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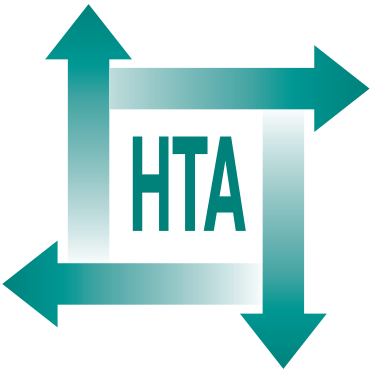

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Abstract

Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis

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Objectives: To estimate the diagnostic accuracy of non-invasive tests for proximal deep vein thrombosis (DVT) and isolated calf DVT, in patients with clinically suspected DVT or high-risk asymptomatic patients, and identify factors associated with variation in diagnostic performance. Also to identify practical diagnostic algorithms for DVT, and estimate the diagnostic accuracy, clinical effectiveness and cost-effectiveness of each.

Data sources: Electronic databases (to April 2004). A postal survey of hospitals in the UK.

Review methods: Selected studies were assessed against validated criteria. A postal survey of hospitals in the UK was undertaken to describe current practice and availability of tests, and identify additional diagnostic algorithms. Pooled estimates of sensitivity, specificity and likelihood ratios were obtained for each test using random effects meta-analysis. The effect of study-level covariates was explored using random effects metaregression. A decision-analytic model was used to combine estimates from the meta-analysis and estimate the diagnostic performance of each algorithm in a theoretical population of outpatients with suspected DVT. The net benefit of using each algorithm was estimated from a health service perspective, using cost–utility analysis, assuming thresholds of willingness to pay of £20,000 and £30,000 per quality-adjusted life-year (QALY). The model was analysed probabilistically and cost-effectiveness acceptability curves were generated to reflect uncertainty in estimated cost-effectiveness.

Results: Individual clinical features are of limited diagnostic value, with most likelihood ratios being close to 1. Wells clinical probability score stratifies proximal, but not distal, DVT into high-, intermediate- and low-risk categories. Unstructured clinical assessment by experienced clinicians may have similar performance to Wells score. In patients with clinically suspected DVT, D-dimer has 91% sensitivity and 55% specificity for DVT, although performance varies substantially between assays and populations. D-dimer specificity is dependent on pretest clinical probability, being higher in patients with a low clinical probability of DVT. Plethysmography and rheography techniques have modest sensitivity for proximal DVT, poor sensitivity for distal DVT, and modest specificity. Ultrasound has 94% sensitivity for proximal DVT, 64% sensitivity for distal DVT and 94% specificity. Computed tomography scanning has 95% sensitivity for all DVT (proximal and distal combined) and 97% specificity. Magnetic resonance imaging has 92% sensitivity for all DVT and 95% specificity. The diagnostic performance of all tests is worse in asymptomatic patients. The most cost-effective algorithm discharged patients with a low Wells score and negative D-dimer without further testing, and then used plethysmography alongside ultrasound, with venography in selected cases, to diagnose the remaining patients. However, the cost-effectiveness of this algorithm was dependent on assumptions of test independence being met and the ability to provide plethysmography at relatively low cost. Availability of plethysmography and venography is currently limited at most UK hospitals, so implementation would involve considerable reorganisation of services. Two algorithms were identified that offered high net benefit and would be feasible in most hospitals without substantial reorganisation of services. Both involved using a combination of Wells score, D-dimer and above-knee

ultrasound. For thresholds of willingness to pay of £10,000 or £20,000 per QALY the optimal strategy involved discharging patients with a low or intermediate Wells score and negative D-dimer, ultrasound for those with a high score or positive D-dimer, and repeat scanning for those with positive D-dimer and a high Wells score, but negative initial scan. For thresholds of £30,000 or more a similar strategy, but involving repeat ultrasound for all those with a negative initial scan, was optimal.

Conclusions: Diagnostic algorithms based on a combination of Wells score, D-dimer and ultrasound (with repeat if negative) are feasible at most UK hospitals and are among the most cost-effective. Use of repeat scanning depends on the threshold for willingness to pay for health gain. Further diagnostic testing for patients with a low Wells score and negative D-dimer is unlikely to represent a cost-effective use of resources. Recommendations for research include the evaluation of the costs and outcomes of using the optimal diagnostic algorithms in routine practice, the development and evaluation of algorithms appropriate for specific groups of patients with suspected DVT, such as intravenous drug abusers, pregnant patients and those with previous DVT, the evaluation of the role of plethysmography: interaction with other diagnostic tests, outcome of low-risk patients with negative plethysmography and measurement of the costs of providing plethysmography, and methodological research into the incorporation of meta-analytic data into decision-analytic modelling.

Contents

List of abbreviations

CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CT	computed tomography
DD	D-dimer
DVT	deep vein thrombosis/thromboses
ED	emergency department
ELISA	enzyme-linked immunosorbent assay
LR	likelihood ratio
MAICER	maximum acceptable incremental cost-effectiveness ratio
MR	magnetic resonance
MRI	magnetic resonance imaging
NA	not applicable
NR	not reported
PE	pulmonary embolus
PTS	post-thrombotic syndrome
QALY	quality-adjusted life-year
RCT	randomised controlled trial
ROC	receiver operating characteristic
SROC	summary receiver operating characteristic
TOF	time of flight
US	ultrasound

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

A wide range of diagnostic tests may be useful in diagnosing deep vein thrombosis (DVT), including clinical assessment, D-dimer, plethysmography, rheography, ultrasound, computed tomographic (CT) scanning, magnetic resonance imaging (MRI) and venography. These may be used in isolation or combined as an algorithm.

Objectives

The objectives of the study were:

- To estimate the diagnostic accuracy of non-invasive tests for proximal DVT and isolated calf DVT, in patients with clinically suspected DVT or high-risk asymptomatic patients, and identify factors associated with variation in diagnostic performance.
- To identify practical diagnostic algorithms for DVT, and estimate the diagnostic accuracy, clinical effectiveness and cost-effectiveness of each.

Methods

Data sources

Diagnostic test data and diagnostic algorithms were sought from electronic searches of MEDLINE, EMBASE, CINAHL, Web of Science, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, Database of Reviews of Effectiveness, NHS Economic Evaluations Database, Health Technology Assessment database, BIOSIS and the ACP Journal Club, 1966–2004. Additional diagnostic test data were sought from the bibliographies of articles included in the review and contact with manufacturers of assays and instruments.

A postal survey of hospitals in the UK was undertaken to describe current practice and availability of tests, and identify additional diagnostic algorithms.

Study selection

Diagnostic cohort studies published in English, French, Spanish or Italian that compared a non-invasive diagnostic test for DVT to an acceptable reference standard were included in the review.

Data extraction

Details of study setting, recruitment, exclusions, population characteristics, reference standard, operator and results were extracted. Quality was judged against validated criteria.

Data synthesis

Pooled estimates of sensitivity, specificity and likelihood ratios were obtained for each test using random effects meta-analysis (MetaDISC software). The effect of study-level covariates was explored using random effects metaregression. A decision-analytic model was used to combine estimates from the metaanalysis and estimate the diagnostic performance of each algorithm in a theoretical population of outpatients with suspected DVT. The net benefit of using each algorithm was estimated from a health service perspective, using cost–utility analysis, assuming thresholds of willingness to pay of £20,000 and £30,000 per quality-adjusted life-year (QALY). The model was analysed probabilistically and cost-effectiveness acceptability curves were generated to reflect uncertainty in estimated cost-effectiveness.

Results

Individual clinical features are of limited diagnostic value, with most likelihood ratios being close to 1. Wells clinical probability score stratifies proximal, but not distal, DVT into high-, intermediate- and low-risk categories. Unstructured clinical assessment by experienced clinicians may have similar performance to Wells score. In patients with clinically suspected DVT, D-dimer has 91% sensitivity and 55% specificity for DVT, although performance varies substantially between assays and populations. D-dimer specificity is dependent on pretest clinical probability, being higher in patients with a low clinical probability of DVT. Plethysmography and rheography techniques have modest sensitivity for proximal DVT, poor sensitivity for distal DVT, and modest specificity. Ultrasound has 94% sensitivity for proximal DVT, 64% sensitivity for distal DVT and 94% specificity. Computed tomography

scanning has 95% sensitivity for all DVT (proximal and distal combined) and 97% specificity. Magnetic resonance imaging has 92% sensitivity for all DVT and 95% specificity. The diagnostic performance of all tests is worse in asymptomatic patients.

The most cost-effective algorithm discharged patients with a low Wells score and negative D-dimer without further testing, and then used plethysmography alongside ultrasound, with venography in selected cases, to diagnose the remaining patients. However, the cost-effectiveness of this algorithm was dependent on assumptions of test independence being met and the ability to provide plethysmography at relatively low cost. Availability of plethysmography and venography is currently limited at most UK hospitals, so implementation would involve considerable reorganisation of services.

Two algorithms were identified that offered high net benefit and would be feasible in most hospitals without substantial reorganisation of services. Both involved using a combination of Wells score, D-dimer and above-knee ultrasound. For thresholds of willingness to pay of £10,000 or £20,000 per QALY the optimal strategy involved discharging patients with a low or intermediate Wells score and negative D-dimer, ultrasound for those with a high score or positive D-dimer, and repeat scanning for those with positive D-dimer and a high Wells score, but negative initial scan. For thresholds of £30,000 or more a similar strategy, but involving repeat ultrasound for all those with a negative initial scan, was optimal.

Conclusions

Implications for healthcare

Diagnostic algorithms based on a combination of Wells score, D-dimer and ultrasound (with repeat if negative) are feasible at most UK hospitals and are among the most cost-effective. Use of repeat scanning depends on the threshold for willingness to pay for health gain. Further diagnostic testing for patients with a low Wells score and negative D-dimer is unlikely to represent a cost-effective use of resources.

Recommendations for research

The recommendations for further research include the following:

- Evaluation of the costs and outcomes of using the optimal diagnostic algorithms in routine practice,
- The development and evaluation of algorithms appropriate for specific groups of patients with suspected DVT, such as intravenous drug abusers, pregnant patients and those with previous DVT,
- The evaluation of the role of plethysmography: interaction with other diagnostic tests, outcome of low-risk patients with negative plethysmography and measurement of the costs of providing plethysmography,
- Methodological research into the incorporation of meta-analytic data into decision-analytic modelling.

Chapter 1
Introduction

Background

Venous thromboembolism consists of a spectrum of clinical disorders, including asymptomatic deep vein thrombosis (DVT), symptomatic DVT and pulmonary embolus (PE). DVT limited to the calf veins (below-knee or distal DVT) is often asymptomatic and rarely associated with adverse outcomes.[1] DVT that extend above the knee (proximal DVT) carry a significant risk of propagation to form PE, resulting in cardiac or respiratory compromise and, in severe cases, death. In addition, DVT may itself be associated with significant morbidity through the development of post-thrombotic syndrome (PTS).

Incidence of DVT

Venous thromboembolism affects approximately 100 persons per 100,000 population per year.[2] Approximately one-third present with features of PE (such as chest pain or difficulty in breathing), while two-thirds present with features of DVT (such as calf pain or swelling).[2] Incidence increases with age, rising exponentially from less than 5 per 100,000 per year in those aged under 15 to over 500 per 100,000 per year in those aged over 80 years.[2] A number of risk factors have been identified for venous thromboembolism. Strong risk factors are: major general surgery, major trauma, hip or knee replacement surgery, hip or leg fractures and spinal cord injury. Other risk factors include malignancy, previous DVT or PE, cardiac or respiratory failure, prolonged immobility, pregnancy, oestrogen therapy and obesity.[3]

Diagnostic testing for DVT is thus typically indicated for two distinct groups: patients presenting with clinically suspected DVT and asymptomatic patients with strong risk factors for DVT. The distribution of DVT differs markedly between these two groups. Most patients with clinically suspected DVT have proximal DVT, whereas most asymptomatic patients have isolated distal DVT.[1] This has important implications for their diagnosis and treatment.

Treatment of DVT

Treatment for DVT is well established.[4,5] Anticoagulation is initially provided by intravenous or subcutaneous heparin, followed by oral warfarin for a period of between 6 weeks and 6 months. Anticoagulation aims to reduce the risk of recurrent DVT, post-thrombotic syndrome and development of PE. The benefit of treatment is thus related to the risks of these outcomes and is substantially greater for patients with proximal DVT. Anticoagulation carries a significant risk of haemorrhage, which in severe cases may be fatal.[6] Thus, decision-making involves weighing the potential benefits and risks of anticoagulant treatment. It is generally accepted that, for patients with proximal DVT, the benefits outweigh the risks and anticoagulation is indicated. For patients with distal DVT the decision is much less clear. Although distal DVT do not usually require treatment they may extend over time to form proximal DVT.[7]

Diagnostic testing for DVT

Traditionally, DVT has been diagnosed by contrast venography. This technique allows excellent visualisation of the venous system and identification of both proximal and distal DVT. It is thus regarded as the reference standard for DVT diagnosis. However, it has a number of limitations. The use of intravenous contrast may be contraindicated by pregnancy, renal failure or known allergy; the procedure may be technically difficult; it is expensive and requires expert interpretation, and it is often uncomfortable for the patient. This has led to the search for cheaper, simpler, non-invasive tests for DVT.

Clinical assessment

The simplest approach to diagnosis involves using the clinical history and examination. A number of individual clinical symptoms and signs may be useful in diagnosis. These may be used by an experienced clinician to estimate an overall clinical probability of DVT (an empirical estimate of clinical probability). Recent research has focused on developing clinical scores that risk-stratify patients by combining a number of clinical features. The most widely used of these is the Wells score.[8] Patients are categorised using a clinical model into high-, intermediate- and low-risk groups. A recent modification of the score uses only two categories: DVT likely and DVT

unlikely.[9] Clinical scores have the theoretical advantages over empirical estimates of clinical probability of being more easily reproducible and less dependent on clinician skill and experience.

D-dimer

D-dimer is a plasmin-mediated proteolytic derivative that is specific for cross-linked fibrin and can be detected on routine blood testing. Elevated plasma D-dimer levels are seen with a number of conditions, including DVT. There are three main methods of D-dimer detection: enzyme-linked immunosorbent assay (ELISA), latex-agglutination assay and whole-blood agglutination. ELISA appears to be highly sensitive, but assays may be time consuming to perform and lack specificity.[10] Latex-agglutination and whole-blood agglutination assays are rapid, but are usually considered to have poorer sensitivity,[10] although more recent latex assays have better sensitivity. ELISA and latex-agglutination assays are usually quantitative, laboratory-based assays, whereas the commonly used whole-blood agglutination assay (SimpliRED) is a qualitative test, available for point-of-care use.

A substantial amount of research has been published relating to the diagnostic accuracy of D-dimer for DVT.[11] These studies have used a variety of different assays and diagnostic thresholds, and have varied in their inclusion of patients with conditions know to cause elevations of D-dimer: malignancy, infection, pregnancy, trauma and surgery. This has led to substantial variation in reported sensitivity and specificity, and confusion regarding the appropriate role for D-dimer.

Plethysmography and rheography techniques

Plethysmography is the measurement of changes in volume of a limb in response to changes in blood volume. In the diagnosis of DVT, changes in limb volume with respiration and the rate of change in response to release of an occlusive cuff on the proximal thigh give information about the patency of the venous system of the lower limb. Changes in limb volume can be measured directly by surrounding the limb in an air-filled cuff or by the use of strain gauges placed circumferentially around the limb, or indirectly by measuring changes in the electrical impedance of the limb.

Phleborheography is based on the measurement of changes in lower limb volume, and thus lower limb venous outflow, in response to respiration. It involves the simultaneous measurement of changes of pressure in cuffs placed around the epigastrium, thigh and calf. The normal phasic pattern of venous outflow with respiration is lost or diminished in acute DVT.

In light reflection rheography near-infrared light is beamed into the skin of the limb being studied and the quantity reflected is measured. The degree of reflection is determined by the filling of the dermal venous plexus. Changes in the degree of reflection, and therefore the filling of the venous plexus, in response to manoeuvres such as repeated dorsiflexion of the foot give an indication of the patency of the deep veins of the lower limb.

Plethysmography and rheography techniques have been investigated for over 30 years, so it is surprising that consensus has not yet been reached regarding their role. Variation in technique and operator may contribute to variation in the reported accuracy. Most data are available on impedance plethysmography.[12] Sensitivity and specificity appear to be reasonable for proximal DVT in symptomatic patients, but poor for distal DVT and asymptomatic patients.

Ultrasound

Ultrasound scanning has made considerable technological progress over the past 30 years. Continuous wave Doppler assessment is a non-invasive imaging method to assess the presence of flowing blood in arteries or veins. The simplest imaging ultrasound technique is grey-scale (B-mode) ultrasound imaging, which allows direct visualisation of the vessel lumen. Grey-scale imaging has more recently been supplemented by a range of Doppler ultrasound techniques that add to the analysis of blood flow by the grey-scale image, using techniques such as gated flow velocity waveform analysis, colour flow imaging and power Doppler. The advantages of colour flow imaging are mainly in helping to identify the deep veins, particularly in the calf. The ultrasound techniques used to diagnose DVT include assessment of venous compressibility (normal veins can be completely compressed), direct clot visualisation on the grey-scale image and using Doppler, colour flow and power Doppler imaging to help further identify areas of venous thrombosis. Although readily acceptable to patients, ultrasound requires an expert operator, and can be time consuming, particularly if the calf veins are examined.

The diagnostic accuracy of ultrasound has been widely studied.[12–15] As with plethysmography, variation in the technique used and the operator may limit the conclusions that can be drawn.

Ultrasound seems to have better sensitivity and specificity than impedance plethysmography,[12] although sensitivity for distal DVT[14] and sensitivity in asymptomatic patients[15] are far from optimal.

Repeat or serial ultrasound

In many centres initial ultrasound scanning is followed by a repeat scan 1 week later if the initial scan is normal.[16–20] From an epidemiological perspective this approach makes little sense. If the repeat scan is independent of the first then, having detected most cases of DVT by the initial scan, one would expect most positive results on the repeat scan to be false positives.

The rationale for this approach is therefore pathophysiological. Ultrasound does not detect distal DVT very well, but distal DVT do not require treatment unless they propagate to form proximal DVT. It is estimated that a substantial proportion of distal DVT propagate in this way.[7] The aim of the repeat scan is to detect distal DVT that have propagated to form proximal DVT. This approach seems to assume that the repeat scan has very high specificity and does not generate many false-positive results. This is probably reasonable because patients with conditions likely to cause a false-positive scan will have had a positive initial scan and will therefore not have proceeded to repeat scanning. However, the empirical evidence to support this is very limited.

Computed tomography and magnetic resonance imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) are powerful imaging tools that allow a detailed assessment of patient anatomy and can be used throughout the body. Their role in the diagnosis of DVT is relatively new.

CT uses a technique that usually depends on conventional iodinated contrast being present in the deep veins of the lower limb during scanning. This can be achieved by techniques similar to lower limb venography, with contrast injected into the foot. More usually, contrast is injected into a peripheral arm vein and the scan timed to coincide with the passage of the bolus of contrast into the deep veins of the leg. The diagnosis of DVT can be made by the direct visualisation of thrombus in the vein, or by inference when a section of vein does not fill with contrast.

MRI can use techniques to image blood flow that do not require the use of contrast agents, and rely on the intrinsic properties of flowing blood and how this appears on a magnetic resonance (MR) image to visualise the veins. However, the imaging of vascular structures is often improved by the use of MRI contrast agents. These can be either injected into a vein in the foot or given as a peripheral arm injection with imaging timed for optimal imaging of lower limb veins, these techniques being analogous to those described for CT imaging. MRI can produce subtracted images to highlight vascular structures, both arteries and veins. In a similar way to CT the presence of thrombus can be assessed by direct visualisation, or by inference when a section of vein is not visualised as would be expected if it contained normal flowing blood. MR techniques have also been described that allow direct thrombus imaging within the deep veins.

CT and MRI share many of the disadvantages of contrast venography. They are relatively expensive techniques that require expert interpretation. Contrast agents can be more easily injected via an arm vein, but still carry risks of anaphylaxis. CT has an additional disadvantage of requiring a substantial radiation dose.

Diagnostic algorithms

None of these diagnostic modalities has the ideal characteristics of being low cost, perfectly accurate, reliable, easy to operate and convenient for the patient. Indeed, it is apparent that non-invasive tests for DVT form a spectrum from the low cost and relatively inaccurate (clinical scores, D-dimer) to the more expensive and accurate (ultrasound, CT and MRI). This has two important implications:

- It is likely that an optimal approach to diagnosis involves a combination of tests, with low-cost, simple methods (such as a clinical score) being used to select patients for subsequent diagnostic testing, and expensive, accurate tests being reserved for cases where they are of greatest value.
- It is likely that deciding what constitutes an optimal diagnostic approach will involve weighing the risks and benefits of treating patients with and without DVT. This in turn involves weighing the benefit of accurate testing against its cost. The choice of an optimal diagnostic strategy, from the health service perspective, is thus ultimately determined by considerations of cost-effectiveness.

Current practice in the NHS

Before making judgements regarding the appropriate combination of tests for diagnosing

DVT the researchers needed to know more about current practice in the NHS. This will help to determine what tests are currently available and what variations in practice exist. A postal survey of 255 emergency departments in the UK was carried out to determine what diagnostic tests are currently used for patients presenting with suspected DVT. The response rate was 73% (186/255). The results are shown in *Figure 1*.

Ultrasound and laboratory-based D-dimer were the most commonly used tests. Three-quarters of departments reported that they had a protocol or an algorithm to guide diagnosis (135/180) and 61 departments sent a copy of their algorithm. Review of these algorithms revealed that 16 were actually management algorithms, concerning diagnosed DVT, while 45 were genuine diagnostic algorithms. In most cases the protocol involved a combination of Wells clinical score, D-dimer and ultrasound, although the decisions made on the basis of test results varied among protocols. For example, some protocols advised no further testing for patients with a low Wells score, whereas others advised D-dimer or ultrasound. This survey therefore shows that current practice in the UK reflects uncertainty as to the role of non-invasive diagnostic tests for DVT, and that strategies involving a combination of tests are widely used.

An optimal approach to diagnostic testing

Despite the substantial amount of literature available there does not appear to be a consistent approach to the diagnosis of DVT. There are several reasons for this. These issues must be addressed in order to develop an optimal approach to diagnostic testing.

- There is considerable heterogeneity in the findings of primary studies into diagnostic modalities.[10,12] This may be due to variation in setting, selection of patients, techniques used, methodological standards or reporting of results. Few existing reviews have explored these potential causes of heterogeneity.
- Even if the diagnostic parameters of individual tests are known, there is a need to know how these tests perform when combined; specifically, whether they are independent of each other and whether diagnostic performance is dependent on pretest probability.
- Little attention has been paid to the health benefits of diagnostic tests. Knowledge of the sensitivity and specificity of a testing regimen should only guide practice if the benefits of treating true positives and the risks of treating false positives and not treating false negatives

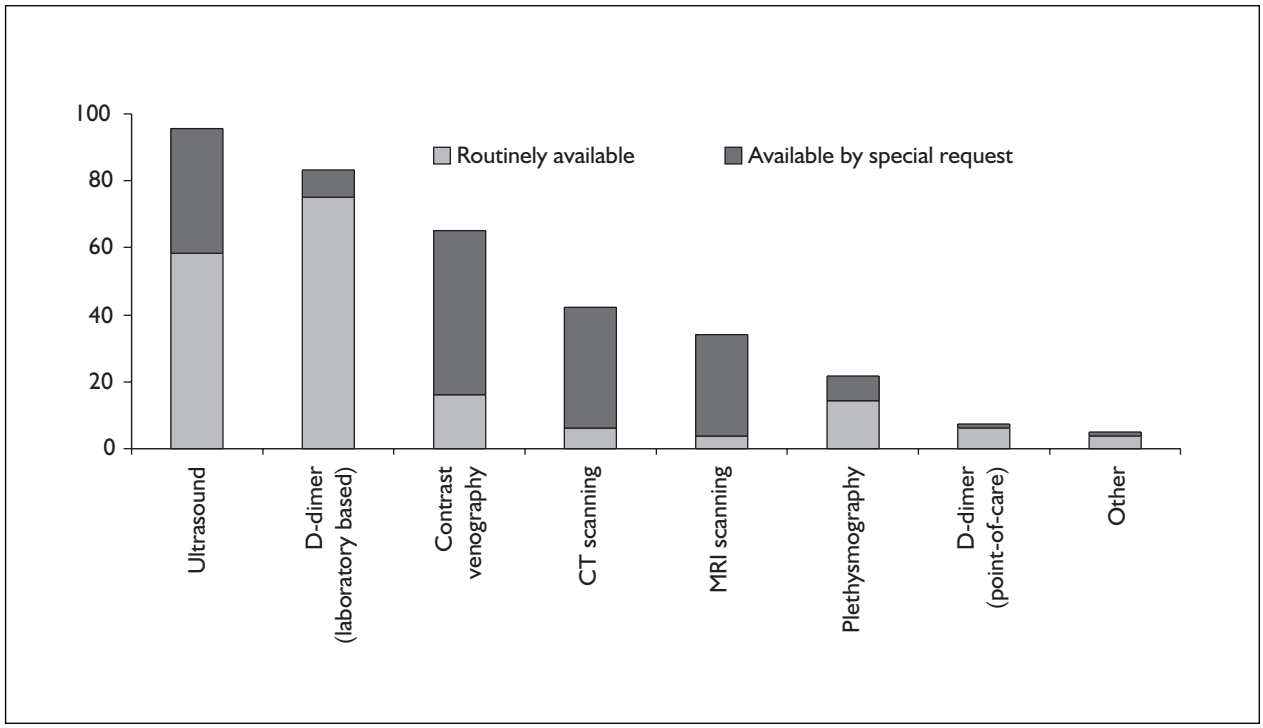

FIGURE 1 *Availability of diagnostic tests for DVT in the UK*

are considered and analysed. The sensitivity and specificity of diagnostic strategies must be combined with treatment/non-treatment outcomes to estimate final health outcomes that are meaningful to patients.
- Much of the advantage of using clinical assessment and non-invasive tests lies in reducing health service costs. Assimilation of data needs to include evaluation of the trade-off between increasing the cost and increasing the effectiveness of assessment.

These latter issues have been explored using modelling techniques. Perone and colleagues[21] concluded that combining clinical probability with a single ultrasound examination was the most cost-effective strategy, whereas Kim and colleagues[22] concluded that bilateral ultrasound with a repeat examination was a cost-effective approach. It is not clear how strategies were selected for evaluation in these studies, whether analyses were based on a systematic review of the best available data, what criteria were used for decision making and whether the results are applicable to the NHS.

Hence, it is apparent that, despite a substantial volume of primary research, few firm conclusions can be drawn regarding appropriate diagnostic strategies for suspected DVT. Yet there is a strong demand for implementation of a non-invasive strategy, as contrast venography is invasive and has a limited availability. While there may be limitations in the primary data, it is clear that a more rigorous and extensive secondary analysis is needed to guide decision making. This needs to go beyond systematic review and meta-analysis. Modelling is needed to define and explore the trade-offs involved in diagnosis, to handle uncertainty produced by limitations of empirical data and to identify the areas where further primary research would be most valuable.

Aims and objectives

The aim was to use secondary research methods to measure the accuracy, clinical effectiveness and cost-effectiveness of diagnostic tests for DVT. The specific objectives were:

- to estimate the diagnostic accuracy of clinical assessment, D-dimer, plethysmography and rheography techniques, ultrasonography, MRI and CT scanning for proximal and isolated calf DVT
- to identify factors that are associated with variation in diagnostic performance
- to identify feasible algorithms for the diagnosis of DVT involving combinations of clinical assessment and diagnostic tests, and measure the diagnostic accuracy of each algorithm
- to assess the benefit of diagnostic strategies in clinically relevant terms, such as mortality and quality of life
- to estimate the cost-effectiveness (net benefit) of each diagnostic algorithm
- to explore the consistency of findings in different settings and different patient groups (symptomatic versus asymptomatic patients, postoperative patients, patients with recent trauma, pregnancy, past history of thromboembolism, malignancy or obesity), and for different baseline prevalences of DVT
- to determine what future research is required to improve the reliability of estimates.

Chapter 2

Systematic reviews and meta-analysis of non-invasive diagnostic tests: methods

A systematic review of the literature and meta-analysis was undertaken to estimate the diagnostic accuracy for proximal and distal DVT of each of the following tests:

- clinical assessment: individual clinical characteristics and composite clinical scores
- D-dimer assays: latex, ELISA and whole-blood agglutination
- plethysmography and rheography techniques: impedance, strain-gauge and air plethysmography, phleborheography and light-reflex rheography
- ultrasonography
- CT scan
- MRI scan.

The aim was to identify all diagnostic cohort studies that compared the test in question to a reference standard for DVT. The ideal reference standard would be venography. However, since non-invasive testing has become more widespread and accepted as a potential reference standard, few studies now use venography as a reference standard. Therefore, different reference standards were accepted for the different tests.

- Ultrasound: only studies using venography as a reference standard were sought.
- Plethysmography, rheography, CT and MRI: studies using venography or ultrasound as a reference standard were sought.
- Clinical features and D-dimer: studies using any other non-invasive test or venography as a reference standard were sought.

Literature search

The following electronic databases were searched using the search strategies outlined in Appendix 1: 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). The bibliographies of all articles selected for the review were scanned for potentially relevant articles that were not identified by the original search. Manufacturers of assays and instruments were contacted to identify unpublished studies.

Selection of studies

The titles and abstracts of all articles identified by the search strategy were screened by two reviewers (FS and SG), who independently determined whether the article could potentially describe the diagnostic performance of the non-invasive test under review, compared with the appropriate reference standard. A kappa score was calculated and disagreements were resolved by discussion. Full copies of all selected articles were retrieved. These articles were then reviewed by the same two reviewers, who independently selected articles that measured the diagnostic performance of the non-invasive test, compared with the appropriate reference standard test. A kappa score was calculated and disagreements were resolved by discussion.

Exclusion criteria

The following studies were excluded:

- prognostic studies (i.e. cohort studies that measured the risk of DVT developing after testing, rather than the probability of DVT being present at the time of testing)
- case–control studies (i.e. studies in which patients were selected on the basis of the results of their reference standard test)
- studies with fewer than ten patients
- studies published in languages other than English, French, Spanish or Italian
- studies of patients with suspected PE, except for the review of CT scanning, where such studies provide most of the available evidence.

If a study was published as an abstract or letter the authors were contacted to ask for details of the data. If it was not possible to extract the necessary

data from the published report the authors were contacted for clarification, provided the study was published in the past 10 years.

Quality of studies

The quality of each study was assessed according to the following criteria:

- Was application of the reference standard:
  - independent of the results of the non-invasive test
  - dependent on the results of the non-invasive test
  - unclear?
- Was non-invasive testing performed/interpreted by observers who were:
  - blind to the reference standard result
  - aware of the reference standard result
  - unclear?
- Was the reference standard performed/interpreted by observers who were:
  - blind to the results of the non-invasive test
  - aware of the results of the non-invasive test
  - unclear?

Independence of the reference standard relates to circumstances where more than one reference standard was applied, or where a single reference standard could be applied in different ways. If all study participants received the same reference standard applied in the same way, then the reference standard was clearly independent. If the reference standard was applied by carers or researchers who were blind to the non-invasive test result, then the reference standard would also be considered to be independent. However, if application of the reference standard could have varied between patients (e.g. if some received ultrasound scanning and follow-up, whereas others received scanning without follow-up) and the decision to apply the reference standard was made by someone who was, or could have been, aware of the non-invasive test result, then the reference standard was considered to be either dependent or unclear.

Several checklists have been published that can be used to assess the quality of articles evaluating diagnostic tests.[23–25] However, most criteria on these 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 composite score. Therefore, three key quality indicators were selected that have been shown empirically to be associated with design-related bias in studies of diagnostic tests.[26]

Data extraction

The following data were extracted from each article:

- whether patients were being investigated for clinically suspected DVT or were asymptomatic patients being screened because of a high risk of DVT
- the setting for patient recruitment: emergency department, primary care, outpatient clinic, in-hospital or mixed setting
- patient groups excluded from the study
- whether patient recruitment was consecutive or not
- whether data collection was prospective or not
- population characteristics: mean age, age range, gender balance
- the prevalence of all DVT, and proximal and distal DVT if reported separately
- the operator or observer performing/interpreting the test
- the interobserver error of interpretation of the non-invasive test
- the reference standard(s) used
- the quality criteria outlined above
- the reported sensitivity and specificity of the non-invasive test
- the number of true positives (all DVT, proximal DVT and distal DVT), true negatives, false positives and false negatives (all, proximal and distal)

Full details of proximal and distal DVT were only available if an adequate reference standard was used (usually venography) and if data were fully reported. In these circumstances 'all DVT' referred to proximal and distal DVT combined. Sensitivity was calculated for all DVT combined, and for proximal and distal DVT separately. In other circumstances 'all DVT' referred to all the cases of DVT reported, with no attempt being made to analyse proximal and distal DVT separately.

For ultrasound, where the reference standard was always venography, an attempt was made to identify how proximal and distal DVT had been handled if they were not reported separately. Studies were classified as:

- proximal and distal DVT reported together
- only proximal DVT reported
- only distal DVT reported
- reporting not clear.

This was not possible for other technologies, for two reasons: (1) when a reference standard other than venography was used it was usually unclear how proximal and distal DVT were handled; and (2) if follow-up or repeat scanning was used to identify DVT, it was impossible to determine whether DVT had been proximal or distal at the time of presentation.

Other data items were recorded for specific tests:

- clinical assessment: whether clinical features were recorded on a standard pro forma or abstracted from case notes
- D-dimer: the type of assay (latex, ELISA or whole-blood agglutination), name of assay, threshold used and manufacturer
- plethysmography: type of plethysmograph (impedance, strain-gauge or air), and whether results were interpreted by an observer or generated automatically
- ultrasound: compression, continuous wave Doppler or colour Doppler
- MRI and CT: whether intravenous contrast was used.

Statistical analysis

Meta-analysis

Meta-analysis was undertaken to obtain pooled estimates of sensitivity specificity and likelihood ratios. Estimates of sensitivity for all DVT and specificity were obtained using data from all studies. Estimates of sensitivity for proximal and distal DVT were obtained using data from studies that reported these separately. In all analyses specificity refers to the ability of the test to identify correctly cases without DVT. No attempt was made to recalculate specificity assuming that distal DVT were classified as normal.

Analyses of all diagnostic tests were undertaken, with the exceptions noted below, using MetaDiSc statistical software.[27] Cohorts of patients with clinically suspected DVT, asymptomatic cohorts and mixed cohorts were analysed separately. For each diagnostic test a random effects model was used to calculate, with 95% confidence intervals, the pooled sensitivity for all DVT, pooled sensitivity for proximal DVT, pooled sensitivity for distal DVT and pooled specificity for no DVT. Where zero counts occurred for study data, a continuity correction of 0.5 was added to every value for that study in order to make the calculation of sensitivity and specificity defined. A χ^2 test of heterogeneity was performed for each analysis.

A different approach was used for clinical assessment. For individual clinical characteristics a random effects model was used, as implemented by MetaDiSc software, to calculate pooled estimates of the positive and negative likelihood ratios with 95% confidence intervals. This approach was used because individual clinical features are unlikely to be used in isolation to rule in or rule out DVT. Instead, they are more likely to be used in a Bayesian approach to modify estimates of the likelihood of DVT. Hence, likelihood ratios give a better impression of the potential value of each clinical feature.

Clinical scores tend to use three categories, so analysis was more complex than for a dichotomous test. Results are usually reported as the prevalence of DVT in each category. This is similar to reporting the positive and negative predictive values of a dichotomous test, and would be expected to vary with the population prevalence of DVT. Therefore, data were analysed by determining for each study how cases with DVT and those without DVT were categorised. This is similar to analysing the sensitivity and specificity of a dichotomous test.

In addition, a different approach to meta-analyses of clinical scores had to be developed because statistical software, such as MetaDiSc, does not allow for meta-analysis of diagnostic tests with more than two categories. Ordinal logistic regression, including a random study effect coefficient, was carried out to estimate the probability of being categorised as high, intermediate and low risk using separate models for those with any DVT, those with a proximal DVT, those with a distal DVT and those without DVT. From this analysis, it was possible to estimate sensitivity and specificity for two possible decision thresholds: high versus intermediate and low, and high and intermediate versus low. A combination of the NLMIXED procedure in SAS[28] and WinBUGS software[29] was used for the analysis. Pooled estimates of likelihood ratios for high-risk (versus intermediate and low risk) and low-risk (versus high and intermediate risk) categories were calculated using MetaDiSc software.

Metaregression

Meta-analysis of diagnostic test data often reveals substantial heterogeneity between the results of individual studies. In these circumstances, if sufficient numbers of studies are available, metaregression may be useful for identifying

study-level covariates that predict variation in diagnostic performance. Metaregression was undertaken if a test supported by a substantial number of studies was identified, but with evidence of heterogeneity among results.

Random effects metaregression was undertaken using STATA statistical software. Any covariate that showed an association with sensitivity or specificity ($p < 0.1$) was selected, and subgroups of studies identified by such covariates were meta-analysed separately. A different approach was used for clinical scores that had more than two diagnostic categories. The ordinal regression model outlined above was extended to fit a summary receiver operating characteristic (SROC) curve through the data, and the influence of adding covariates into the model on the shape of the curve was explored.[30]

The following covariates were used in metaregression:

- population characteristics: age, gender and prevalence of DVT
- exclusion criteria used (if reported in a sufficient number of studies)
- the reference standard used
- the setting for patient recruitment (emergency department, primary care, outpatient clinic, in-hospital, or a combination of these)
- quality criteria.

If the analysis was supported by only a limited number of studies, or studies of poor quality, then heterogeneity was explored in a more subjective manner. Articles were reread by reviewers and attempts made to identify potential factors that could explain the observed heterogeneity.

Chapter 3

Systematic reviews and meta-analysis of non-invasive diagnostic tests: results

Over 10,000 articles were scanned for the literature review. The results of the selection process are summarised in *Table 1*.

Clinical assessment

In total, 3332 titles/abstracts were scanned and 97 potentially relevant articles selected for retrieval (kappa=0.85). Review of the full articles identified 68 that met the inclusion criteria (kappa=0.86). Three of these duplicated data published elsewhere and were excluded. No appropriate data could be extracted or analysed from a further 18 articles, despite attempts to contact the authors. Review of the bibliographies of the selected articles identified two additional articles for inclusion. Thus, 49 articles were included in the meta-analysis: 29 reported clinical features[31–59] and 24 reported clinical scores.[8,9,31,34,35,58,60–77] Four reported both.[31,34,35,58]

Individual clinical features

Data were extracted from 29 studies, reporting 31 cohorts evaluating individual clinical features, outlined in Appendix 2 (*Table 30*). DVT prevalence ranged from 12 to 70% (median 33%). Prevalence of proximal and distal DVT was reported by 13 cohorts, with a proportion of proximal DVT (of all DVT detected) ranging from 18 to 92% (median 75%). Mean age ranged from 45 to 69 (median 56) years. The male to female ratio ranged from 30% male to 61% male (median 40% male).

Cohorts were recruited from the following settings: outpatient clinic (nine), inpatients (eight), emergency department (three), mixed (four) and not stated (seven). Recruitment was reported to be consecutive in 14 cohorts and prospective in 20. Most cohorts did not report exclusion criteria. The only exclusions reported with any frequency were past history of thromboembolism (six cohorts), anticoagulated patients (five) and pregnancy (three).

Data were collected on a standardised pro forma for nine cohorts, were abstracted from case notes for five and were not reported by 17. Data were recorded by a physician for 11 cohorts, a trained nurse for one and were not reported for 19. The reference standard was venography for 18 cohorts and ultrasound for 13.

Quality criteria were recorded as follows:

- The reference standard was applied independently of the results of clinical assessment in 28 cohorts, was dependent in two and was unclear in one.
- Clinical features were interpreted blind to the reference standard in ten cohorts and interpretation was unclear in 21.
- The reference standard was interpreted blind to the clinical features in five cohorts, was interpreted by unblinded observers in one and interpretation was unclear in 25.

The results of meta-analysis are outlined in *Table 2*. If a likelihood ratio of greater than 2 is

TABLE 1 *Selection of articles from literature searches*

	Clinical assessment	D-dimer	Plethysmo-graphy	Ultrasound	CT	MRI
Abstracts/titles scanned	3332	1140	995	3992	2038	1291
Articles selected for retrieval	97	247	254	400	42	35
Kappa for retrieval	0.85	0.87	0.85	0.85	0.76	0.84
Retrieved articles selected for inclusion	68	131	114	151	14	16
Kappa for inclusion	0.86	0.94	0.92	0.90	0.93	0.91
Unable to extract relevant data	18	15	22	9	3	1
Same data published elsewhere	3	6	8	6	2	2
Additional articles identified from bibliography or other sources	2	0	4	6	0	1
Articles included in the meta-analysis	49	110	88	142	9	14

TABLE 2 *Diagnostic value of clinical features for DVT*

Clinical feature	Number of studies	Likelihood ratio of positive feature (95% CI)	*p*-Value for heterogeneity	Likelihood ratio of negative feature (95% CI)	*p*-Value for heterogeneity
Calf pain	12	1.08 (0.96 to 1.2)	0.005	0.90 (0.78 to 1.03)	0.005
Calf swelling	13	1.34 (1.17 to 1.53)	<0.001	0.66 (0.56 to 0.77)	0.047
Past history of DVT	9	2.54 (1.79 to 3.61)	<0.001	0.88 (0.85 to 0.92)	0.173
Malignancy	17	2.61 (2.03 to 3.36)	0.004	0.88 (0.83 to 0.94)	<0.001
Recent immobilisation	14	1.93 (1.63 to 2.28)	0.227	0.89 (0.83 to 0.95)	<0.001
Recent surgery	14	1.72 (1.35 to 2.19)	0.002	0.93 (0.88 to 0.97)	<0.001
Obesity	4	1.02 (0.75 to 1.38)	0.81	0.99 (0.97 to 1.03)	0.853
Difference in calf diameter	7	1.76 (1.43 to 2.18)	<0.001	0.51 (0.37 to 0.71)	0.001
Homan's sign	11	1.40 (1.18 to 1.66)	0.254	0.87 (0.79 to 0.96)	0.019
Warmth	11	1.31 (1.08 to 1.60)	0.001	0.85 (0.75 to 0.98)	<0.001
Tenderness	12	1.18 (1.06 to 1.32)	0.008	0.78 (0.69 to 0.89)	0.249
Erythema	6	1.30 (1.02 to 1.67)	0.059	0.88 (0.80 to 0.98)	0.278
Oedema	10	1.18 (0.99 to 1.41)	<0.001	0.89 (0.77 to 1.03)	0.076

CI, confidence interval.

considered useful for ruling in DVT, and less than 0.5 useful for ruling out, then only a past history of DVT and malignancy are useful for ruling in, and no individual feature is useful for ruling out. Recent immobilisation, recent surgery or a measured difference in calf diameter are of borderline value in ruling in, while absence of calf swelling or a difference in calf diameter are of borderline value in ruling out DVT.

The results of individual studies and the pooled estimates for each likelihood ratio are shown in the additional figures in Appendix 3 (*Figures 31–56*).

