D-Dimer tests for the diagnosis of deep venous thrombosis in symptomatic hospital outpatients with a clinical prediction rule

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[Diagnostic Test Accuracy Protocol]

D-Dimer tests for the diagnosis of deep venous thrombosis in symptomatic hospital outpatients with a clinical prediction rule

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ABSTRACT

This is a protocol for a Cochrane Review (Diagnostic test accuracy). The objectives are as follows:

To estimate the sensitivity and specificity of the various types of D-dimer test in the diagnosis of deep vein thrombosis (DVT) of the lower limb in symptomatic outpatients with a clinical prediction rule score. Patients' clinical prediction rule scores will be used to assess D-dimer test accuracy in different risk groups.

BACKGROUND

Venous thromboembolism (VTE) is a single disease affecting the venous circulation. It has two distinct presentations: deep vein thrombosis (DVT) and pulmonary embolism (Goldhaber 2012). A DVT is a venous thrombosis (blood clot) commonly found in the deep veins of the lower limb or pelvis. Thromboses may break off, or embolise, and travel through the veins to other parts of the body. If a thrombosis reaches the lungs it will cause pulmonary embolism by blocking one or more of the pulmonary arteries. DVT is more common than pulmonary embolism, affecting around 70,000 people each year in the UK, and it is potentially fatal if left untreated. The annual incidence of VTE in studies from Western Europe, North America, Australia, and Southern Latin America ranges from 0.75 to 2.69 per 1000 individuals (Raskob 2014). An epidemiological model developed by Cohen 2007 estimated that within six countries of the European Union, the total number of symptomatic DVTs per annum is 465,715 (range 404,664 to 538,189), the number of cases of pulmonary embolism per annum is 295,982 (range 242,450 to 360,363) and the number of cases of VTE-related deaths per annum is 370,012 (range 300,193 to 483,108) (Cohen 2007).

There are many risk factors associated with DVT, but the incidence of the condition rises dramatically in people over the age of 60 years (White 2003). Major surgery, trauma, fractures or surgery to the hip or knee, malignancy, cardiac or respiratory failure, prolonged immobility, pregnancy, oestrogen therapy, previous DVT or pulmonary embolism, and obesity are all known to increase the likelihood of DVT (Anderson 2003). Affected individuals may have no symptoms but have a history of one or more risk factors, which creates a suspicion that a DVT is present, with subsequent testing confirming the presence of the blood clot (Goodacre 2006). Those with symptoms may have calf pain and swelling. In general, symptomatic DVT are usually found proximally in the large veins of the thigh, whereas asymptomatic DVT are found more distally in the smaller veins of the calf. DVT in the large proximal veins is associated with poorer patient outcomes as they are more likely to embolise to the lungs and result in fatalities (NCGC 2012).

A patient with symptoms consistent with DVT will initially be assessed with a clinical prediction rule such as the Wells score, and categorised as being likely or unlikely of having a DVT. Clinical prediction rules such as the Wells score are recommended in clinical guidelines and are an important part of the patient pathway in routine clinical practice (NCGC 2012). Patients will then undergo further testing, usually D-dimer or imaging (duplex ultrasound, ascending venography, or computer tomography (CT) venography. Uncertainty exists about the most accurate method to diagnose DVT, and this creates a great deal of variation in clinical practice (Goodacre 2006).

Duplex ultrasound, ascending venography, and CT venography may be used to give patients a diagnosis of DVT. Duplex ultrasound is the most widely available and commonly used test and is less invasive than the venography tests, although it may not be as accurate. Both CT and ascending venography use X-rays, thus giving a dose of radiation, and require administration of a contrast agent, making them unsuitable for patients with renal failure. CT and ascending venography are not recommended for pregnant patients.

