assessment study, in which the same samples (one low, one high D-dimer) were sent to around 500 users in the UK NEQAS BC, assessed variability between 13 different kits and 18 different instruments (most commonly HemosIL D-dimer HS on ACL TOP device which was used in 190 sites). Of the 474 sites that responded for the low D-dimer result, VTE was unlikely in 430 (only 1 centre used semi-quantitative and returned an "unlikely" result) and not excluded in 25. Of the 478 sites that responded for the high D-dimer result, VTE was unlikely in 4 centres and not excluded in 450.

10. Similarly, a sample assessing 66 centres looking at the point-of-care test D-dimer results for test samples using the Cobas h232 machine found that DVT was not excluded in 82% of sites. The expert witness highlighted the wide variability between responses in the D-dimer results returned, showing an example with estimates of the D-

dimer count in the high D-dimer sample ranging from 295-2945 ng/ml for laboratory tests (sample previously discussed in point 9) and ranging from 0.1-0.75 ug/ml for a sample distributed for a point of care D-dimer test.

11. For qualitative tests, there was discussion surrounding human error based on the need to read the test at exactly the right time to get a valid result.

12. There was also discussion about whether any differences in test accuracy when D-dimer tests are used in people with suspected DVT compared to people with suspected PE were likely to be real given that the CV for laboratory D-dimer tests using common samples can be up to 30% between laboratories. The expert witness did not think that there was a reason that the D-dimer test would be more or less accurate in people with suspected PE compared to suspected DVT given that the biological basis for the test giving a positive result was the same in both cases, but was unable to confirm this categorically.