Clinical scores

Data were extracted from 24 studies, reporting 25 cohorts evaluating clinical probability scores, outlined in Appendix 2 (*Table 31*). Of these, 21 cohorts evaluated the Wells score,[8,31,34,35,58,60–73,76] two cohorts used a dichotomised version of the Wells score,[9,77] four cohorts evaluated empirical risk assessment in which clinicians categorised patients into high, intermediate and low risk of DVT on the basis of an unstructured risk assessment,[60,63,75,76] and four cohorts evaluated other scores.[34,35,74]

DVT prevalence ranged from 10 to 47% (median 25%). Prevalence of proximal and distal DVT was reported by 13 cohorts, with a proportion of proximal DVT ranging from 46 to 92% (median 76%). Mean age ranged from 45 to 68 (median 60) years. The male to female ratio ranged from 25% male to 63% male (median 40% male).

Cohorts were recruited from the following settings: outpatient clinic (12), inpatients (two), emergency department (five), mixed (three) and not stated (three). Recruitment was reported to be consecutive in 17 and prospective in 23. Patients with a past history of thromboembolism were excluded from ten cohorts, anticoagulated patients were excluded from 12 and pregnant patients from nine.

Data were collected on a standardised proforma for 11 cohorts and were not reported by 14. Data were recorded by a physician for 15 cohorts, a trained nurse for one and were not reported for nine. The reference standard was venography for three cohorts and ultrasound for 22.

Quality criteria were recorded as follows:

- The reference standard was applied independently of the clinical probability in 17 cohorts and was dependent on the clinical probability in eight.
- Clinical probability was estimated blind to the reference standard in eight cohorts and was unclear in 17.
- The reference standard was interpreted blind to the clinical probability in three cohorts, was interpreted by unblinded observers in one and interpretation was unclear in 21.

Wells clinical probability score

This is a clinical score that categorises patients into high, intermediate and low risk of DVT

TABLE 3 *Wells clinical probability score*

Clinical characteristic	Score
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden >3 days or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below the tibial tuberosity)	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	–2

according to a number of defined criteria (outlined below). A score of 3 or higher indicates high probability of DVT, 1 or 2 a moderate probability, and 0 or lower a low probability (*Table 3*).

The results of the 21 studies of Wells score are plotted on a receiver operating characteristic (ROC) plane in *Figure 2*. Sensitivity and specificity are plotted for two thresholds: high risk versus intermediate and low risk, and high and

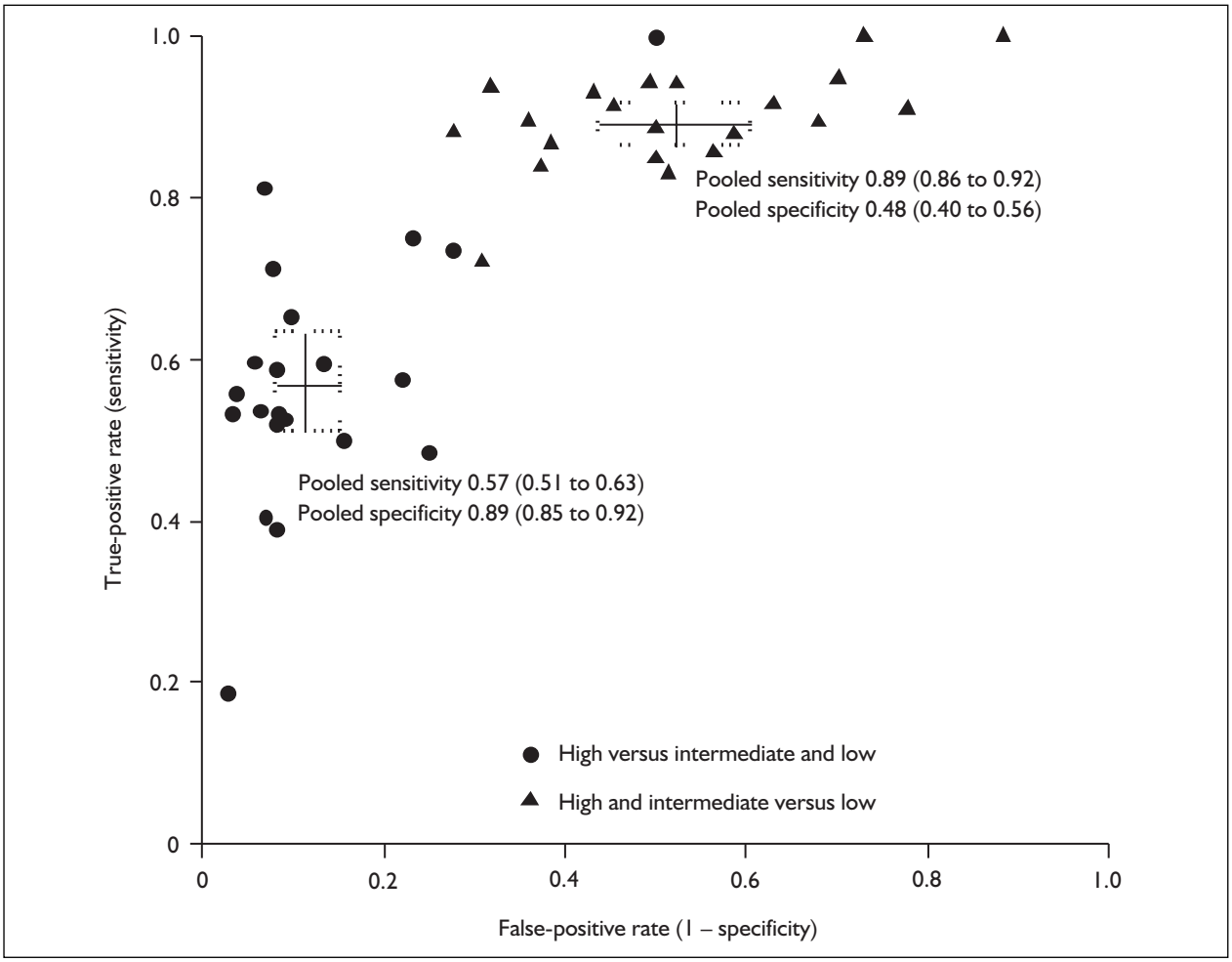

FIGURE 2 *Performance of Wells clinical risk score for detecting all DVT represented on the ROC plane with 95% CI*

TABLE 4 *Summary estimates from meta-analysis of Wells score*

	High risk	Intermediate risk	Low risk
Categorisation of all cases with DVT (n = 21)	56.6% (51.0 to 62.1)	32.2% (28.0 to 36.1)	11.1% (8.4 to 13.8)
Categorisation of proximal DVT (n = 6)	67.7% (56.0 to 80.2)	25.5% (16.0 to 34.6)	6.5% (3.2 to 11.4)
Categorisation of distal DVT (n = 6)	34.0% (21.7 to 49.1)	47.9% (36.2 to 59.3)	17.6% (8.6 to 28.8)
Categorisation of cases without DVT (n = 21)	11.3% (8.4 to 15.0)	40.9% (35.8 to 45.5)	47.7% (39.7 to 55.6)

95% CI in parentheses.

intermediate risk versus low risk. This demonstrates substantial heterogeneity among the results.

The summary estimates from meta-analysis are outlined in *Table 4*. This shows pooled estimates of how all patients with DVT, patients with proximal DVT patients with distal DVT and patients without DVT will be categorised by the Wells score. The values in the top left and right corners of the table are summary estimates of the sensitivity and (1 – specificity) of the high versus intermediate and low threshold values shown in *Figure 2*. The values in the bottom left and right corners of the table are summary estimates of (1 – sensitivity) and the specificity of the high and intermediate versus low threshold values in *Figure 2*.

The likelihood ratio, calculated using MetaDiSc software, of high risk versus intermediate and low categorisation is 5.4 (95% CI 4.1 to 7.2, p-value for heterogeneity <0.001) and for low risk versus intermediate and high categorisation is 0.25 (95% CI 0.21 to 0.29, p-value for heterogeneity = 0.194). The individual study data and pooled estimates of likelihood ratios are plotted in the additional figures in Appendix 3 (*Figures 57* and *58*).

Because clinicians may be more familiar with clinical scores being reported as the prevalence of DVT in each category, the results of meta-analysis were converted into this measure by applying the estimates of categorisation of all DVT (proximal and distal) and no DVT to two theoretical populations. First, a population with a prevalence of DVT of 33% (the same as the median prevalence of the cohorts included in the meta-analysis) was categorised as follows: 26% would be high risk with a DVT prevalence of 71%, 38% would be intermediate risk with a prevalence of 28%, and 36% would be low risk with a prevalence of 10%. However, cohorts enrolled in research studies are likely to have a higher prevalence than the general population with suspected DVT. A population with a DVT prevalence of 15% would be categorised as follows: 18% would be high risk with a DVT prevalence of 47%, 40% would be intermediate risk with a prevalence of 12%, and 42% would be low risk with a prevalence of 4%.

Fitting an SROC to the data in *Figure 2* and examining the influence of study-level covariates using metaregression identified the following as potentially important covariates, associated with improved diagnostic performance: lower mean subject age (p = 0.009), exclusion of persons with a previous history of DVT (p = 0.016) and assessment of the reference standard blind to the results of clinical assessment (p = 0.03). Covariates examined but not statistically significant were: setting for recruitment (p-values for all settings >0.07), exclusion of patients with suspicion of pulmonary embolus (p = 0.66), exclusion of pregnant women (p = 0.30), percentage male (p = 0.98), whether the original or modified Wells criteria were used (p = 0.42), prevalence of DVT in cohort (p = 0.86), whether a standardised pro forma was used for data collection (p = 0.13), whether assessment was carried out by a physician (p = 0.30), use of single ultrasound as a reference standard, compared with venogram or ultrasound with follow-up or repeat (p = 0.85), use of an independent reference standard (p = 0.22) and performance of clinical assessment blind to the reference standard (p = 0.22).

Empirical risk assessment

The results of meta-analysis of the four studies of empirical assessment of clinical probability are shown in *Table 5*. None of the studies reported data for proximal and distal DVT separately.

The pooled estimate of the likelihood ratio of high-risk categorisation is 5.6 (95% CI 1.9 to 16.6, p-value for heterogeneity <0.001) and low-risk categorisation is 0.20 (95% CI 0.10 to 0.41, p-value for heterogeneity = 0.069). The individual study data and pooled estimates of likelihood ratios are plotted in the additional figures in Appendix 3 (*Figures 59* and *60*).

TABLE 5 *Results of meta-analysis of studies of empirical assessment of clinical probability*

	High risk	Intermediate risk	Low risk
Categorisation of all cases with DVT (n = 4)	51.5% (44.3 to 58.9)	40.0% (33.7 to 46.5)	8.3% (5.3 to 12.2)
Categorisation of cases without DVT (n = 4)	11.0% (2.1 to 33.5)	55.1% (23.9 to 62.8)	33.2% (10.9 to 74.1)

95% CI in parentheses.

Wells and colleagues[9] and Tick and colleagues[77] both reported dichotomised versions of the Wells score to stratify into high and low risk. Wells split the intermediate probability group, while Tick combined the high and intermediate probability groups. Wells' study categorised 81% of patients with DVT as high risk and 19% as low risk, and categorised 43% of patients without DVT as high risk and 57% as low risk. Tick's study categorised 90% of patients with DVT as high risk and 10% as low risk, and categorised 47% of patients without DVT as high risk and 53% as low risk.

Other risk scores

Kahn and colleagues[42] used multivariate analysis to develop a four-item clinical prediction index for DVT that stratified patients into low, moderate or high probability of DVT. Constans and colleagues developed a six-item score, the St Andre score, and compared it with the Wells and Kahn scores.[34] A further evaluation prospectively compared the Wells, Kahn and St Andre scores, and developed a new six-item ambulatory score.[35] The new score had similar diagnostic utility to the nine-item Wells score and outperformed the Kahn score. However, this score has yet to be validated in any other setting, so there is currently no opportunity for meta-analysis.

Summary

Individual clinical features are of limited value in the diagnosis of clinically suspected DVT. The Wells score provides a consistent, reproducible way of stratifying patients into high, intermediate and low risk of DVT that has been validated in a variety of different settings and provides useful information to guide further diagnostic testing. Wells risk stratification alone is unlikely to be considered sufficiently accurate to allow treatment or ruling out of DVT without further diagnostic testing. Empirical assessment of clinical probability may be as accurate as Wells stratification, but lacks reproducibility. Other risk assessment scores have yet to be validated and cannot be recommended for routine use.

D-dimer

In total, 1140 titles/abstracts were scanned and 247 potentially relevant articles were selected for retrieval (kappa = 0.87). Review of the full articles identified 131 that met the inclusion criteria (kappa = 0.94). Six of these duplicated data published elsewhere and were excluded. No appropriate data could be extracted or analysed from a further 15 articles, despite attempts to contact the authors. Review of the bibliographies of the selected articles identified no additional articles for inclusion. Thus, 110 articles were included in the meta-analysis: 101 were published in English, five in French, two in Spanish, and one each in Italian and German. Two articles reported two cohorts of patients, so a total of 112 cohorts was reported: 99 had clinically suspected DVT[41,55,60–72,78–160] and 13 received asymptomatic screening.[161–173] The number of assays tested on each cohort varied from one to 13. Overall, 213 analyses of D-dimer assays were reported: 198 involved patients with clinically suspected DVT and 15 asymptomatic screening.

Cohorts with clinically suspected DVT

DVT prevalence varied from 2 to 78% (median 36%). Prevalence of proximal and distal DVT was reported by 51 cohorts, with a proportion of proximal DVT (of all DVT detected, in studies that reported proximal and distal DVT separately) ranging from 27 to 100% (median 77%). The mean or median age ranged from 51 to 69 (median 59) years, with the exception of one cohort that recruited exclusively people aged over 70. The male to female ratio was reported by 81 cohorts, with the proportion of males ranging from 17 to 62% (median 42%).

Cohorts were recruited from the following settings: outpatient clinic (31), inpatients (nine), emergency department (16), mixed (29) and not stated (14). Recruitment was reported to be consecutive in 76 and prospective in 68. There were no exclusions reported by 50 cohorts, ten excluded postoperative

patients, 19 excluded pregnant patients, 33 excluded anticoagulated patients, 23 excluded those with previous thromboembolism, three excluded those with recent trauma, four excluded those with sepsis and 18 excluded patients with a prolonged history.

The reference standard was venography for 34 cohorts, ultrasound alone for 28, ultrasound with clinical follow-up for ten, serial ultrasound for six, ultrasound or venography for 13, and another reference standard for eight (combinations of ultrasound and plethysmography). The threshold value for D-dimer was defined before analysis in 82 cohorts, was defined after analysis in ten and was not clear in seven.

Quality criteria were recorded as follows:

- The reference standard was applied independently of the results of D-dimer testing in 86 cohorts, was dependent on D-dimer in four and was unclear in nine.
- D-dimer was measured blind to the reference standard in 43 cohorts and measurement was unclear in 56.
- The reference standard was interpreted blind to the D-dimer result in 50 cohorts and interpretation was unclear in 49.

Figure 3 shows the results for all analyses plotted on an ROC plane. The point estimates for sensitivity and specificity are 90.5% and 54.7%, respectively, but the results show substantial heterogeneity, particularly for specificity. Sensitivity ranged from 48 to 100% (χ^2 test for heterogeneity, $p < 0.001$). Specificity ranged from 5 to 100% (χ^2 test for heterogeneity, $p < 0.001$). Therefore, random effects weighted meta-regression was undertaken to identify covariates that predicted sensitivity or specificity.

All analyses: metaregression

The results of metaregression are shown in *Table 6*. A threshold of $p < 0.1$ was used for statistical significance. Variation in sensitivity was predicted by an outpatient or a mixed setting for patient recruitment, exclusion of patients who were pregnant, anticoagulated or had a long history of symptoms, age, prospective analysis, the D-dimer threshold used and whether the D-dimer threshold was determined before or after the study. Variation in specificity was predicted by an outpatient, an emergency department or a mixed setting, exclusion of patients who were pregnant, anticoagulated or had a past history of thromboembolism, age, consecutive recruitment, prospective analysis, the reference standard used, and quality criteria relating to blinding of

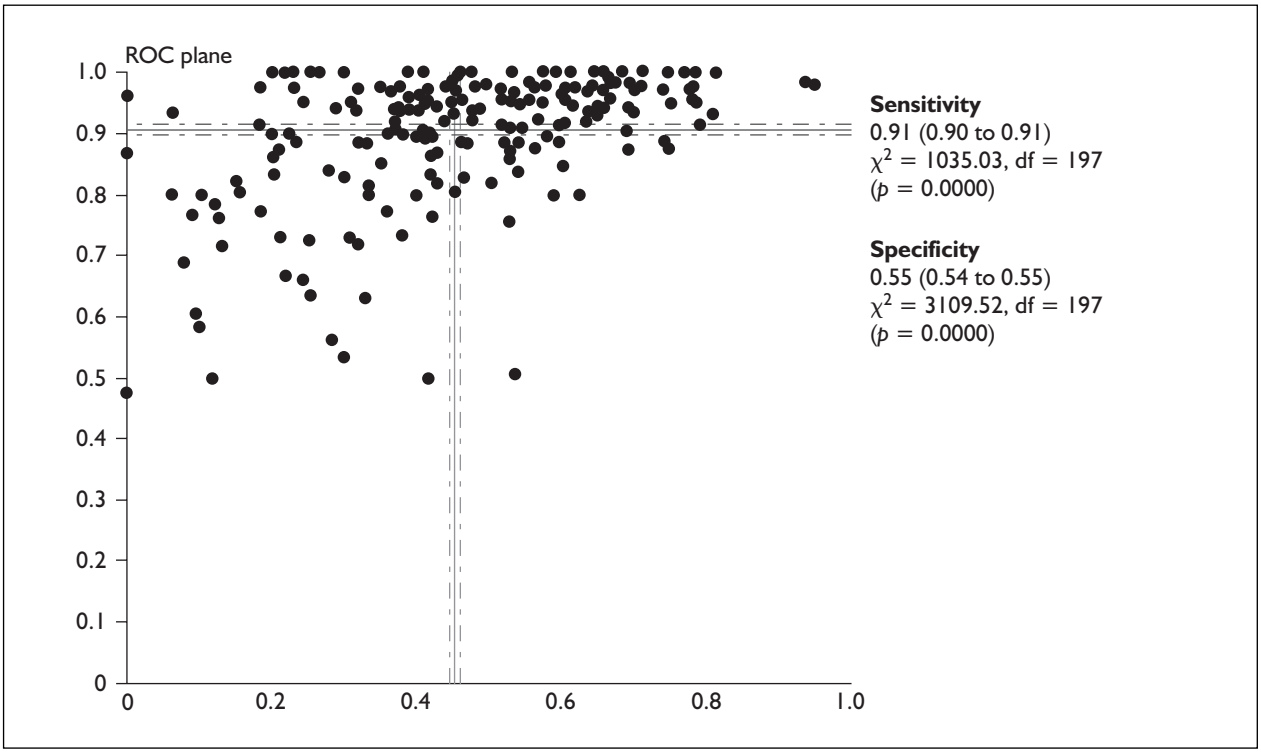

FIGURE 3 *D-dimer ROC plane for all studies of clinically suspected DVT*

observers measuring D-dimer and blinding or observers interpreting the reference standard.

The meta-analysis was repeated, stratified by each significant predictor, to estimate sensitivity and specificity for studies with, or without, the relevant predictor. The results are shown in *Table 7*. More selected cohorts (i.e. recruited from outpatient or emergency department only, or reporting exclusion criteria) tended to have higher sensitivity and specificity. Higher quality studies (prospective studies, those recruiting consecutive

TABLE 6 *Metaregression for factors associated with variation in sensitivity and specificity of D-dimer*

Variable		Sensitivity (*p*-value)	Specificity (*p*-value)
Patients recruited	Mixed	0.030	0.010
	ED only	0.32	0.065
	Outpatient only	0.010	0.022
	Inpatient only	0.944	0.236
Patients excluded	Postoperative	0.85	0.92
	Pregnant	0.049	0.079
	Anticoagulated	0.011	0.007
	Past history of DVT	0.38	<0.001
	Trauma	0.47	0.21
	Sepsis	0.76	0.89
	Long history	0.061	0.82
Mean age		0.046 (0.11)[a]	0.01 (0.21)[a]
% Male		0.30	0.13
Prevalence of DVT		0.27	0.38
Consecutive patients recruited		0.47	0.016
Prospective study		0.026	0.047
D-dimer threshold used		0.090 (0.97)[b]	0.68 (0.45)[b]
Reference standard used (venography vs other)		0.372	<0.001
Reference standard independent of D-dimer result		0.11	0.21
D-dimer measured blind to reference standard		0.40	0.054
Reference standard measured blind to D-dimer		0.98	0.035
D-dimer threshold defined before the study		0.002	0.34

p-Value when included in random effect weighted metaregression.
[a] The revised value excluded one study with an extreme value for mean age.
[b] The revised value excluded one study that used an extreme threshold value.
ED, emergency department.

TABLE 7 *Sensitivity and/or specificity of D-dimer for selected groups identified by metaregression*

Variable	Sensitivity (overall = 90.5%)	Specificity (overall = 54.7%)
Mixed patient selection	87% (86 to 88)	50% (49 to 51)
ED patients only	89% (87 to 91)	62% (60 to 64)
Outpatients only	94% (93 to 95)	59% (58 to 60)
Studies excluding pregnant patients	95% (93 to 97)	57% (56 to 58)
Studies excluding anticoagulated patients	93% (92 to 94)	61% (60 to 62)
Studies excluding patient with past history of thromboembolism	91% (90 to 93)	65% (63 to 66)
Studies excluding patients with a prolonged history	93% (92 to 94)	54% (52 to 56)
Consecutive patients recruited	91% (90 to 92)	57% (56 to 58)
Prospective study	90% (89 to 91)	58% (57 to 59)
Venographic reference standard	91% (90 to 92)	62% (61 to 64)
D-dimer measured blind to reference standard	90% (89 to 91)	56% (55 to 57)
Reference standard measured blind to D-dimer	90% (89 to 91)	57% (56 to 58)
D-dimer threshold derived from data	95%[a] (94 to 96)	41% (39 to 44)

p-Value for heterogeneity <0.001 except for [a]$p = 0.245$.

patients, those using venography as a reference standard, D-dimer and reference standard measured blind) tended to have higher specificity. Studies that determined the D-dimer threshold after data analysis had higher sensitivity. However, stratification by these covariates failed to identify any homogeneous group of results. The χ^2 test for heterogeneity remained highly significant for all analyses.

Stratification by type of D-dimer assay

The reviewers planned a priori to analyse D-dimer results stratified by assay. *Figures 4–6* show the results of studies using ELISA, latex and whole-blood agglutination assays, respectively. ELISA were reported by 91 analyses in 58 cohorts (35 analyses reported proximal and distal DVT separately). Sensitivity was 94% (95% CI 93 to 95%, *p*-value for heterogeneity <0.001) and specificity 45% (44 to 46, $p < 0.001$). Latex assays were reported by 74 analyses in 52 cohorts (22 analyses reported proximal and distal DVT separately). Sensitivity was 89% (88 to 90, $p < 0.001$) and specificity 55% (54 to 56, $p < 0.001$). Whole-blood agglutination assays were reported by 29 analyses in 29 cohorts (ten analyses reported proximal and distal DVT separately). Sensitivity was 87% (85 to 88, $p < 0.001$) and specificity 68% (67 to 69, $p < 0.001$). The results of individual studies and pooled estimates of sensitivity and specificity are summarised in the additional figures in Appendix 3 (*Figures 61–66*).

To explore further the potential differences between D-dimer assays each individual assay that had been reported in three or more analyses was analysed. The results are outlined in *Table 8*. These show that, although ELISAs are generally more sensitive than latex assays, there are substantial differences between individual assays and some newer latex assays have sensitivity comparable to ELISAs. However, even when each assay is analysed individually this does not explain the heterogeneity observed between individual study results.

Proximal and distal DVT

Analysis of studies that reported proximal and distal DVT separately showed that all assays had higher sensitivity for proximal than for distal DVT. These are outlined in *Table 9*.

Studies reporting results stratified by clinical probability

The results of five studies, using six assays (five whole-blood agglutination and one latex), reported results stratified by Wells clinical risk score.[61,70,71,92,110] *Figures 7* and *8* show the sensitivity and specificity of these individual studies, stratified by Wells score. Meta-analyses

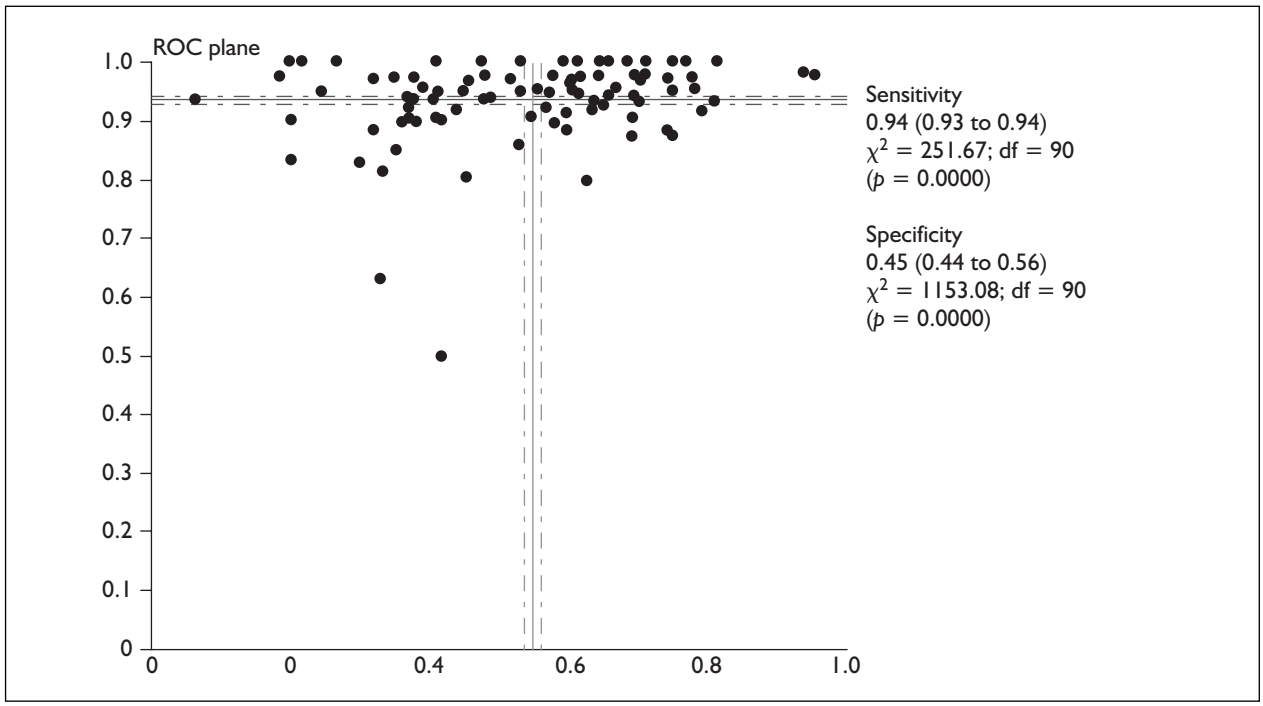

FIGURE 4 *ROC plane for analyses of ELISAs*

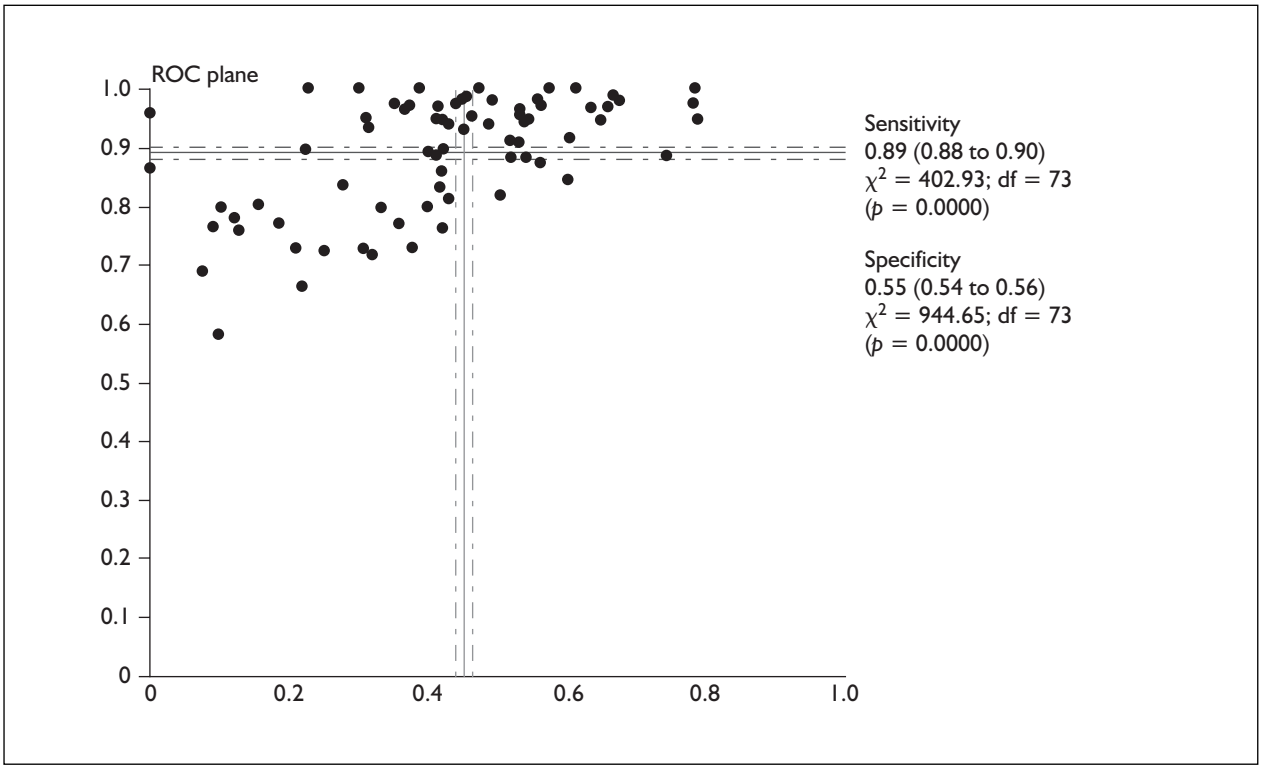

FIGURE 5 *ROC plane for analyses of latex assays*

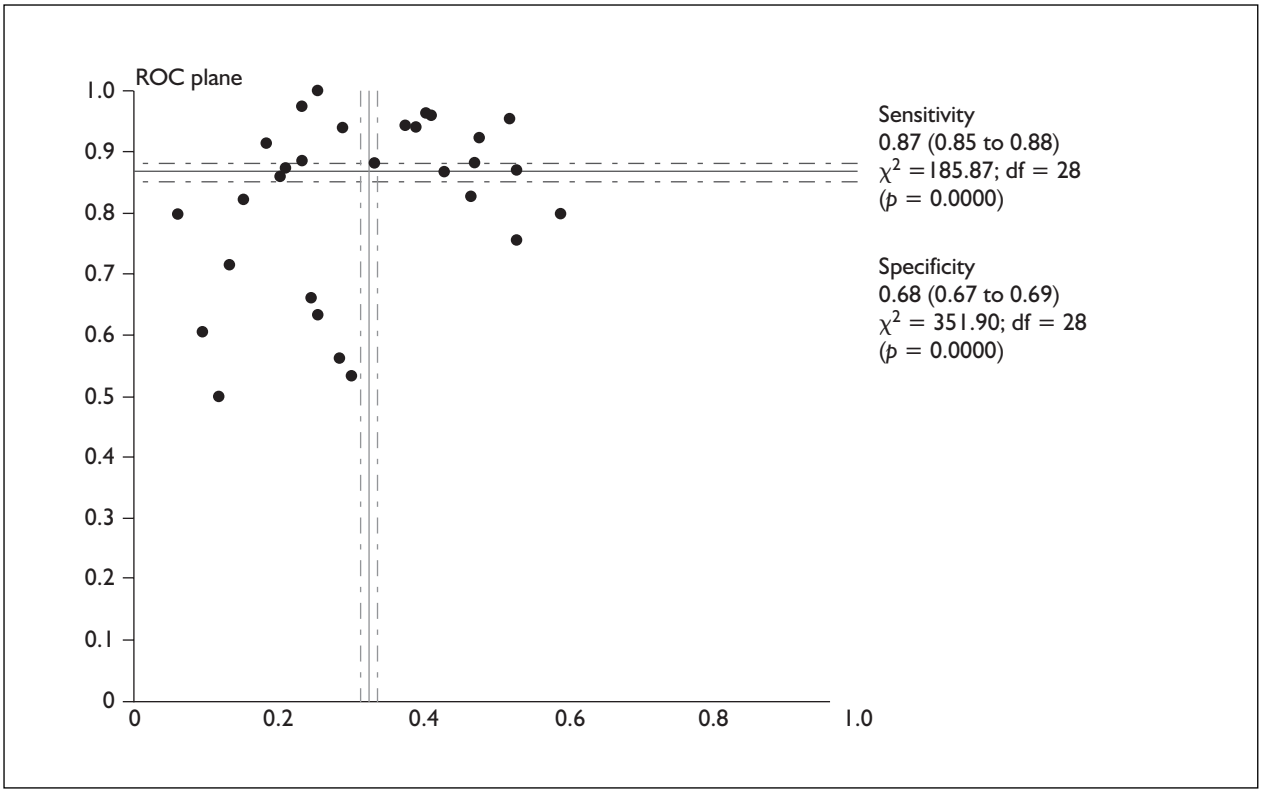

FIGURE 6 *ROC plane for analyses of whole-blood agglutination assays*

TABLE 8 *Sensitivity and specificity (95% CI and* p*-value for heterogeneity) for each D-dimer assay*

Test	Assay type	Manufacturer	Sensitivity	Specificity
Asserachrom (n = 19)[66,68,71,90,95,97,102,106,109,115,118,124,129,134,139,146,154,159]	Classical ELISA	Diagnostica Stago	95% (93 to 96) p = 0.005	36% (34 to 38) p < 0.001
Enzygnost (n = 5)[71,97,100,120,124]	Classical ELISA	Dade Behring	96% (92 to 98) p = 0.046	62% (57 to 67) p < 0.001
Fibrinostika (n = 3)[97,124,125]	Classical ELISA	Organon Teknika	95% (90 to 98) p = 0.063	37% (30 to 45) p = 0.761
Dimertest EIA Gold (n = 6)[90,103,116,126,132,151]	Classical ELISA	Agen	90% (85 to 93) p = 0.023	67% (62 to 71) p < 0.001
VIDAS (n = 17)[60,66,68,69,78,81,87,97,98,103,104,106,116,123,124,159,160]	Rapid ELISA	Biomerieux	96% (95 to 98) p = 0.008	39% (36 to 42) p < 0.001
Nycocard (n = 14)[55,81,91,94,97,102,107,111,116,120,122,124,130,157]	Rapid ELISA	Nycomed	89% (87 to 91) p < 0.001	50% (47 to 54) p < 0.001
Instant IA (n = 8)[97,102,106,114,116,120,121,124]	Rapid ELISA	Diagnostica Stago	92% (90 to 94) p = 0.478	54% (49 to 58) p < 0.001
Minutex (n = 8)[71,84,87,97,102,107,116,123]	Latex	Biopool	92% (90 to 94) p < 0.001	45% (42 to 49) p < 0.001
D-Di latex (n = 4)[102,129,139,154]	Latex	Diagnostica Stago	80% (72 to 86) p < 0.001	58% (51 to 64) p < 0.001
LPIA (n = 3)[116,150,151]	Latex	Mitsubishi Kasei	98% (94 to 99) p = 0.482	58% (51 to 65) p = 0.244
BC (n = 4)[71,97,100,103]	Latex	Dade Behring	90% (84 to 94) p < 0.001	53% (47 to 60) p < 0.001
IL test (n = 6)[60,87,88,96,97,148]	Latex	Instrumentation Laboratories, Milano	94% (91 to 97) p = 0.077	52% (47 to 56) p < 0.001
Miniquant (n = 4)[82,87,90,159]	Latex	Biopool	96% (91 to 99) p = 0.528	36% (31 to 40) p < 0.001
STA-latest (n = 8)[41,60,65,79,80,85,97,109]	Latex	Diagnostica Stago	94% (92 to 96) p = 0.883	46% (43 to 50) p = 0.002
Tinaquant (n = 7)[65,66,97,98,113,123,147]	Latex	Roche	96% (93 to 97) p = 0.023	52% (47 to 56) p = 0.014
Turbiquant (n = 3)[60,97,98]	Latex	Dade Behring	88% (81 to 93) p = 0.439	46% (41 to 52) p = 0.042
SimpliRED (n = 29)[61,64,67,70–72,83,88,90,92,93,97,99,101,105,108,110,112,117,119,123,126,128,146,149,153,157,159]	Whole-blood agglutination	Agen	87% (85 to 88) p < 0.001	68% (67 to 69) p < 0.001

TABLE 9 *Pooled sensitivity and specificity for D-Dimer for proximal and distal DVT*

	Overall sensitivity (95% CI)	Proximal sensitivity (95% CI)	Distal sensitivity (95%CI)	Specificity (95% CI)
All D-dimers	90% (89 to 91)	94% (93 to 95)	82% (80 to 84)	55% (54 to 56)
ELISAs	94% (93 to 95)	99% (98 to 99)	86% (84 to 88)	45% (44 to 46)
Latex assays	89% (88 to 90)	94% (92 to 95)	79% (75 to 83)	55% (54 to 56)
Whole-blood agglutination assays	87% (85 to 88)	84% (80 to 88)	64% (55 to 73)	68% (67 to 69)

$p < 0.001$ for heterogeneity in all analyses.

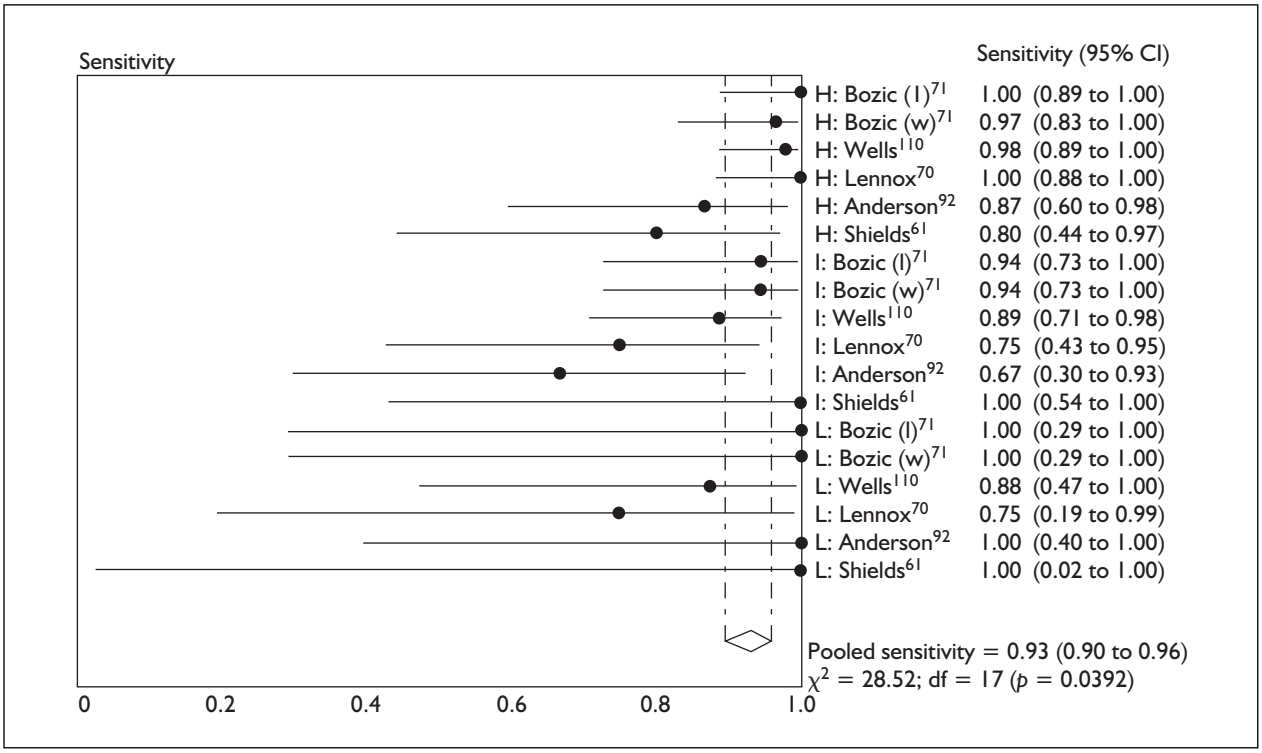

FIGURE 7 *Sensitivity of D-dimer in studies reporting results stratified by Wells score. H, high risk; I, intermediate risk; L, low risk; l, latex assay; w, whole-blood agglutination assay.*

showed that, in patients with a high Wells score, D-dimer had a sensitivity (95% CI, p-value for heterogeneity) of 96% (92 to 99, $p = 0.047$) and specificity of 51% (48 to 53, $p = 0.001$); in patients with an intermediate score, sensitivity was 88% (79 to 94, $p = 0.18$) and specificity was 67% (62 to 72, $p = 0.003$); and in patients with a low Wells score, sensitivity was 91% (72 to 99, $p = 0.69$) and specificity was 78% (74 to 81, $p < 0.001$). The specificity of D-dimer appears to be dependent on Wells score ($p = 0.095$, using a random effects model), whereas there is no evidence that sensitivity is dependent ($p = 0.228$).

Studies reporting patients with malignancy separately

Five studies reported patients with malignancy separately.[70,82–84,149] Meta-analysis of these studies showed that D-dimer had a sensitivity of 95% (95% CI 90 to 97, $p = 0.026$) and a specificity of 46% (95% CI 39 to 52, $p = 0.0026$) in patients with malignancy.