DVT is usually treated with anticoagulant therapy (NCGC 2012). The purpose of treatment is to prevent recurrent episodes of DVT, post-thrombotic syndrome and the development of a pulmonary embolism. The accurate diagnosis of DVT is essential to avoid morbidity and mortality and expense of unnecessary anticoagulation (NCGC 2012). This Review protocol is complementary to other Cochrane Review protocols by the same authors on the use of D-dimer for excluding pulmonary embolism (Crawford 2013), and the diagnosis of DVT by duplex ultrasound (Chappell 2014).

A previous Review included patients recruited with VTE (i.e. both DVT and pulmonary embolism) and both inpatient and outpatient settings (Di Nisio 2007). However, Di Nisio 2007 did not consider the combination of D-dimer with different clinical probabilities. Our Cochrane Review will focus on symptomatic patients in the outpatient or emergency department setting. There is also a Cochrane Review protocol on the diagnosis of DVT in the upper extremity by ultrasound (Di Nisio 2011), however there is no overlap between the two protocols, as they are concerned with distinct (upper and lower) limbs. Non-Cochrane Reviews on this topic include one focusing on the effect of age on the accuracy of D-dimer (Schouten 2013).

Target condition being diagnosed

Symptomatic deep vein thrombosis (DVT) of the lower limb.

Index test(s)

D-dimer tests can work in various ways. D-dimer is a piece of protein released into the circulation when a blood clot breaks down, either as a result of normal body processes or prescribed fibrinolytic medication. The normal level of plasma D-dimer is usually less than 500 micrograms per litre (µg/L), though the upper limit of normal can vary depending on the method of measurement. A higher level of D-dimer may indicate the presence of a DVT or pulmonary embolism. Some D-dimer tests use coated latex particles that agglutinate in the presence of plasma containing D-dimer. The degree of agglutination is directly proportional to the concentration of D-dimer in the plasma (Than 2009). These agglutination methods are very quick, but can lack accuracy. Others use enzyme-linked immunosorbent assays (ELISA) to determine D-dimer concentration. These are more accurate but require laboratory processing and so cannot be performed at the bedside. D-dimer tests also include newer immunofiltration methods, which can be carried out in less than five minutes at the bedside, and may be more accurate than latex agglutination. Since D-dimer is a blood test, its use is not restricted by the availability of scanner or radiologist time.

Pre-test probability score using clinical prediction rules

As an assessment of the pre-test probability of a DVT is considered a standard component of current clinical practice, we intend to include only studies which assess the pre-test probability of DVT using a clinical prediction rule (Wells 2003). There are many clinical prediction rules in existence for assessing the pre-test probability of venous thromboembolism (VTE) and can be used to score the pre-test probability of pulmonary embolism as well as DVT (Ceriani 2010). We intend to include studies which assess the pre-test probability of DVT using any one of the following clinical prediction rules as part of the diagnostic strategy involving any D-dimer test: Revised and Revised Simplified Geneva, the Wells rule and the Charlotte rule (Ceriani 2010; Wells 2006).

Clinical pathway

Patients presenting with symptoms of DVT in the outpatient or emergency setting will be scored using the DVT Wells score or similar (Wells 2006). The Wells score is a clinical prediction rule that gives the patient a point for each criterion met (e.g. pitting oedema in the symptomatic leg, previous known DVT), and subtracts 2 points if an alternative diagnosis is considered just as likely. The maximum score is 9 points. Current National Health Service (NHS) guidance recommends that patients with a score of 2 or more undergo ultrasound testing within four hours, and those with a score of 1 or less or without access to ultrasound within 4 hours undergo D-dimer testing (NCGC 2012). Patients with a Wells score of 1 or less but a positive D-dimer test are also recommended to undergo ultrasound within four hours of request. This NHS guidance has been available for less than one year, and so we do not expect that all studies will have dichotomised the Wells score at 1 or less and 2 or more. For example, some studies will have used three subgroups where a patient is graded as low risk if he or she has a score of 0 or less, moderate (or intermediate) risk if scored 1 or 2, and high risk if scored 3 or more, as this is the categorisation used by the developers of the Wells score (Wells 1997). In addition, the availability of other clinical prediction rules means that studies may have used other scores to screen for DVT.