Cohorts of asymptomatic patients

DVT prevalence ranged from 8 to 49% (median 24%). Prevalence of proximal and distal DVT was reported separately by eight cohorts, with a proportion of proximal DVT ranging from 14 to

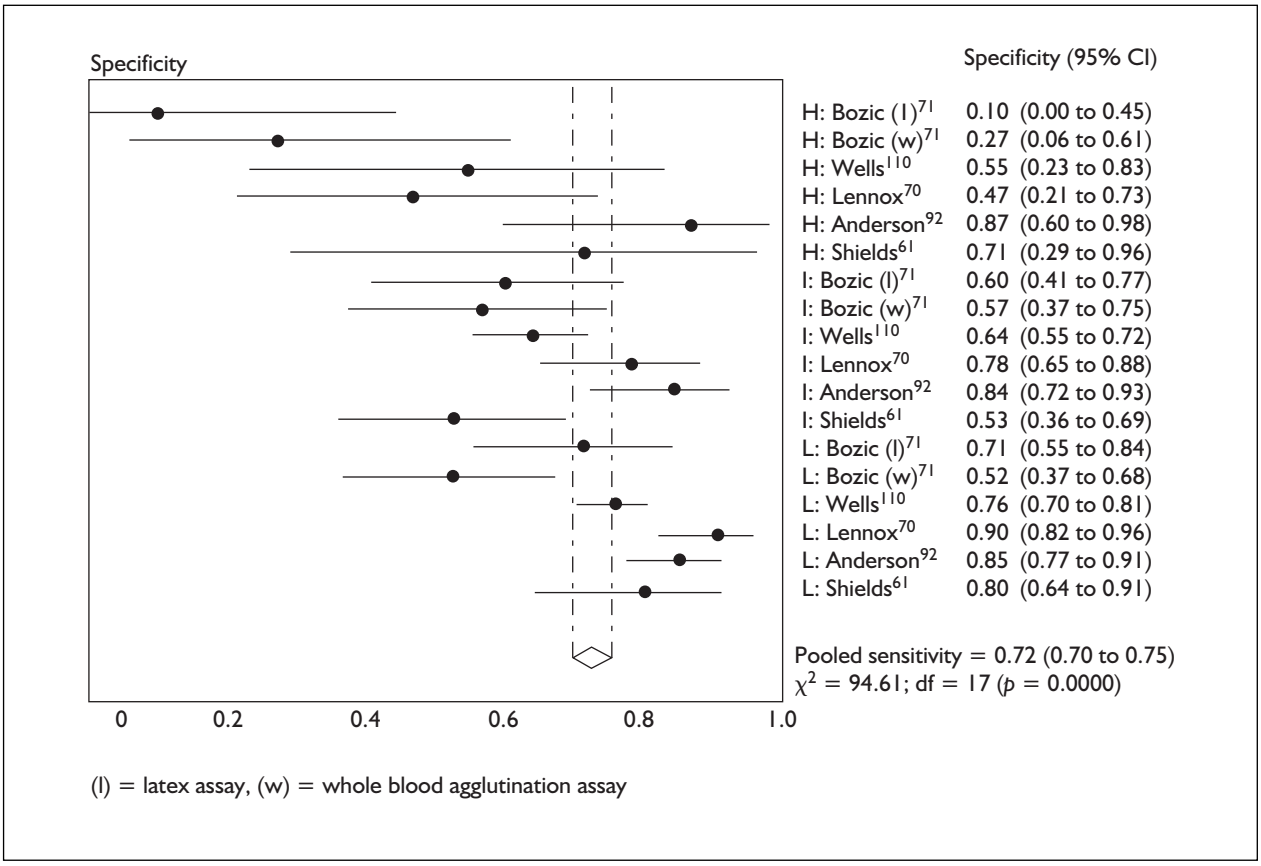

FIGURE 8 *Specificity of D-dimer in studies reporting results stratified by Wells score. H, high risk; I, intermediate risk; L, low risk; l, latex assay; w, whole-blood agglutination assay.*

44% (median 33%). The mean or median age was reported by ten studies, and ranged from 34 to 72 years. The male to female ratio was reported by ten studies. The proportion of males ranged from 10 to 77%.

Eight cohorts were screened following orthopaedic surgery, whereas the other five were screened after mixed surgery, gastrointestinal surgery, cerebrovascular accident, burns and spinal trauma. Recruitment was reported to be consecutive in seven and prospective in 12. Only four cohorts reported exclusions. These included anticoagulated patients (three cohorts), previous thromboembolism (two cohorts), post-trauma, sepsis and burns (one cohort each).

The reference standard was venography for seven cohorts, ultrasound alone for five and ultrasound with clinical follow-up for one. The 13 cohorts were used to analyse 15 different assays: nine ELISA, five latex and one whole-blood agglutination. The threshold value for D-dimer was defined before analysis in six cohorts, was defined after analysis in six and was not clear in one.

Quality criteria were recorded as follows:

- The reference standard was independent in all 13 cohorts.
- D-dimer was measured blind to the reference standard in nine cohorts and measurement was unclear in four.
- The reference standard was interpreted blind to the D-dimer result in seven cohorts and interpretation was unclear in six.

The results of all studies of asymptomatic patients are shown in *Figure 9*. Pooled sensitivity (95% CI) was 88% (84 to 91, $p < 0.001$) and pooled specificity was 43% (40 to 46, $p < 0.001$). The nine studies of ELISAs had a pooled sensitivity of 84% (74 to 88, $p < 0.001$) and specificity of 45% (41 to 48, $p < 0.001$). The five studies of latex assays had a pooled sensitivity of 96% (89 to 99, $p = 0.445$) and specificity of 50% (43 to 58, $p < 0.001$). The single study of a whole-blood agglutination assay had a sensitivity of 100% (88 to 100) and specificity of 13% (8 to 21). The results of individual studies and pooled estimates of sensitivity and specificity are outlined in the additional figures in Appendix 3 (*Figures 67* and *68*).

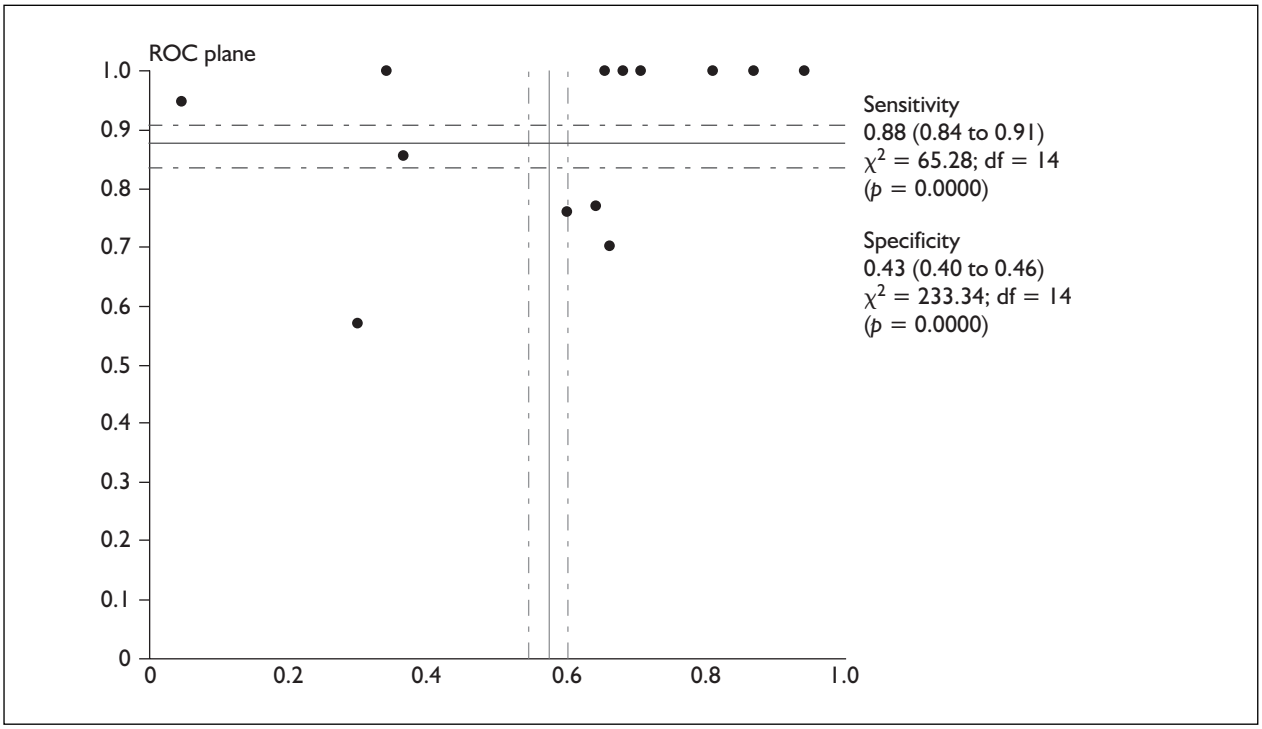

FIGURE 9 *ROC plane for studies of D-dimer in asymptomatic cohorts*

Summary

In patients with clinically suspected DVT D-dimer has good sensitivity (91%) but poor specificity (55%). ELISAs have the best sensitivity, but poor specificity. Whole-blood agglutination assays have better specificity but poorer sensitivity. There is substantial heterogeneity in estimates of sensitivity, and particularly specificity, for all assays. Although several factors were identified that contributed to this heterogeneity, stratification of studies by significant factors did not markedly reduce the heterogeneity. It appears that there are other, unmeasured factors producing heterogeneity in the results.

Studies that separately analysed patients with malignancy or according to Wells risk stratification showed that specificity is lower in patients with malignancy or a higher clinical risk. This observation, along with the finding that D-dimer has reasonable sensitivity, suggest that the most useful role for D-dimer may lie in ruling out DVT in patients with a low clinical probability.

D-dimer has slightly poorer diagnostic performance in asymptomatic patients. Overall sensitivity was 88% and specificity 43%. Again, there was substantial heterogeneity between the results of individual studies.

Plethysmography and rheography

In total, 995 titles/abstracts were scanned and 254 potentially relevant articles were selected for retrieval (kappa = 0.85). Review of the full articles identified 114 that met the inclusion criteria (kappa = 0.92). Eight of these duplicated data published elsewhere and were excluded. No appropriate data could be extracted or analysed from a further 22 articles, despite attempts to contact the authors. Review of the bibliographies of the selected articles identified four additional articles for inclusion. Thus, 88 articles were included in the meta-analysis.

These 88 articles reported a total of 98 cohorts of patients: 82 with clinically suspected DVT, 14 asymptomatic cohorts and two mixed cohorts. Impedance plethysmography was evaluated in 52 cohorts: 42 symptomatic,[36,52,54,56,75,128,174–208] eight asymptomatic[177,184,191,209–213] and two mixed.[214,215] Strain-gauge plethysmography was evaluated in 23 cohorts: 20 symptomatic[152,216–232] and three asymptomatic.[218,233,234] Air plethysmography was evaluated in five cohorts: four symptomatic[235–238] and one asymptomatic.[239] Light-reflex rheography was evaluated in nine cohorts, all of which were symptomatic.[240–248] Phleborheography was evaluated in nine cohorts: seven symptomatic[191,249–254] and two asymptomatic.[191,249]

TABLE 10 *Sensitivity and specificity of plethysmography techniques for clinically suspected DVT*

	n[a]	Sensitivity for all DVT	Sensitivity for proximal DVT	Sensitivity for distal DVT	Specificity
Impedance plethysmography	42 (28)	75% (73 to 77) $p < 0.001$	88% (86 to 90) $p < 0.001$	28% (24 to 33) $p < 0.001$	90% (89 to 91) $p < 0.001$
Strain-gauge plethysmography	20 (10)	83% (81 to 85) $p < 0.001$	90% (88 to 92) $p < 0.001$	56% (50 to 63) $p = 0.033$	81% (79 to 82) $p < 0.001$
Air plethysmography	4 (2)	85% (79 to 90) $p = 0.005$	98% (93 to 100) $p = 0.18$	39% (22 to 58) $p = 0.216$	91% (81 to 95) $p = 0.02$
Light-reflex rheography	9 (4)	91% (87 to 94) $p = 0.001$	94% (88 to 98) $p = 0.315$	92% (74 to 99) $p = 0.179$	71% (66 to 75) $p < 0.001$
Phleborheography	7 (4)	86% (83 to 89) $p < 0.001$	92% (88 to 94) $p = 0.001$	58% (48 to 68) $p < 0.001$	93% (91 to 95) $p < 0.001$

[a] *n* = number of cohorts. Numbers in parentheses are cohorts that reported proximal and distal DVT separately. Elsewhere, numbers in parentheses are 95% CIs. *p*-Values are for χ^2 test for heterogeneity.

The characteristics of the cohorts are outlined in Appendix 2 (*Tables 32–35*). Most cohorts were recruited from inpatients. Asymptomatic cohorts were nearly all recruited from patients who had recently undergone orthopaedic surgery, most commonly arthroplasty of the hip or knee or fixation of femoral neck fractures. Cohorts with clinically suspected DVT tended to be younger and more likely to be predominantly male than cohorts receiving asymptomatic screening. They also had a slightly lower prevalence of DVT and a higher proportion of cases with proximal DVT.

The results of meta-analysis for cohorts with clinically suspected DVT are shown in *Table 10*. Impedance and strain-gauge plethysmography both had modest sensitivity and specificity. Strain-gauge plethysmography had better sensitivity (83% versus 75%), while impedance plethysmography had better specificity (90% versus 81%). Analysis of studies reporting proximal and distal DVT separately revealed that sensitivity was particularly poor for distal DVT (impedance 28%, strain gauge 56%), but potentially useful for proximal DVT (88% and 90%). Results for air plethysmography appeared to be slightly better (sensitivity 85%, specificity 91%), but these findings were based on a small number of studies. Light-reflex rheography had reasonable sensitivity (91%), but poor specificity (71%). Phleborheography had similar diagnostic performance to air plethysmography (sensitivity 86%, specificity 93%).

The results of meta-analysis for asymptomatic cohorts are shown in *Table 11*. Only impedance plethysmography had been investigated by a significant number of studies. Sensitivity was too poor for any of the techniques to be useful in decision-making.

The results of all studies of impedance and strain-gauge plethysmography in clinically suspected DVT are shown in *Figures 10* and *11*, respectively. The results for individual studies of plethysmography and rheography techniques in symptomatic and asymptomatic patients are shown, with pooled estimates of sensitivity and specificity, in additional figures in Appendix 3 (*Figures 69–82*).

Metaregression

Significant heterogeneity was present whenever there were more than a very few studies in the analysis. There were sufficient numbers of studies available to allow metaregression analyses of the use of impedance plethysmography and strain-gauge plethysmography in patients with clinically suspected DVT.

Impedance plethysmography

The results of metaregression for impedance plethysmography are outlined in *Table 12*. Using a threshold of $p < 0.1$ for statistical significance, setting for recruitment ($p = 0.098$) and blind reporting of the reference standard ($p = 0.056$)

TABLE 11 *Sensitivity and specificity of plethysmography techniques for asymptomatic patients*

	n[a]	Sensitivity for all DVT	Sensitivity for proximal DVT	Sensitivity for distal DVT	Specificity
Impedance plethysmography	8 (7)	18% (15 to 21) $p < 0.001$	27% (22 to 33) $p = 0.096$	13% (9 to 17) $p < 0.001$	96% (95 to 97) $p < 0.001$
Strain-gauge plethysmography	3 (3)	37% (25 to 49) $p = 0.737$	39% (21 to 59) $p = 0.132$	35% (21 to 52) $p = 0.160$	83% (78 to 88) $p < 0.001$
Air plethysmography	1 (1)	4% (1 to 18) NA	No data	4% (1 to 18) NA	99% (92 to 100) NA
Phleborheography	2 (2)	26% (18 to 38) $p = 0.758$	32% (17 to 50) $p = 0.809$	21% (11 to 36) NA	96% (90 to 99) $p = 0.104$

[a] *n* = number of cohorts. Numbers in parentheses are cohorts that reported proximal and distal DVT separately. Elsewhere, numbers in parentheses are 95% CIs. *p*-Values are for χ^2 test for heterogeneity.
NA, not applicable.

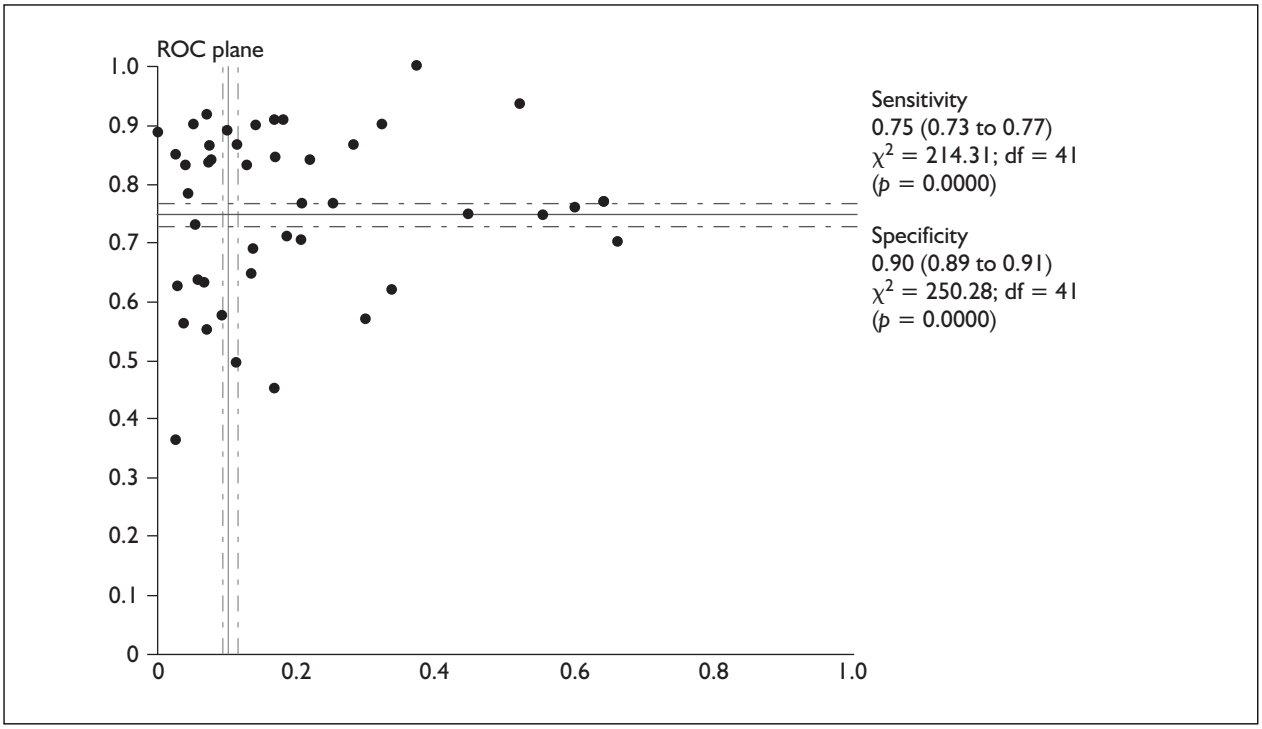

FIGURE 10 *ROC plane for all studies of impedance plethysmography in clinically suspected DVT*

were associated with variation in sensitivity, while proportion of males in the cohort ($p = 0.01$), DVT prevalence ($p = 0.043$), setting for recruitment ($p = 0.09$), consecutive recruitment ($p = 0.017$) and prospective study ($p = 0.046$) were associated with variation in specificity.

Specificity was lower in cohorts with a higher prevalence of DVT and cohorts with a higher proportion of male patients. Plots of these associations are shown in the additional figures in Appendix 3 (*Figures 83* and *84*). For categorical variables the meta-analysis was repeated, stratified

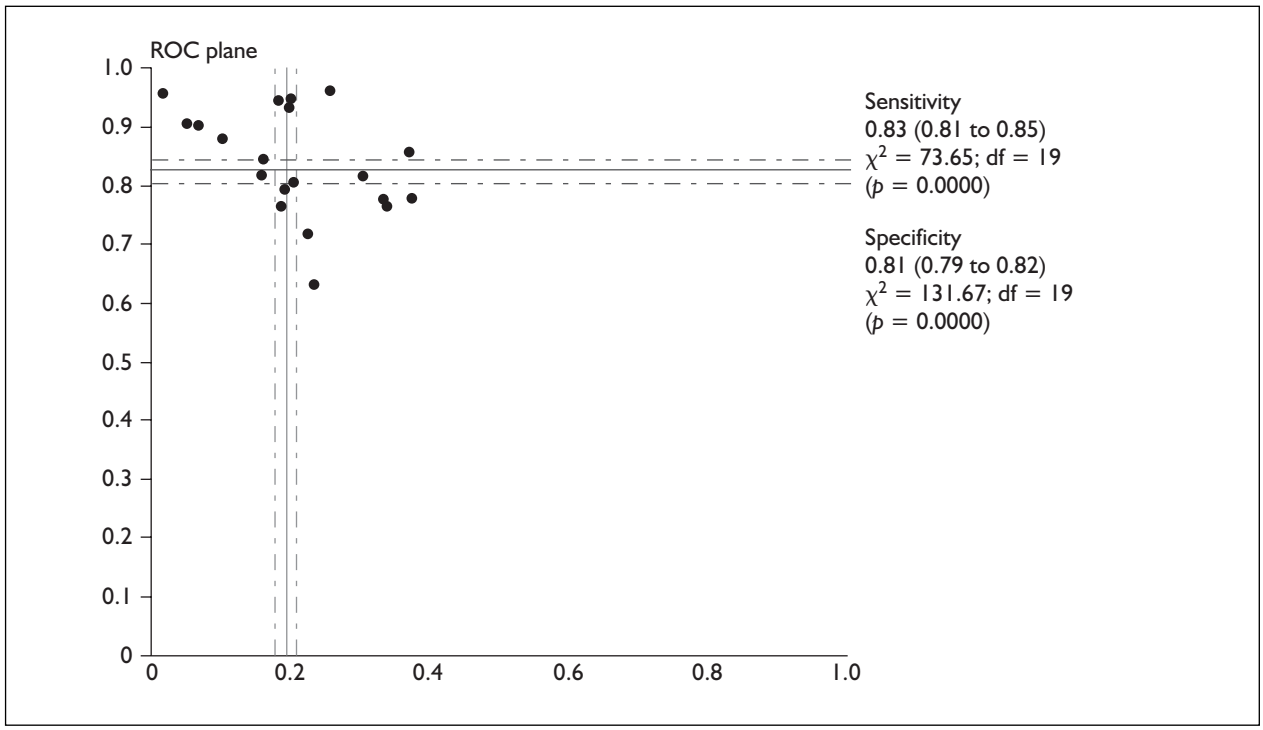

FIGURE 11 *ROC plane for all studies of strain-gauge plethysmography in clinically suspected DVT*

TABLE 12 *Predictors of impedance plethysmography sensitivity and specificity*

Variable	Sensitivity	Specificity
Mean age	0.17	0.37
Proportion of males	0.94	0.010
DVT prevalence	0.666	0.043
Patients with previous DVT excluded	0.660	0.37
Setting	0.098	0.090
Consecutive	0.32	0.017
Prospective	0.026	0.046
Reference standard independent	0.41	0.75
Plethysmography interpreted blind	0.36	0.45
Reference standard interpreted blind	0.056	0.74

p-Value when included in random effect weighted metaregression.

by each of the significant predictors, to estimate sensitivity and/or specificity for studies with, or without, the relevant predictor. The results are shown in *Table 13*. In general, studies that reported their setting had lower sensitivity and higher specificity, compared with those where the setting was not stated. With one exception, studies that were reported as prospective were also reported as having consecutive recruitment. These studies reported lower sensitivity and higher specificity than those that did not report these factors. Overall, therefore, it appears that studies with better reporting had lower sensitivity and higher specificity.

Strain-gauge plethysmography

The results of metaregression for strain-gauge plethysmography are outlined in *Table 14*. Using a threshold of $p < 0.1$ for statistical significance, setting for recruitment ($p < 0.001$) and the proportion of males in the cohort ($p = 0.005$) were associated with variation in sensitivity, while no variables were associated with variation in specificity.

Sensitivity was higher in cohorts with a higher proportion of males. This association is plotted in an additional figure in Appendix 3 (*Figure 85*). The meta-analysis was repeated, stratified by setting (the only significant predictor). The results

TABLE 13 *Sensitivity and specificity for impedance plethysmography stratified by significant predictors*

Variable	Sensitivity	Specificity
Setting: not stated (n = 14)	83% (80 to 86) p = 0.001	84% (81 to 86) p < 0.001
Setting: inpatient (n = 13)	70% (67 to 73) p < 0.001	91% (89 to 92) p < 0.001
Setting: outpatient (n = 6)	73% (68 to 77) p < 0.001	93% (91 to 95) p = 0.013
Setting: mixed (n = 7)	69% (63 to 74) p < 0.001	88% (85 to 91) p = 0.003
Setting: primary care (n = 2)	83% (74 to 91) p = 0.976	93% (88 to 97) p = 0.743
Consecutive (n = 16)	70% (67 to 73) p < 0.001	93% (91 to 94) p < 0.001
Prospective (n = 17)	69% (66 to 72) p < 0.001	93% (91 to 94) p < 0.001

95% CI in parentheses. p-Values are for χ^2 test for heterogeneity.

TABLE 14 *Predictors of strain-gauge plethysmography sensitivity and specificity*

Variable	Sensitivity	Specificity
Mean age	0.57	0.47
Proportion of males	0.005	0.28
DVT prevalence	0.57	0.84
Setting	<0.001	0.20
Consecutive	0.62	0.49
Prospective	0.33	0.99
Reference standard independent	0.93	0.20
Plethysmography interpreted blind[a]	0.87	0.49
Reference standard interpreted blind[a]	0.87	0.49
Interpretation (automatic vs others)	0.55	0.14
Venographic reference standard	0.40	0.28

p-Value when included in random effect weighted metaregression.
[a] All studies that interpreted the reference standard blind also reported plethysmography blind.

are shown in *Table 15*. Sensitivity was higher in outpatient and mixed cohorts, and lower in those that did not report the setting.

Limited reporting restricted the reviewers' ability to identify potential causes of heterogeneity. In the majority of studies of symptomatic patients the entry criterion was merely clinical suspicion of DVT, with no specification of the symptoms and signs required for entry into the study, and often no description of these features for those patients who were entered. As the studies span a considerable period and cover a number of differing healthcare systems it is likely that the clinical index of suspicion, and thus the entry criteria, vary between studies. For each type of test there was often variation in the equipment and methodology used to perform the test. The equipment used ranged from the commercially produced to equipment developed by the investigators for the purpose of the study. The methods of interpretation of test results also often differed. Although the principle of the test remains the same, this variation in equipment, methodology and interpretation may be a further source of heterogeneity. The skill and training of the operator performing the test often were not described. Both the performance and in many cases interpretation of the test will be highly dependent on the experience of the operator.

TABLE 15 *Sensitivity and specificity for strain-gauge plethysmography stratified by setting for recruitment*

Variable	Sensitivity	Specificity
Setting: not stated (n = 4)	82% (77 to 86) p = 0.013	78% (75 to 81) p < 0.001
Setting: ED (n = 1)	63% (52 to 73)	77% (67 to 84)
Setting: inpatient (n = 10)	84% (81 to 87) p < 0.001	81% (79 to 83) p < 0.001
Setting: outpatient (n = 3)	86% (83 to 89) p = 0.119	87% (84 to 90) p = 0.001
Setting: mixed (n = 2)	89% (85 to 92) p = 0.476	91% (88 to 94) p = 0.219

95% CI in parentheses. p-Values for χ^2 test for heterogeneity.

Interpretation of the results of individual tests was often not blind and there is therefore considerable scope for the appearance of the limb to influence interpretation of the test result. In many studies it was not possible to determine whether blinding had occurred.

Studies reporting results stratified by clinical probability

One study reported diagnostic performance of impedance plethysmography stratified by Wells criteria.[75] Among patients with a high Wells score, sensitivity (95% CI) was 81.4% (69.6 to 89.3) and specificity was 69.2 % (42.4 to 87.3). Among patients with an intermediate Wells score sensitivity was 47.6% (33.4 to 62.3) and specificity was 90.6% (82.5 to 95.2). Among patients with a low Wells score sensitivity was 40.0% (19.8 to 64.3) and specificity was 95.3% (91.8 to 97.4). The test therefore had higher sensitivity (p = 0.001) and lower specificity (p = 0.001) in high-risk patients. This finding suggests that unreported differences between cohorts in the clinical risk of DVT may be responsible for the unexplained heterogeneity between studies.

Summary

Plethysmography and rheography techniques appear to have a limited role in the diagnosis of clinically suspected DVT. The two most widely investigated tests are impedance and strain-gauge plethysmography in symptomatic patients. Impedance plethysmography has sensitivity and specificity of 75% and 90% respectively. The equivalent values for strain-gauge plethysmography are 83% and 81%. In asymptomatic patients sensitivity is too poor for any of the techniques to be useful. Metaregression was limited by poor reporting of studies. There was some evidence that diagnostic performance depended on prevalence of DVT in the cohort and reported setting for recruitment.

Ultrasound

In total, 3992 titles/abstracts were scanned and 400 potentially relevant articles were selected for retrieval (kappa = 0.85). Review of the full articles identified 151 that met the inclusion criteria (kappa = 0.90). Six of these duplicated data published elsewhere and were excluded. No appropriate data could be extracted or analysed from a further nine articles, despite attempts to contact the authors. Review of the bibliographies of the selected articles identified six additional articles for inclusion. Thus, 142 articles were included in the meta-analysis.

The 142 studies reported a total of 150 cohorts (eight studies reported two separate cohorts): 100 reported patients with clinically suspected DVT,[46,114,176,178,185,186,190,193,199,210,222–224,228,236,249,250,255–336] 45 reported asymptomatic patients[43,53,171,210,249,259,267,302,317,337–371] and five reported mixed cohorts.[206,282,372–374]

Cohorts with clinically suspected DVT

The 100 cohorts of patients with clinically suspected DVT were reported as follows: 53 reported proximal and distal DVT separately, 19 only reported proximal DVT, three only reported distal DVT, and 25 were unclear or reported proximal and distal DVT together. DVT prevalence varied from 20 to 94% (median 48%). The proportion of proximal DVT (of all DVT detected) ranged from 48 to 100% (median 78%). The mean or median age was reported by 60

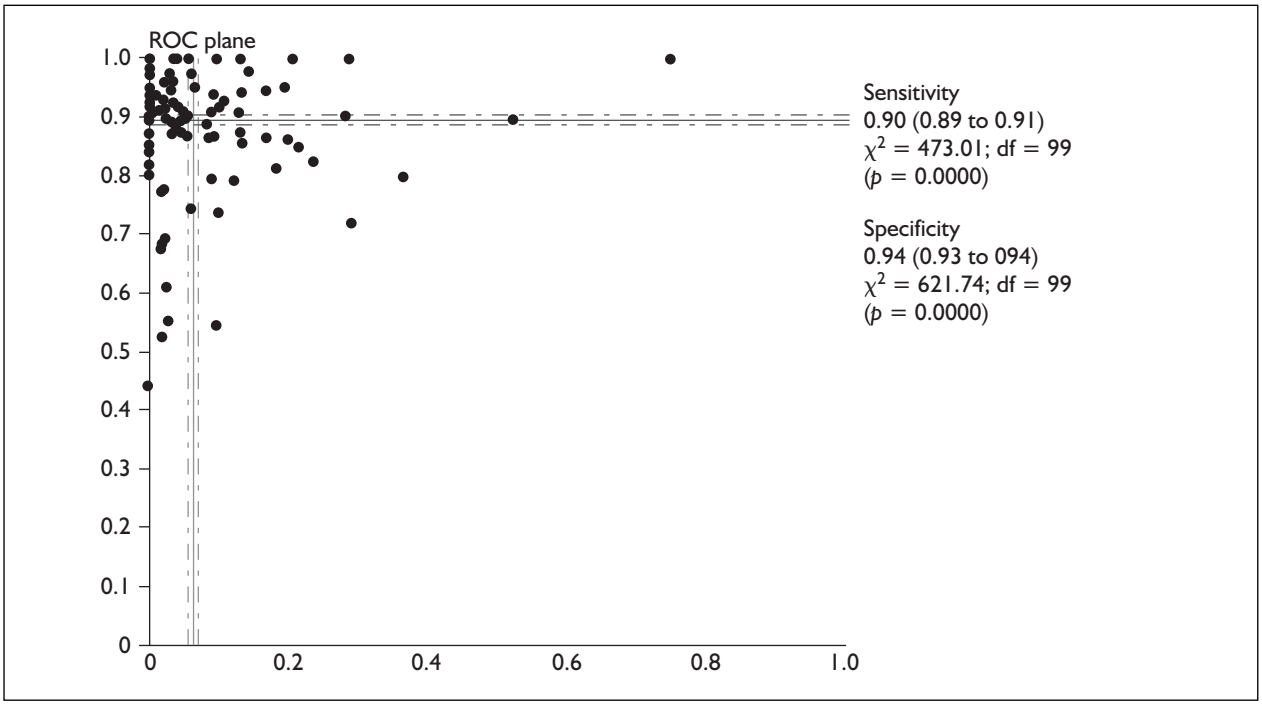

FIGURE 12 *Ultrasound ROC plane for studies of clinically suspected DVT*

cohorts, and ranged from 39 to 68 (median 57 years). The male to female ratio was reported by 65 cohorts, with the proportion of males ranging from 15 to 95% (median 45%).

Cohorts were recruited from the following settings: outpatient clinic (11), inpatients (12), emergency department (4), mixed (18) and not stated (55). Recruitment was reported to be consecutive in 48 and prospective in 67. Twelve papers excluded patients with previous DVT and 45 papers did not report any exclusion criteria.

The following techniques were used: 22 used compression ultrasonography alone, five used colour Doppler alone, 16 used continuous-wave Doppler alone, 28 used duplex (compression and colour Doppler), 25 used triplex (compression, colour Doppler and continuous-wave doppler) and four used other techniques.

Quality criteria were recorded as follows:

- The reference standard was independent of ultrasound in all studies (all patients had to have venography for the study to be included).
- Ultrasound was interpreted blind to the results of venography in 62 cohorts and was unclear in 38.
- Venography was interpreted blind to the ultrasound result in 56 cohorts, was interpreted by observers aware of ultrasound result in two and was unclear in 42.

Results of meta-analysis

Pooled sensitivity (95% CI, *p*-value for heterogeneity) for detecting any DVT was 89.7% (88.8 to 90.5, $p < 0.001$). Pooled sensitivity for detecting proximal DVT was 94.2% (93.2 to 95.0, $p < 0.001$) and for distal DVT was 63.5% (59.8 to 67.0, $p < 0.001$). Pooled specificity, calculated using data from all 98 studies, was 93.8% (93.1 to 94.4, $p < 0.001$). When restricted to the 53 studies reporting full data, specificity was 94.2% (93.4 to 95.0, $p < 0.001$). *Figure 12* shows the ROC plane for the studies. The data for individual studies and pooled estimates of sensitivity and specificity are outlined in the additional figures in Appendix 3 (*Figures 86* and *87*).

Results of metaregression

The results of metaregression of studies of ultrasound for patients with clinically suspected DVT are outlined in *Table 16*. Using a threshold of $p < 0.01$ for statistical significance, use of compression ultrasound, interpretation by a radiologist, prevalence of DVT and the proportion of proximal DVT were all significant predictors of sensitivity. Only the use of compression ultrasound predicted specificity.

There were 33 studies in which the operator was reported as being a radiologist. Meta-analysis surprisingly showed that diagnostic performance was generally slightly worse among these studies. Overall sensitivity (95% CI) was 86.1% (83.8 to

TABLE 16 *Metaregression of studies of ultrasound in patients with clinically suspected DVT*

Variable	Sensitivity	Specificity
Setting for recruitment	0.14	0.43
Consecutive recruitment	0.78	0.55
Mean age	0.36	0.17
Proportion of males	0.66	0.24
Prospective	0.26	0.24
Compression ultrasound used	0.024	0.023
Colour Doppler used	0.93	0.44
Radiologist interpreted	0.064	0.52
Sonographer interpreted	0.52	0.44
Ultrasound performed blind to reference standard	0.44	0.52
Reference standard performed blind to ultrasound	0.59	0.56
DVT prevalence	<0.001	0.11
Proportion of proximal DVTs	0.04	0.14

p-Value when included in random effect weighted metaregression.

88.3), sensitivity for proximal DVT was 94.4% (92.3 to 96.1), sensitivity for distal DVT was 62.6% (55.4 to 69.4) and specificity was 92.4% (90.9 to 93.7). Cohorts with a higher prevalence of DVT and cohorts with a higher proportion of proximal DVT tended to have higher sensitivity. The relationship between DVT prevalence and ultrasound sensitivity is plotted in an additional figure in Appendix 3 (*Figure 88*), while the relationship between the proportion of proximal DVT and sensitivity is plotted in *Figure 89* (Appendix 3).

Table 17 shows the results of analysis stratified by the technique used. Optimal sensitivity is achieved by using duplex or triplex techniques, while optimal specificity is achieved by using compression alone.

Studies reporting results stratified by clinical probability

One study reported diagnostic performance of ultrasound stratified by Wells criteria.[8] Among patients with a high Wells score, sensitivity was 91% (95% CI 81 to 96) and specificity was 100 % (77 to 100). Among patients with an intermediate Wells score sensitivity was 61% (95% CI 46 to 74) and specificity was 99% (94 to 100). Among patients with a low Wells score sensitivity was 67% (95% CI 42 to 85) and specificity was 98% (95 to 99).

Asymptomatic cohorts

The 45 cohorts of asymptomatic patients were reported as follows: 25 reported proximal and distal DVT separately, ten reported only proximal DVT, two reported only distal DVT, and eight were unclear or reported proximal and distal DVT together. DVT prevalence varied from 6 to 58% (median 21%). The proportion of proximal DVT (of all DVT detected) ranged from 7 to 86% (median 36%). The mean or median age was reported by 30 cohorts, and ranged from 51 to 82 (median 67) years. The male to female ratio was reported by 27 cohorts, with the proportion of males ranging from 20 to 72% (median 41%).

Most of the cohorts (36/45) were recruited from patients who had just received orthopaedic surgery (hip or knee replacement). Recruitment was reported to be consecutive in 28 and prospective in 40. Eight papers excluded patients with previous DVT, while 12 papers did not report any exclusion criteria.

The following techniques were used: 12 cohorts used colour Doppler, 16 used compression ultrasonography, 16 used a combination of techniques and five did not clarify the techniques used.

Quality criteria were recorded as follows:

- The reference standard was independent of ultrasound in all studies.
- Ultrasound was interpreted blind to the results of venography in 41 cohorts and was unclear in four.
- Venography was interpreted blind to the ultrasound result in 38 cohorts, was interpreted by observers aware of ultrasound result in one and was unclear in six.

Results of meta-analysis

Pooled sensitivity (95% CI, *p*-value for heterogeneity) for detecting any DVT was 50.7% (47.1 to 54.4, $p < 0.001$). Pooled sensitivity for

TABLE 17 *Results of meta-analysis stratified by ultrasound technique used*

	Sensitivity for all DVT	Sensitivity for proximal DVT	Sensitivity for distal DVT	Specificity
Compression only (n = 22)	90.3% (88.4 to 92.0) $p < 0.001$	93.8% (92.0 to 95.3) $p = 0.005$	56.8% (49.0 to 66.4) $p < 0.001$	97.8% (97.0 to 98.4) $p = 0.01$
Colour Doppler only (n = 5)	81.7% (77.4 to 85.5) $p < 0.001$	95.8% (85.7 to 99.5) $p = 0.427$	43.5% (23.2 to 66.5) $p = 0.009$	92.7% (89.7 to 95.1) $p = 0.003$
Continuous wave Doppler only (n = 16)	81.1% (78.2 to 83.7) $p < 0.001$	87.8% (84.7 to 90.5) $p < 0.001$	41.8% (32.5 to 51.6) $p = 0.015$	84.0% (81.4 to 86.3) $p < 0.001$
Triplex (n = 25)	91.1% (89.0 to 93.0) $p < 0.001$	96.4% (94.4 to 97.9) $p < 0.001$	75.2% (67.7 to 81.6) $p < 0.001$	94.3% (92.5 to 95.8) $p < 0.001$
Duplex (n = 28)	92.1% (90.7 to 93.5) $p < 0.001$	96.5% (95.1 to 97.6) $p < 0.001$	71.2% (64.6 to 77.2) $p < 0.001$	94.0% (92.8 to 95.1) $p < 0.001$
Others (n = 4)	93.3% (88.8 to 96.4) $p = 0.338$	–	–	96.0% (92.2 to 98.2) $p < 0.001$

95% CI in parentheses. p-Values are for χ^2 test for heterogeneity.

detecting proximal DVT was 66.7% (61.9 to 71.3, $p < 0.001$) and for distal DVT was 39.0% (34.5 to 43.6, $p < 0.001$). Pooled specificity, calculated using data from all 45 studies, was 96.5% (95.9 to 97.1, $p < 0.001$). When restricted to the 25 studies reporting full data specificity was 97.0% (96.2 to 97.7, $p < 0.001$). *Figure 13* shows the ROC plane for these 25 studies. The data for individual studies and pooled estimates of sensitivity and specificity are outlined in the additional figures in Appendix 3 (*Figures 90* and *91*).

Results of metaregression

The only significant predictors of sensitivity were prospective study ($p = 0.040$) and prevalence of DVT ($p = 0.019$). No significant predictors of specificity were identified. Pooled estimates from the 39 studies that reported that they were prospective were: sensitivity (all DVT) 55.6% (95% CI 52.3 to 58.8, p-value for heterogeneity <0.001) and specificity 96.4% (95.8 to 97.0, $p < 0.001$). The association between sensitivity and prevalence is shown in an additional figure in Appendix 3 (*Figure 92*). In contrast to the findings of metaregression in clinically suspected cohorts, studies with a higher prevalence of DVT reported lower sensitivity.

Mixed cohorts

Three of the five mixed cohorts reported proximal and distal DVT separately, one reported proximal only and the other was unclear. Pooled sensitivity (95% CI, p-value for heterogeneity) for detecting any DVT was 75.9% (66.7 to 83.6, $p < 0.001$). Pooled sensitivity for detecting proximal DVT was 93.2% (84.7 to 97.7, $p = 0.085$) and for distal DVT was 55.8% (41.3 to 69.5, $p = 0.513$). Pooled specificity, calculated using data from all five studies, was 97.9% (93.6 to 98.9, $p = 0.212$).

Repeat ultrasound

No studies were identified that compared the results of repeat scanning with venography in a complete cohort of patients, so no studies of repeat scanning were included in the meta-analysis. However, several excluded studies provided some useful data to guide practice. Five studies were identified that reported the results of repeat scanning in cohorts of patients with suspected DVT. Three of these used venography in some patients to confirm the results of positive repeat scanning. Details of these studies are summarised in *Table 18*.

Repeat scanning had a positive rate of 0–2%. Where venography was used to confirm positive findings, the positive predictive value of ultrasound was 82–94%. Overall, the best estimate of the positive rate of repeat scanning is 35/2610 = 1.34% (95% CI 0.97 to 1.86%), with a positive predictive value of 146/164 = 89.0% (95% CI 83.3 to 92.9%).

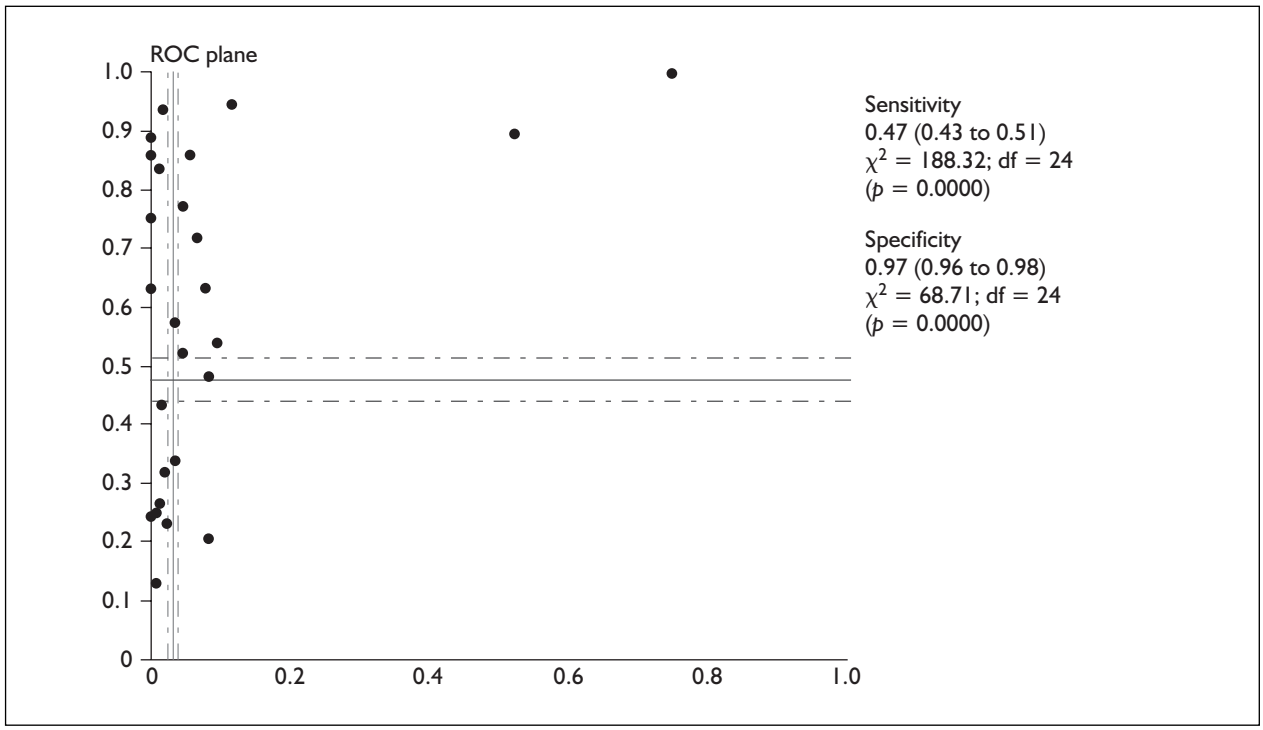

FIGURE 13 *Ultrasound ROC plane for studies of asymptomatic patients with full reporting*

TABLE 18 *Studies of repeat ultrasound scanning*

Study	Number (%) of initial scans positive	Number (%) of repeat scans positive	Number (%) of positive scans (initial or repeat) confirmed by venography
Heijboer, 1993[20]	93/491 (19)	7/397 (1.8)	84/89 (94)
Cogo, 1998[16]	400/1702 (24)	12/1252 (1.0)	–
Sluzewski, 1991[17]	67/174 (39)	0/98 (0)	–
Birdwell, 1998[18]	63/405 (16)	7/342 (2.0)	23/28 (82)
Birdwell, 2000[19]	95/709 (13)	9/521 (1.7)	39/47 (83)

The use of repeat scanning has been restricted in some strategies on the basis of clinical probability or D-dimer result. These are outlined in *Table 19*. The results suggest that a selective approach can produce a higher rate of positive scans, although none of the studies used venographic confirmation. For example, two studies of repeat ultrasound limited to patients with a positive D-dimer produced an overall positive scan rate of 22/606 = 3.63% (95% CI 2.42 to 5.44%).

Summary

In patients with clinically suspected DVT, ultrasound can rule out proximal but not distal DVT. In asymptomatic patients neither proximal nor distal DVT can be ruled out by ultrasound. In both patient groups specificity is good, but not perfect, so use of this technique in low-risk patients carries the risk of producing significant numbers of false-positive results. Optimal sensitivity (particularly for distal DVT) is achieved by the combined use of compression ultrasound and colour Doppler, while optimal specificity is achieved by using compression ultrasound alone. Sensitivity of ultrasound appears to be dependent on the prevalence of DVT in the cohort, although the association differs between clinically suspected and asymptomatic cohorts. This is probably explained by the relative proportions of proximal and distal DVT in symptomatic and asymptomatic cohorts. Symptomatic cohorts include predominantly proximal DVT, which are more easily identified by ultrasound, whereas asymptomatic cohorts include predominantly distal DVT, which are frequently missed by ultrasound. Higher prevalence of DVT is likely to

TABLE 19 *Studies of repeat ultrasound scanning for subgroups of patients*

Study	Group	Initial scan	Repeat scan
Wells, 1997[58]	Intermediate Wells score	27/193 (14%)	3/166 (1.8%)
Tick, 2002[77]	Intermediate or high Wells score and positive D-dimer	300/531 (57%)	13/83 (15.7%)
Bernardi, 1998[375]	Positive D-dimer	260/946 (27%)	5/88 (5.7%)
Kraaijenhagen, 2002[62]	Positive D-dimer	391/1739 (22%)	17/518 (3%)

imply more proximal DVT in symptomatic cohorts and more distal DVT in asymptomatic cohorts.

CT scan

In total, 2038 titles/abstracts were scanned and 42 potentially relevant articles were selected for retrieval (kappa=0.76). Review of the full articles identified 14 that met the inclusion criteria (kappa=0.93). Two of these duplicated data published elsewhere and were excluded. No appropriate data could be extracted or analysed from a further three articles, despite attempts to contact the authors. Review of the bibliographies of the selected articles identified no additional articles for inclusion. Thus, nine articles were included in the meta-analysis.[376–384]

The characteristics of the studies are outlined in Appendix 2 (*Table 36*). Most studies compared CT with ultrasound in patients with suspected PE. Only three studies included patients with clinically suspected DVT and only one compared CT with venography. The only exclusion criteria reported by the studies related to contraindications to intravenous contrast or failure to obtain a reference standard test. The majority of scans were performed using helical CT scanners, with contrast injected into an arm vein and imaging timed to coincide with opacity of the deep veins of the legs to allow assessment of these veins for thrombus. A radiologist interpreted the scans in all studies, but only one study reported the experience or grade of the radiologist. One study measured interobserver error of CT interpretation, reporting a kappa score of 0.88. The criteria for a positive CT result were clearly defined in eight of the nine studies.

Quality criteria were scored as follows:

- The reference standard was applied independently of the results of CT scanning in six studies and was unclear in three.
- CT was interpreted blind to the reference standard in five studies and was unclear in four.
- The reference standard was interpreted blind to the CT result in four studies, was interpreted by observers aware of the CT result in two and was unclear in three.

Figures 14 and *15* show the forest plots for sensitivity and specificity. The pooled estimate of sensitivity was 95% (95% CI 91 to 97%) and the pooled estimate of specificity was 97% (95% CI 95 to 98%). However, both estimates were subject to significant heterogeneity ($p = 0.01$ and $p < 0.001$, respectively). Reported sensitivity ranged from 71 to 100% in the individual studies, while specificity ranged from 93 to 100%.

There was significant heterogeneity between studies, but there were too few studies to use metaregression to examine this. Reasons for this heterogeneity are probably multiple. There was a number of differences in technical aspects of acquiring the scans. The type of scanner varied, although the majority were spiral (helical) scanners. In addition, the way in which they were used varied, for example, scan time and table movement speed varied, and this had an impact on the quality of the images obtained. Different techniques to acquire venous images were described, with variable anatomical areas investigated in various papers. The diagnostic criteria used in the papers to diagnose DVT were quite variable and the level of expertise of the readers also varied considerably. Although the majority of papers examined cases with suspected PE, one of the papers with a lower sensitivity[383] did not, and in this paper the prevalence of DVT was considerably lower. Overall, in many of the papers the risk of verification bias was quite large and the degree to which this was a problem probably varied between papers, and the reason for patients proceeding to CT venography when having CT pulmonary angiography was often not clear.

Summary

CT scanning appears to have excellent sensitivity and specificity for DVT. However, this finding is based on a limited number of studies that mostly recruited patients with suspected PE. The

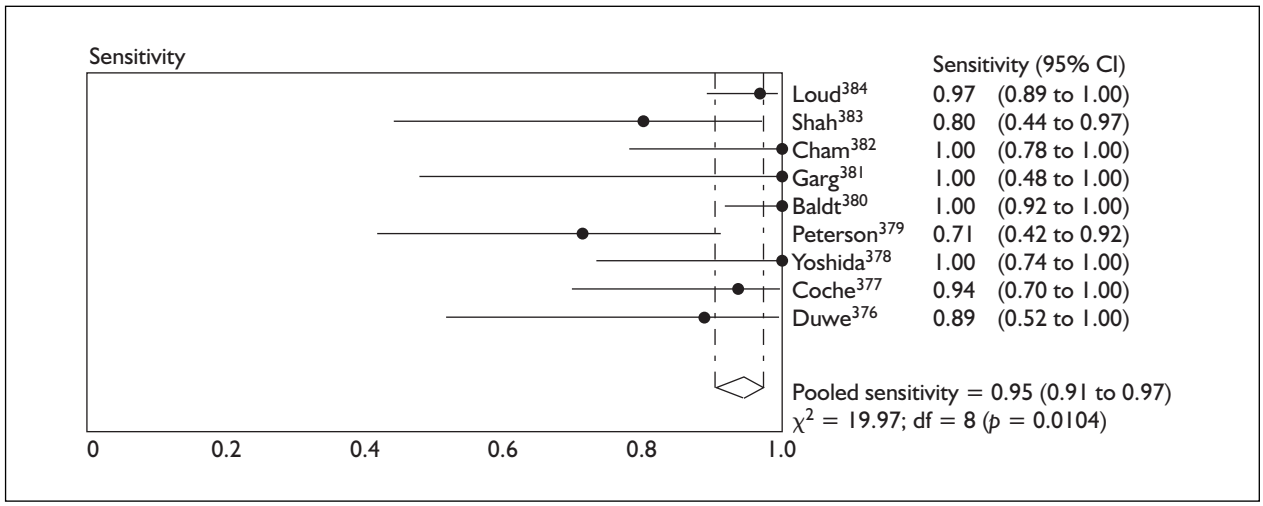

FIGURE 14 *Sensitivity of CT scanning for DVT*

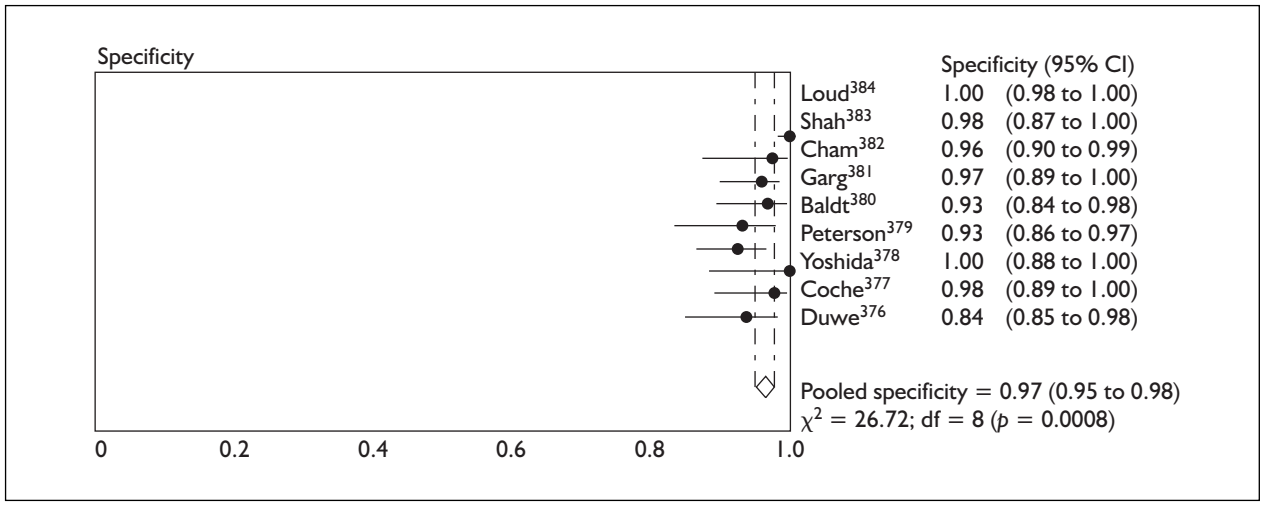

FIGURE 15 *Specificity of CT scanning for DVT*

reference standard in all but one study was ultrasound, which is known to have imperfect sensitivity and specificity. The use of intravenous contrast for CT scanning means that this technique incurs many of the risks of venography. Current data are therefore insufficient to recommend any role for CT scanning in routine diagnostic evaluation for DVT.

MRI scan

In total, 1291 titles/abstracts were scanned and 35 potentially relevant articles were selected for retrieval (kappa = 0.84). Review of the full articles identified 16 that met the inclusion criteria (kappa = 0.91). Two of these duplicated data published elsewhere and were excluded. No appropriate data could be extracted or analysed from one further article, despite attempts to contact the authors. Review of the bibliographies of the selected articles identified one additional article for inclusion. Thus, 14 articles were included in the meta-analysis.[313,315,385–396] The characteristics of the studies are outlined in Appendix 2 (*Table 37*). Most studies compared MRI with contrast venography in patients with suspected DVT. The only exclusion criteria reported by the studies related to contraindications to MRI or venography, or failure to obtain a reference standard test. The majority of studies used a two-dimensional time of flight (ToF) technique to image flowing blood in the veins of the leg. Some also incorporated phase-contrast imaging for equivocal cases, but only a few later studies used contrast-enhanced venous

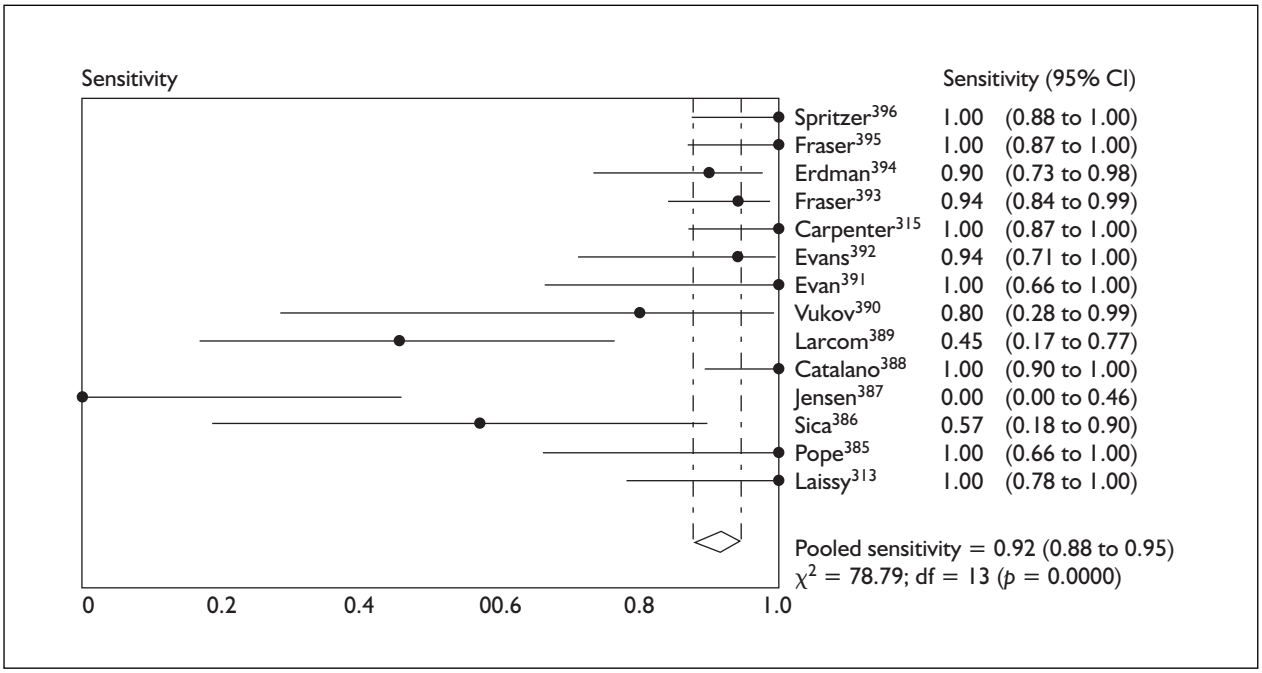

FIGURE 16 *Sensitivity of MRI scanning for DVT*

imaging and only one study used direct thrombus imaging. A radiologist interpreted the scans in all studies, but only two studies reported the experience or grade of the radiologist, stating that they were "experienced" and a "specialist". Two studies measured interobserver error of MRI interpretation: one reported a kappa score of 0.94, the other a kappa score of 0.85 for femoral vein interpretation and 0.97 for the iliac vein. The criteria for a positive MRI result were clearly defined in 11 studies.

Quality criteria were scored as follows:

- The reference standard was applied independently of the results of MRI scanning in all of the studies.
- MRI was interpreted blind to the reference standard in 11 studies and was unclear in three.
- Reference standard was interpreted blind to the MRI result in 11 studies and was unclear in three.

Figures 16 and *17* show the forest plots for sensitivity and specificity. The pooled estimate of sensitivity was 92% (95% CI 88 to 95%) and the pooled estimate of specificity was 95% (95% CI 93 to 97%). However, both estimates were subject to significant heterogeneity ($p < 0.001$ for both). Reported sensitivity ranged from 0 to 100% in the individual studies, while specificity ranged from 43 to 100%.

As with the studies on CT venography, there were insufficient studies to use metaregression to examine the causes for significant heterogeneity between studies on MR venography. Review of the papers suggests a number of probable causes for this heterogeneity. The MR technique described was usually a TOF MR venography technique, although other techniques such as contrast-enhanced MR venography, direct thrombus imaging, phase-contrast MR venography and cine MRI were reported in more recent papers, either as the sole modality to diagnose DVT or as a supplement to TOF imaging. In addition, the way in which the images were reviewed varied, with some describing using maximum intensity projection images and others purely examining source axial images. The anatomical areas examined varied between studies, with some papers examining the whole leg and pelvic veins, and others focusing on one anatomical area alone. The experience of the person interpreting the images was also variable, and this was probably an important determinant of how well MR venography performed. This is suggested by the paper by Larcom and colleagues,[389] who initially used a non-specialist radiologist to interpret the MR venograms, with a reported sensitivity of 45% (5/11). Retrospective interpretation by a specialist MR angiographer produced a sensitivity of 91% (10/11). Using these results in the meta-analysis produces a pooled estimate of sensitivity of 94% (95% CI 90 to 96%), but there was still significant

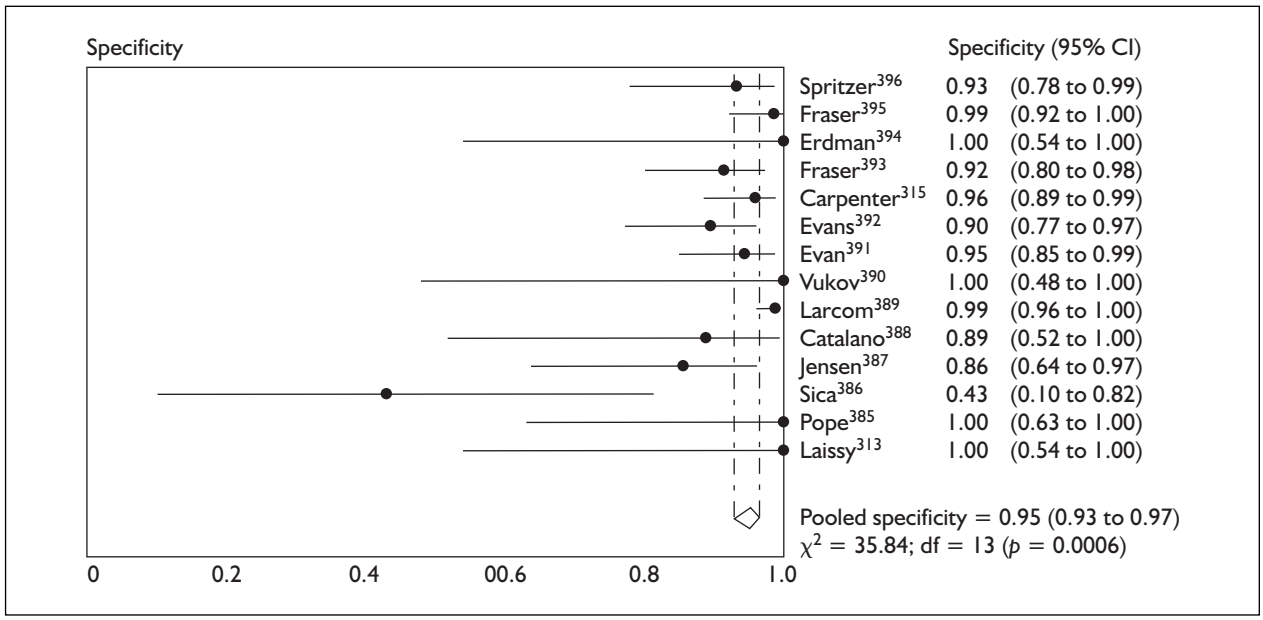

FIGURE 17 *Specificity of MRI scanning for DVT*

heterogeneity ($p < 0.001$). The degree of verification bias was also difficult to gauge, and may have varied between studies.

In examining the papers by Larcom,[389] Sica[386] and Jensen,[387] the three papers whose results appear as the most obvious outliers, there are probably specific reasons for this. Two of the papers[387,389] were reports on asymptomatic patients following surgery or lower limb injury, in which the prevalence of DVT was low. In the other paper[386] the imaging was limited to diagnosis of calf vein DVT only. In the only other paper, examining asymptomatic papers by Montgomery and colleagues[397] MR performed better. This paper limited imaging to the pelvis, where contrast venography may perform badly, and where certain veins, for example the internal iliac veins, will not be visualised by conventional contrast venography.

Summary

MRI scanning appears to have similar sensitivity and specificity to ultrasound. These findings are supported by a number of studies comparing MRI to venography in patients with clinically suspected DVT. MRI scanning requires specialist interpretation, which will limit its usefulness in routine practice. There is currently insufficient evidence of any superiority over ultrasound to justify using MRI as an alternative to either ultrasound or venography.

Chapter 4

Discussion: systematic reviews and meta-analysis of non-invasive diagnostic tests

The principal findings of the meta-analyses are:

- Individual clinical features have little diagnostic value in suspected DVT.
- The Wells score provides useful diagnostic information by using standardised clinical assessment to categorise patients into high-, intermediate- and low-risk categories. Diagnostic performance may vary between populations and only proximal DVT appears to be reliably categorised.
- Other recently developed clinical scores require further validation.
- Unstructured assessment of clinical probability may have comparable diagnostic performance to Wells score, but is supported by fewer data and is not standardised.
- D-dimer is sensitive, particularly for proximal DVT, but has poor specificity. There is some variation between assays: ELISAs have better sensitivity and poorer specificity, while whole-blood agglutination assays have better specificity and poorer sensitivity. Specificity appears to be dependent on the clinical probability of DVT, being higher in patients with a lower probability of DVT.
- Plethysmography and rheography techniques have modest sensitivity for proximal DVT, poor sensitivity for distal DVT and modest specificity.
- Ultrasound has good sensitivity for proximal DVT, modest sensitivity for distal DVT and good specificity.
- CT scanning has good sensitivity and specificity for DVT, but this is based on a very limited amount of data, mostly from studies of patients with suspected PE.
- MRI scanning has similar sensitivity and specificity to ultrasound, but is more expensive to perform and difficult to interpret.
- Non-invasive tests generally have worse diagnostic performance when used in asymptomatic patients, compared with use in patients with clinically suspected DVT. D-dimer has comparable sensitivity and slightly worse specificity, while ultrasound and plethysmography techniques have poor sensitivity in asymptomatic patients.

Interpretation of these findings

Individual clinical features

The poor performance of clinical features in DVT diagnosis may be explained by the way in which the study cohorts are assembled. 'Suspected DVT' is a clinical entity that is generated by the clinician, rather than the patient. Patients do not present with "suspected DVT", but with symptoms of pain, swelling or some other concern. To be put in a study cohort they need to be labelled by a clinician and then referred for diagnostic testing. This referral filter is likely to be based on the clinical features evaluated in studies. For example, a patient is unlikely to be considered to have suspected DVT if there if no leg pain or swelling. Therefore, we should not conclude that clinical features have little value in DVT diagnosis in any circumstances, but simply that, once the diagnosis of DVT has been suspected sufficiently to warrant consideration for further investigation, clinical features are unlikely to be helpful. These conclusions are thus more relevant to secondary than primary care. The process by which patients acquire a label of having "suspected DVT" requires further investigation.

Wells clinical score

Wells clinical score provides a useful, reproducible way of estimating the pretest probability of DVT. Variation in performance of Wells score is probably explained by differences in population characteristics and between users of the score. Two studies estimated interobserver error for Wells score,[8,58] recording kappa values of 0.75 and 0.85, indicating excellent agreement. However, these studies were undertaken in settings in which the observers were well trained and very familiar with the score. It would be useful to measure the interobserver error among different clinicians working in different settings. Wells score effectively categorises proximal, but not distal, DVT. This is probably because distal DVT are less likely to produce measurable clinical signs, such as a difference in calf diameter, and thus are unlikely to be categorised as high risk.

Unstructured, empirical clinical assessment

Although appearing to have similar diagnostic value to Wells score, the estimates of diagnostic parameters for unstructured clinical assessment had wide confidence intervals, being based on only four studies and showing considerable heterogeneity. By its very nature unstructured clinical assessment is not reproducible and will rely on clinicians sharing the same skills and training. Furthermore, some of the studies of unstructured assessment were performed alongside studies of Wells score,[60,63,70] so it is perhaps unsurprising that similar estimates of diagnostic performance were obtained.

D-dimer

D-dimer has good sensitivity, but poor specificity. The poor specificity of D-dimer is explained by the wide variety of different conditions that may elevate D-dimer levels. Smoking, pregnancy, recent trauma or operations, malignancy and infection may all elevate D-dimer, and may also either coexist with, or be a differential diagnosis for, suspected DVT.[398] This was demonstrated by metaregression, which showed that cohorts that excluded some of these groups of patients were more likely to report higher specificity. Hence, it appears that D-dimer specificity may be better in selected groups of patients with no alternative cause for D-dimer elevation. Metaregression also showed that D-dimer has higher sensitivity in studies that excluded anticoagulated patients and those with a prolonged history. This supports recent guidance that advises caution in using D-dimer if the patient has had symptoms for more than 2 weeks or if they have received anticoagulant therapy.[399]

Co-morbidities associated with false-positive D-dimer probably also explain why D-dimer appears to have markedly better specificity in patients stratified to Wells low clinical probability. Some co-morbidities, such as malignancy, automatically put patients in a higher Wells risk category and also generate false-positive D-dimer results. Regardless of the reasons, it is fortunate that D-dimer has better diagnostic performance in clinically low-risk patients, because this is the group where it may be most valuable. The relatively high sensitivity of D-dimer may be considered adequate to rule out DVT in clinically low-risk patients, but not high-risk patients.

Choice of diagnostic threshold did not appear to influence sensitivity or specificity in the meta-analysis. This is probably because, where possible, either the manufacturer's recommended threshold or the most frequently used threshold was chosen, thus deliberately reducing heterogeneity. The importance of using an appropriate threshold for D-dimer must be emphasised.

Two previous meta-analyses of D-dimer produced conflicting conclusions. Stein and colleagues[10] reviewed the use of D-dimer for ruling out DVT and PE, and concluded that ELISAs were more useful than other assays by virtue of higher sensitivity, and were as diagnostically useful for ruling out DVT as a negative ultrasound scan. Heim and colleagues[400] reviewed the use of D-dimer for ruling out DVT, and concluded that D-dimer should not be used as a stand-alone test for DVT, because variation among results of individual studies meant that many reported sensitivity below 90%, and were thus unsuitable as a rule-out test. These meta-analyses did not include as many studies as the present analysis, and only undertook limited analyses to identify potential causes of variation. By undertaking metaregression, analysing proximal and distal DVT separately, and analysing results stratified by clinical probability, this study has provided insight into the factors that may influence the diagnostic performance of D-dimer. Deciding whether D-dimer is sufficiently sensitive to rule out DVT clearly involves an element of subjectivity, but is best addressed with a full understanding of how D-dimer performs in different circumstances.

Plethysmography techniques

Air, strain-gauge and impedance plethysmography all rely on changes in volume to detect DVT. It is therefore theoretically likely that the ability of these techniques to detect DVT accurately will depend on the size and location of the thrombus, with smaller, distal DVT being more likely to be missed. This is reflected by the comparative sensitivities of all three techniques for proximal and distal DVT. Sensitivity for distal DVT is much lower in all three cases.

This may also explain the findings of the only study to stratify results by Wells criteria.[75] Impedance plethysmography had lower sensitivity in low-risk patients, perhaps indicating that smaller, more distal thrombi are likely to result in lower Wells categorisation and a greater risk of being missed. It could be argued that this is fortuitous, because smaller, more distal thrombi are less likely to propagate to form PE, and are thus more 'forgiving' if missed. Alternatively, it could be argued that low sensitivity in low-risk patients makes impedance plethysmography less

useful for ruling out DVT in low-risk patients, particularly compared with the performance of D-dimer in this group. However, it should be recognised that this finding has only been demonstrated in one study of impedance plethysmography and needs to be explored further in other studies and other techniques.

Ultrasound

Comfort and convenience have made ultrasound a popular choice for DVT diagnosis. This meta-analysis confirms that ultrasound has good sensitivity for proximal DVT and good specificity, although sensitivity for distal DVT is less impressive. Use of ultrasound therefore requires a strategy for managing possible distal DVT or a conviction that these DVT are of little pathological significance.

The present estimates of sensitivity and specificity were slightly lower than estimates from previous meta-analyses.[12,15] This is probably because, in this study, very few restrictions were placed on selection of studies and thus studies were included from a wide range of settings, with operators of varying skills and experience. Therefore, these estimates may not reflect the best potential diagnostic performance for ultrasound, but probably do reflect real practice.

Stratifying analysis by ultrasound technique showed that duplex and triplex techniques had optimal sensitivity, while using compression ultrasound alone resulted in better specificity. This suggests that the ultrasound technique could be tailored to the clinical situation. If the aim of ultrasound is simply to rule out proximal DVT in a low-risk population then it is probably appropriate to use compression ultrasound alone to avoid generating too many false positives. If, however, ultrasound is being used in a high-risk population, or is intended to detect distal DVT, then duplex or triplex techniques should be used.

Repeat ultrasound scanning

No studies were found comparing the results of repeat scanning to venography in all cases and thus no studies suitable for inclusion in the meta-analysis. The evidence base for repeat scanning seems to be observational studies reporting the rate of positive repeat scans. These suggest that 1.3% of repeat scans will be positive, although it may be possible to increase this rate by selecting patients on the basis of clinical risk or D-dimer result.

If the rationale for repeat scanning is to detect initially distal DVT that propagate proximally, then findings from other elements of the meta-analyses cast some doubt on the use of Wells score to select patients for repeat scanning. Wells score appropriately categorised patients with proximal DVT into high-, intermediate- and low-risk groups, but patients with distal DVT were more likely to be categorised as intermediate risk than high. Limiting repeat scanning to high-risk patients thus makes little sense if the aim is to detect extending distal DVT. Selection on the basis of D-dimer result is perhaps more appropriate. Although the sensitivity of D-dimer for distal DVT is only modest it does provide some degree of discrimination. Patients with a positive D-dimer and negative initial scan are more likely to have a distal DVT than those with both tests negative. Observational studies of selected groups of patients undergoing repeat ultrasound provide some weak evidence that selection on the basis of D-dimer produces a higher positive rate.[58,62,77,375]

CT scanning

Most studies of CT scanning for DVT have been undertaken on convenience samples of patients undergoing CT for suspected pulmonary embolus. These patients are probably more likely to have proximal DVT and thus produce inflated estimates of sensitivity. Furthermore, the reference standard in most studies was ultrasonography, which has imperfect sensitivity and specificity. CT scanning for DVT therefore requires further evaluation. Since CT is a relatively expensive test and accurate thrombus identification requires injection of intravenous contrast, it seems that CT carries many of the costs, risks and inconveniences that have led to the recent decline in the use of venography. Furthermore, CT requires a substantial radiation dose. This would have important implications if CT were to become widely used for a common complaint such as suspected DVT.

MRI scanning

MRI scanning has been subject to more appropriate evaluation than CT scanning and does not appear to have quite the same diagnostic performance as CT. One crucial limitation associated with MRI scanning is the need for expert radiological interpretation, without which diagnostic performance can be markedly impaired. MRI scanning also shares with CT and venography the disadvantages of high cost and the need for intravenous contrast. Access to MRI scanning is currently very limited, so using MRI for urgent complaints such as suspected DVT will increase waiting times for other important, but less urgent conditions. Since diagnostic performance

appears similar to ultrasound, the role of MRI is likely to remain limited.

Asymptomatic cohorts

All of the diagnostic tests appeared to have poorer performance in asymptomatic patients. Sensitivity was markedly lower for plethysmography and ultrasound, whereas the sensitivity of D-dimer was only slightly reduced. This may be explained by the size and distribution of thrombi. In asymptomatic patients thrombi are more likely to be smaller and more distal.[12] This creates substantial difficulties for techniques that rely on size and proximal location for detection.

Specificity, in contrast, was decreased for D-dimer and, if anything, higher for plethysmography and ultrasound. This is explained by the fact that asymptomatic patients usually undergo screening for DVT because of a risk factor that may itself be a cause of false-positive D-dimer results. The most common group of patients receiving asymptomatic screening is postoperative orthopaedic patients. These patients often have elevated D-dimer levels without DVT.

Limitations

Systematic review and meta-analysis of diagnostic test data is a relatively new research field. Techniques for literature searching, reviewing and undertaking meta-analysis are developing. Studies of diagnostic tests are easier to perform than clinical trials because they usually involve less experimental intervention and can be more easily integrated into routine care. This can make the task of identifying, retrieving and analysing all relevant data much harder. There are currently no systems for registering diagnostic test studies and the Standards for Reporting of Diagnostic Accuracy (STARD) criteria[23] for reporting have only recently been introduced. These factors mean that the problems that affect meta-analysis of clinical trial data are even more pronounced in meta-analysis of diagnostic test data.

Publication bias

Only limited attempts were made to identify and retrieve unpublished data. The potential effect of publication bias on diagnostic test data is an issue that has only recently been investigated. Most published meta-analyses of diagnostic tests have only searched electronic databases and reference lists, and have not addressed the possibility of publication bias.[401] If diagnostic test data are subject to the same sort of bias as clinical trails, then one might expect that publication bias would lead to an overestimate of diagnostic performance in meta-analyses.

Heterogeneity between studies

Substantial heterogeneity was identified between individual study results whenever there were sufficient numbers of studies to permit analysis. Where appropriate, metaregression was carried out to identify covariates that might explain some of this heterogeneity. Although several covariates were identified that were associated with better, or worse, diagnostic performance, stratification of studies by these covariates did not produce a homogeneous group.

Metaregression was limited by poor reporting of studies. Many studies did not report even the most basic population characteristics, such as age and gender, and most studies did not report exclusion criteria. However, six studies of D-dimer and one each of impedance plethysmography and ultrasound reported data stratified by Wells clinical score. These showed that diagnostic performance of these tests appeared to be dependent on clinical probability of DVT. It is therefore very likely that unreported differences in case mix and clinical probability could explain much of the heterogeneity between studies.

The stratified analyses and the results of metaregression suggest that the diagnostic performance of non-invasive tests for DVT is dependent on population characteristics. This implies that diagnostic performance will vary between patients and will depend on individual patient characteristics. Care should therefore be taken in using the results of these analyses. Clinicians should consider what effect the characteristics of the patients or population may have on diagnostic performance.

Poor reporting of primary data

Poor reporting undermined other analyses and conclusions in the meta-analysis. In many studies, even when venography was used as a reference standard, it was not clear whether proximal or distal DVT were being reported. Nevertheless, sufficient numbers of studies did report these data clearly, and reasonably reliable estimates of sensitivity for proximal and distal DVT were obtained for most diagnostic tests. The exceptions to this were Wells score, where estimates for proximal and distal DVT were based on a small number of studies, and individual clinical signs, where no separate analysis of proximal and distal DVT could be performed.

Study quality

Study quality was assessed using the same three criteria in all the reviews. Failure to meet these criteria has been associated with overestimation of diagnostic performance.[26] However, there was some evidence that the diagnostic performance of tests for DVT tended to be higher in studies that met the quality criteria. In studies of Wells score, assessment of the reference standard blind to the results of Wells scoring was associated with better diagnostic performance. In studies of D-dimer, blind measurement of D-dimer and blind assessment of the reference standard were both associated with higher diagnostic specificity.

These findings are difficult to explain, as one would logically expect lack of blinding to lead to overestimates of diagnostic performance. It is possible that the relationship between blinding and diagnostic performance is confounded. Quality criteria (or their reporting) may act as markers for the overall care taken, and degree of control involved, in a diagnostic evaluation. In 'high-quality' studies the diagnostic tests may be performed in a tightly controlled, experimental setting, whereas in 'low quality' studies they are performed in a more pragmatic, 'real-life' manner. If this is true, then estimates of diagnostic performance from lower quality studies may better represent how these tests perform in everyday practice.

This explanation may also apply to other study-level covariates, such as prospective data collection and consecutive recruitment, that can be used as markers of quality and appeared, at least in the case of D-dimer specificity, to be associated with better diagnostic performance. One exception to these observations is the association between post hoc determination of the D-dimer threshold and higher sensitivity for D-dimer. Generating a threshold for positivity from the same data set will tend to overestimate the predictive or diagnostic power of any feature or test.

Interdependence of tests

As discussed previously, five studies of D-dimer[61,70,71,92,110] and one each of impedance plethysmography[75] and ultrasound[8] suggested that the diagnostic performance of these tests were dependent on clinical probability. However, it is not known whether other diagnostic tests show similar characteristics. It seems reasonable to assume that, although different D-dimer assays have different specificity, this value will vary with clinical probability of DVT.

As well as being dependent on clinical probability, diagnostic tests may be dependent on each other. For example, the type of conditions that produce a false-positive test for plethysmography may also produce a false-positive ultrasound result. This has potential implications if wanting to use tests in combination, but the lack of appropriate data limits the ability to draw conclusions.

Applicability to specific patient groups

With a few exceptions, such as the performance of D-dimer in patients with malignancy, there were very few data reporting the diagnostic performance of tests in specific patient groups, such as pregnant women or intravenous drug abusers. Care should therefore be taken in extrapolating findings to these patients. In particular, the findings may not be applicable to patients who develop DVT while hospital inpatients. Although many cohorts reported investigation of patients defined as being inpatients, many of these may be patients who were (historically) admitted for DVT investigation, rather than being inpatients who developed suspected DVT.

Implications of the meta-analyses

The implications of these meta-analyses can be summarised as follows:

- The most useful approach to clinical assessment is probably to use the Wells score to estimate the clinical probability of proximal DVT. However, it is unlikely that this categorisation will be considered accurate enough to allow treatment decisions to be made without further testing. Clinical probability scoring should therefore be used as a basis for selecting further tests, rather than treatment decisions.
- D-dimer testing is likely to be most usefully applied to patients with a low clinical probability of DVT. Specificity appears to be higher in these patients and sensitivity, applied to a low-risk population, may be considered adequate to rule out DVT (proximal, if not distal).
- The role of plethysmography and rheography remains unclear. Neither sensitivity nor specificity is likely to be considered adequate to rule out or rule in DVT without further testing. Using impedance plethysmography to rule out DVT in low-risk patients seems to be undermined by the finding, albeit from only one study,[75] that sensitivity is lower in these patients. Since it is likely that these techniques will need to be used in conjunction with other

diagnostic tests, more data are required to investigate how plethysmography and rheography interact with clinical probability and other diagnostic tests.
- Ultrasound will probably be considered to have adequate sensitivity to rule out proximal DVT and specificity to rule in DVT, but inadequate sensitivity to rule out distal DVT. However, these judgements need to take into account clinical probability of DVT. In a high-risk patient it may be argued that the imperfect sensitivity of ultrasound means that the risk of missed DVT will be unacceptable. The potential consequences of missing distal DVT also need to be considered in relation to the risk of extension and propagation.
- Using non-invasive testing in asymptomatic patients presents substantial problems. D-dimer may offer a simple, sensitive way of detecting DVT in at-risk asymptomatic patients, but poor specificity means that most patients will have a positive result and further testing will be required to confirm the diagnosis. Plethysmography and ultrasound have poor sensitivity in these patients.

Implications for future research

Although several hundred studies were included in these meta-analyses there remain substantial areas of uncertainty. This suggests that, while more research is required, researchers need to aim for quality, rather than quantity. Most importantly, the reporting of future research must be improved:

- All future studies should report their findings according to STARD criteria.
- The selection process must be clearly described and specifically state whether patients with conditions that could reduce diagnostic performance, such as co-morbidities or previous DVT, were excluded.
- The characteristics of the study population must be clearly described: mean/median age, gender balance, whether DVT were proximal or distal, and the proportion of patients with characteristics that may reduce diagnostic performance.
- A Wells score should be reported for all patients and diagnostic performance reported stratified by clinical probability.

There are plenty of data describing how non-invasive tests perform in unselected, or haphazardly selected, populations. These data suggest that there is no ideal test that can be used in all patients and all situations, so tests need to be used selectively in different populations or in combination. Data are needed that examine how tests perform in different patient groups and how different tests interact with each other.

Chapter 5

Evaluation of diagnostic algorithms for deep vein thrombosis: background and methods

Background

There is no perfect diagnostic test for DVT. Venography is considered to be the reference standard for diagnosis, yet it is invasive, uncomfortable, technically difficult to perform and interpret, requires a significant radiation dose, and carries risks associated with the injection of intravenous contrast material, or inducing DVT. Non-invasive tests are cheaper and more convenient, but none has perfect specificity or sensitivity, especially for distal DVT. Diagnosis is therefore likely to involve selection from a number of different tests. This can be done on an individual patient basis, using the data provided in previous chapters to determine which tests are likely to be appropriate. However, this approach has some disadvantages. Application of diagnostic test data to each individual patient requires considerable clinical (and statistical) skill. If tests are selected in an inconsistent or inappropriate manner this may result in unacceptable variation in diagnostic performance and inefficient use of resources.

Diagnostic algorithms applicable to patients with suspected DVT may be used to address this problem. Tests are selected and applied sequentially according to the algorithm until a decision to treat or discharge without treatment is reached. The algorithm is applied to a population of patients with suspected DVT and aims to maximise the benefit of diagnostic testing (in terms of accurate identification of patients with and without DVT), while minimising the costs of testing and subsequent treatment. A substantial number of diagnostic algorithms for DVT has been evaluated and published.

The diagnostic performance of algorithms can be assessed in the same way as diagnostic tests by measuring sensitivity (for proximal and distal DVT) and specificity. Yet to be able to make rational choices regarding which algorithm to use, the costs and benefits of using the algorithm also need to be weighed up. The costs of an algorithm are not simply those of the tests used, but must include the costs of subsequent treatment, and the costs of treating complications of treatment or lack of treatment. The benefits of diagnostic testing relate directly to the sensitivity and specificity of testing: optimising sensitivity allows cases of DVT to be treated, thus reducing the risk of complications of DVT, while optimising specificity allows treatment of patients without DVT to be avoided, thus avoiding the risks of treatment in those who will not benefit.

Evaluation of diagnostic algorithms thus involves:

- estimation of sensitivity (for proximal and distal DVT) and specificity
- estimation of the health outcomes of detecting and treating patients with, and without, DVT
- estimation of the costs of testing, the costs of treating positive cases, and the costs of managing the consequences of treatment or lack of treatment
- comparing the costs and benefits of providing each algorithm to a 'zero option' alternative, involving no testing and no treatment
- estimation of the net benefit of providing each algorithm, compared with no testing and no treatment, assuming a willingness to pay of £20,000 or £30,000 per quality-adjusted life-year (QALY) gained.