Symptomatic patients thought to be at low risk by the clinical prediction rule will generally undergo D-dimer testing. Doctors look for non-DVT causes of the symptoms if a low risk score is combined with a negative D-dimer test. Patients with a low risk score but a positive D-dimer test will be referred for ultrasound imaging. Patients with an intermediate or high risk score may be referred straight to ultrasound imaging. Therefore, patients with low scores will generally be offered D-dimer testing, patients with intermediate or high scores may or may not be offered D-dimer testing according to the availability of other tests and clinical need. We will stratify patients according to whether they are scored as intermediate, high, or low risk by the clinical prediction rule and analyse these groups separately.

Rationale

Symptomatic DVT is difficult to diagnose clinically as many of the symptoms occur in other diseases. To send all patients with DVT symptoms for definitive diagnostic imaging would not be an efficient use of resources. There is therefore a need for diagnostic tests that can quickly triage patients into those who require further tests, those who can be offered antithrombotic therapy, and those for whom other diagnoses should be considered.

OBJECTIVES

To estimate the sensitivity and specificity of the various types of D-dimer test in the diagnosis of deep vein thrombosis (DVT) of the lower limb in symptomatic outpatients with a clinical prediction rule score. Patients' clinical prediction rule scores will be used to assess D-dimer test accuracy in different risk groups.

Secondary objectives

To investigate the following as potential sources of heterogeneity: age, sex, cancer, previous venous thromboembolism (VTE), prolonged immobilisation, anticoagulant treatment, time lapse between onset of symptoms and testing, and type of reference standard. However, we recognise that all of these listed items, except type of reference standard, are patient-specific rather than study-specific, and so study reports may lack the necessary level of detail to enable an informative analysis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include cross-sectional studies evaluating the diagnostic test accuracy of D-dimer and diagnostic cohort study designs including both prospective and retrospective designs. We will exclude diagnostic case-control studies. Case-control designs are known to overestimate the sensitivity and specificity that a diagnostic test has in clinical practice (Rutjes 2005). In this review, we will consider studies that use a clinical prediction rule with D-dimer testing to rule out patients with deep vein thrombosis (DVT) in hospital outpatient and emergency departments. Specifically, we will use studies that recruited symptomatic outpatients with low, intermediate, or high risk clinical prediction rule scores. We will only include studies which obtain a reference standard test for all those who receive a D-dimer test.

Participants

We will include hospital outpatients presenting with symptoms consistent with a DVT of the lower limb, who have undergone assessment with a clinical prediction rule such as the Wells score. We will exclude patients who do not have a clinical prediction rule score.The specific symptoms are: leg pain and possibly swelling, redness, and heat. Other signs may include the presence of pitting oedema and fever (Wells 2006). We recognise that the index tests are likely to perform differently in patients with different prior clinical prediction rule results, and we will not combine data from low risk and high risk groups. It will only be possible to include studies where these data are presented separately.

Index tests

We plan to include, (but not be limited to) latex agglutination, enzyme-linked immunosorbent assays (ELISA), and immunofiltration D-dimer tests. We will include studies that use a variety of index tests and aim to include all blood tests for D-dimer.

Target conditions

Symptomatic DVT of the lower limb, including both distal and proximal thrombi.

Reference standards

We will include duplex ultrasound, ascending venography, or CT venography, or a combination of these as reference standards in the Review. We will also include studies where patients had a low probability of DVT and normal D-dimer upon first assessment, but were followed up within three months of the reference standard.

Search methods for identification of studies

Electronic searches

We will not use a diagnostic search filter because these have not proved sensitive enough (Whiting 2011b). We will not apply any language restriction to the electronic searches; we will endeavour to have non-English language papers translated.

We will search the following databases using the search strategies shown in Appendix 1 and Appendix 2.