Most published studies of diagnostic algorithms report cohorts of patients managed by the algorithm and use a period of follow-up to identify complications due to "missed" or untreated DVT. These management studies can provide valuable reassurance that in practice these algorithms are unlikely to result in an unacceptable rate of adverse outcomes. However, the sparse data available on the natural course of untreated DVT suggest that most do not lead to symptomatic recurrence, pulmonary embolism or death.[402,403] In fact, if patients have no other underlying pathology and remain mobile then the rate of symptomatic progression may be very low. Therefore, it is not known whether an apparently safe algorithm is associated with few complications because it is highly sensitive for detecting DVT, or because the missed DVT do not naturally tend to

lead to complications. It is also not known whether the algorithm has resulted in inadvertent treatment of patients without DVT.

While acknowledging the importance of management studies in guiding policy in this area, the reviewers took a different approach to the assessment of algorithms for DVT diagnosis. The aim was to estimate the overall sensitivity and specificity of a variety of different algorithms by using modelling to combine estimates of the sensitivity and specificity of individual diagnostic tests. The results of this analysis could then be used to model the effectiveness and cost-effectiveness of these algorithms.

Aims and objectives

The aim of this phase of the evaluation was to model the use of diagnostic algorithms for patients presenting with suspected DVT to determine their effectiveness and cost-effectiveness. The specific objectives were to estimate:

- the sensitivity and specificity of each algorithm
- the health outcomes of using each algorithm
- the costs associated with each algorithm
- the cost-effectiveness of each algorithm compared with no testing, expressed as net benefit.

Methods

Identification of potential algorithms

The potential range of combinations of diagnostic tests that could be used in an algorithm is huge. Rather than simply testing every possible combination of tests in an algorithm, the authors sought algorithms that were likely to be feasible in routine practice. Algorithms were identified from two sources: (1) a literature search for algorithms that have been tested in clinical practice, and (2) a national survey of emergency departments in the UK.

Algorithms identified by literature search

An electronic search of the literature was done to identify articles that reported cohorts of patients with suspected DVT, who underwent diagnostic testing according to an algorithm combining two or more tests, and were then followed up or received a reference standard diagnosis. Eighteen articles were identified that fulfilled these criteria.[9,31,58,62,67,73,77,78,92,375,404–411] One article compared two algorithms in a randomised trial,[9] and the others were all cohort studies of a single algorithm. Two articles[92,411] reported data that were published elsewhere. Hence, there were 17 cohorts available for analysis. The results of follow-up are summarised in *Table 20*.

All of the studies used follow-up to determine whether the strategy was safe. The rate of

TABLE 20 *Studies of algorithms for diagnosing DVT*

Study	Total	Number treated	Number not treated	Number of DVT/PE during follow-up	Duration of follow-up (months)	% treated	% of untreated suffering DVT or PE
Wells(I) 2003[9]	566	85	481	2	3	15	0.4
Wells(C) 2003[9]	530	77	453	6	3	15	1.4
Wells, 1999[67]	150	40	110	2	3	27	1.8
Anderson, 1999[31]	344	43	301	2	3	12	0.7
Wells, 1997[58]	593	92	501	3	3	16	0.6
Kraaijenhagen, 2002[62]	1739	410	1329	15	3	24	1.1
Bernardi, 1998[375]	946	265	681	3	3	28	0.4
Walsh, 2002[78]	194	39	155	0	6	20	0
Bates, 2003[410]	556	51	505	5	3	9	1.0
Schutgens, 2003[404]	812	309	503	8	3	38	1.6
Anderson, 2003[409]	1075	193	882	4	3	18	0.5
Janes, 2001[406]	431	93	338	1	3	22	0.3
Perrier, 1999[407]	474	111	363	9	3	23	2.6
Tick, 2002[77]	811	343	462	7	3	43	1.5
Ruiz-Giménez, 2002[73]	569	150	419	3	3	26	0.7
Ginsberg, 1997[408]	398	66	332	4	3	17	1.2
Kearon, 2001[405]	445	63	382	1	3	14	0.3

C, control group; I, intervention group.

thromboembolic events in untreated patients varied from 0 to 2.6%, but was generally around 1%. However, it was not always clear whether all patients had been followed up and in most cases follow-up was limited to telephone contact.

No study compared the algorithm to a reference standard, such as venography. This is not surprising, given the logistic and ethical difficulties presented by such a study, but it does mean that it is not known whether the low rate of thromboembolic events among untreated patients is due to the sensitivity of the algorithm or due to a low rate of recurrence in mobile, untreated patients with DVT. Nevertheless, it is reasonable to assume that these algorithms would be acceptable in the NHS.

There was some duplication among the algorithms: three of the studies evaluated the same algorithm in different groups of patients, the studies by Bernardi[375] and Kraaijenhagen[62] evaluated essentially the same algorithm, and the study by Ruiz-Giménez[73] evaluated the same algorithm as the control group in the Wells randomised trial. Hence, there were 13 different algorithms. However, three of the algorithms could be interpreted in different ways, so two versions of each were tested. Overall, therefore, 16 algorithms derived from the literature review were tested.

Algorithms identified by the national survey

As outlined in Chapter 1, all NHS emergency departments were surveyed regarding current diagnostic approaches to DVT. D-dimer assays and ultrasound were routinely available to most departments. Venography was available to most departments by special request. Other tests (CT, MRI and plethysmography) were only available in a minority of departments.

A copy of the diagnostic algorithm used to diagnose DVT was received from 45 departments. The diagnostic tests used in the algorithms are outlined in *Table 21*. Most algorithms used a combination of a clinical score (usually Wells), D-dimer and ultrasound. Each algorithm was reviewed to determine whether it was similar to any of the published algorithms or whether it was similar to other algorithms identified by the survey. This process identified 11 additional algorithms that were being used in the UK, but were unlike any of the published algorithms.

Additional algorithms

In addition to algorithms identified by literature search and national survey, five other strategies were tested. Although not strictly algorithms, because each only uses one test, they represent either common approaches to diagnosis or theoretical extremes:

- no testing or treatment for any patient
- venography for all patients
- above-knee ultrasound for all patients, repeated 1 week later if negative
- full-leg ultrasound for all patients
- above-knee ultrasound for all patients without repeat.

Summary of algorithms tested

Ultimately 32 algorithms were tested: 16 from the published literature, 11 from the national survey and five additional algorithms. These are outlined in Appendix 4. The characteristics of the algorithms are summarised in *Tables 22* and *23*. *Table 22* shows the tests used in each algorithm.

The 'minimum' criteria for discharge without treatment in each algorithm (i.e. the simplest test or combination of tests used to discharge without treatment) are outlined as follows (*Table 23*):

- Algorithm 21 discharges on the basis of a low Wells score alone.
- Algorithms 13 and 25 discharge on the basis of negative D-dimer alone.

TABLE 21 *Use of DVT diagnostic tests in UK algorithms*

Diagnostic test	Number (%) of algorithms incorporating test (*n* = 45)
Wells score	32 (71)
Other clinical risk score	5 (11)
D-dimer	41 (91)
Ultrasound	42 (93)
Repeat ultrasound	22 (49)
Plethysmography	8 (18)
Venography	19 (42)

TABLE 22 *Diagnostic tests used in each algorithm tested in the model*

Algorithm number	Wells score	D-dimer	Plethysmography	Above-knee ultrasound	Full-leg ultrasound	Venography
0						
1						+
2				+		
3					+	
4				+		
5	+			+		+
6		+		+		
7	+			+		+
8	+				+	+
9	+	+		+		
10	+	+		+		
11	+	+		+		+
12	+	+			+	
13	+	+		+		+
14	+	+		+		
15	+	+		+		
16	+	+		+		
17	+			+		
18	+			+		
19		+	+			+
20	+	+	+	+		+
21	+			+		
22	+	+				+
23	+	+				+
24	+	+		+		+
25		+		+		
26	+	+	+		+	
27	+	+	+		+	
28	+	+	+		+	
29	+	+	+		+	
30		+	+		+	
31	+		+		+	

- Algorithms 9, 10, 11, 12, 15, 16, 20, 22, 23, 24, 27 and 28 discharge on the basis of a combination of Wells score and D-dimer.
- Algorithm 31 discharges on the basis of a combination of Wells score and plethysmography.
- Algorithms 19, 26, 29 and 30 discharge on the basis of negative plethysmography and D-dimer.
- Algorithms 2, 3, 4, 5, 6, 7, 8, 14, 17 and 18 require all patients to have ultrasound.

Treatment for DVT required patients to have a positive venogram or ultrasound result in all algorithms except for algorithm 26, which recommended treatment on the basis of a high Wells score and positive plethysmography result alone.

Model description

A decision-analytic model was developed to compare algorithms for the diagnosis of DVT in a hypothetical cohort of 1000 patients presenting with suspected DVT. This number is likely to be similar to that observed per annum in a large hospital.[412] The model principally applies to patients presenting as outpatients, without known co-morbidity (such as malignancy). The potential impact of applying the algorithms to other populations was explored in the sensitivity analysis.

The model allows the following comparisons to be made:

- number of patients with proximal DVT who are correctly diagnosed
- number of patients with distal DVT that propagates proximally and are treated
- number of patients without DVT or with non-propagating distal DVT who are not treated
- total direct costs of testing
- total costs of each algorithm
- outcomes in terms of QALYs
- the net benefit of each algorithm compared with no testing, assuming thresholds of willingness to pay of £20,000 and £30,000 per QALY.

TABLE 23 *Criteria used for discharge*

Algorithm number	Wells and D-dimer	Plethysmography and D-dimer	Wells only	Wells and plethysmography	D-dimer alone	Ultrasound for all
0						
1						
2						+
3						+
4						+
5						+
6						+
7						+
8						+
9	+					
10	+					
11	+					
12	+					
13					+	
14						+
15	+					
16	+					
17						+
18						+
19		+				
20	+					
21			+			
22	+					
23	+					
24	+					
25					+	
26		+				
27	+					
28	+					
29		+				
30		+				
31				+		

The model was constructed as a decision tree, which is outlined in *Figure 18*.

The key elements of the model are:

- The sensitivity (proximal and distal) and specificity of the algorithm are estimated from the diagnostic parameters of the constituent tests.
- The sensitivity and specificity of the algorithm are applied to the population to determine the proportion of patients with and without DVT who receive treatment.
- Depending on whether they have DVT or not, and whether they are treated or not, individuals in the population will be exposed to a number of events related to DVT, treatment, or both.
- Following these events individuals will have health outcomes determined by the events they have suffered.
- Costs are accrued by performing diagnostic tests, treating DVT and treating events.

Estimation of sensitivity and specificity for each algorithm

Each algorithm consists of up to five separate diagnostic tests. The sensitivity and specificity of each of these tests are based on meta-analyses reported in previous chapters, and are reproduced in Appendix 5 along with details of the probability distributions applied to these parameters. In each case independent beta distributions were applied. Combining the diagnostic parameters of the individual tests to estimate the overall diagnostic performance of the algorithm involved making a number of assumptions that are outlined below.

Independence of constituent diagnostic tests

The simplest way to estimate the sensitivity and specificity of an algorithm is to assume that each of the individual tests used in the algorithm is independent of the other tests. Sensitivities and specificities of individual tests can thus be combined in a simple multiplicative manner to estimate overall values. However, this assumption

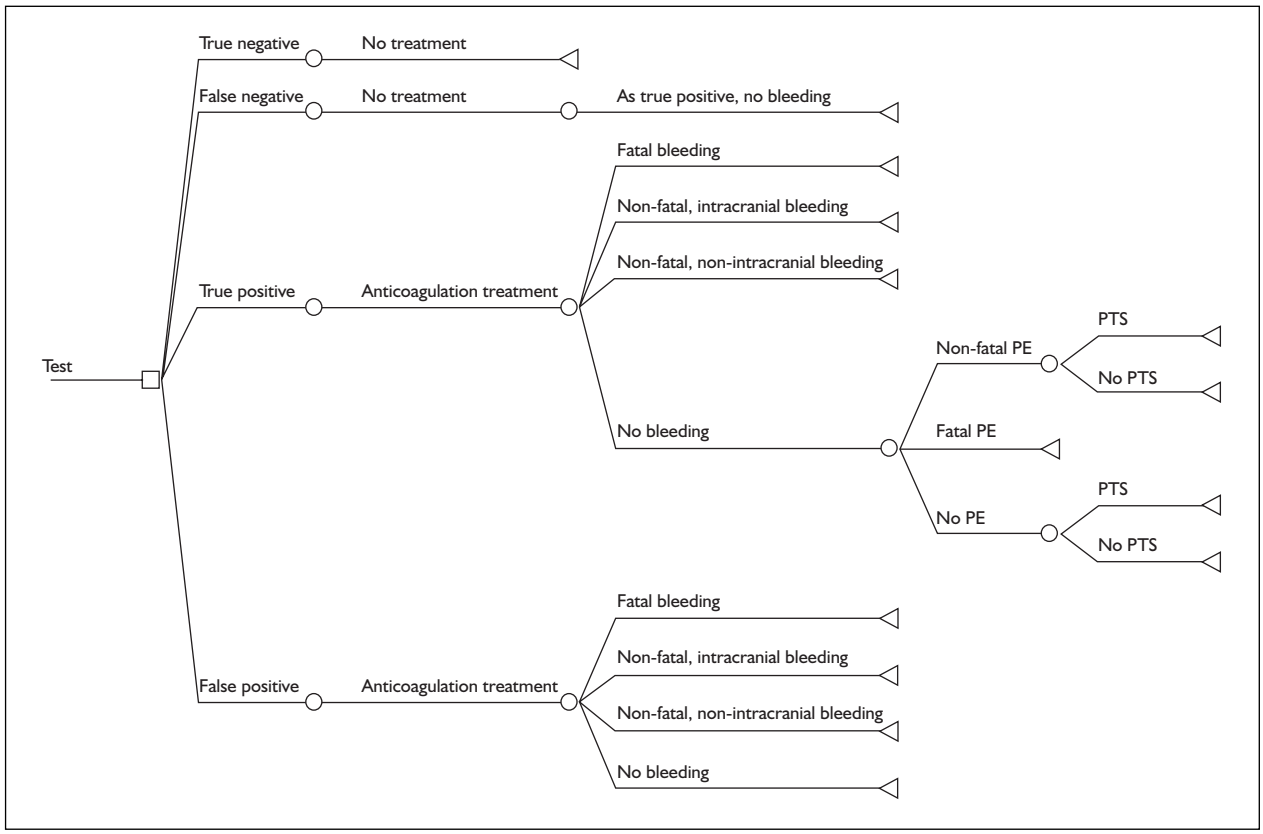

FIGURE 18 *Key features of decision tree*

of independence may not hold. So one needs to consider whether the tests considered for inclusion in algorithms will be independent.

Five studies of D-dimer assays included in the meta-analysis[61,70,71,92,110] evaluated sensitivity and specificity by Wells categorisation. Specificity was consistently lower in subgroups with higher clinical risk of DVT. No such relationship was observed for sensitivity. This finding is biologically plausible. Pathologies that are associated with a higher clinical risk of DVT, particularly malignancy, are also known to be associated with elevated levels of D-dimer.

Only two studies, one of impedance plethysmography[75] and one of ultrasound,[8] were identified that reported any diagnostic tests other than D-dimer stratified by Wells score. These suggested that both tests had higher sensitivity in patients with a high risk of DVT. However, both of these studies reported low overall sensitivities for impedance plethysmography and ultrasound, so findings may not be generalisable. No studies were found reporting strain-gauge plethysmography by Wells categorisation, and no studies examining interactions between any other diagnostic tests.

In view of these findings, it was assumed that D-dimer specificity was dependent on Wells categorisation. It was also assumed that specificity for intermediate-risk patients is the same as overall specificity for each assay. Data from the six studies reporting D-dimer by Wells categorisation were then used to estimate the ratio of high-risk or low-risk specificity to intermediate-risk specificity (i.e. high 51/67 = 0.76; low 78/67 = 1.16). These ratios were applied to the estimate of the overall specificity for each assay to estimate specificity in high- and low-risk patients. For all other diagnostic parameters the overall values derived from the meta-analyses were used, assuming that tests were independent of each other.

Proximal and distal DVT

Proximal and distal DVT appear to carry different risks of propagation for PE and thus different risk–benefit ratios for treatment with anticoagulation. Hence, proximal and distal DVT were handled separately. Meta-analyses showed that Wells stratification, D-dimer, plethysmography and ultrasound all have higher sensitivity for proximal than for distal DVT. Therefore, meta-analysis of studies that reported

proximal and distal DVT separately was used to obtain estimates of sensitivity.

Plethysmography

Meta-analysis suggested that impedance and strain-gauge plethysmography have slightly different sensitivities and specificities. The survey of current practice revealed that the use of plethysmography was not widespread in the UK, and those hospitals that did use plethysmography used strain-gauge. Therefore, it was assumed that plethysmography was always strain-gauge.

Ultrasound techniques

Ultrasound is sensitive for detecting proximal DVT, but has relatively poor sensitivity for distal DVT. Given that distal DVT are only likely to be of pathological significance if they propagate to form proximal DVT, many sonographers do not examine below the knee, but only look for proximal DVT. This approach may be augmented by a repeat scan 1 week later, to detect proximal propagation, either in all patients or in those selected by D-dimer or Wells categorisation.

Therefore, two alternative approaches to ultrasound were considered in the analysis:

- above-knee ultrasound, in which only the proximal veins are scanned
- full-leg ultrasound, in which the whole leg is scanned.

It was assumed that above-knee ultrasound could be undertaken by anyone with training in sonography and would have the same sensitivity for proximal DVT as the overall estimate from the meta-analysis, but would not detect distal DVT. Instead, distal DVT would be classified as negative or (false) positive according to the specificity of ultrasound. It was assumed that full-leg ultrasound would have proximal sensitivity, distal sensitivity and specificity derived from the meta-analysis. It was also assumed that false-negative proximal or distal DVT were reported as having a normal ultrasound, while false-positive patients without DVT were reported as having a proximal DVT (for both above-knee and full-leg techniques).

Repeat ultrasound

Repeat ultrasound is intended to detect distal DVT that have propagated proximally, and thus negate the potential risk associated with missing distal DVT. Implicit in this is the assumption that repeat ultrasound has a much better specificity than initial ultrasound, because all of the conditions causing false positives will be 'weeded out' by the initial ultrasound. Presumably this also means that cases of proximal DVT that were missed by the initial ultrasound will also be missed by the repeat. These are reasonable assumptions. False positives and false negatives are unlikely to be random events, but may be determined by anatomical or physiological characteristics. Thus, patients for whom a false-positive or false-negative result is likely on initial scan will have the same characteristics, making a false-positive or false-negative result likely on the repeat scan.

The use of repeat scanning was modelled using the following assumptions:

- Distal DVT that are going to propagate to the proximal veins will do so within the first week.
- Only patients with a negative initial scan will undergo repeat scanning.
- Patients with a false-negative initial scan for proximal DVT will have a false-negative repeat scan
- Patients with a true-negative initial scan for no DVT will have a true-negative repeat scan.
- Repeat scanning will detect distal DVT that have propagated proximally with the sensitivity for proximal DVT derived from the meta-analysis.
- Patients with distal DVT that do not propagate proximally will be effectively DVT negative at the time of repeat scanning.
- Repeat scanning usually follows a negative initial above-knee scan. However, it may also be used following an initial full-leg scan or venogram that has detected distal DVT to determine whether proximal propagation has occurred.

Therefore, the results of repeat scanning were estimated by modelling one specific event occurring after initial presentation: the proximal propagation or resolution of distal DVT over the initial week. All other diagnostic tests were modelled at presentation.

This approach to modelling repeat ultrasound involves making a number of assumptions that have few empirical data to support them. Some empirical data do exist, as outlined in Chapter 3, although they did not meet the required standard for inclusion in the meta-analysis. Therefore, a separate cost-effectiveness analysis specifically of repeat ultrasound was undertaken, using data from follow-up studies to determine whether repeating an initially negative ultrasound scan is likely to be cost-effective. The details are outlined in the section 'Cost-effectiveness of repeat ultrasound scanning' (p. 56).

Venography

It was assumed that venography had perfect (100%) sensitivity and specificity. However, venography has a number of limitations due to its being an invasive procedure. The following assumptions were used to reflect these limitations:

- Venography would be unsuccessful in 10% of patients and ultrasound would be performed instead.
- Allergic reaction to intravenous contrast would lead to fatal reactions in 1 in 55,000 patients receiving venography.[413,414]
- Venography would cause proximal DVT in 1/303 and distal DVT in 2/303 patients.[415,416] It was assumed that half of these would be detected and treated, and half would not be treated. These would, respectively, carry the same costs and outcomes as treated and untreated DVT (see later descriptions).

Applying the algorithms to a typical population

Each algorithm was applied to a hypothetical population of 1000 people with suspected DVT. The sensitivity and specificity of the algorithm determined how many patients with, and without, DVT would receive treatment. Treatment decisions are usually stipulated as part of the algorithm. The final decision for any pathway will usually be to treat or discharge without treatment. However, in some cases the treatment decision may not be clear. Typically, this occurs when the diagnostic test is able to determine the location of DVT (proximal or distal), rather than simply a positive or negative result. In these cases there may be confusion as to the appropriate treatment decision. It was assumed that this situation would be handled in a consistent way in all algorithms. Because of the assumptions made in the model, the most appropriate decision upon identifying a proximal DVT would be to treat, the most appropriate decision upon identifying a distal DVT would be to repeat an above-knee scan 1 week later, and the most appropriate decision for no DVT would be to discharge without treatment.

Population prevalence of proximal and distal DVT

The performance of diagnostic algorithms will depend on the population prevalence of proximal and distal DVT. The idea was to estimate a prevalence that reflected a typical population presenting with suspected DVT. However, studies that reported prevalence of proximal and distal DVT separately, such as those identified in the meta-analysis of ultrasound, required all patients to undergo venography. Because the use of venography in routine practice has declined recently, this meant that such cohorts were either highly selected or historical. Either way, overall DVT prevalence would be expected to be lower in a typical population presenting with suspected DVT.

To obtain a more typical estimate the population prevalence of proximal DVT reported in a recent study of D-dimer in a typical NHS hospital was used,[72] which reported unselected patients presenting with suspected DVT. Because the reference standard for this study was ultrasound only proximal DVT were reported. To estimate the prevalence of (undiagnosed) distal DVT in this population, the median estimate of the proximal to distal ratio reported in ultrasound studies (78% proximal:22% distal) was used, assuming that a similar ratio existed in the study population.

Age and gender distribution of the population

It was assumed that the diagnostic performance of the algorithm would be independent of the age distribution of the population, but that quality-adjusted life expectancy would depend on age. Therefore, it was assumed that the population had a mean age of 60 years, derived from data from the VERITY registry of patients presenting for diagnostic testing for suspected DVT in the UK.[412] The VERITY registry also reported that among patients with diagnosed DVT there were equal numbers of men and women. Therefore, it was assumed that there was an equal gender balance in the study population.

Estimation of the probability of events after diagnosis and treatment

It was assumed that patients would have proximal DVT, distal DVT or no DVT, and would receive either treatment or no treatment. Treatment would consist of initial anticoagulation with subcutaneous heparin followed by at least 3 months of oral anticoagulation with warfarin. These factors would determine the probability of the following events:

- among patients with DVT: fatal PE, non-fatal PE and development of PTS. Proximal and distal DVT were modelled separately and the risks of events were assumed to be reduced by treatment
- among treated patients: fatal haemorrhage, non-fatal intracranial haemorrhage and other non-fatal major haemorrhage (defined as any haemorrhage requiring hospitalisation or blood transfusion).

Patients with DVT may also suffer recurrent DVT. This outcome was not included in the model because: (1) recurrent DVT offers a new opportunity for diagnosis and treatment and is therefore effectively a new episode and (2) the important consequences of recurrent DVT (PE and PTS) are measured and included in the model regardless of whether they occur as a result of initial or recurrent DVT.

In some cases there may be a short delay between patient presentation and full availability of diagnostic testing, for example, if the patient presents outside normal working hours. In this analysis no attempt was made to address the question of whether patients should receive treatment during this delay. This would involve weighing two very small risks: the risk of bleeding after a single dose of anticoagulant versus the risk of DVT propagation over a time period of typically less than 24 hours, multiplied by the probability of DVT. These risks are very uncertain and highly dependent on individual circumstances (patient risk of DVT or bleeding, time delay before diagnosis), and are thus best addressed on a case-by-case basis.

Probability of events due to distal DVT

A number of studies compared treatment of distal DVT to no treatment. These are outlined in *Table 24*. In addition, Schwartz and colleagues[422] found that, without treatment, 8/32 (25%) patients with muscle vein thrombosis propagated to more proximal calf veins, compared with 0/52 of a historical treated cohort. No patient developed PE. Meanwhile, in an RCT of two different treatment regimens for calf DVT, Pinede and colleagues[423] reported that 1/197 (0.5%) treated patients developed PE.

From these data it appears that distal DVT carry a significant risk of propagating proximally if untreated, but a low risk of directly causing PE. If treated, the risk of proximal propagation or PE is very small. The most reliable data to determine the risk of proximal propagation without treatment are from the randomised trial by Largerstedt.[417] Observational studies carry the risk of bias owing to patients being selected to receive treatment on the basis of factors such as size and location of DVT.

It was therefore assumed that:

- Without treatment, 21% of patients with a distal DVT will develop proximal DVT. This is based on the data from Largerstedt,[417] in which 28 patients with distal DVT were randomised to no treatment: five developed symptomatic proximal extension and one suffered symptomatic PE.
- Patients who develop proximal DVT (21%) have the same risks of fatal and non-fatal PE as those with initial proximal DVT. Patients who do not develop proximal DVT (79%) have no risk of fatal or non-fatal PE.
- Treatment effectively abolishes any risk of DVT extension.

There are very few data regarding the risk of PTS after treated and untreated DVT. It was assumed that the 21% of untreated patients who develop proximal DVT have the same risk of post-thrombotic syndrome as any other patient with untreated proximal DVT, and that the risk of post-thrombotic syndrome with treated distal DVT is zero.

Probability of events due to proximal DVT

Anticoagulation has been standard treatment for proximal DVT for over 40 years, so there are

TABLE 24 *Studies comparing treatment of distal DVT with no treatment*

Study	Design	Propagation to form proximal DVT		Propagation to form PE	
		Treated	Untreated	Treated	Untreated
Largerstedt, 1985[417]	RCT	0/23 (0%)	5/28 (18%)	0/23 (0%)	1/28 (3.6%)
Nielsen, 1994[403]	RCT	NR	NR	0/7 (0%)	0/9 (0%)
Hull, 1979[402]	RCT	NR	NR	0/16 (0%)	0/16 (0%)
Masuda, 1998[418]	Observational	0/28 (0%)	2/26 (8%)	0/28 (0%)	0/26 (0%)
Meissner, 1997[419]	Observational	NR	NR	1/21 (5%)	0/8 (0%)
Labropoulis, 2002[420]	Observational	2/19 (11%)	5/29 (17%)	0/19 (0%)	1/29 (3%)
Lohr, 1995[421]	Observational	0/23 (0%)	21/169 (12%)	NR	NR

NR, not reported; RCT, randomised controlled trial.

substantial data relating to treated proximal DVT, but very few relating to untreated proximal DVT. The data relating to treated proximal DVT were summarised in a recent meta-analysis by Douketis and colleagues.[424] The summary estimate of the probability of fatal PE was 0.4% (17/4221) and of non-fatal thromboembolism was 3.8% (156/4104). Of those with non-fatal thromboembolism, 21.4% had PE and 78.6% had recurrent DVT, so the rate of non-fatal PE was 0.8%. Meanwhile, Prandoni and colleagues[425] estimated the incidence of PTS in patients with treated proximal DVT: 5.3% of 528 presented severe post-thrombotic manifestations. These estimates were used in the present model.

The evidence for treating DVT is largely based on an RCT by Barritt and Jordan,[426] published in 1960, that compared anticoagulation to no treatment for symptomatic PE. Both groups were prescribed 2 weeks of bed rest. In the untreated group five of the 19 (26%) patients died from recurrent PE, while another five suffered a non-fatal recurrence. Since this trial only two small trials of anticoagulation have been performed. Hull and colleagues[402] compared 'inadequate' low-dose treatment to full anticoagulation for DVT. Among the 19 patients with proximal DVT receiving 'inadequate' treatment one suffered a non-fatal PE and was anticoagulated, and there were no deaths. Nielsen and colleagues[403] compared non-anticoagulant treatment with phenylbutazone (an anti-inflammatory drug) to anticoagulation for DVT. Patients were mobilised soon after diagnosis. Over the following 3 months one of the 35 untreated patients with proximal DVT suffered non-fatal PE and was anticoagulated, and there were no deaths.

These data suggest that the risk of PE in untreated proximal DVT is relatively low (3–4%) and that approximately one-quarter of patients with untreated PE will die (giving an overall mortality of 1% for untreated DVT). However, data from the 1940s, reporting cohorts of patients with DVT who were managed before anticoagulation became widespread, suggest a much higher mortality of approximately 16%. Several factors need to be taken into account when attempting to reconcile these conflicting estimates:

- Historical comparisons are known to exaggerate treatment effects.
- Diagnosis of DVT in the 1940s was based on clinical criteria, so cohorts are likely to include many high-risk cases.
- Standard treatment in the 1940s (and in the Barritt and Jordan study[426]) was bed rest, which probably worsens prognosis. By contrast, Nielsen's study[403] prescribed early mobilisation.
- The recent randomised trials reported only small numbers, so confidence intervals for estimates are wide.
- The control groups in the randomised trials both received some form of treatment. Hull[402] used low-dose heparin and Nielsen[403] used phenylbutazone, an anti-inflammatory that has antiplatelet activity.

Hence, it is likely that the true risks of fatal and non-fatal PE in patients with untreated proximal DVT lie somewhere between these two extremes. Furthermore, it might be argued that the present model is interested in the risks of 'missed' DVT, rather than untreated DVT. The two are not necessarily the same. Non-invasive tests might be more likely to misdiagnose small, non-occlusive DVT in otherwise healthy people that may carry a better prognosis.

Therefore, an alternative method was used to estimate the risks of untreated (missed) proximal DVT. Management studies were identified that reported the use of non-invasive strategies in cohorts of patients with suspected DVT and then provided follow-up for at least 3 months to identify subsequent cases of thromboembolism. These included the management studies of diagnostic algorithms outlined earlier and management studies of ultrasound.

For each study estimates of sensitivity for each diagnostic test, derived from the meta-analyses, were used to estimate the number of DVT that the diagnostic strategy would have failed to detect. The same assumptions regarding distal DVT as used in the model were used to estimate the number that would extend to form proximal DVT and the number that would be identified by repeat ultrasound scanning. Then, the expected total number of "missed" proximal DVT in all studies and the total number of fatal and non-fatal PE identified during 3-month follow-up were calculated. From this, the proportion of patients predicted to have had missed DVT who developed fatal or non-fatal PE was derived. The results are outlined in *Table 25*.

From these data it was estimated that the probability of fatal PE would be 1.9% (5/268) and the probability of non-fatal PE would be 9.3% (25/268) among patients with untreated proximal DVT.

Unfortunately, none of the data sources identified allowed the probability of PTS in untreated

TABLE 25 *Predicted numbers of 'missed' DVT patients who develop fatal or non-fatal PE*

Diagnostic strategy	Study	Number of DVT diagnosed at initial assessment	Predicted number of untreated proximal DVT	Actual number of fatal PE during follow-up	Actual number of non-fatal PE during follow-up
Serial ultrasound	Cogo, 1998[16]	400	34.0	1	1
	Heijboer, 1993[20]	93	3.7	0	1
	Sluzewski, 1991[17]	39	4.5	0	1
	Sluzewski, 1991[17]	28	3.2	0	0
	Birdwell, 1998[18]	63	3.0	0	1
	Wolf, 2000[427]	117	11.6	0	1
Single full-leg ultrasound	Schellong, 2003[428]	121	15.2	1	0
	Elias, 2003[429]	112	16.3	0	0
	Stevens, 2004[430]	42	4.4	0	0
	Shields, 2002[61]	17	2.0	0	0
Diagnostic algorithm	Bernardi, 1998[375]	260	24.9	1	1
	Kraaijenhagen, 2002[62]	391	28.0	2	4
	Wells, 2003[9]	82	7.5	0	0
	Wells, 2003[9]	76	7.7	0	6
	Wells, 1999[67]	38	2.0	0	1
	Anderson, 1999[31]	40	2.2	0	0
	Wells, 1997[58]	89	4.1	0	0
	Walsh, 2002[78]	39	2.7	0	0
	Bates, 2003[410]	50	5.8	0	0
	Schutgens, 2003[404]	294	25.1	0	4
	Anderson, 2003[409]	189	12.5	0	0
	Janes, 2001[406]	93	11.9	0	1
	Perrier, 1999[407]	111	11.3	0	2
	Tick, 2002[77]	330	24.9	0	1

proximal DVT to be estimated. Therefore, an expert panel consisting of ten consultants working in emergency medicine, general internal medicine and haematology was asked to estimate this probability. Their estimates ranged from 5 to 50%, with a mean of 33%.

Probability of events due to anticoagulant treatment

A recent meta-analysis by Linkins and colleagues[6] estimated the risks of bleeding among patients taking anticoagulant therapy for venous thromboembolism. Among 10,757 patients who received anticoagulant therapy there were 37 fatal bleeding episodes (0.34%), 13 non-fatal intracranial haemorrhages (0.12%) and 226 other non-fatal major bleeding episodes (2.1%). These estimates were used in the model.

Valuation of health outcomes

After diagnosis and treatment, according to the algorithm, the 1000 individuals in the population would suffer events over the following 3 months, as outlined above. Having suffered, or avoided, these events, the anticipated number of QALYs that each individual would accrue was then estimated. Individuals who died were assigned zero QALYs. Those who avoided all adverse events were assumed to have a normal expected quality-adjusted, discounted life expectancy for an individual aged 60 years of 11.58 QALYs, based on interim life tables[431] and estimates of age-specific quality of life.[432]

QALYs for those who suffered non-fatal events were estimated by adjusting normal expected quality-adjusted, discounted life expectancy. Decrements in quality of life for PTS and for non-fatal intracranial haemorrhage are those reported by O'Meara and colleagues[433] and are based on valuation exercises conducted using the standard gamble technique with a small sample (n = 36) of individuals both with and without DVT. Other non-fatal (non-intracranial) haemorrhage was assumed to be equal to hospitalisation for 2 weeks. During this time patients were assumed to accrue no QALYs, but afterwards were assumed to have a normal quality-adjusted life expectancy. No studies were identified that estimated the impact of non-fatal pulmonary embolism on quality of life. Values estimated by the expert panel were therefore used. It was assumed that if a patient had more than one non-fatal event then decrements in quality of life would be multiplicative.

The only other factors affecting health outcome were adverse events associated with the use of venography: the 1:55,000 risk of a fatal reaction to intravenous contrast and the 1% risk of inducing DVT (half of which are detected and treated). These were modelled by applying a mean QALY loss to each individual receiving venography according to the model.

No QALY loss related to DVT itself was assumed, because the health impact of DVT is mainly due to its complications (PE and PTS) rather than DVT itself, and because patients with suspected DVT who ultimately do not have DVT will presumably have other pathologies (such as muscular injury or cellulitis) that will have a similar impact on quality of life to DVT. Hence, if one assumes a QALY loss for DVT, one should assume a QALY loss for all patients in the cohort, thus negating any impact.

Valuation of health service costs

Costs to the health service arose from two sources: (1) diagnostic tests required by the algorithm, and (2) treatment of DVT and adverse events.

Costs of the tests

The cost of clinical risk assessment was estimated as 5 minutes of a hospital consultant.[434] SimpliRED whole-blood agglutination D-dimer test costs were obtained from the manufacturer (Axis Shield: personal communication, 2004) plus an additional 5 minutes of consultant time to administer and interpret the test result. Laboratory-based D-dimer was also assumed to require 5 minutes of consultant time and the unit cost of the test was obtained from a large NHS trust (Newcastle upon Tyne NHS Trust; personal communication, 2004). NHS reference costs were used to estimate ultrasound and venogram values.[435] Full-leg ultrasound was distinguished from the simpler above-knee ultrasound. Normal probability distributions were applied to these parameters. The cost of plethysmography is based on the costs of the equipment (£14,500 per machine), maintenance costs (£1450 per annum) and consumables (Amtec Medical: personal communication, 2004). Assumptions of a working life of 5000 tests for the equipment and 15 minutes of a grade 1 technician per test were made, as reported by McNally and colleagues.[436] This is for the Belfast DVT screener (a strain-gauge plethysmograph). Training costs were not included in the estimates of any of the diagnostic test unit costs.

Treatment costs

Where possible, NHS reference costs were used. These were available directly for fatal and non-fatal PE. PTS was valued as one new vascular surgery outpatient visit plus two follow-up visits per annum[435] and a further two GP consultations per annum.[434] The lifetime cost was therefore estimated at £3866.

It was assumed that treatment for proximal DVT was provided as an outpatient and consisted of a mean 8.6 days of low molecular weight heparin (enoxaparine, dose estimated for a 70-kg patient), followed by 90 days of warfarin. Treatment beyond 90 days was assumed to be determined on a case-by-case basis and not influenced by the initial diagnostic strategy. It was assumed that heparin treatment required two additional nursing visits and two GP home visits, based on data from Boccalon and colleagues,[437] and warfarin treatment would require four anticoagulant clinic visits (NHS reference cost). Drug costs were drawn from the British National Formulary (BNF, 2004)[438] and unit costs of GP and nursing from Netten and Curtis.[434]

Haemorrhagic adverse events associated with anticoagulant treatment were costed from various sources. Non-fatal, non-intracranial bleeding was based on NHS reference cost data for gastrointestinal bleeding, while fatal bleeding and non-fatal intracranial bleeding, in both the first and subsequent years, were based on data reported by Sandercock and colleagues.[439]

Model analysis

The model was analysed to estimate the expected mean costs and mean QALYs that would be accrued by each algorithm, compared with no testing (algorithm zero), for every 1000 patients with suspected DVT. To estimate cost-effectiveness two net benefit analyses were undertaken, using thresholds for willingness to pay of £20,000 and £30,000 per QALY. These analyses involve assuming a willingness to pay of up to £20,000 and £30,000 per QALY gained, respectively, and calculating the net benefit that would be expected to accrue. These values were chosen because they represent reasonable levels for the willingness to pay threshold in the NHS, based on judgements by the National Institute for Health and Clinical Excellence.[440] Using these assumptions the algorithm with the highest estimated mean value for net benefit would thus be the most cost-effective algorithm.

The model was analysed probabilistically. Probability distributions were assigned to parameters used in the model, Monte Carlo

simulation was used to sample randomly from those distributions and the model was recalculated for each simulation. This approach permits the uncertainty in model inputs to be reflected in the key model outputs, namely costs, effects and the cost-effectiveness ratio. Distributions for the parameters are outlined in Appendix 5.

Uncertainty in these estimates is reflected using cost-effectiveness acceptability curves (CEACs). The net benefits of each strategy compared with no testing were calculated for each of the Monte Carlo simulations by the following equation:

$$\text{Expected net benefit } T_i = \lambda Q(T_i) - C(T_i)$$

where λ represents the maximum acceptable incremental cost-effectiveness ratio (MAICER) or 'willingness to pay' threshold, $Q(T_i)$ is the expected health benefit of treatment strategy T_i, and $C(T_i)$ is the expected cost of treatment strategy T_i.[441,442] The CEAC plots the proportion of simulations for each strategy that generates the maximum net benefit across a λ range of £0–100,000. The CEAC frontier plots the extent of uncertainty surrounding decisions based on mean net benefits across a similar range of λ values.[443]

The time horizon was the lifetime of the patient. The analysis assumes a health and social services perspective and a discount rate of 3.5% was applied to all future costs and benefits. Costs are expressed in 2003/04 UK sterling values.

Sensitivity analysis

In addition to the probabilistic sensitivity analysis outlined above, a number of other parameters and assumptions was explored using one-way deterministic sensitivity analysis. Analyses were planned of the effect of varying the population prevalence of DVT and the specificity of D-dimer, because these parameters were most likely to vary between populations, and may be useful in identifying an algorithm that is more suitable for a particular patient group. For example, D-dimer appears to have lower specificity in patient groups with co-morbidity, such as inpatients and those with malignancy. It was also planned to repeat the probabilistic sensitivity analysis, only including algorithms that used widely available tests. Finally, unplanned sensitivity analyses were undertaken to determine whether the cost-effectiveness of apparently optimal algorithms was sensitive to variation in key parameters, and whether minor modifications might alter cost-effectiveness.

Population prevalence of proximal DVT

The prevalence of proximal DVT in the model population reflects a typical population of patients presenting to hospital with clinically suspected DVT. However, this value may depend on local factors, such as the presence of referral filters (e.g. GPs or patients) that may select patients for investigation, or may be different in specific groups of patients, such as those with malignancy. Therefore, estimation of the mean net benefit of each algorithm was repeated for values of the prevalence of proximal DVT varying from 0 to 30%.

Specificity of D-dimer

Although there was substantial heterogeneity in the estimates of diagnostic parameters for all tests used in the algorithms, no subgroups in whom test performance was predictably different could be reliably identified. One exception to this was the specificity of D-dimer. This test is known to produce false-positive results in certain groups of patients, such as those with malignancy. Meta-analysis showed that specificity of D-dimer is lower among patients with malignancy (46%) than among the general population. This example was used to explore the possibility that the cost-effectiveness of algorithms in subgroups of patients in whom D-dimer has lower specificity will differ from the cost-effectiveness in the general population with suspected DVT. Estimation of the mean net benefit of each algorithm was repeated with estimates of D-dimer specificity reduced to 84% of their baseline value. This reflects the estimate of specificity derived from meta-analysis of patients with malignancy.

Algorithms only using widely available tests

The national survey showed that D-dimer and ultrasound are widely available throughout the NHS, whereas the availability of plethysmography and venography is much more limited. The wells score is a simple clinical score that requires no special equipment and is therefore widely available. Full-leg ultrasound requires a degree of skills and experience that may not be routinely available throughout the NHS. Therefore, it was assumed that algorithms using venography, plethysmography and full-leg ultrasound may not currently be feasible throughout the NHS and may require substantial organisational change to implement, whereas algorithms only using Wells score, D-dimer and above-knee algorithms could be implemented throughout the NHS with minimal reorganisation. The probabilistic sensitivity analysis was repeated, limiting inclusion of algorithms to those based only on Wells score, D-dimer and above-knee ultrasound.

Cost-effectiveness of repeat ultrasound scanning

As outlined earlier, a separate analysis of repeat ultrasound scanning, using data from follow-up studies, was undertaken to determine whether repeating an initially negative scan is likely to be cost-effective in unselected patients and in patients with a positive D-dimer.

Data from observational studies of repeat scanning suggest that a repeat scan in an unselected population will be positive in 1.34% of cases (Chapter 3): 89% will be true positive and 11% false positive. If only patients with a positive D-dimer undergo repeat scanning, 3.63% will be positive. These data were used to estimate the additional costs incurred and QALYs accrued by performing a repeat scan on 10,000 unselected patients with a negative initial scan, and on 10,000 patients with a positive D-dimer and negative initial scan. These data were used to estimate the incremental cost per QALY gained in each of these scenarios.