- MEDLINE (OvidSP).
- Embase (OvidSP).

In addition, we will design search strategies for:

- CINAHL (via EBSCO);
- LILACS (Bireme);
- DARE (Database of Abstracts of Reviews of Effects) and the Health Technology Assessment Database (HTA) in the Cochrane Library;
- ISI Conference Proceedings Citation Index - Science;
- British Library Zetoc conference search.

Similarly, we will design structured search strategies for each database using controlled vocabulary and search terms appropriate for each database.

We will also search MEDION (www.mediondatabase.nl/), using the 'Systematic Reviews of Diagnostic Studies' search filter.

Searching other resources

We will handsearch the reference lists of the primary studies and Reviews identified from the electronic searches.

Data collection and analysis

Selection of studies

One review author (LR) will screen the titles and abstracts retrieved by the electronic searches, and a second review author (MS) will check a random sample of 10% of the screened titles and abstracts. Full papers will be obtained for potentially eligible studies, including those identified by non-electronic means. Two review authors (LR and MS) will independently apply the exclusion criteria to the full papers and resolve any disagreements by discussion or refer to a third review author as necessary. We will use a PRISMA flow diagram to show the selection process (PRISMA 2009), and will use Endnote version 4 (endnote.com) as our reference management system.

The exclusion criteria for abstracts are: D-dimer is not used, patients do not have symptoms consistent with DVT, study uses a case-control design, study is not a diagnostic test accuracy study. We shall report the number of excluded abstracts in the PRISMA flow diagram. For studies that fulfil the abstract criteria, we will assess the full-text. Given that the reporting in abstracts is necessarily sparse, we will check the full-text articles for meeting the abstract criteria and also for fulfilling the following: a 2x2 contingency table is either supplied or can be back-calculated, all patients are symptomatic or data for the symptomatic patients can be extracted, the reference standard is either duplex ultrasound, ascending venography, or CT venography. We will also include studies with a three month follow-up within the reference standard. We will report the number of studies failing these criteria in the PRISMA flow diagram. We will undertake a more in-depth evaluation of studies that pass the initial screening of the full-text and we will fully report these in the review.

Data extraction and management

Two review authors (LR and MS) will independently extract data using a standard form, which will include an assessment of study quality (Whiting 2011a). The reviewer authors will corroborate their data extraction and quality assessment decisions and disagreements will be resolved by discussion or referred to a third review author as necessary. Patient level 2x2 contingency tables (true positives (TP) true negatives (TN), false positives (FP) and false negatives (FN) will be extracted as reported. If necessary, they will be back-calculated from estimates of sensitivity, specificity, positive and negative predictive values, and the total number of patients.

We will collect data on mortality, adverse events, and the number of technical failures for all tests along with prognostic factors from the patient history including the proportion with cancer, recent surgical procedures, prolonged periods of immobilisation, and time to reference standard (mean or median, with range if available). We shall report if studies reached diagnoses through consensus (where more than one person tests each patient). We will also extract data required for assessment of heterogeneity: age, sex, cancer, previous VTE, prolonged immobilisation, anticoagulant treatment (specifically where patients began taking anti-coagulants after D-dimer testing and before the reference standard), time from onset of symptoms to testing, and type of reference standard. We will also record data on the technical aspects of D-dimer and the reference standards, for example, type of scanner and contrast agent.

We will save data in Microsoft Excel 2010.

Assessment of methodological quality

We will use the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) to develop a quality assessment tool, incorporating the review question; a flow diagram for the study and an assessment of risk of bias and applicability judgements (Whiting 2011a). Review-specific signalling questions, appropriate items concerning the applicability of primary studies relative to the review, together with guidance about rating can be found in Appendix 3. We propose that two review authors working independently will pilot the tool and agree on the interpretation of questions. Disagreements will be resolved by discussion or referral to a third review author.