Chapter 6

Evaluation of diagnostic algorithms for deep vein thrombosis: results

Accuracy of the algorithms

The accuracy of the algorithms for detecting and treating proximal and distal DVT, and for correctly identifying patients without DVT, was evaluated by estimating the mean value for each parameter in each algorithm. *Figures 19–22*, respectively, show the proportion of patients with proximal DVT who are treated, the proportion of patients with distal DVT that propagates proximally who are treated, the proportion of patients with distal DVT that does not propagate proximally who are treated and the proportion of patients without DVT who are treated. The data comprising *Figures 19–22* are in Appendix 2 (*Table 38*).

The more sensitive strategies all use venography to some degree and typically have sensitivities greater than 95%. Three algorithms (excluding algorithm zero) have sensitivities below 90%. These were algorithms where patients were immediately discharged following a low Wells test, or were discharged following a negative D-dimer test.

There is much greater variation in the proportion of propagating distal DVT that receives treatment. In general, the more repeat ultrasound scanning or venography is used, the more distal DVT are treated.

Most strategies treat approximately 6% of distal DVT that do not propagate proximally. This reflects the assumption that distal DVT would only be treated if demonstrated to be propagating proximally on repeat ultrasound: 6% is the false-positive rate of repeat ultrasound. Two algorithms (excluding algorithm 0) have markedly different values: algorithm 1, which uses venography on all patients, and thus fewer ultrasounds; and algorithm 26, the only algorithm that treats on the basis of a test result other than positive venography or ultrasound (positive D-dimer and strain-gauge plethysmography).

All algorithms have 6% or lower of patients without DVT treated, the exact figure being dependent on the proportion of patients in each algorithm who

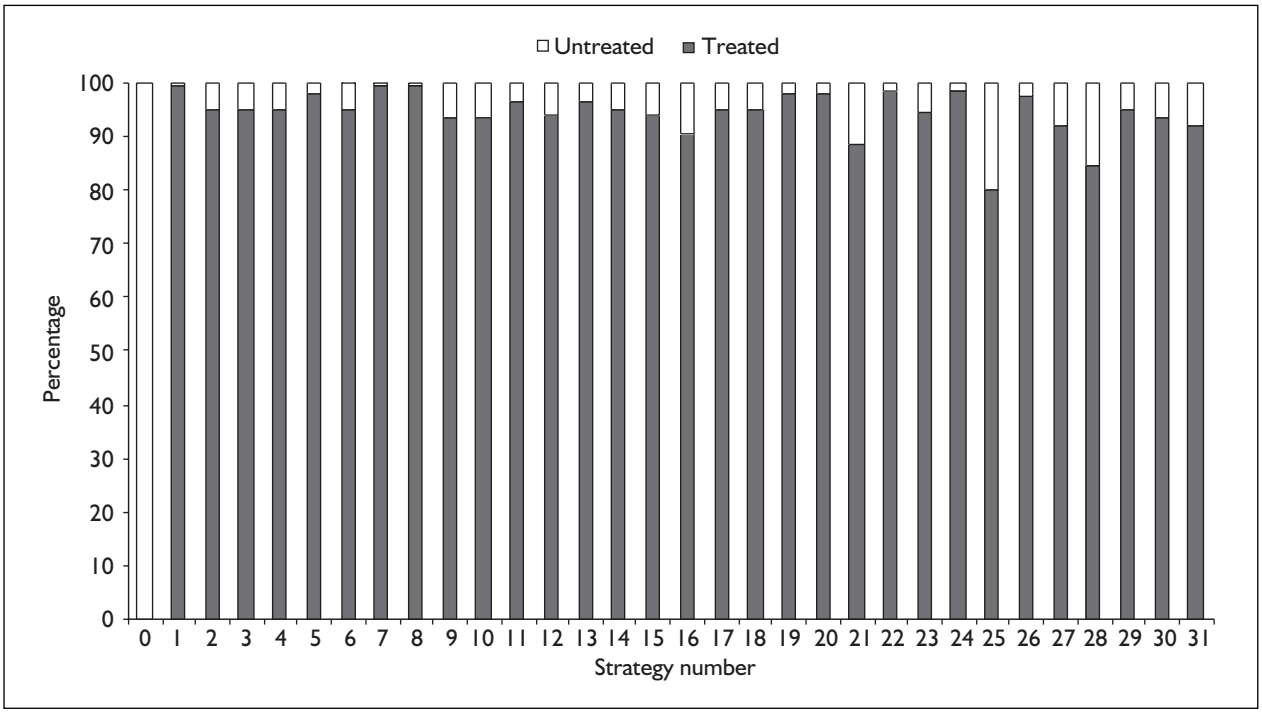

FIGURE 19 *Proportion of patients with proximal DVT who are treated*

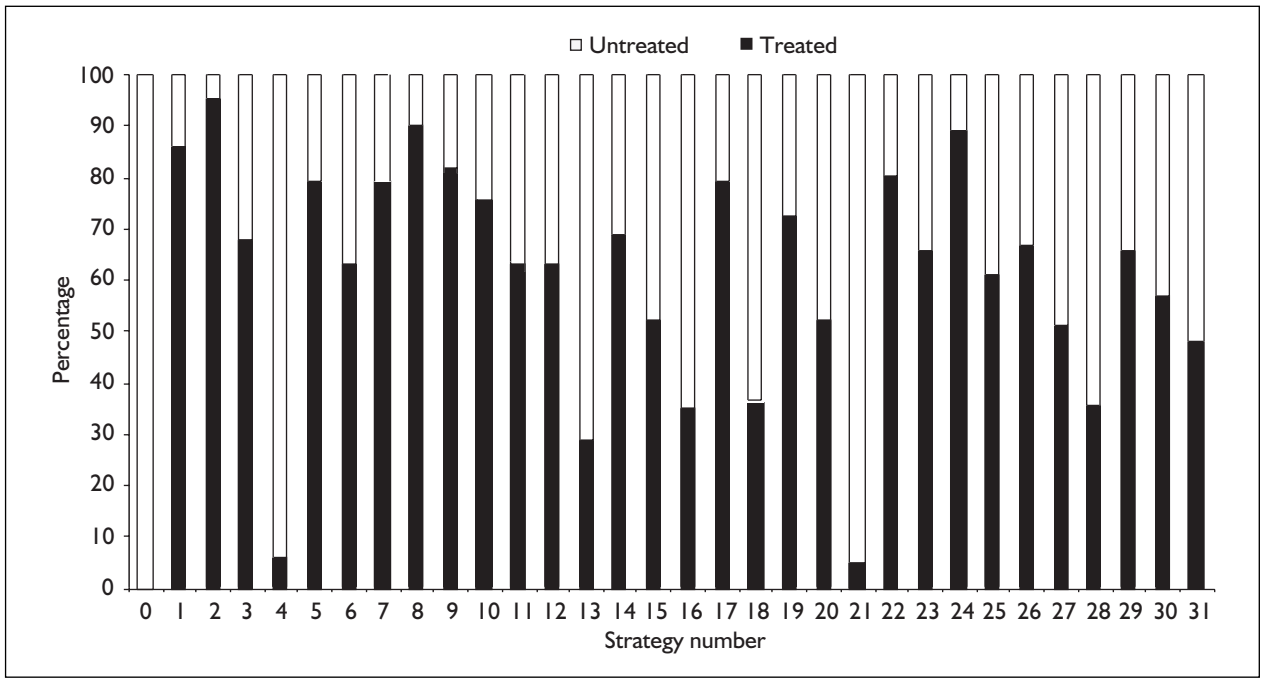

FIGURE 20 *Proportion of patients with distal DVT that propagates proximally who are treated*

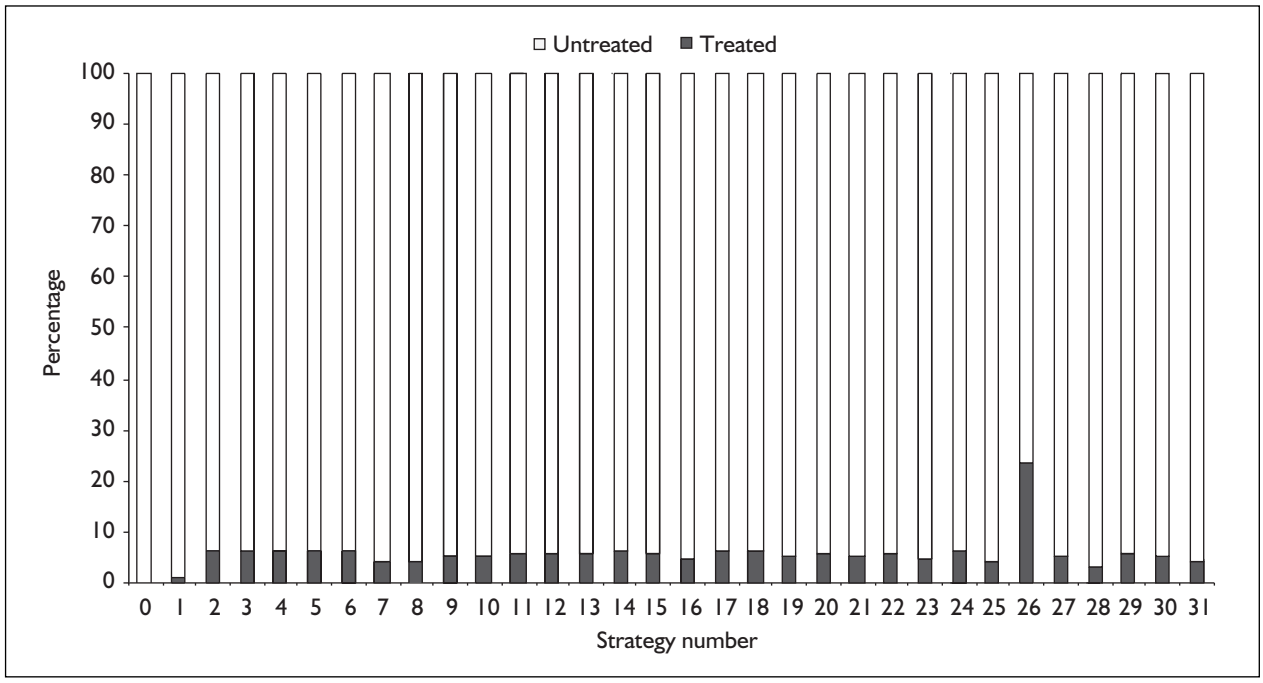

FIGURE 21 *Proportion of patients with distal DVT that does not propagate proximally who are treated*

receive ultrasound. Algorithms that make extensive use of venography have lower false-positive rates.

Use of tests within each algorithm

Table 26 summarises the number of tests required per 1000 patients with suspected DVT under each algorithm. This shows the substantial variation between the algorithms. The logistic implications of each algorithm need to be appreciated. Wells score can be simply implemented by any clinician, and the survey suggested that most hospitals have routine access to D-dimer testing and ultrasound. Availability of venography is more limited and only a few hospitals have access to plethysmography. Access to testing may have the following implications for the feasibility of algorithms:

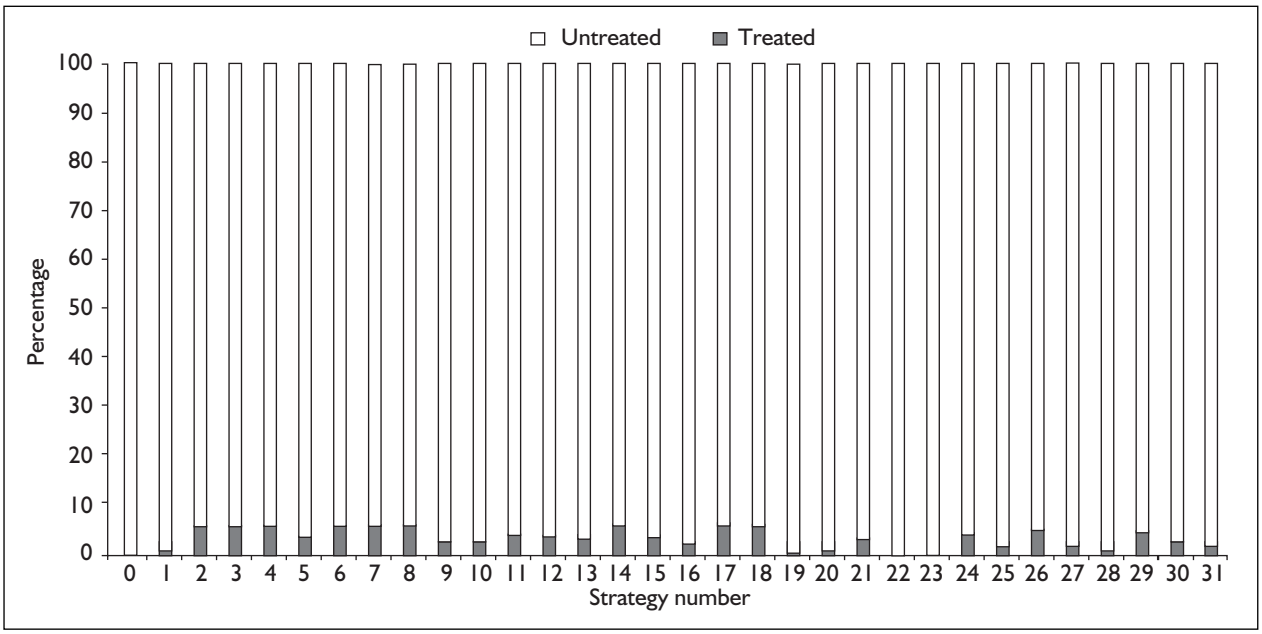

FIGURE 22 *Proportion of people without DVT who are treated*

TABLE 26 *Number of tests performed per 1000 patients with suspected DVT*

Algorithm number	Number of Wells tests performed	Number of above-knee ultrasounds performed	Number of full-leg ultrasounds performed	Number of D-dimer tests performed	Number of venograms performed	Number of plethysmographies performed
0	0	0	0	0	0	0
1	0	162	0	0	1000	0
2	0	1826	0	0	0	0
3	0	57	1000	0	0	0
4	0	1000	0	0	0	0
5	1000	1346	0	0	162	0
6	0	1286	0	1000	0	0
7	1000	1086	0	0	439	0
8	1000	106	1000	0	399	0
9	462	1038	0	1000	0	0
10	462	991	0	1000	0	0
11	1000	902	0	860	65	0
12	1000	50	707	1000	0	0
13	478	657	0	1000	90	0
14	1000	1271	0	439	0	0
15	1000	881	0	860	0	0
16	1000	556	0	900	0	0
17	1000	1439	0	0	0	0
18	1000	1128	0	0	0	0
19	0	110	0	1000	550	1000
20	1000	759	0	1000	173	707
21	1000	579	0	0	0	0
22	1000	128	0	421	707	0
23	1000	97	0	772	491	0
24	1000	818	0	421	551	0
25	0	696	0	1000	0	0
26	1000	40	479	772	0	1000
27	1000	38	398	1000	0	425
28	1000	28	254	421	0	707
29	1000	54	768	421	0	421
30	0	46	550	1000	0	1000
31	1000	40	422	0	0	772

- Algorithms 1, 7, 8, 19, 22, 23 and 24 make substantial use of venography (over one-third of patients), and thus require venography to be routinely available. This is not the case at most NHS hospitals.
- Algorithms 5, 11, 13 and 20 require venography for a few patients, so they will be feasible if venography is available on special request.
- Algorithms 19, 20, 26, 27, 28, 29, 30 and 31 require plethysmography. Currently these will only be feasible in a minority of NHS hospitals.
- Algorithms 3, 8, 12, 26, 27, 28, 29, 30 and 31 require full-leg ultrasonography, so these will only be feasible if sonographers with appropriate skills are routinely available.
- Algorithms 2, 4, 6, 9, 10, 14, 15, 16, 17, 18, 21 and 25 use combinations of Wells score, D-dimer and above-knee ultrasound, so will be widely feasible throughout the NHS.

Costs and QALYs accrued by each algorithm

Table 27 shows the mean costs and QALYs associated with each algorithm per 1000 patients with suspected DVT. The costs have been broken down into those associated with the diagnostic tests and those associated with complications of DVT or treatment. The no-testing, no-treatment strategy (algorithm 0) by definition has no costs associated with testing. It also has lower total costs and accrues fewer QALYs than the other strategies. Excluding algorithm 0, the mean costs of diagnostic testing per 1000 patients with suspected DVT range from £42,026 to £202,847, while the mean costs of treatment range from £155,037 to £197,075. The total costs of testing and treating range from £212,002 to £399,733. In general, the algorithms based on Wells score,

TABLE 27 *Costs and QALYs accrued per 1000 patients with suspected DVT for each algorithm*

Algorithm number	Costs associated with diagnostic testing (£)	Costs associated with DVT treatment or complications (£)	Total costs (£)	Number of QALYs accrued
0	–	144,040	144,040	11,523
1	200,177	158,688	358,864	11,560
2	107,402	197,075	304,477	11,558
3	113,678	196,909	310,587	11,557
4	59,364	196,536	255,900	11,556
5	113,453	179,394	292,847	11,559
6	86,253	196,881	283,134	11,557
7	154,018	196,819	350,837	11,559
8	202,847	196,886	399,733	11,559
9	73,207	174,521	247,728	11,558
10	70,938	174,483	245,420	11,558
11	78,782	181,190	259,972	11,558
12	97,538	180,936	278,473	11,557
13	66,898	177,069	243,967	11,558
14	87,437	196,916	284,353	11,557
15	67,797	180,870	248,667	11,557
16	47,527	168,556	216,082	11,556
17	92,058	196,978	289,036	11,557
18	72,268	196,719	268,987	11,556
19	136,314	157,295	293,609	11,560
20	105,078	162,551	267,630	11,560
21	42,026	175,697	217,723	11,554
22	149,945	155,812	305,757	11,560
23	106,934	155,037	261,971	11,559
24	156,866	181,639	338,505	11,559
25	49,498	165,130	214,628	11,553
26	86,959	193,461	280,420	11,558
27	71,672	165,967	237,638	11,557
28	53,646	158,356	212,002	11,555
29	105,101	184,095	289,196	11,558
30	91,068	172,425	263,493	11,558
31	67,912	166,154	234,066	11,557

D-dimer and above-knee ultrasound were cheapest, while those using venography were more expensive.

The mean QALYs per 1000 patients with suspected DVT ranged from 11,523 if no treatment is offered to 11,560 where venography is used on all patients. Compared with doing nothing (algorithm 0), the additional number of QALYs accrued varied from 30 to 37 per 1000 patients. In general, the more expensive algorithms accrued more QALYs. There were some exceptions, however, and on the basis of the mean estimates the following algorithms were dominated (i.e. another algorithm accrued more QALYs at lower cost):

- Algorithms 0, 21 and 25 were dominated by algorithm 28.
- Algorithms 4 and 18 were dominated by algorithm 31.
- Algorithms 3, 6, 12, 14, 15 and 17 were dominated by algorithm 13.
- Algorithms 2, 26, 29 and 30 were dominated by algorithm 23.
- Algorithms 5, 7, 8 and 24 were dominated by algorithm 20.

The net benefit of each algorithm

Figure 23 shows the expected net benefit of each strategy, compared with no testing (algorithm 0), assuming a maximum willingness to pay of either £20,000 per QALY or £30,000 per QALY. The data for this figure are given in Appendix 2, (*Table 39*), Unsurprisingly, all of the algorithms evaluated are better options than offering no treatment. Regardless of whether a £20,000 or £30,000 threshold was used for cost per QALY, algorithm 20 had the greatest net benefit. This algorithm used Wells score and D-dimer as an initial screening test and then used ultrasound and strain-gauge plethysmography to evaluate whether a patient required treatment or not, using a venogram if these tests were discordant. As noted earlier, the availability of venography and plethysmography appears to be limited, so this algorithm is currently not feasible in many hospitals unless services are developed. Two further algorithms (9 and 10) also had a consistently high net benefit regardless of the threshold used. Both of these algorithms used D-dimer and Wells score as an initial screening tool, before progressing to ultrasound with repeat.

The individual tests incorporated in each algorithm do not seem to determine cost-effectiveness. Algorithms incorporating Wells score or D-dimer tend to have a high net benefit, but there are exceptions: algorithms 19 and 30 do not use Wells score but have a high net benefit, and algorithm 31 does not use D-dimer but has a high net benefit. Use of plethysmography, ultrasound (above-knee or full-leg) and venography does not seem to be associated with higher or lower net benefit values. Hence, it appears to be the way in

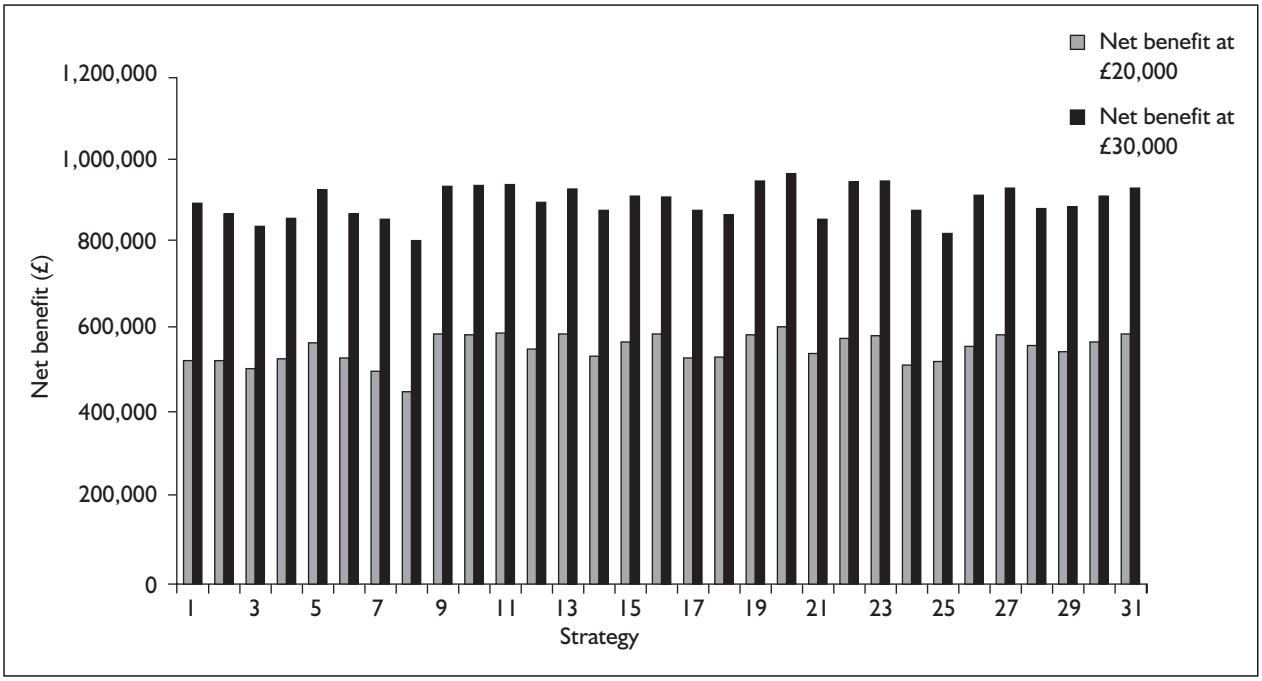

FIGURE 23 *Net benefit of each algorithm per 1000 patients with suspected DVT compared with no testing*

which the tests are used, rather than the tests themselves, that determines cost-effectiveness.

In this respect, the most striking trend is that algorithms that discharge patients with a low Wells score and a negative D-dimer have a relatively high net benefit, while those that require all patients to have an ultrasound or venogram have a relatively low net benefit. This is probably because ultrasound is a relatively expensive way of ruling out DVT in low-risk patients, compared with D-dimer.

Comparison of algorithms 1–4 shows how the model estimates the relative cost-effectiveness of ultrasound or venographic strategies for unselected patients. If one is willing to pay £20,000 per QALY gained, then a single above-knee ultrasound (algorithm 4) has higher net benefit than above-knee ultrasound with repeat (algorithm 2), which in turn has higher net benefit than venography (algorithm 1). This order is reversed if one is willing to pay £30,000 per QALY. This may explain other variations in net benefit when the threshold is changed: a higher threshold favours venography-based strategies. Full-leg ultrasound (algorithm 3) has lower net benefit than other options, regardless of the willingness to pay threshold.

Probabilistic sensitivity analysis

The results presented thus far have ignored the uncertainty that exists in the parameter values. Probabilistic sensitivity analysis was undertaken, sampling all parameters 1000 times from the distributions contained in Appendix 5. This allowed the effect of uncertainty in parameter values upon estimates of cost-effectiveness to be observed, and the results are presented in *Figure 24*. This figure shows the probability of each algorithm being the most cost-effective at each £10,000 increment in the threshold for willingness to pay per QALY gained. For reasons of clarity only those strategies that have a 5% or greater probability of being optimal have been included.

Algorithm 0 (no treatment) is most likely to be the most cost-effective option at a threshold of £0 per QALY. If one is not willing to pay for any health gain, then no testing is very likely to be the most cost-effective strategy. At a threshold of £10,000 per QALY algorithm 16 is most likely to be the most cost-effective strategy, with a 55% probability of being optimal. Algorithm 20 is the optimal strategy at thresholds of £20,000 and above.

Some algorithms with high estimates of mean net benefit, such as algorithms 19, 22 and 23, appear

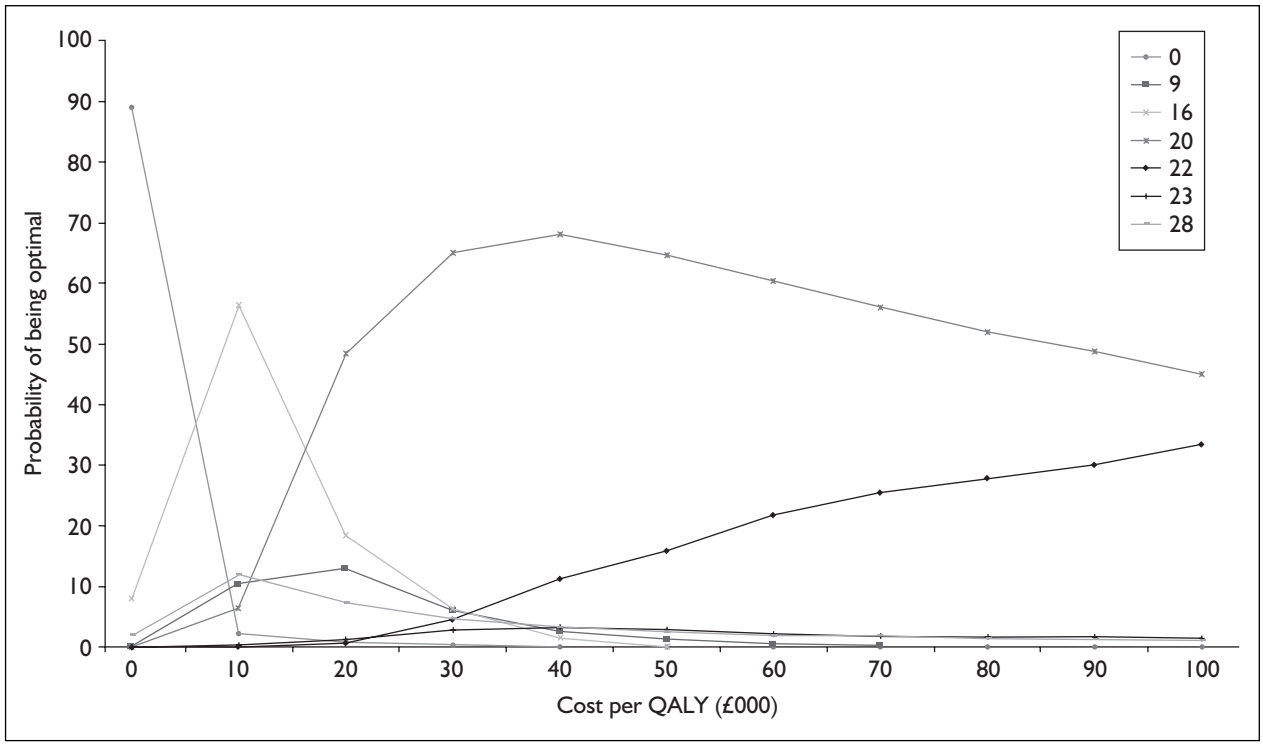

FIGURE 24 *Probability that each strategy is optimal at different cost per QALY thresholds*

unlikely to be optimal in the probabilistic analysis. This is because the advantage of these algorithms, in terms of gaining QALYs through accurate diagnosis, are less certain than their disadvantages, in terms of higher testing costs.

These results suggest that at low thresholds (around £10,000 per QALY) a strategy of selecting patients for ultrasound with repeat scanning, based on Wells score and D-dimer, will be most cost-effective. At thresholds of £20,000 per QALY and above this approach should be augmented by using strain-gauge plethysmography to select patients for venography instead of repeat ultrasound scanning. At high thresholds venography becomes more attractive, in the form of a strategy of performing venography for all patients except for those with a low Wells score and negative D-dimer. It is noticeable that all of these strategies involve discharging patients with a low Wells score and negative D-dimer. Strategies using ultrasound or venography in all low-risk patients are unlikely to be optimal even when a threshold of £100,000 per QALY is used.

Deterministic sensitivity analyses

Prevalence of proximal DVT in the population

The results of varying the prevalence of proximal DVT in the population, assuming a threshold for willingness to pay of £20,000 per QALY, are shown in *Figure 25*. For each value of proximal DVT prevalence the mean net benefit of the algorithm is plotted. To enhance clarity only selected algorithms are included: those with a high mean net benefit at one of the values of proximal DVT prevalence. All algorithms have a negative net benefit if the prevalence of proximal DVT is less than 1%, so diagnostic testing is unlikely to be cost-effective if DVT prevalence is very low. Algorithms 28, 31 and 16 are more cost-effective when DVT prevalence is 5–10%. Although algorithm 20 is optimal for values of prevalence of 15% and above, algorithms 5, 9, 11 and 13 appear to be more cost-effective at higher prevalence of DVT.

D-dimer specificity

The mean net benefit for each algorithm if D-dimer specificity is 84% of baseline value is shown in *Table 28*, assuming willingness to pay of £20,000 and £30,000 per QALY. As expected, algorithms incorporating D-dimer have a lower net benefit if D-dimer specificity is lower, but the loss of net benefit is not sufficient to alter substantially the relative cost-effectiveness of the algorithms. Those using D-dimer and Wells score to rule out DVT in low-risk patients remain the most cost-effective, and algorithm 20 remains optimal. Two algorithms that do not use D-dimer, algorithms 31 and 5, appear to be more attractive in this analysis.

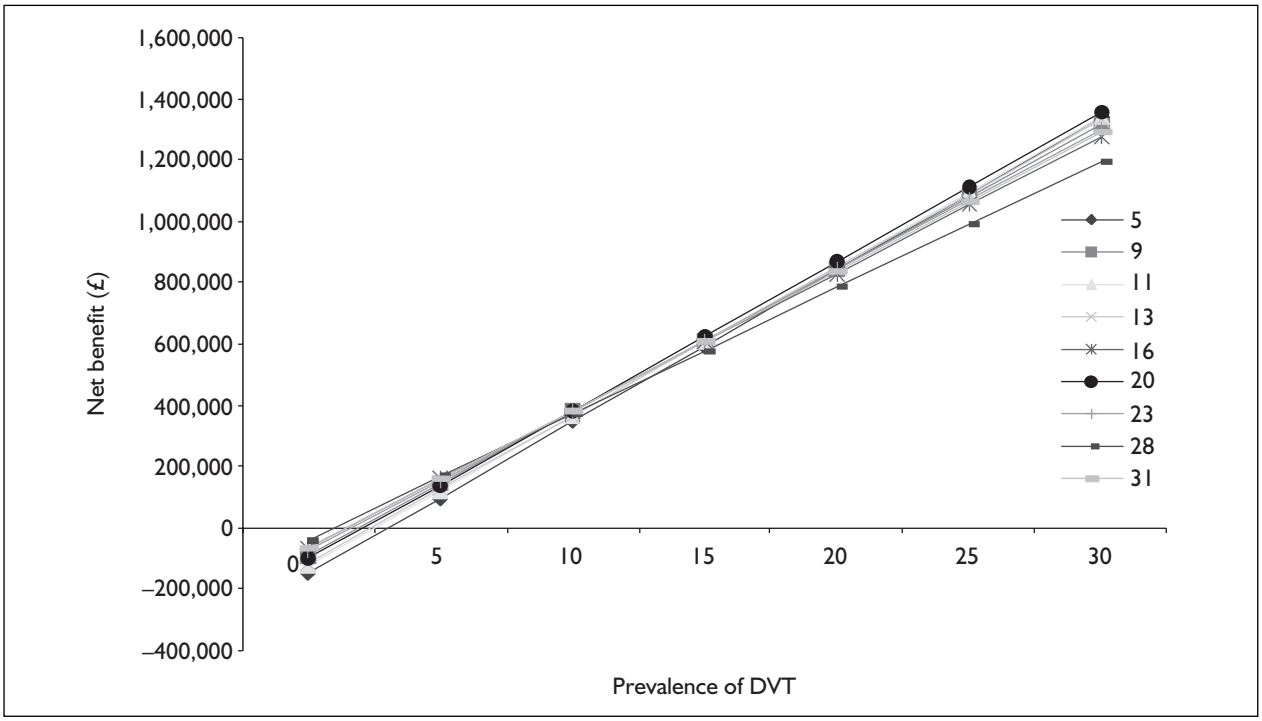

FIGURE 25 *Variation in ranking of mean net benefit of algorithms with prevalence of DVT in the population*

TABLE 28 *Mean net benefit of algorithms when D-dimer specificity is 84% of baseline value*

Algorithm number	Net benefit (£) at £20,000 per QALY	Net benefit (£) at £30,000 per QALY
1	531,267	904,313
2	533,961	881,159
3	515,396	856,367
4	542,167	869,180
5	578,971	942,859
6	535,587	875,519
7	510,408	869,011
8	458,422	815,480
9	582,511	931,101
10	581,603	928,752
11	581,143	933,894
12	545,406	889,348
13	582,232	927,361
14	540,574	881,822
15	570,459	911,940
16	576,880	906,268
17	542,135	885,700
18	542,806	876,682
19	573,665	942,920
20	602,602	969,085
21	554,601	868,743
22	573,253	945,619
23	578,843	935,692
24	510,012	869,561
25	510,699	809,062
26	553,060	903,427
27	584,482	927,220
28	563,272	880,126
29	541,355	887,868
30	558,340	903,372
31	596,499	939,761

Algorithms only using widely available tests

Figure 26 shows the results of repeating probabilistic sensitivity analysis limited to algorithms that use only widely available tests: Wells score, D-dimer and above-knee ultrasound. At a threshold of willingness to pay of 0, algorithm 0 is again most likely to be optimal. At thresholds of £10,000 and £20,000 per QALY algorithm 16 is most likely to be optimal, and at thresholds of £30,000 per QALY and above algorithm 9 is most likely to be optimal. Therefore, if plethysmography or venography is not available and cannot be implemented, either algorithm 16 or algorithm 9 is likely to be the most cost-effective strategy, depending on the threshold for willingness to pay.

Algorithm 20

This algorithm appears to be optimal at conventionally used thresholds for willingness to pay. However, it uses strain-gauge plethysmography, which is not routinely available in hospitals throughout the UK. The costing for strain-gauge plethysmography was based on assuming that it could be performed by the clinician assessing the patient (doctor or DVT nurse) and that the machine would be used 5000 times during its lifetime. These assumptions may not be appropriate in hospitals with a relatively small number of patients with suspected DVT, or if the machine is used by junior doctors, who change jobs frequently and require retraining, rather than permanent staff, such as DVT nurses. Therefore, a one-way sensitivity analysis was performed in which the cost of providing plethysmography was varied in £5 increments up to a maximum of £50 per patient. The results are shown in *Table 29*.

If a £20,000 per QALY threshold is used then algorithm 20 is only optimal if the cost of strain-gauge plethysmography is £35 per patient or less. If a £30,000 per patient threshold is used, then algorithm 20 remains optimal unless the cost of plethysmography exceeds £50 per patient.

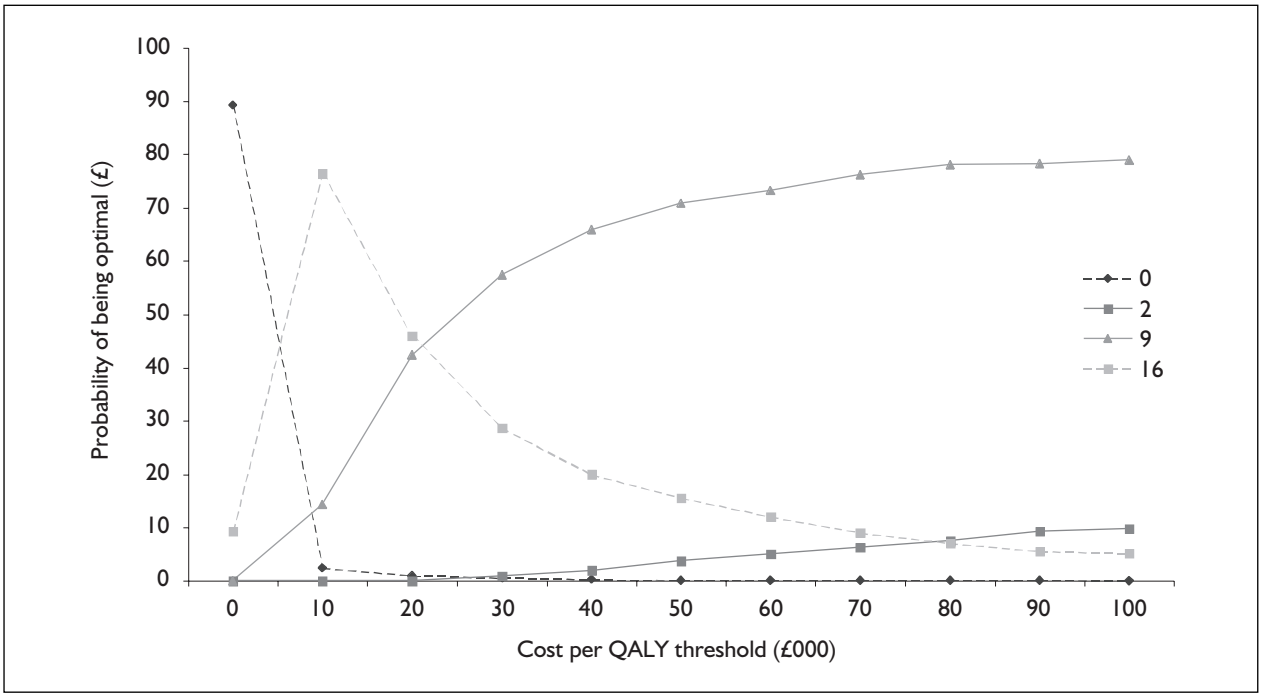

FIGURE 26 *Probability that each algorithm is optimal at different cost per QALY thresholds. Only algorithms using Wells test, ultrasound and D-dimer were analysed*

TABLE 29 *One-way sensitivity analysis on the cost of providing plethysmography*

Price (£)	Net benefit (£) at £20,000 per QALY	Net benefit (£) at £30,000 per QALY
20	609,890	976,908
25	606,452	973,470
30	603,015	970,033
35	599,578	966,596
40	596,141	963,159
45	592,704	959,722
50	589,267	956,285

Algorithm 16

This algorithm only uses Wells score, D-dimer and above-knee ultrasound, and is likely to be feasible throughout the NHS. However, clinicians may be interested to know whether the cost-effectiveness of this algorithm is influenced by the D-dimer assay used or the approach to ultrasound. In the main analysis the algorithm used a SimpliRED D-dimer assay, above-knee ultrasound and repeat ultrasound scanning for high- or intermediate-risk patients with a positive D-dimer. The analysis was repeated using (1) latex D-dimer, (2) ELISA D-dimer, (3) no repeat ultrasound scanning, and (4) full-leg ultrasound. The mean estimates of net benefit using the £20,000 and £30,000 per QALY thresholds, respectively, were:

- SimpliRED D-dimer: £591,904 and £923,878
- latex D-dimer: £594,497 and £934,654
- ELISA D-dimer: £589,218 and £931,510
- single above-knee ultrasound only: £586,097 and £919,391
- full-leg ultrasound: £578,053 and £922,909.

Hence, it appears that using a latex assay is more cost-effective than SimpliRED or ELISA at both thresholds, whereas the original strategy is more cost-effective than modified versions that either do without a repeat ultrasound or use a full-leg scan.

Analysis of repeat ultrasound

If 10,000 unselected patients with a negative initial scan undergo repeat ultrasound, 119 will have a true-positive result and gain the additional costs and QALYs of treated proximal DVT, 15 will have a false-positive result and gain additional

costs and lose QALYs associated with treating no DVT, while 9866 will have a negative repeat scan and not gain or lose any costs or QALYs. Analysis results in an estimated cost per QALY gained of £21,059 for repeat ultrasound in unselected patients. This approach is therefore of borderline cost-effectiveness and depends on the threshold for willingness to pay.

If 10,000 patients with a positive D-dimer and negative initial scan undergo repeat ultrasound, 323 will have a true-positive result. Assuming that D-dimer is independent of ultrasound and the number of false positives is unchanged, 15 will have a false-positive result and 9662 will have a negative repeat scan. Analysis results in an estimated cost per QALY gained of £7804 for repeat ultrasound in patients with positive D-dimer. Hence, if an unselective approach to repeat scanning is not considered cost-effective, selection on the basis of a positive D-dimer is likely to be considered cost-effective.

Summary

- Assuming a threshold for willingness to pay of £20,000 per QALY or more, algorithm 20 is most likely to be the optimal strategy.
- For a threshold of willingness to pay of £10,000 per QALY algorithm 16 is most likely to be optimal.
- Algorithm 20 requires routine availability of plethysmography (for most patients) and venography (for a minority). Assuming a £20,000 per QALY threshold, algorithm 20 will only be optimal if plethysmography can be provided at a cost of £35 per patient or less. Assuming a £30,000 per QALY threshold, algorithm 20 will be optimal if plethysmography can be provided at a cost of less than £50 per patient.
- If venography or plethysmography is not routinely available, then algorithm 16 is most likely to be the optimal strategy, given willingness to pay of £10,000 or £20,000 per QALY, while algorithm 9 is most likely to be the optimal strategy, given willingness to pay of £30,000 per QALY or more.
- If the prevalence of proximal DVT is very low (1% or less) then diagnostic testing for DVT is unlikely to be cost-effective. If DVT prevalence is 5% algorithm 28 appears to be cost-effective, provided plethysmography is available. Otherwise, algorithm 16 appears to be more appropriate in populations with low DVT prevalence, while algorithm 9 is more appropriate in populations with high DVT prevalence.
- Algorithms involving D-dimer are likely to be cost-effective even when used in patient groups such as those with malignancy, in whom D-dimer would be expected to have lower specificity.
- If algorithm 16 is used, then a latex D-dimer assay may be more cost-effective than ELISA or SimpliRED, and above-knee ultrasound with repeat if negative is likely to be more cost-effective than a single above-knee or full-leg ultrasound.
- Although repeat ultrasound scanning will produce few positive results, it is likely to be cost-effective, particularly if patients are selected on the basis of D-dimer result or Wells score.