Statistical analysis and data synthesis

We will present and use the 2x2 contingency tables to estimate sensitivity and specificity for each study. We will use these estimates to create receiver operating characteristic (ROC) curves and forest plots for all studies. We will group data according to type of D-dimer test and prior clinical prediction rule result.

Quantitative D-dimer tests are used with explicit thresholds and 500 µg/L is a common choice (Schouten 2013). If there are sufficient studies using this threshold, we shall perform a bivariate random-effects meta-analysis of sensitivity and specificity in order to produce clinically applicable summary estimates of sensitivity and specificity. However, we expect to have studies using qualitative D-dimer tests and these will have no explicit threshold, and so we will consider presenting the results as summary ROC curves to give an indication of the global performance of the qualitative D-dimer tests (Harbord 2007).

If the model fit of the bivariate or hierarchical summary receiver operating characteristic (HSROC) model is not acceptable, we shall consider performing univariate meta-analyses for sensitivity and specificity. The programs used to fit the model must converge. However, convergence is a necessary but not sufficient measure of a model having a satisfactory fit, and further checks are necessary. In particular, the covariance parameter can be poorly estimated even when convergence is achieved.

A small number of studies, is one, but not the only common reason for non-convergence (and we would not attempt to fit the five parameter bivariate or HSROC models with fewer than six studies). It can also happen when there is a lack of variation in threshold between studies - a possibility here given the clinical acceptance and frequent use of 500 µg/L. We note that there are many possible reasons, both statistical and clinical, why we would not undertake a summary receiver operating characteristic (SROC) curve method of meta-analysis and we would want to consider both clinical and statistical sources of heterogeneity.

Performing univariate analyses, one each for sensitivity and specificity is not always recommended. However, where studies do use a common threshold, the univariate meta-analyses could be informative and would also allow meta-regression in a situation where use of the bivariate or HSROC models may not be valid.

We will perform all analyses in R 8.0 (cran.r-project.org) and SAS 9.3 (www.sas.com).

Investigations of heterogeneity

In our investigations of heterogeneity we will specifically investigate the type of reference standard and age, where these data are available, by including them as covariates in the meta-analysis. Each meta-regression will be carried out separately for each D-dimer test and each patient group as defined by clinical prediction rule score by adding the items as covariates to the bivariate model (or the univariate models, as appropriate). If the data for our prespecified variables are insufficient, we may consider analysing one or two other items if the data are available and they are considered to be clinically relevant - any such analysis, if undertaken, will be reported as posthoc in the final review. We will examine graphically other potential sources (age, sex, cancer, previous VTE, prolonged immobilisation, anticoagulant status (anticoagulant treatment may cause disease progression bias if it is administered between the D-dimer testing and the reference standard), and the time from onset of symptoms to testing) for signs that they are a cause of heterogeneity (Deeks 2013). We will group estimates according to all the items listed as potential sources of heterogeneity and present them in forest and ROC plots for visual assessment of heterogeneity.

Sensitivity analyses

We will carry out further meta-analyses where studies are grouped according to type of D-dimer (quantitative, semi-quantitative, and qualitative), rather than individual D-dimer tests.

Assessment of reporting bias

Methods for dealing with publication bias in reviews of diagnostic accuracy studies are relatively underdeveloped. Consequently, we shall interpret our results cautiously, and with an awareness of the likelihood of publication bias, rather than use funnel plots, which can be challenging to interpret in this context. We shall consider using a funnel plot of the log of the diagnostic odds ratio (lnDOR), providing there is low heterogeneity in the lnDOR (Deeks 2005).