Chapter 7

Discussion: cost-effectiveness analysis

Implications of the analysis

Many algorithms are available for diagnosing suspected DVT. In general, the more expensive an algorithm, the more accurate it will be. Deciding whether an algorithm is sufficiently accurate involves a subjective judgement, which is not always made explicit. In this report cost-effectiveness analysis was used to ensure that the criteria for judging each algorithm are rational and explicit. This has involved estimating the diagnostic performance of each algorithm, estimating the benefits of accurate diagnosis, estimating the costs of testing and treating patients, and then placing a value on the benefits of accurate diagnosis to determine the overall net benefit of each algorithm, taking both costs and benefits into account.

Using this approach conclusions may be drawn regarding the potential roles of diagnostic tests within algorithms and it is possible to determine what might be an appropriate algorithm for the NHS. This process needs to draw on the findings of the systematic reviews along with other data sources, particularly management studies of DVT diagnosis. The results of cost-effectiveness analysis are unlikely to influence practice if clinicians feel that, by using an apparently cost-effective algorithm, they will expose their patients to risks of adverse outcomes. Management studies report follow-up of patients who have been discharged without treatment after a particular combination of negative tests. As such they provide valuable data to inform clinicians of the anticipated rate of adverse outcome.

Wells score

Most of the algorithms used the Wells score. Those that did not (algorithms 1–4, 6, 19, 25 and 30) tended to have lower estimates of mean net benefit. Wells score is simple and cheap, and provides useful diagnostic data at low cost, so it is likely to be a useful component of a cost-effective algorithm.

D-dimer

The meta-analyses in Chapter 3 established that D-dimer was likely to be most useful in patients with a low or intermediate Wells score. Most algorithms that used D-dimer used it to rule out DVT in low- or intermediate-risk patients. Cost-effectiveness analysis showed that these algorithms tended to have relatively high estimates of mean net benefit. Algorithms that recommended testing low-risk patients with ultrasound or venography, regardless of D-dimer result (algorithms 2–8, 14, 17 and 18), tended to have lower estimates of mean net benefit, particularly if the £20,000 per QALY threshold was used. This is probably because low-risk patients with a negative D-dimer have a very low probability of having proximal DVT. Estimates from the meta-analysis suggest that the probability of proximal DVT in these patients is about 0.3%. Further testing to detect DVT is unlikely to be cost-effective in such circumstances.

D-dimer and Wells score: management studies

Management studies of patients with a low or intermediate Wells score and negative D-dimer have recently been reviewed[444] and provide reassurance that discharging these patients without further testing is likely to be acceptable to clinicians. The overall 3-month incidence of venous thromboembolism was 0.5% (95% CI 0.07 to 1.1) among patients with a low clinical probability of DVT and normal SimpliRED D-dimer concentration, and 0.4% (0.04 to 1.1) among outpatients with a low or moderate clinical probability of DVT and a normal ELISA or latex D-dimer concentration. The authors concluded that these combinations 'safely excluded' a diagnosis of DVT. The analysis suggests that this judgement is supported by cost-effectiveness analysis.

The authors of this review also suggested that decision analysis was required to determine whether the less sensitive, but more specific SimpliRED D-dimer assay was more appropriate than more sensitive, but less specific, latex assays or ELISAs. The sensitivity analysis of algorithm 16 suggests that using latex D-dimer produces the highest mean net benefit.

Above-knee ultrasound

Above-knee ultrasound was used in most of the algorithms tested and was the principal test for

patients with a high Wells score or positive D-dimer in some of the most cost-effective algorithms (9, 10 and 16). However, algorithms that advocated scanning all patients (2–8, 14, 17, 18) were less cost-effective. So a selective approach to ultrasound seems to be preferable.

Repeat ultrasound scanning

The cost-effectiveness of repeat ultrasound scanning depends on whether a higher risk group of patients is selected or not (on the basis of D-dimer result or Wells score), and whether a £20,000 or £30,000 per QALY threshold for willingness to pay is used. If one is willing to pay up to £20,000 per QALY then repeat ultrasound will only be cost-effective if higher risk patients are selected. If one is willing to pay £30,000 per QALY, then repeat scanning will always be cost-effective, regardless of whether patients are selected or not. These findings were consistent when repeat ultrasound data were analysed as a discrete entity and when comparing the results of algorithms incorporating single versus repeat scanning (e.g. algorithms 2 and 4, sensitivity analysis of algorithm 16).

Full-leg ultrasound scanning

It was assumed that performing a full-leg ultrasound would require additional skill and experience and would therefore have a higher unit cost than above-knee ultrasound. This meant that full-leg ultrasound did not appear to be cost-effective when directly compared with above-knee ultrasound (with or without repeat) or venography, and algorithms using full-leg ultrasound (3, 8, 12, 26–31) tended to be less cost-effective. It is important to recognise that it is not the technique of full-leg scanning that makes it appear less cost-effective, but the additional costs of performing the test. If a full-leg ultrasound can be performed without incurring additional costs then it is likely to be cost-effective.

Ultrasound: management studies

A substantial number of studies has been published reporting follow-up of patients with negative serial above-knee ultrasound results[16–18,20,427] or negative single full-leg ultrasound results.[61,428–430] These show a low rate of thromboembolic events over the subsequent 3 months and have been used to provide evidence that these approaches allow 'safe' discharge without further testing or follow-up. The analysis suggests that they are also cost-effective, provided testing is not extended to those at low risk with a negative D-dimer.

Plethysmography

This test is not widespread in the UK. Where plethysmography is used the predominant technique appears to be the Belfast venometer, a type of strain-gauge plethysmograph. For this reason it was assumed that all algorithms using plethysmography would use strain-gauge and the unit costs of this technique were calculated from assumptions regarding use of the venometer: that it could be used as a near-patient test by a DVT nurse or junior doctor, and would take 15 minutes to perform. Under these assumptions plethysmography appears to be a useful element of many algorithms, despite having modest sensitivity and specificity.

Two of the most cost-effective algorithms (20 and 31) used plethysmography in different ways. Algorithm 20 used plethysmography alongside ultrasound, once low-risk patients with a negative D-dimer had been discharged, to determine which patients could be discharged without further testing (ultrasound and plethysmography negative) and which patients required venography (one or other test positive), thus avoiding repeat ultrasound scanning. However, the apparent cost-effectiveness of this approach depends on two assumptions. First, plethysmography must be available at the relatively low cost assigned in the analysis. Hospitals that do not manage many patients with suspected DVT (and thus do not conduct as many tests over the lifetime of the equipment) or do not have DVT nurses may incur higher costs. If the cost exceeds £35 per patient then algorithm 20 is no longer optimal, assuming a £20,000 per QALY threshold. Second, plethysmography and ultrasound must detect DVT independently of each other, that is, they must not detect the same true-positive cases of DVT and miss the same false negatives. There were no data to address this issue, but basic principles suggest that this assumption of independence may not hold. Both ultrasound and plethysmography rely on the size and 'occlusiveness' of DVT for detection. Smaller or non-occluding clots are more likely to be missed. If this is the case then the assumption of independence will not hold and cost-effectiveness will be reduced.

Algorithm 31 uses plethysmography in conjunction with Wells score to discharge patients with a low or intermediate Wells score and negative plethysmography result. As with algorithm 20, the apparent cost-effectiveness of this approach may be undermined if costs of plethysmography are higher than estimated here, or if assumptions of independence do not hold.

In this case the assumption is that the accuracy of plethysmography is independent of Wells score. The only study of (impedance) plethysmography[75] suggests that sensitivity is lower in Wells low-risk patients. If this is the case then more patients with DVT will be discharged than we have assumed in the model and cost-effectiveness will be lower.

Plethysmography: management studies

Management studies have measured the outcomes of patients assessed by serial impedance plethysmography, rather than a single investigation.[20,445–448] The prevalence of recurrent thromboembolism following negative serial impedance plethysmography is estimated to be 1.5% (95% CI 0.8 to 2.2),[12] which is similar to serial ultrasound. However, a much greater proportion of DVT was detected during serial testing, rather than the initial test (6.1% for impedance plethysmography[12] versus 1.3% for ultrasound). There are also problems with applying these data to the UK. The algorithms identified in the survey used strain-gauge, rather than impedance, plethysmography, and the plethysmography was used for single, rather than serial, testing.

Venography

Concerns about costs, complications and radiation dose have led to a decrease in the use of venography, such that a technique that was once the standard test for DVT is now routinely available in only a minority of hospitals in the UK. The analysis suggests that venography is only likely to have a role in diagnosis if it is limited to a selected group of patients, such as in algorithm 20. Although some venography-based strategies appeared cost-effective when mean net benefit estimates were compared, probabilistic analysis suggested that they were unlikely to be optimal. This is because the high costs associated with venography are relatively certain, while the potential benefits, in terms of high diagnostic accuracy leading to health gain, are more doubtful.

The potential effects of radiation dose were not taken into account in the analysis, either for the individual patient or for the wider community. These factors would be extremely difficult to include in the model. However, the need to reduce radiation exposure provides an additional rationale for reducing the reliance on contrast venography.

Diagnostic algorithms

Many hospitals use algorithms to guide diagnosis, and cost-effectiveness analysis may be used to justify the choice of algorithm. This process needs to involve a consideration of the practicalities of implementing an algorithm, uncertainties surrounding the analysis, features of the population or individual patient, acceptability of the algorithm to the clinical staff who will implement it, and how much one is willing to pay for additional health gains. Despite these sometimes conflicting considerations a number of conclusions may be drawn from the analysis, and a few algorithms identified that appear to be optimal for use in the NHS.

Algorithm 9

This algorithm (*Figure 27*), derived from a study by Bates and colleagues,[410] uses Wells score, latex D-dimer and above-knee ultrasound, so it will be

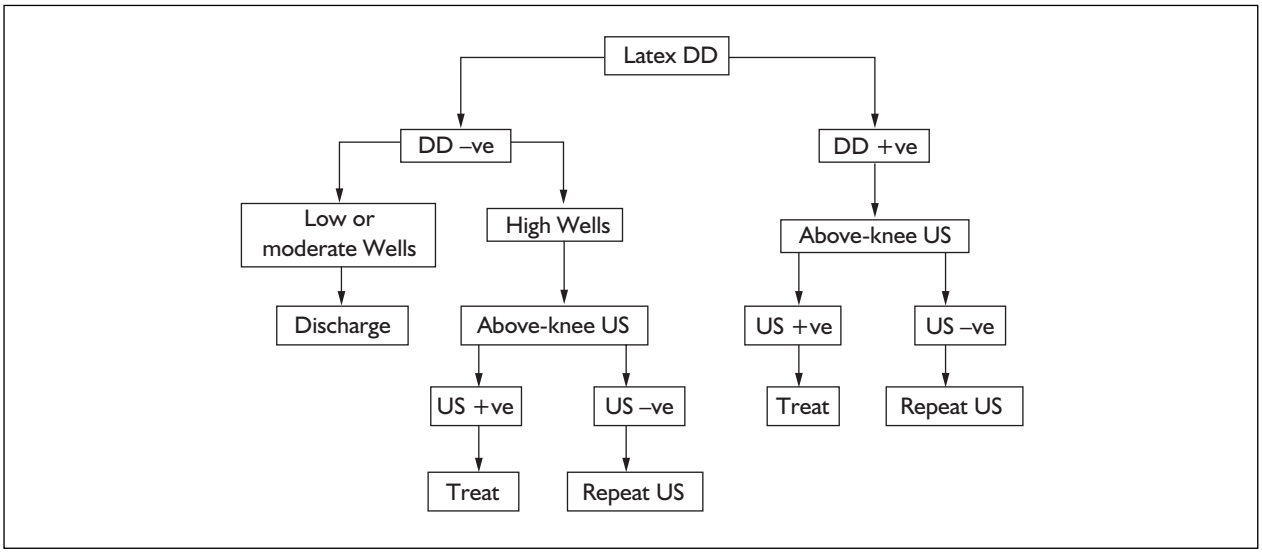

FIGURE 27 *Algorithm 9. DD, D-dimer; US, ultrasound.*

feasible in most UK hospitals. Patients with a positive D-dimer or high Wells score receive ultrasound with repeat scanning if negative. Those with a negative D-dimer and intermediate or low Wells score are discharged home. The published study followed up 505 untreated patients for 3 months and identified five thromboembolic events. This is compatible with the analysis, which suggests that out of every 1000 patients with suspected DVT there will be 10.24 cases of untreated proximal DVT and 1.5 cases of untreated distal DVT that propagate proximally. If the threshold for willingness to pay is £30,000 per QALY or more, then this is likely to be the optimal algorithm for most hospitals in the UK.

Algorithm 16

This algorithm (*Figure 28*) was derived from a study by Wells and colleagues.[9] It was used as the intervention arm of a randomised trial and compared with algorithm 18, the control arm of which involved performing ultrasound on all patients. The precise algorithm used in the trial used a dichotomised version of the Wells score to divide patients into 'DVT likely' and 'DVT unlikely' groups. Patients in the DVT likely group received ultrasound and D-dimer. If both tests were negative the patients were discharged, whereas if ultrasound was negative and D-dimer positive a repeat ultrasound was performed. Patients in the DVT unlikely group received D-dimer testing. If positive they received a single ultrasound, whereas if negative they were discharged. Any positive ultrasound was treated. The randomised trial found no significant difference in thromboembolic events over 3 months between the two arms and concluded that, because the D-dimer-based strategy (algorithm 16) required less use of the more expensive ultrasound tests, this strategy should be preferred. Out of some 481 untreated patients in the intervention arm there were two thromboembolic events over 3 months of follow-up. This is compatible with the analysis, which suggests that out of every 1000 patients with suspected DVT there will be 14.8 cases of untreated proximal DVT and 5.7 cases of untreated distal DVT that propagate proximally (although the two algorithms are not absolutely comparable).

Because of a lack of data on the dichotomised version of the Wells score, this algorithm was tested twice: in algorithm 16 patients with an intermediate Wells score were managed in the DVT unlikely group, whereas in algorithm 15 they were managed in the DVT likely group. Algorithm 16 was generally more likely to be cost-effective than algorithm 15 in the analyses.

If the threshold for willingness to pay is £10,000 per QALY then algorithm 16 is most likely to be optimal, regardless of whether analysis includes all algorithms or is limited to those using only routinely available tests. At £20,000 per QALY algorithm 20 is more likely to be optimal, if plethysmography is available and assumptions of independence hold. At £30,000 per QALY algorithm 9 is more likely to be optimal. Algorithm 16 is optimal at lower thresholds of

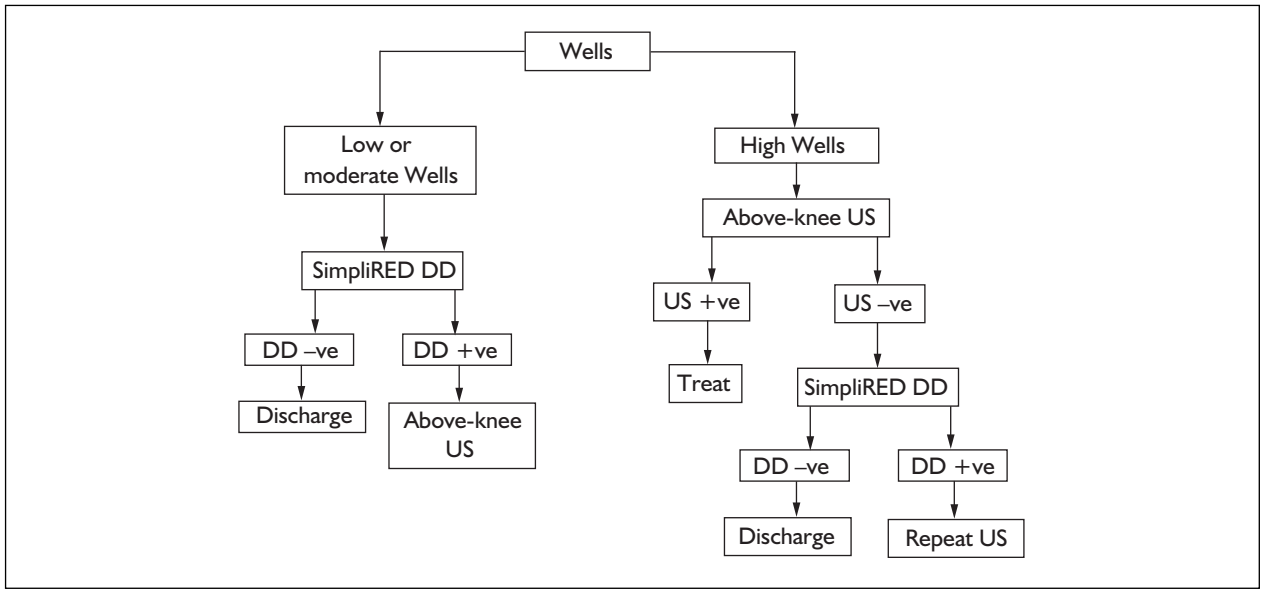

FIGURE 28 *Algorithm 16*

willingness to pay because it involves less use of repeat ultrasound scanning and because it was assumed that the SimpliRED D-dimer assay would be used. Hence, it is cheaper, but less effective, than algorithm 9. Selecting between these two algorithms depends on the threshold for willingness to pay for health gain.

Algorithm 20

This algorithm (*Figure 29*) discharges patients with a low Wells score and negative D-dimer. All other patients receive plethysmography and ultrasound. If both tests are positive the patient is treated, if both are negative they are discharged, and if they disagree then venography is used to resolve the diagnosis. It was optimal in the main analysis for values of willingness to pay of £20,000 per QALY or more. However, it requires the availability of plethysmography and venography, its cost-effectiveness depends upon being able to provide plethysmography reasonably cheaply (if the £20,000 per QALY threshold is used), and it requires an assumption of independence between plethysmography and ultrasound.

The study from which algorithm 20 was derived, by Kearon and colleagues,[405] followed up 382 untreated patients for 3 months and identified one case of thromboembolism. This is compatible with the analysis, which suggests that out of every 1000 patients with suspected DVT there will be 3.09 cases of untreated proximal DVT and four cases of untreated distal DVT that propagate proximally. This low rate of thromboembolism is likely to convince clinical staff that such a strategy is 'safe', but when similar rates of thromboembolism are observed after cheaper, simpler strategies (such as algorithm 16),[9] they may question whether the complexity and cost of testing are justified. The advantage of this algorithm is that it does not require the patient to return for repeat ultrasound scanning, which may be seen as a practical advantage for staff and patients.

Algorithm 31

This algorithm (*Figure 30*) discharges patients with a low or intermediate Wells score and negative plethysmography result. All other patients receive a full-leg ultrasound. In the analysis it was highly cost-effective at both thresholds for willingness to pay. Although it requires the availability of plethysmography, unlike algorithm 20 it does not require venography and is considerably cheaper to run.

The disadvantage of this algorithm is that, being derived from the UK survey, it does not have published data to support it. Furthermore, its diagnostic performance in the model depends on the assumption that the diagnostic performance of plethysmography does not depend on Wells score. If sensitivity is lower among patients with a low Wells score then this algorithm will discharge more patients with untreated proximal DVT than estimated and may not be cost-effective or acceptable to staff and patients.

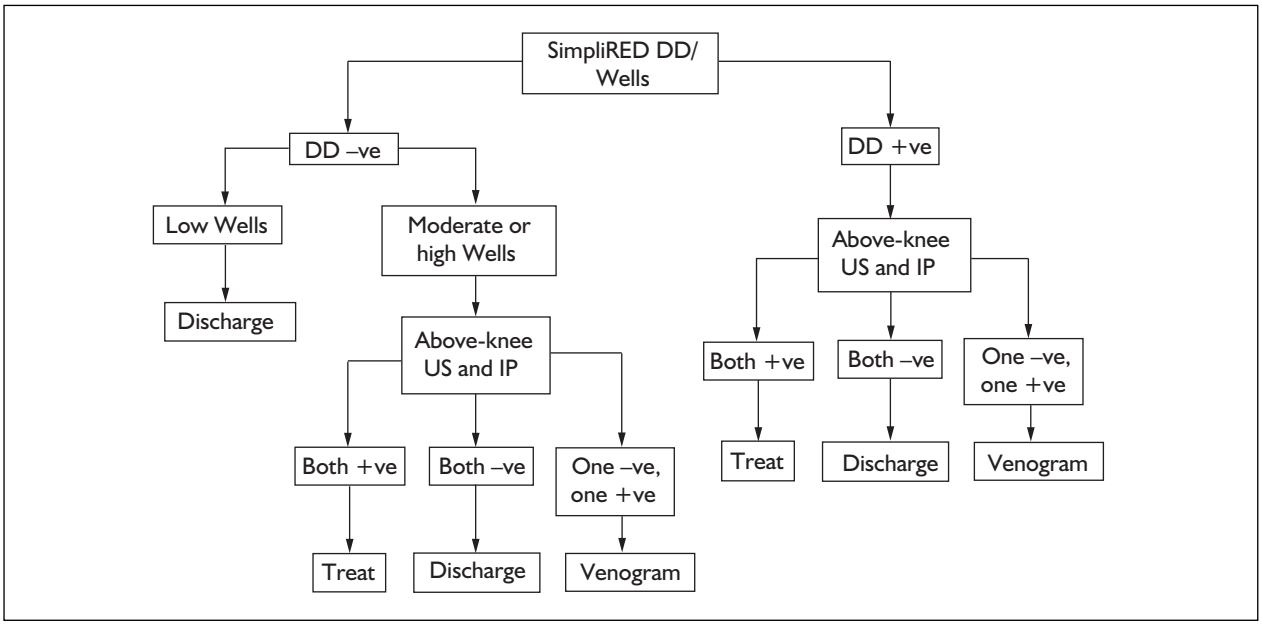

FIGURE 29 *Algorithm 20. IP, impedance plethysmography.*

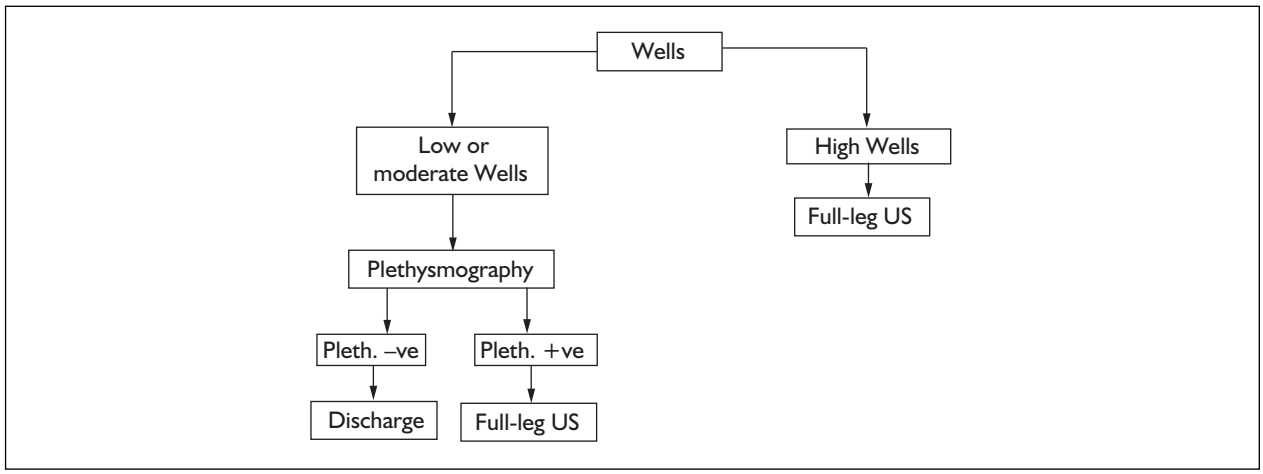

FIGURE 30 *Algorithm 31*

Diagnostic algorithms in specific patient groups

Variation in the prevalence of DVT or the performance of diagnostic tests may influence the cost-effectiveness or the appropriateness of diagnostic algorithms when they are applied to specific patient groups. Unfortunately, shortcomings in the reporting of primary data limited the authors' ability to draw conclusions about the performance of diagnostic tests in most of the specific groups. This means that consideration of the use of diagnostic algorithms in specific groups is limited to a crude analysis of the effect of varying prevalence, some consideration of the effect of varying D-dimer specificity (where the evidence is strongest) and drawing upon pathophysiological concepts.

Effect of variation in DVT prevalence

Sensitivity analysis showed that variation in DVT prevalence could affect the relative estimates of cost-effectiveness of the algorithms. The main analysis assumed that the prevalence of proximal DVT was 15%. At lower estimates of prevalence algorithm 16 (the Wells trial intervention arm) was more cost-effective, whereas at higher prevalence algorithms 9, 11 and 13 appeared to be more cost-effective. These latter two algorithms were derived from studies by Anderson and colleagues[409] and Perrier and colleagues[407] respectively. Both make selective use of venography to resolve the diagnosis in patients with a high Wells score, positive D-dimer and negative ultrasound.

Drawing a broad general conclusion from this analysis, it would seem that a cheaper, simpler strategy (algorithm 16) is appropriate if DVT prevalence is likely to be low, while a strategy involving more use of repeat ultrasound (algorithm 9) or using venography for patients with high Wells score, positive D-dimer and negative ultrasound (algorithms 11 and 13) is appropriate in populations where DVT prevalence is likely to be high.

Effect of variation in D-dimer specificity

The systematic review of D-dimer identified substantial heterogeneity in estimates of D-dimer specificity. It is well recognised that a number of clinical conditions will cause elevations of D-dimer, other than venous thromboembolism. In the metaregression D-dimer specificity was higher in studies that excluded pregnant patients, anticoagulated patients, those with a prolonged clinical history and those with a past history of thromboembolism. It is likely that D-dimer will have lower specificity in populations with greater co-morbidity, such as inpatient populations.

The only direct estimate of D-dimer specificity identified involved studies of D-dimer in patients with malignancy,[70,82–84,149] in which D-dimer had a specificity of 46%. Sensitivity analysis using proportionately lowered estimates of D-dimer specificity showed that algorithms using D-dimer were less cost-effective than in the main analysis, but remained more cost-effective than those recommending ultrasound or venography for all.

Inpatient populations

The main analysis relates to patients presenting as outpatients with suspected DVT. Patients presenting as inpatients are likely to have more co-morbidities and thus D-dimer would be expected to have lower specificity. Therefore, it may be expected that algorithms using D-dimer would not be appropriate in these patients. However, as outlined above, D-dimer-based strategies appear

to be more cost-effective than strategies involving ultrasound or venography for all, even when D-dimer specificity is proportionately lower. This suggests that D-dimer can still be a valuable test for ruling out DVT in low-risk patients, even if its specificity is expected to be poor. Since it is a cheap and simple test it is worthwhile using it to rule out DVT in a relatively small proportion of patients, even if many others will then need to receive further testing. The main risk with this approach, which cannot be addressed by the model, is that D-dimer could be used to investigate patients who would not otherwise have received investigation. The poor specificity of D-dimer makes it unsuitable for asymptomatic screening for DVT. This is an important consideration for the inpatient population, where the dividing line between suspected DVT and asymptomatic screening may be blurred.

Asymptomatic patients

The cost-effectiveness analysis was designed to analyse algorithms for diagnosing clinically suspected DVT and should not be applied to asymptomatic patients. Few of the parameters or assumptions used in the model apply to asymptomatic patients. They have different prevalences of proximal and distal DVT, and a different natural history,[1] diagnostic tests have very different performance; the risks and benefits of treatment are different; and prophylactic treatment may be indicated among those at highest risk, regardless of the results of diagnostic testing.[449]

The performance of diagnostic tests is generally poorer among patients at risk of asymptomatic DVT. D-dimer has reasonable sensitivity, but poor specificity means that further diagnostic testing is required if D-dimer is positive. Ultrasound and plethysmography have poor sensitivity in asymptomatic patients, so cannot reliably rule out DVT. Meanwhile, CT and MRI have not been extensively investigated in asymptomatic patients. These factors, along with the fact that the term 'asymptomatic patients' includes a heterogeneous group of medical and surgical patients, mean that it is difficult to construct diagnostic algorithms, and even more difficult to assess their cost-effectiveness.

Pregnant patients

Because of the need to avoid using intravenous contrast or X-rays in pregnancy, non-invasive tests have long been the mainstay of diagnosis in pregnant patients. Many studies exclude pregnant patients, particularly studies of Wells score and D-dimer, so it may be inappropriate to apply the present findings to these patients. Ultrasound and impedance plethysmography have been studied in pregnant patients. Given the superior diagnostic performance of ultrasound, the most appropriate approach is probably to perform an ultrasound on all pregnant patients, with repeat if negative, rather than using a diagnostic algorithm.

Intravenous drug abusers

These patients constitute a growing proportion of the population with suspected DVT, but are often excluded from studies without necessarily being reported as exclusions. For example, intravenous drug abusers did not form a significant proportion of the population in the studies that developed the Wells score (Wells P: personal communication). Yet, they cause specific problems with diagnosis. Intravenous drug use is associated with thrombophlebitis and sepsis, which may generate false positives and reduce D-dimer specificity, and lack of venous access may make venography impossible. Meanwhile, it may be expected that ultrasound would be an appropriate test, because thrombi should be associated with femoral vein injection, a location that is easily visualised by ultrasound. Since the prevalence of DVT is high among intravenous drug abusers presenting with suspected DVT (audit data, Sheffield Teaching Hospitals Trust) the most appropriate approach is probably to treat these patients in a similar way to patients with a high Wells score and perform ultrasound with repeat if negative in all cases. However, this may be problematic owing to poor compliance.

Comparison to other studies of cost-effectiveness

Perone and colleagues[21] used decision analysis modelling to compare four strategies, incorporating combinations of clinical risk scoring, D-dimer and ultrasound, with a 'no treatment' alternative. They estimated that the cheapest strategy (combining clinical risk scoring and D-dimer with a single ultrasound) was also the most cost-effective. This strategy was the same as algorithm 13 in the present analysis. Alternative strategies of ultrasound with repeat for all patients (present algorithm 2), ultrasound with repeat if D-dimer is positive (algorithm 6) and ultrasound with repeat or venography based on Wells score (algorithm 5), were all less cost-effective, with incremental costs per QALY gained of $61,616–95,080.

Although there is a number of differences in the methods, assumptions and parameters used, these results broadly concur with the present analysis. At the £20,000 per QALY threshold algorithm 13 was more cost-effective than algorithm 2, 5 or 6. At £30,000 per QALY algorithm 13 was more cost-effective than algorithms 2 and 6, but slightly less cost-effective than algorithm 5. Thus, the present analysis supports their conclusion that combining clinical probability and D-dimer with a single ultrasound is probably the most cost-effective option among those tested. However, by testing a larger number of potential algorithms the current study identified that, once patients with a low or intermediate Wells score and negative D-dimer have been excluded from further testing, a policy of repeat ultrasound scanning is probably cost-effective. This alternative was not tested by Perone's group, who only compared algorithm 13 with strategies that involved performing ultrasound on all patients.

Other cost-effectiveness analyses have tended to focus on the cost-effectiveness of one particular non-invasive technology and are less easily comparable to the present analysis. Kim and colleagues[22] evaluated strategies for using compression ultrasonography in patients with suspected DVT and concluded that bilateral above-knee ultrasound, with repeat if negative, was the most cost-effective option, with an incremental cost-effectiveness ratio of $39,000 per QALY gained. Conversely, Hillner and colleagues[450] found that repeat scanning cost an additional $390,000 per additional life saved, and concluded that future research should focus on identifying clinical predictors of high-risk patients who would be suitable for repeat scanning. Crippa and colleagues[451] evaluated the role of D-dimer in diagnosis and concluded that using D-dimer to rule out DVT in symptomatic patients was likely to be cost-effective, particularly for those with a low clinical risk, but was unlikely to be cost-effective in asymptomatic patients.

Limitations of the analysis

This analysis has a number of limitations that should be recognised. Some of these relate to limitations in the data and assumptions used in the model. Others relate to the principles behind the model, such as the use of diagnostic algorithms and the use of cost-effectiveness analysis per se.

Uncertainty regarding the outcome of untreated proximal DVT

Most of the parameters in this analysis were supported by excellent data, including a substantial number of systematic reviews. Yet three crucial variables, the probabilities of fatal PE, non-fatal PE and PTS in untreated patients with proximal DVT, had very limited data to support them. This is not surprising because anticoagulation has been standard treatment for DVT for over 40 years.

The solution to this problem for two of the variables (fatal and non-fatal PE) was to use data from follow-up studies of patients in whom DVT was ruled out by imperfect non-invasive tests. The authors believe that this approach, although relying on an element of modelling, provides very appropriate estimates. The estimates of the probability of fatal and non-fatal PE (2% and 9%, respectively) may seem rather low, but probably reflect what we really want to measure: the risks associated with missed DVT, rather than the risks of untreated DVT. It is likely that the DVT missed by diagnostic testing differ from those that are detected, perhaps being smaller and more distally located. If this is the case then the risks of propagation will also differ. By estimating the risks of missed DVT from studies of ultrasound and D-dimer, hopefully, an estimate has been obtained that reflects the risks of DVT missed by these modalities. The limitations of this approach are, first, the assumption that DVT missed by one diagnostic test (e.g. D-dimer) are the same as DVT missed by another (e.g. ultrasound), and second, that estimates from these two diagnostic tests are applied to other, unrelated diagnostic tests.

Independence of diagnostic tests

When combining diagnostic tests in an algorithm, one needs to know whether the tests are independent of each other. The greater the correlation between diagnostic tests, the less information will be added by each test. Good data were found relating to the interaction between D-dimer and Wells score, and these were used in the model. Only one study each was found relating to the interaction between Wells score and plethysmography[75] or ultrasound.[8] A decision was made not to use this limited information in the model, but to assume independence. Finally, no data were found relating to potential interactions between D-dimer, plethysmography and ultrasound. The implications of this are that findings involving any interaction between tests, other than those involving D-dimer and Wells score, may be undermined if assumptions of

independence do not hold. This problem is likely to be greatest for algorithms involving plethysmography.

Interaction between D-dimer and Wells score was included in the model. The one study that examined interaction between ultrasound and Wells score[8] suggested that ultrasound had higher sensitivity in patients with a high Wells score. If this is true then the present study may have underestimated the performance of algorithms, such as algorithms 9 and 16, that restrict use of ultrasound in patients with a low Wells score. Meanwhile, the opposite effect may occur for studies that involve discharging low-risk patients with a negative plethysmography result, such as algorithm 31. The one study that examined interaction between Wells score and plethysmography[75] suggested that sensitivity was lower in those with a low Wells score. Therefore, by assuming independence the performance of algorithm 31 may have been overestimated.

Variation between populations and providers of care

All the meta-analyses identified substantial heterogeneity among results. The authors had only very limited success in using metaregression to identify factors that predicted diagnostic performance. It is likely that differences in patient populations and in the providers of care who undertook diagnostic testing are responsible for much of the heterogeneity. This means that diagnostic algorithms may have very different performance if they are used in different populations or by different providers of care.

An attempt was made to include all potentially eligible studies in the systematic reviews, and studies were not excluded on the basis of quality criteria, such as consecutive recruitment or prospective data collection, that may not be strongly related to validity.[26] This means that the estimates of diagnostic performance tended to be slightly lower than those reported in previous meta-analyses. It is therefore possible that diagnostic algorithms applied to carefully selected populations by well-trained providers may perform better than estimated here, whereas algorithms applied to 'all-comers' by poorly trained providers may perform worse.

Potential algorithms not included in the analysis

The range of potential algorithms that could be included in the analysis is huge. The number of algorithms in the analysis was limited by only including algorithms currently used in the UK, published algorithms and a few hypothetical algorithms. It is possible that other combinations of tests could be more cost-effective than those included in the analysis. However, it is unlikely that any algorithm that is not currently being used or has not been published will be acceptable to providers and patients.

The use of algorithms

Diagnostic algorithms provide a standardised way of managing patients that can be used to guide inexperienced staff. This has advantages of reducing variation in practice, allowing safe management by the inexperienced and providing some control over risk management, but it also has disadvantages. The systematic review of clinical scores found that unstructured estimation of clinical probability by experienced staff had similar diagnostic performance to Wells score. Experienced staff may be able to select individual patients for appropriate diagnostic testing and use tests in an intelligent manner. Furthermore, they may be able to incorporate patient preferences into decision-making. None of this can be done by diagnostic algorithms.

The use of cost-effectiveness analysis

Cost-effectiveness is only one of the considerations that need to be taken into account when deciding on an appropriate strategy for diagnosing suspected DVT. For example, the analysis does not take into account patient perceptions of diagnostic testing or the acceptability of particular tests. Non-invasive tests have the advantages, compared with venography, of being more comfortable for patients and less technically demanding for clinicians. These factors are not taken into account in the analysis, except for very crudely estimated complication and failure rates. Repeat ultrasound may be cost-effective (if selectively applied or a £30,000 per QALY threshold is used), but the analysis does not include the effect of diagnostic uncertainty on patients who are waiting for a definitive diagnosis. Patients may have a strong preference for an immediate diagnosis.

Cost-effectiveness analysis involves making a value judgement regarding the monetary value of a QALY. The analysis principally examined the cost-effectiveness of algorithms at the £20,000 and £30,000 per QALY thresholds. However, other factors, such as equity, need to be taken into account in decision-making. Finally, although the aim of cost-effectiveness analysis is to ensure that decision-making is explicit and rational, this aim may be impaired by poor understanding of the

concepts and methods of cost-effectiveness analysis. Clinicians who do not understand the methods used in this analysis are likely to be sceptical of the findings and may be unwilling to implement them.

Implications for future research

This analysis identified two algorithms (9 and 16) that are likely to be cost-effective and feasible throughout the NHS. Choosing between these algorithms depends on the threshold for willingness to pay for health gain, but both could be implemented in a similar manner. Future research into these algorithms should focus on the practicalities of implementation, and how their use may be linked to developments in emergency diagnosis (such as clinical decision units) and outpatient management of DVT. The analysis also identified two other algorithms (20 and 31) that may be more cost-effective, but doubts were raised about the assumptions used in modelling their cost-effectiveness. Future research into these algorithms should therefore focus on providing empirical data to address these assumptions.

Implementation of algorithms based on Wells, D-dimer and ultrasound (9 and 16)

As these algorithms only use tests that are widely available, there are no theoretical reasons why they should not be implemented throughout the NHS in a cost-effective manner. However, some practical issues need to be examined:

- What are the costs and outcomes in routine practice? The cost estimates were based on national unit costs, while outcomes were based on the results of meta-analyses, modelling and empirical data from management studies. The latter are typically undertaken in specialist centres, where standards of training, monitoring and performance may be higher than elsewhere. Audit, observational studies and collection of cost data need to be undertaken alongside routine practice to determine whether implementation reflects the performance assumed in the model.
- How do the algorithms perform in subgroups of patients? Data used in the model were derived from either selected groups of patients that excluded subgroups (e.g. intravenous drug abusers, pregnant patients or those with previous DVT) or heterogeneous groups in which these subgroups constituted a small proportion. Further research is required to determine whether different algorithms are required in specific patient groups.
- How do the algorithms perform when implemented by different providers? The costs and accuracy of algorithms and their constituent tests will vary depending on who is implementing them. The development of specialist DVT nurses in the NHS offers the opportunity to concentrate skills and enhance cost-effectiveness. For example, if DVT nurses could develop the skills required to perform ultrasound then this test could be provided as a cheap, point-of-care test.
- How do algorithms compare to non-protocol care? This is a more fundamental question, but still important to implementation. Although algorithms may be a useful way of standardising care, there is no strong reason why algorithm-guided care should be any better than unstandardised care, and some reasons why it may be worse than individualised patient care undertaken by an experienced clinician. Research is required to determine whether algorithms improve care, or even change it.

Evaluation of algorithms using plethysmography

Incorporating plethysmography into algorithms has the potential to improve cost-effectiveness, but is undermined by uncertainty surrounding assumptions of independence of tests and the costs of providing plethysmography. Research is required to determine how plethysmography interacts with other tests, particularly Wells score and ultrasound. This could involve either experimental studies comparing the results of all three tests with venography, or observational studies determining the incidence of thromboembolism after using plethysmography-based algorithms. Research is also required in hospitals that are currently using plethysmography to determine the costs of providing the test and to explore whether these are generalisable throughout the NHS.

Methodological issues

The approach of using data from meta-analysis to inform the decision analysis model is based on a number of simplifications that require further investigation. These include the assumptions regarding independence of tests discussed earlier and the difficulty in applying results to specific groups of patients. Other issues include:

- evaluation of the optimal cut-off used when determining sensitivity and specificity of a test in a decision model: it was assumed that all tests were operating at the same threshold and therefore parameters were only estimated for one threshold. These estimates were then used as fixed values in the decision model. However, deriving the optimal cut-off for a particular test could be part of the decision modelling process.
- the selection of appropriate ranges for values of sensitivity and specificity used in probabilistic sensitivity analysis, when these two variables are recognised to be interdependent.

Diagnostic testing for pulmonary embolus

The analysis was limited to evaluation of diagnostic tests for DVT, yet many of the same issues are relevant to the diagnosis of suspected PE. Substantial research has been undertaken into diagnostic tests for PE, such as clinical scores, D-dimer, VQ scanning and spiral CT scanning, yet there is widespread variation in practice and uncertainty regarding the appropriate diagnostic approach. Systematic review, meta-analysis and decision analysis modelling are required to address this problem.

Acknowledgements

Contribution of authors

Steve Goodacre (Senior Lecturer in Health Service Research and Emergency Medicine) drafted the protocol, selected articles for inclusion, extracted data, undertook statistical analyses, provided cost-effectiveness data, wrote the final report, and assisted with designing the decision-analysis model and undertaking cost-effectiveness analyses. Fiona Sampson (Research Fellow in Health Service Research) undertook the postal survey of UK hospitals, selected articles for inclusion, extracted data and assisted with writing the final report. Matt Stevenson (Operational Research) designed the decision-analysis model, undertook cost-effectiveness analyses, and assisted with drafting the protocol and writing the final report. Allan Wailoo (Health Economics) provided cost-effectiveness data, and assisted with drafting the protocol, designing the decision-analysis model, undertaking cost-effectiveness analysis and writing the final report. Alex Sutton (Senior Lecturer in Statistics) undertook the statistical analyses and assisted with writing the final report. Steve Thomas (Senior Lecturer in Vascular Radiology) provided vascular radiology expertise, extracted data and assisted with drafting the protocol, designing the decision-analysis model and writing the final report. Tom Locker (Specialist Registrar in Emergency Medicine) extracted data and assisted with writing the final report. Angie Ryan (Information Resources) undertook the electronic literature searches and assisted with writing the final report.