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APPENDICES

Appendix 1. MEDLINE search strategy

Database: Ovid MEDLINE(R)

1. Thromboembolism/
2. Venous Thromboembolism/
3. Thrombosis/
4. Venous Thrombosis/
5. Upper Extremity Deep Vein Thrombosis/
6. (vein$ adj3 (thromb$ or clot$)).ti,ab.
7. (ven$ adj3 (thromb$ or clot$)).ti,ab.
8. (calf adj3 (thromb$ or clot)).ti,ab.
9. (thigh adj3 (thromb$ or clot)).ti,ab.
10. (proximal adj3 (thromb$ or clot)).ti,ab.
11. (limb adj3 (thromb$ or clot$)).ti,ab.
12. (leg adj3 (thromb$ or clot$)).ti,ab.
13. (DVT or VTE).ti,ab.
14. (blood adj3 clot).ti,ab.
15. or/1-14
16. Fibrin Fibrinogen Degradation Products/
17. Biological Markers/
18. Enzyme-Linked Immunosorbent Assay/

(Continued)

19. "Nephelometry and Turbidimetry"/
20. d-dimer.ti,ab.
21. (fibrin adj2 d).ti,ab.
22. dimeri?ed plasmin.ti,ab.
23. elisa?.ti,ab.
24. elfa?.ti,ab.
25. enzyme linked.ti,ab.
26. latex agglutination.ti,ab.
27. (latex adj3 assay?).ti,ab.
28. blood agglutination.ti,ab.
29. Immunoturbidimetr$.ti,ab.
30. turbidimetr$.ti,ab.
31. SimpliRed.ti,ab.
32. Minutex.ti,ab.
33. NycoCard.ti,ab.
34. "Instant I.A".ti,ab.
35. Vidas.ti,ab.
36. LIATEST.ti,ab.
37. ("IL test" or IL-DD).ti,ab.
38. Turbiquant.ti,ab.
39. Asserachrom.ti,ab.
40. Enzygnost.ti,ab.
41. Fibrinostika.ti,ab.
42. "BC DD".ti,ab.
43. (Tinaquant or Tina-quant).ti,ab.
44. TriniLIZE.ti,ab.
45. biopool.ti,ab.
46. TintElize.ti,ab.

(Continued)

47. HemosIL.ti,ab.
48. Innovance-DD.ti,ab.
49. stratus.ti,ab.
50. FDP.ti,ab.
51. Dimertest.ti,ab.
52. (LPIA or EIA).ti,ab.
53. or/16-52
54. 15 and 53

Appendix 2. EMBASE search strategy

1. thromboembolism/
2. venous thromboembolism/
3. deep vein thrombosis/
4. lower extremity deep vein thrombosis/
5. upper extremity deep vein thrombosis/
6. thrombosis/
7. vein thrombosis/
8. leg thrombosis/
9. (vein$ adj3 (thromb$ or clot$)).ti,ab.
10. (ven$ adj3 (thromb$ or clot$)).ti,ab.
11. (calf adj3 (thromb$ or clot)).ti,ab.
12. (leg adj3 (thromb$ or clot)).ti,ab.
13. (thigh adj3 (thromb$ or clot)).ti,ab.
14. (proximal adj3 (thromb$ or clot)).ti,ab.
15. (limb adj3 (thromb$ or clot$)).ti,ab.
16. (DVT or VTE).ti,ab.
17. (blood adj3 clot).ti,ab.

(Continued)

18. or/1-17
19. fibrin degradation product/
20. biological marker/
21. D dimer/
22. enzyme linked immunosorbent assay/
23. turbidimetry/
24. d-dimer.ti,ab.
25. (fibrin adj2 d).ti,ab.
26. dimeri?ed plasmin.ti,ab.
27. elisa?.ti,ab.
28. elfa?.ti,ab.
29. enzyme linked.ti,ab.
30. Immunoturbidimetr$.ti,ab.
31. turbidimetr$.ti,ab.
32. latex agglutination.ti,ab.
33. (latex adj3 assay?).ti,ab.
34. blood agglutination.ti,ab.
35. SimpliRed.ti,ab.
36. Minutex.ti,ab.
37. NycoCard.ti,ab.
38. "Instant I.A".ti,ab.
39. Vidas.ti,ab.
40. LIATEST.ti,ab.
41. ("IL test" or IL-DD).ti,ab.
42. Turbiquant.ti,ab.
43. Asserachrom.ti,ab.
44. Enzygnost.ti,ab.
45. Fibrinostika.ti,ab.

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46. "BC DD".ti,ab.
47. (Tinaquant or Tina-quant).ti,ab.
48. TriniLIZE.ti,ab.
49. biopool.ti,ab.
50. TintElize.ti,ab.
51. (HemosIL-DD or HemosIL-DDHS).ti,ab.
52. Innovance-DD.ti,ab.
53. stratus.ti,ab.
54. FDP.ti,ab.
55. Dimertest.ti,ab.
56. (LPIA or EIA).ti,ab.
57. or/19-56
58. 18 and 57

Appendix 3. QUADAS-2 form

Domain 1: Patient selection	Rating criteria
A. Risk of bias	Describe the methods of patient selection. Describe included patients (prior testing, presentation, intended use of index test, and setting).
SQ1. Was a consecutive or random sample of patients enrolled?	**Yes:** It is stated that the patients were a consecutive or random sample. **No:** It is stated that the patients were not a consecutive or random sample, for example, they were a convenience sample. **Unclear:** It is not clear how the patients were recruited.
SQ2. Did the study avoid inappropriate exclusions?	**Yes:** All symptomatic outpatients with a CPR score were included. **No:** Some patients who meet our inclusion criteria (symptomatic, outpatient, CPR score) were not included. **Unclear:** The exclusion criteria are not sufficiently described.
SQ3. Did the study avoid inappropriate inclusions?	**Yes:** The sample did not include hospital inpatients, or asymptomatic patients, or anyone without a prior CPR score. **No:** The sample included hospital inpatients, asymptomatic patients, or patients without a prior CPR score. **Unclear:** The inclusion criteria are not sufficiently described.

(Continued)

Risk of bias: could the selection of patients have introduced bias?	**High:** The patient sample does not reflect our inclusion/exclusion criteria. **Low:** The patient sample reflects our inclusion/exclusion criteria. **Unclear:** Not enough information is given about the study population.
B. Concerns regarding applicability. Are there concerns that the included patients do not match the review question?	**Low:** The patients sample matches those in our review. **High:** The patients do not match the review question - the sample is skewed in some way, for example, patients with risk factors such as recent surgery were excluded. **Unclear:** The study does not give sufficient detail about the patients.
Domain 2: Index test	**Rating criteria**
A. Risk of bias	Describe the index test and how it was conducted and interpreted, including the training and background of the individual carrying out the test.
SQ4. Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes:** The readers of the index test were blind to the reference standard. **No:** The readers of the index test knew the results of the reference standard. **Unclear:** The study does not say whether or not the readers of the index test were blind to the reference standard.
SQ5. If a threshold was used, was it prespecified?	**Yes:** Either no explicit threshold was used (for the qualitative tests) or a prespecified threshold (e.g. 500µg/l) was used for the quantitative tests. **No:** A threshold was used and the choice of threshold was based on results from the study. **Unclear:** A threshold was used, but how the threshold was chosen is not clear.
Risk of bias. Could the conduct or interpretation of the index test have introduced bias?	**Low:** The readers of the index were blind to the results of the reference standard and either no explicit threshold was used or it was prespecified. **High:** The readers of the index test were not blind to the reference standard results, and/or a threshold was used and was not prespecified. **Unclear:** It is not clear whether the readers of the index test were blind to the results of the reference standard and/or how the threshold was chosen.
B. Concerns regarding applicability. Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low:** The conduct and interpretation of the index test match the review question. The D-dimer test used validated methods. **High:** The conduct or interpretation of the index test do not match the review question. The D-dimer test used unvalidated methods. **Unclear:** The conduct and interpretation of the index test are not sufficiently described.
Domain 3: Reference standard	**Rating criteria**
A. Risk of bias	Describe the reference standard and how it was conducted and interpreted.
SQ6. Is the reference standard likely to classify correctly the target condition?	**Yes:** The reference standard was conducted by a trained and/or experienced individual using appropriate methods. The reference standard was either ultrasound, CT venography, MR venography, or ascending venography. **No:** The reference standard was not conducted by a trained and/or experienced individual, or the methods were not suitable for the diagnosis of DVT.

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	Unclear: The background of the individual carrying out the test is not clear, or the methods not described in sufficient detail.
SQ7. Were the reference standard results interpreted without knowledge of the results of the index test?	**Yes:** The study says that the reference standard was performed blind to the results of the D-dimer test. **No:** The readers of the reference standard knew the results of the D-dimer test. **Unclear:** It is not clear whether the readers of the reference standard knew the results of the D-dimer test.
Risk of bias. Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low:** The reference standard was performed blind to the results of the D-dimer test by suitably trained individuals using validated methods. **High:** The reference standard was not performed blind to the D-dimer test or was performed by individuals lacking training or using unvalidated methods. **Unclear:** The background of the individuals conducting the reference standard is not clear, or whether these individuals were blind to the results of the D-dimer test.
B. Concerns regarding applicability. Is there concern that the target condition as defined by the reference standard does not match the review question?	**Low:** The reference standard is either ultrasound, CT venography, MR venography, or ascending venography and was conducted by a suitably trained/experienced individual blind to the results of the D-dimer test. **High:** The reference standard was not performed by a qualified or trained individual. **Unclear:** The conduct or interpretation of the reference standard is not sufficiently well described.
Domain 4. Flow and timing	**Rating criteria**
A. Risk of bias	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:
SQ8. Was there an appropriate interval between index test(s) and reference standard?	**Yes:** The index and reference standard tests were all conducted within 7 days of each other. **No:** Some of the reference standard test results were obtained after more than 7 days. **Unclear:** No information about the relative timing of the tests is provided.
SQ9. Did all patients receive a reference standard?	**Yes:** A complete set of reference standard test results are available for all study patients. **No:** The reference standard results are not available for all patients, or some patients had follow-up only. **Unclear:** It is not clear whether all patients received an acceptable reference.
SQ10. Did patients receive the same reference standard?	**Yes:** All patients received the same reference standard in a given study. **No:** Patients received different reference standards, possibly depending on the results of either the CPR or D-dimer result. **Unclear:** It is not clear which patients received a particular reference standard or why.
SQ11. Were all patients included in the analysis?	**Yes:** All patients recruited contribute to the final 2x2 table. **No:** Some patients' data are missing from the 2x2 table. **Unclear:** It is not clear whether all the patients recruited were included in the final analysis.
Risk of bias. Could the patient flow have introduced bias?	**Low:** All patients recruited were included in the final analysis and received the same reference standard or, if they are missing from the final analysis, it is for a reason not connected to DVT. **High:** There are patients missing from the final 2x2 table, and the reason for missingness is not explained, or they received different reference standards according to CPR or D-dimer results.

(Continued)

Unclear: The study does not report sufficient details of the patient flow.

CPR: clinical prediction rule
CT: computer tomography
DVT: deep vein thrombosis
MR: magnetic resonance

CONTRIBUTIONS OF AUTHORS

This review will be conducted by a team of individuals who collectively possess all the skills necessary to conduct the review.

LR and MS will be responsible for applying the eligibility criteria to the studies identified by the search strategy and FC will act as the third review author in the event of their disagreement. They will extract the data and undertake assessment of study quality. KW will design the search strategy, MdN will provide clinical advice and he and FC will contribute to the interpretation of statistical analyses. FMC will be responsible for the presentation of the data, any meta-analysis and the investigations of heterogeneity. All will contribute to the final written review.

DECLARATIONS OF INTEREST

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FMC: none known.
AA: none known.
KW: none known.
MdN: has declared that he has received consultancy fees from Bayer, Daiichi Sankyo and Grifols unrelated to this review.
LR: none known.
MS: none known.
FC: none known.

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