Other contributors

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Appendix 1

Literature search strategies

Literature search for studies of clinical features and scores

1 exp Venous Thrombosis/
2 deep vein thrombosis.tw.
3 phlebothrombosis.tw.
4 venous thrombos$.tw.
5 deep venous thrombosis.tw.
6 DVT.tw.
7 or/1-6
8 exp "Sensitivity and Specificity"/
9 exp Diagnostic Errors/
10 Reference Values/
11 Reproducibility of Results/
12 likelihood functions/
13 specificity.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
14 sensitivity.mp.
15 false negative$.mp.
16 false positive$.mp.
17 true negative$.mp.
18 true positive$.mp.
19 predictive value$.mp.
20 reproducibility.mp.
21 ROC curve.mp.
22 Diagnos$.mp.
23 reference value$.mp.
24 likelihood function$.mp.
25 likelihood ratio$.mp.
26 or/8-25
27 exp medical history taking/
28 medical history.tw.
29 history taking.tw.
30 exp physical examination/
31 physical exam$.tw.
32 patient exam.tw.
33 (pre test probability or pretest probability or pre-test probability).tw.
34 ((pre test or pretest or pre-test) adj2 (prob$ or Score$)).tw.
35 probability model$.tw.
36 probability tool$.tw.
37 prediction rule$.tw.
38 wells.ti,ab.
39 clinical scor$ system$.tw.
40 clinical diagnos$ model$.tw.
41 clinical probability$.tw.
42 clinical feature$.tw.
43 clinical finding$.tw.
44 clinical sign$.tw.
45 clinical symptom$.tw.
46 clinical assessment.tw.
47 clinical evaluation.tw.
48 clinical diagnosis.tw.
49 physical sign$.tw.
50 physical symptom$.tw.
51 physical assessment.tw.
55 or/27-51
56 7 and 26 and 55

Literature search for studies of D-dimer

1 exp Venous Thrombosis/
2 deep vein thrombosis.tw.
3 phlebothrombosis.tw.
4 venous thrombos$.tw.
5 deep venous thrombosis.tw.
6 DVT.tw.
7 or/1-6
8 exp "Sensitivity and Specificity"/
9 exp Diagnostic Errors/
10 Reference Values/
11 Reproducibility of Results/
12 likelihood functions/
13 specificity.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
14 sensitivity.mp.
15 false negative$.mp.
16 false positive$.mp.
17 true negative$.mp.
18 true positive$.mp.
19 predictive value$.mp.
20 reproducibility.mp.
21 ROC curve.mp.
22 Diagnos$.mp.
23 reference value$.mp.
24 likelihood function$.mp.
25 likelihood ratio$.mp.
26 or/8-25
27 Fibrin Fibrinogen Degradation Products/ or Enzyme-Linked Immunosorbent Assay/
28 Reagent Kits, Diagnostic/
29 d-dimer.tw.
30 simplired.tw.
31 or/27-30
32 7 and 26 and 31

Literature search for studies of plethysmography techniques

1 exp Venous Thrombosis/
2 deep vein thrombosis.tw.
3 phlebothrombosis.tw.
4 venous thrombos$.tw.
5 deep venous thrombosis.tw.
6 DVT.tw.
7 or/1-6
8 exp "Sensitivity and Specificity"/
9 exp Diagnostic Errors/
10 Reference Values/
11 Reproducibility of Results/
12 likelihood functions/
13 specificity.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
14 sensitivity.mp.
15 false negative$.mp.
16 false positive$.mp.
17 true negative$.mp.
18 true positive$.mp.
19 predictive value$.mp.
20 reproducibility.mp.
21 ROC curve.mp.
22 Diagnos$.mp.
23 reference value$.mp.
24 likelihood function$.mp.
25 likelihood ratio$.mp.
26 or/8-25
27 exp Plethysmography, Impedance/
28 impedance plethysmography.tw.
29 rheography.tw.
30 plethysmography.tw.
31 or/27-30
33 7 and 36 and 31

Literature search for studies of ultrasound

1 exp Venous Thrombosis/
2 deep vein thrombosis.tw.
3 phlebothrombosis.tw.
4 venous thrombos$.tw.
5 deep venous thrombosis.tw.
6 DVT.tw.
7 or/1-6
8 exp "Sensitivity and Specificity"/
9 exp Diagnostic Errors/
10 Reference Values/
11 Reproducibility of Results/
12 likelihood functions/
13 specificity.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
14 sensitivity.mp.
15 false negative$.mp.
16 false positive$.mp.
17 true negative$.mp.
18 true positive$.mp.
19 predictive value$.mp.
20 reproducibility.mp.
21 ROC curve.mp.
22 Diagnos$.mp.
23 reference value$.mp.
24 likelihood function$.mp.
25 likelihood ratio$.mp.
26 or/8-25
27 exp Ultrasonography/
28 ultraso$.tw.
29 sonography.tw.
30 duplex.tw.
31 doppler.tw.
32 echography.tw.
33 echotomography.tw.
34 or/27-33
35 7 and 26 and 34

Literature search for studies of CT scanning

1 exp Venous Thrombosis/
2 deep vein thrombosis.tw.
3 phlebothrombosis.tw.
4 venous thrombos$.tw.
5 deep venous thrombosis.tw.
6 DVT.tw.
7 or/1-6
8 exp "Sensitivity and Specificity"/
9 exp Diagnostic Errors/
10 Reference Values/
11 Reproducibility of Results/
12 likelihood functions/
13 specificity.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
14 sensitivity.mp.
15 false negative$.mp.
16 false positive$.mp.
17 true negative$.mp.
18 true positive$.mp.
19 predictive value$.mp.
20 reproducibility.mp.
21 ROC curve.mp.
22 diagnos$.mp.
23 reference value$.mp.
24 likelihood function$.mp.
25 likelihood ratio$.mp.
26 or/8-25
27 tomography, x-ray computed/ or tomography, spiral computed/

28 cat scan.tw.
29 ct scan.tw.
30 cine ct.tw.
31 compute$ tomography.tw.
32 electron beam.tw.
33 tomodensitometry.tw.
34 compute$ transmission tomography.tw.
35 or/27-34
36 7 and 26 and 35

Literature search for studies of MRI scanning

1 exp Venous Thrombosis/
2 deep vein thrombosis.tw.
3 phlebothrombosis.tw.
4 venous thrombos$.tw.
5 deep venous thrombosis.tw.
6 DVT.tw.
7 or/1-6
8 exp "Sensitivity and Specificity"/
9 exp Diagnostic Errors/
10 Reference Values/
11 Reproducibility of Results/
12 likelihood functions/
13 specificity.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
14 sensitivity.mp.
15 false negative$.mp.
16 false positive$.mp.
17 true negative$.mp.
18 true positive$.mp.
19 predictive value$.mp.
20 reproducibility.mp.
21 ROC curve.mp.
22 Diagnos$.mp.
23 reference value$.mp.
24 likelihood function$.mp.
25 likelihood ratio$.mp.
26 or/8-25
27 exp Magnetic Resonance Imaging/
28 chemical shift imaging.tw.
29 mr tomography.tw.
30 mri.tw.
31 magnetic resonance imaging.tw.
32 magnetization transfer contrast imaging.tw.
33 nmr.tw.
34 proton spin tomography.tw.
35 zeugmatography.tw.
36 or /27-35
37 7 and 26 and 36

Literature search for algorithms

1. exp "Sensitivity and Specificity"/
2. exp Diagnostic Errors/
3. Reference Values/
4. Reproducibility of Results/
5. likelihood functions/
6. 1 or 2 or 3 or 4 or 5
7. specificity.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
8. sensitivity.mp.
9. false negative$.mp
10. false positive$.mp
11. true negative$.mp.
12. true positive$.mp.
13. predictive value$.mp.
14. reproducibility.mp
15. ROC curve.mp.
16. Diagnos$.ti.
17. reference value$.mp.
18. likelihood function$.mp.
19. likelihood ratio$.mp.
20. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. exp Venous Thrombosis/
22. deep vein thrombosis.tw.
23. phlebothrombosis.tw.
24. venous thrombosis.tw.
25. venous thromboembolism.tw.
26. deep venous thrombosis.tw.
27. DVT.tw.
28. 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 20 and 28
30. algorithms/
31. algorithm$.tw.
32. "Guideline [Publication Type]"/
33. exp Guidelines/
34. guideline.tw.
35. Clinical Protocols/
36. protocol$.tw.
37. or/30-36
38. 28 and 37

Appendix 2

Additional tables

TABLE 30 *Cohorts reporting individual clinical features*

First author	Year	*n*	% With DVT	Mean age	% Male	Setting	Reference standard
Anderson[31]	1999	344	13	54	45	ED	Ultrasound and follow-up
Briët[32]	1983	82	49	NR	NR	ED	Venogram
Chan[33]	2000	173	25	55	39	ED	Ultrasound
Constans[34]	2001	273	24	68	38	Inpatient	Ultrasound and follow-up
Constans[35]	2003	282	25	NR	30	Outpatient	Ultrasound
Cooperman[36]	1979	98	23	54	40	NR	Venogram
Cranley[37]	1976	124	54	NR	NR	NR	Venogram
Criado[38a]	1997	916	16	NR	47	Inpatient	Ultrasound
Criado[38a]	1997	610	12	NR	37	Outpatient	Ultrasound
Glover[39a]	1996	1231	24	65	42	Inpatient	Ultrasound
Glover[39a]	1996	1265	14	61	35	Outpatient	Ultrasound
Haeger[40]	1969	72	46	NR	NR	Outpatient	Venogram
Johanning[41]	2002	156	14	60	37	Outpatient	Ultrasound
Kahn[42]	1999	271	27	58	49	Mixed	Venogram and plethysmography
Kiil[43]	1979	58	40	69	40	NR	Venogram
Landefeld[44]	1990	236	27	56	38	Mixed	Venogram
Lee[45]	2002	345	18	NR	61	NR	Ultrasound
Lindqvist[46]	1977	47	51	NR	NR	Mixed	Venogram
Lucchi[47]	1993	102	38	52	34	Outpatient	Ultrasound
Molloy[48]	1982	100	43	54	38	NR	Venogram
Oger[49]	1997	277	58	NR	43	Inpatient	Venogram
Pini[50]	1984	137	52	NR	NR	Outpatient	Venogram
Prandoni[51]	1988	500	32	54	49	Outpatient	Venogram
Richards[52]	1976	150	40	NR	NR	Inpatient	Venogram
Robinson[53]	1998	83	34	69	45	Inpatient	Venogram
Sandler[54]	1984	50	58	56	55	Inpatient	Venogram
Trujillo-Santos[55]	2000	108	70	65	54	Inpatient	Venogram
Vaccaro[56]	1987	152	45	NR	NR	NR	Venogram
Vine[57]	1981	150	33	NR	40	Mixed	Venogram
Wells[58]	1997	593	16	57	42	Outpatient	Ultrasound, repeat and follow-up
Wijeyaratne[59]	2002	137	46	45	30	NR	Ultrasound

[a] Two studies reported two cohorts each (inpatient and outpatient).

TABLE 31 *Cohorts reporting clinical scores*

First author	Year	Score	*n*	% With DVT	Mean age (years)	% Male	Setting	Reference standard
Arrivé[60]	2002	W, E	141	23	NR	NR	NR	Ultrasound
Shields[61]	2002	W	102	17	NR	52	ED	Ultrasound
Kraaijenhagen[62]	2002	W	1726	22	60	37	Outpatient	Ultrasound and follow-up
Dryjski[64]	2001	W	66	10	63	25	ED	Ultrasound
Bucek[65]	2001	W	97	36	59	41	Outpatient	Ultrasound
Fünfsinn[66]	2001	W	92	44	56	49	Outpatient	Ultrasound
Wells[67]	1999	W	150	28	64	50	Inpatient	Ultrasound and follow-up
Borg[68]	1997	W	67	42	63	36	NR	Ultrasound
D'Angelo[69]	1996	W	66	29	59	37	NR	Ultrasound and repeat
Anderson[31]	1999	W	344	13	54	45	ED	Ultrasound and follow-up
Lennox[70]	1999	W	200	23	58	63	Mixed	Ultrasound
Bozic[71]	2002	W	135	39	60	39	Outpatient	Ultrasound and repeat
Kilroy[72]	2003	W	279	15	NR	NR	ED	Ultrasound and follow-up
Ruiz-Giménez[73]	2002	W	569	26	67	36	Outpatient	Ultrasound and follow-up
Cornuz[63]	2002	W, E	278	29	60	62	Mixed	Ultrasound and follow-up
Wells[8]	1995	W	529	25	NR	NR	Outpatient	Venogram
Wojciechowski[74]	1982	O	190	47	64	48	ED	Venogram
Constans[34]	2001	W, O	273	24	68	38	Inpatient	Ultrasound and follow-up
Constans[35 a]	2003	W, O	282	25	NR	30	Outpatient	Ultrasound
Constans[35 a]	2003	W, O	444	28	61	NR	Outpatient	Ultrasound
Wells[58]	1997	W	593	16	57	42	Outpatient	Ultrasound, repeat and follow-up
Wells[75]	1998	E	529	25	NR	NR	Outpatient	Venogram
Miron[76]	2000	W, E	270	21	NR	NR	Outpatient	Ultrasound and follow-up
Wells[9]	2003	DW	520	16	58	40	Mixed	Ultrasound and follow-up
Tick[77]	2002	DW	810	43	62	36	Outpatient	Ultrasound and follow-up

[a] Two cohorts (validation and derivation) reported in one study.
DW, dichotomised Wells score; E, Empirical scoring; O, other score; W, Wells score.

TABLE 32 *Characteristics of plethysmography cohorts with clinically suspected DVT*

Technique	Number of cohorts	Recruitment	Mean/median age (years)	% Male	Prevalence of DVT	Proportion of DVT distal
Impedance plethysmography	42	Primary care: 2 Outpatient: 6 Inpatient: 13 Mixed: 7 Not stated: 14	Reported by 23/42 Median: 58 Range: 48–62	Reported by 24/42 Median: 43% Range: 34–65	Median: 41% Range: 18–78%	Reported by 28/42 Median: 18% Range: 0–40%
Strain-gauge plethysmography	20	ED: 1 Outpatient: 2 Inpatient: 9 Mixed: 2 Not stated: 6	Reported by 10/20 Median: 58 Range: 43–67	Reported by 11/20 Median: 47% Range: 31–60	Median: 32% Range: 15–83%	Reported by 10/20 Median: 32% Range: 14–58%
Air plethysmography	4	Mixed: 1 Not stated: 3	Reported by 3/4 53, 56 and 60 years	Reported by 3/4 33, 51 and 57%	42, 42, 63 and 70%	Reported by 2/4 23 and 26%
Light reflex rheography	9	ED: 1 Inpatient: 1 Mixed: 4 Not stated: 3	Reported by 4/9 43, 58, 60 and 62	Reported by 6/9 Median: 43% Range: 32–51	Median: 35% Range: 17–47%	Reported by 4/9 0, 8, 18 and 30%
Phleborheography	7	ED: 0 Inpatient: 3 Mixed: 2 Not stated: 2	Reported by 1/7 40 years	Reported by 3/7 26, 46 and 51%	Median: 38% Range: 27–64%	Reported by 4/7 14, 16, 20 and 21%

TABLE 33 *Methodology for plethysmography cohorts with clinically suspected DVT*

Technique	Interpretation of plethysmography	Reference standard used	Reference standard independent	Reference standard interpreted blindly	Plethysmography interpreted blindly	Criteria for positive result defined
Impedance plethysmography	Automatic: 2 Operator: 4 Independent observer: 5 Other: 2 Not stated: 29	Venography: 41 Ultrasound: 1	Yes: 32 No: 0 Unclear: 10	Yes: 26 No: 0 Unclear: 16	Yes: 23 No: 0 Unclear: 19	Yes: 22 No: 20
Strain-gauge plethysmography	Automatic: 8 Operator: 3 Not stated: 9	Venography: 16 Ultrasound: 4	Yes: 17 No: 0 Unclear: 3	Yes: 13 No: 0 Unclear: 7	Yes: 13 No: 0 Unclear: 7	Yes: 13 No: 7
Air plethysmography	Operator: 1 Not stated: 3	Venography: 4 Ultrasound: 0	Yes: 4 No: 0 Unclear: 0	Yes: 2 No: 0 Unclear: 2	Yes: 1 No: 0 Unclear: 3	Yes: 3 No: 1
Light-reflex rheography	Operator: 2 Independent observer: 5 Not stated: 2	Venography: 7 Ultrasound: 2	Yes: 9 No: 0 Unclear: 0	Yes: 9 No: 0 Unclear: 0	Yes: 5 No: 0 Unclear: 4	Yes: 4 No: 5
Phleborheography	Independent observer: 1 Other: 1 Not stated: 5	All venography	Yes: 1 No: 0 Unclear: 6	Yes: 1 No: 0 Unclear: 6	Yes: 5 No: 0 Unclear: 2	Yes: 2 No: 5

TABLE 34 *Characteristics of asymptomatic plethysmography cohorts*

Technique	Number of cohorts	Recruitment	Mean/median age (years)	% Male	Prevalence of DVT	Proportion of DVT distal
Impedance plethysmography	8	Orthopaedic: 7 Not stated: 1	Reported 3/8 63, 65 and 73	Reported by 4/8 47, 33, 52 and 24	Median: 26 Range: 8–55	Reported by 7/8 Median: 57% Range: 40–68%
Strain-gauge plethysmography	3	All orthopaedic	Reported by 2/3 68 and 72	Reported by 1/3 14%	9, 37 and 38%	80, 53 and 62%
Air plethysmography	1	Orthopaedic	74 years	43%	28%	100%
Phleborheography	2	Orthopaedic Mixed	None reported	None reported	24 and 54%	22 and 57%

TABLE 35 *Methodology for asymptomatic plethysmography cohorts*

Technique	Interpretation of plethysmography	Reference standard used	Reference standard independent	Reference standard interpreted blindly	Plethysmography interpreted blindly	Criteria for positive result defined
Impedance plethysmography	Automatic: 0 Operator: 2 Independent observer: 1 Other: 0 Not stated: 5	Venography: 8 Ultrasound: 0	Yes: 6 No: 1 Unclear: 1	Yes: 5 No: 1 Unclear: 2	Yes: 4 No: 0 Unclear: 4	Yes: 4 No: 4
Strain-gauge plethysmography	Automatic: 2 Not stated: 1	Venography: 3 Ultrasound: 0	Yes: 3 No: 0 Unclear: 0	Yes: 0 No: 0 Unclear: 3	Yes: 1 No: 0 Unclear: 2	Yes: 1 No: 2
Air plethysmography	Not stated: 1	Venography: 1 Ultrasound: 0	Yes: 1 No: 0 Unclear: 0	Yes: 1 No: 0 Unclear: 0	Yes: 1 No: 0 Unclear: 0	Yes: 1 No: 0
Phleborheography	Not stated: 2	Venography: 2 Ultrasound: 0	Yes: 1 No: 0 Unclear: 1	Yes: 0 No: 0 Unclear: 2	Yes: 1 No: 0 Unclear: 1	Yes: 0 No: 2

TABLE 36 *Characteristics of studies of CT scanning for DVT*

First author	Year	*n*	Setting	Patients	Mean age (years)	% Male	Gold standard	% With DVT
Duwe[376]	2000	74	NR	Suspected PE	78	36	Ultrasound	12
Coche[377]	2001	65	Mixed	Suspected PE	NR	38	Ultrasound	25
Yoshida[378]	2001	42	NR	Suspected DVT	58	48	Ultrasound	29
Peterson[379]	2001	136	Inpatient	Suspected PE	60	40	Ultrasound	10
Baldt[380]	1996	103	Mixed	Suspected DVT	63	58	Venography	43
Garg[381]	2000	70	NR	Suspected PE	61	93	Ultrasound	7
Cham[382]	2000	112	Mixed	Suspected PE	65	43	Ultrasound	13
Shah[383]	1999	52	NR	Mixed	NR	NR	Ultrasound	19
Loud[384]	2001	308	NR	Suspected PE	63	43	Ultrasound	21

TABLE 37 *Characteristics of studies of MRI scanning for DVT*

First author	Year	*n*	Setting	Patients	Mean age (years)	% Male	Gold standard	% With DVT
Laissy[313]	1996	21	NR	Mixed	50	43	Venography	71
Pope[385]	1991	17	NR	Suspected DVT	NR	59	Venography	53
Sica[386]	2001	14	Mixed	Suspected DVT	53	42	Venography	50
Jensen[387]	2001	27	Inpatient	Asymptomatic	41	56	Venography	22
Catalano[388]	1997	43	NR	Suspected DVT	NR	NR	Venography	79
Larcom[389]	1996	203	Inpatient	Asymptomatic	66	41	Venography	5
Vukov[390]	1991	10	ED	Suspected DVT	NR	NR	Venography	50
Evans[391]	1993	64	NR	Suspected DVT	54	56	Venography	14
Evans[392]	1996	65	NR	Suspected DVT	58	45	Venography	26
Carpenter[315]	1993	101	NR	Suspected DVT	NR	NR	Venography	27
Fraser[393]	2002	101	Mixed	Suspected DVT	NR	NR	Venography	52
Erdman[394]	1990	36	NR	Suspected DVT	NR	55	Venography	83
Fraser[395]	2003	98	Mixed	Suspected DVT	62	42	Venography	28
Spritzer[396]	1993	58	NR	NR	NR	NR	Venography	48

TABLE 38 *Estimated clinical accuracy of each test*

Algorithm number	Percentage of proximal DVTs treated	Percentage of distal DVTs that propagate to proximal treated	Percentage of distal DVTs that do not propagate to proximal treated	Percentage of no DVTs treated
0	0.0	0.0	0.0	0.0
1	99.5	86.1	0.6	0.6
2	95.0	95.3	6.0	6.0
3	95.0	67.8	6.0	6.0
4	95.0	6.0	6.0	6.0
5	98.1	79.2	6.0	3.4
6	95.0	63.2	6.0	6.0
7	99.2	79.2	4.0	6.0
8	99.2	90.3	4.0	6.0
9	93.2	82.1	5.2	2.8
10	93.2	75.7	5.2	2.8
11	96.5	63.4	5.6	3.7
12	93.9	63.4	5.6	3.7
13	96.1	28.7	5.6	3.2
14	95.0	69.0	6.0	6.0
15	93.9	52.5	5.6	3.7
16	90.1	34.9	4.6	2.1
17	95.0	79.2	6.0	6.0
18	95.0	36.4	6.0	6.0
19	97.9	72.5	5.0	0.3
20	97.9	52.4	5.6	1.0
21	88.4	4.9	4.9	3.1
22	98.4	80.5	5.6	0.0
23	94.4	65.7	4.6	0.0
24	98.4	89.1	6.0	3.7
25	79.8	61.0	3.8	1.7
26	97.6	66.8	23.3	4.8
27	92.0	51.1	5.3	1.6
28	84.5	35.5	3.1	0.7
29	94.9	65.8	5.8	4.2
30	93.5	57.0	5.0	2.5
31	92.0	48.1	4.3	1.7

TABLE 39 *Net benefit per 1000 patients with suspected DVT for each algorithm, compared with algorithm 0, using a threshold of £20,000 per QALY and £30,000 per QALY*

Strategy	Net benefit (£) assuming cost per QALY threshold of £20,000	Net benefit (£) assuming cost per QALY threshold of £30,000
1	531,267	904,313
2	533,961	881,159
3	515,396	856,367
4	542,167	869,180
5	578,971	942,859
6	540,770	880,702
7	510,408	869,011
8	458,422	815,480
9	597,675	948,356
10	597,100	946,341
11	592,715	947,039
12	556,433	901,866
13	594,157	941,200
14	542,183	883,431
15	581,319	924,291
16	591,904	923,878
17	542,135	885,700
18	542,806	876,682
19	591,155	961,516
20	610,446	977,464
21	554,601	868,743
22	584,168	957,110
23	597,766	955,614
24	528,699	890,281
25	531,757	832,930
26	568,545	921,007
27	594,579	938,667
28	566,313	883,451
29	550,286	898,008
30	575,163	922,471
31	596,499	939,761

Appendix 3

Additional figures

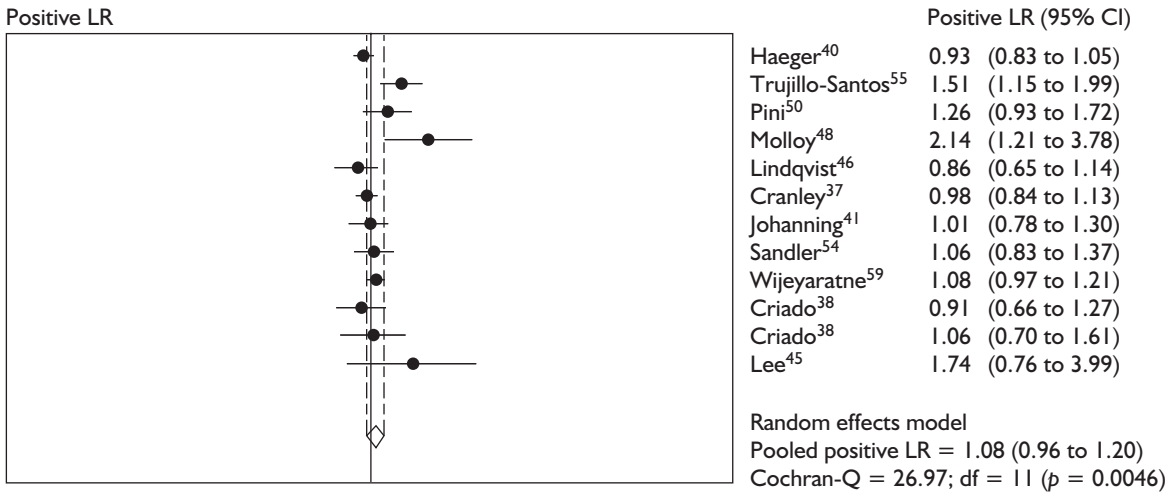

FIGURE 31 *Positive likelihood ratios (LR): calf pain*

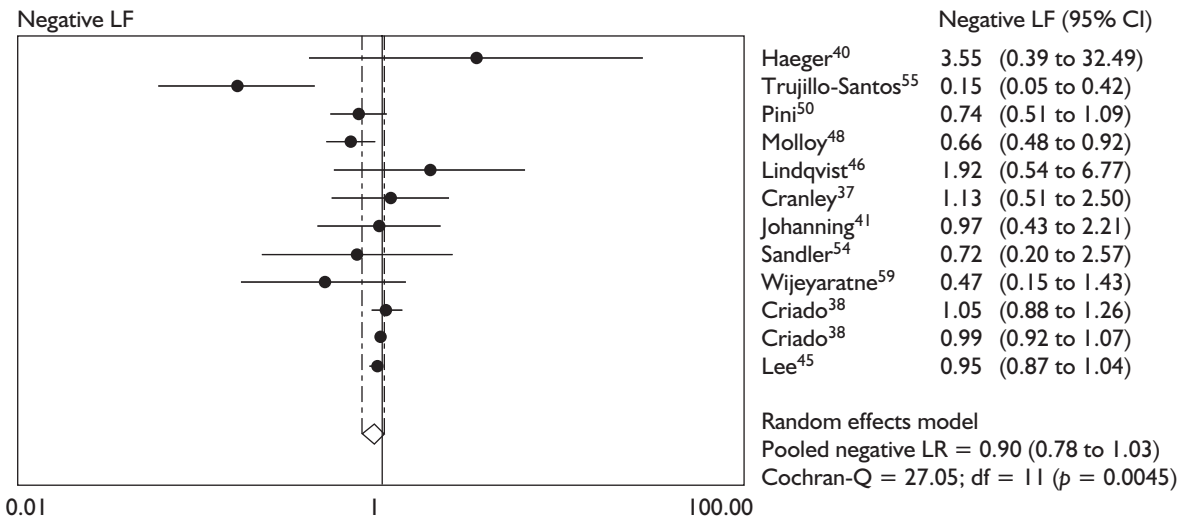

FIGURE 32 *Negative likelihood ratios: calf pain*

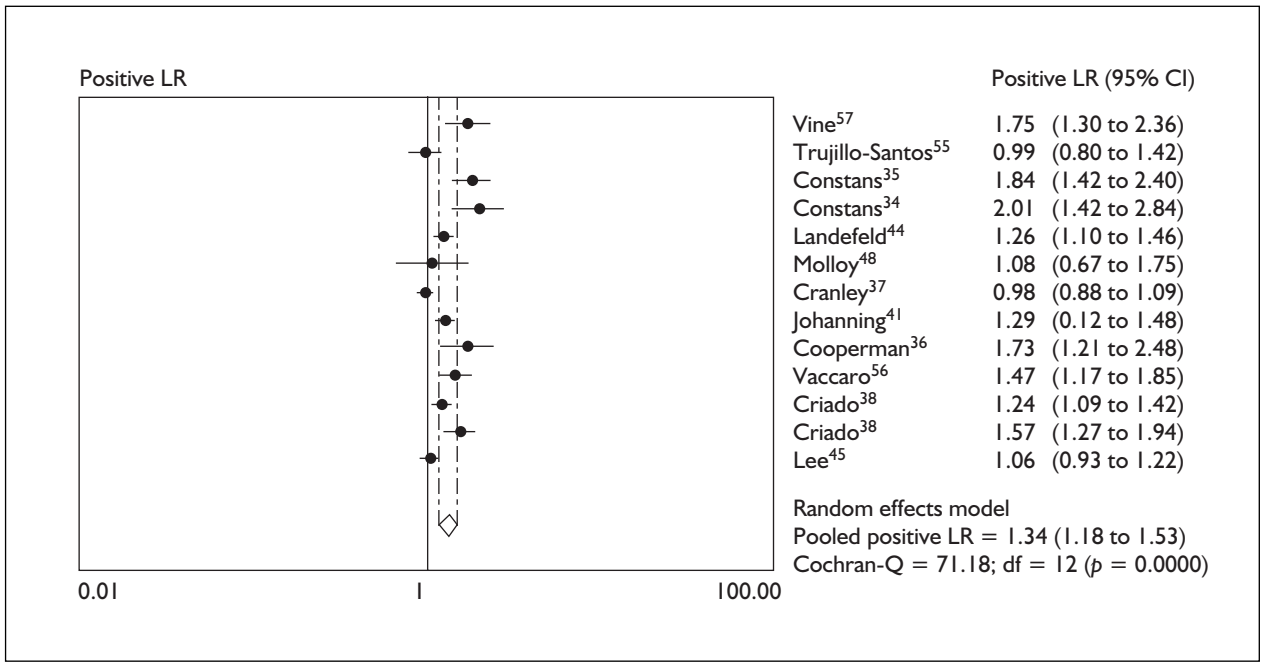

FIGURE 33 *Positive likelihood ratios: calf swelling*

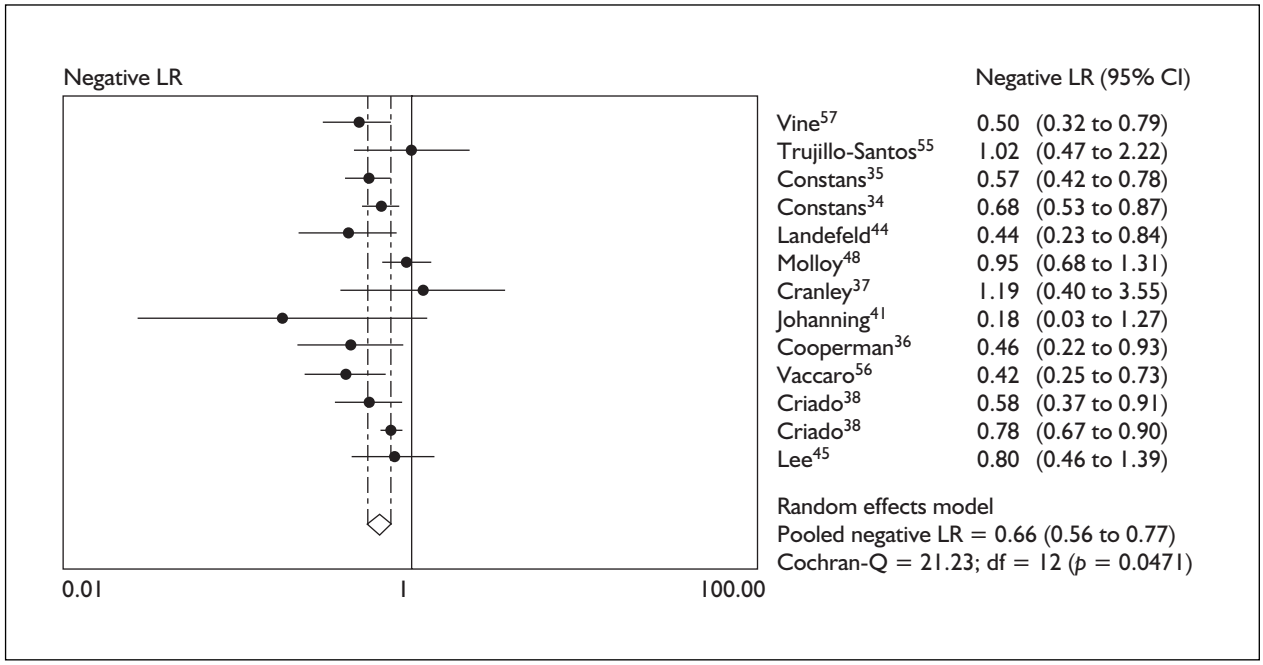

FIGURE 34 *Negative likelihood ratios: calf swelling*

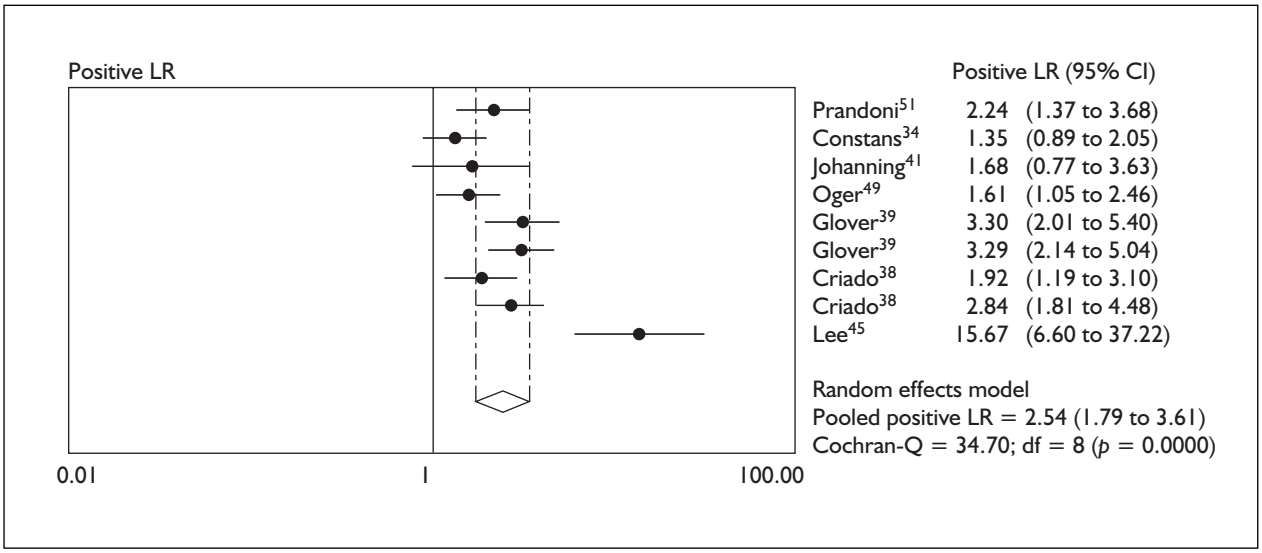

FIGURE 35 *Positive likelihood ratios: past history of DVT*

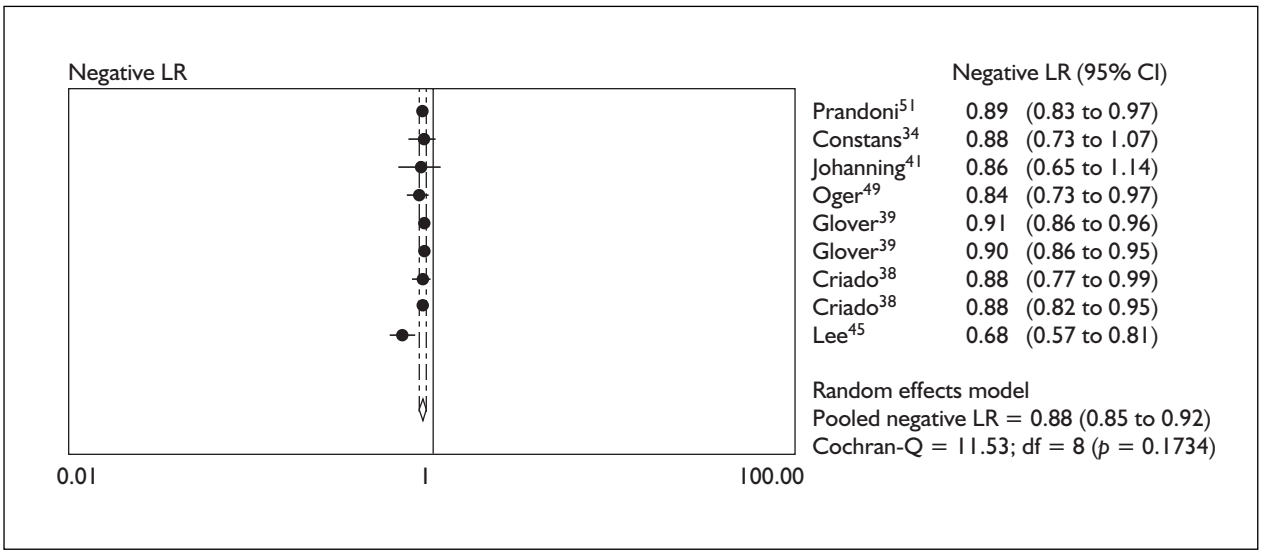

FIGURE 36 *Negative likelihood ratios: past history of DVT*

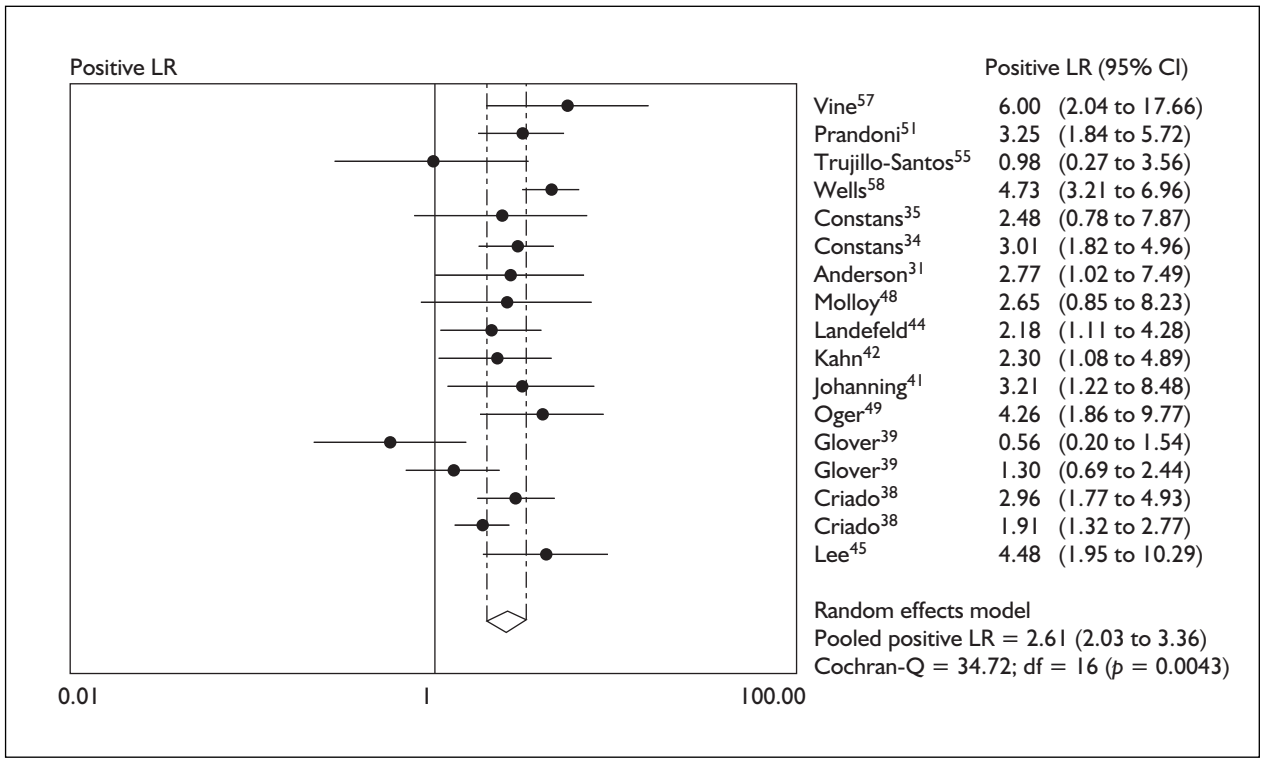

FIGURE 37 *Positive likelihood ratios: malignancy*

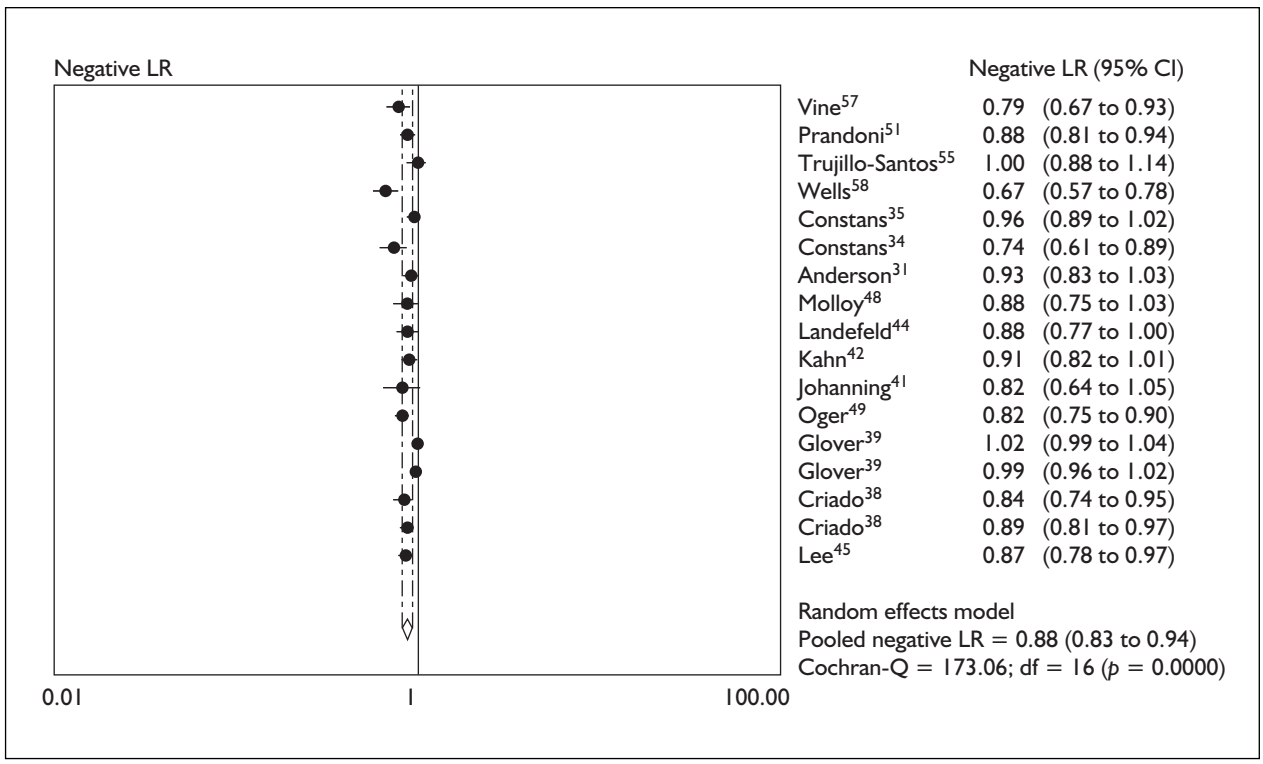

FIGURE 38 *Negative likelihood ratios: malignancy*

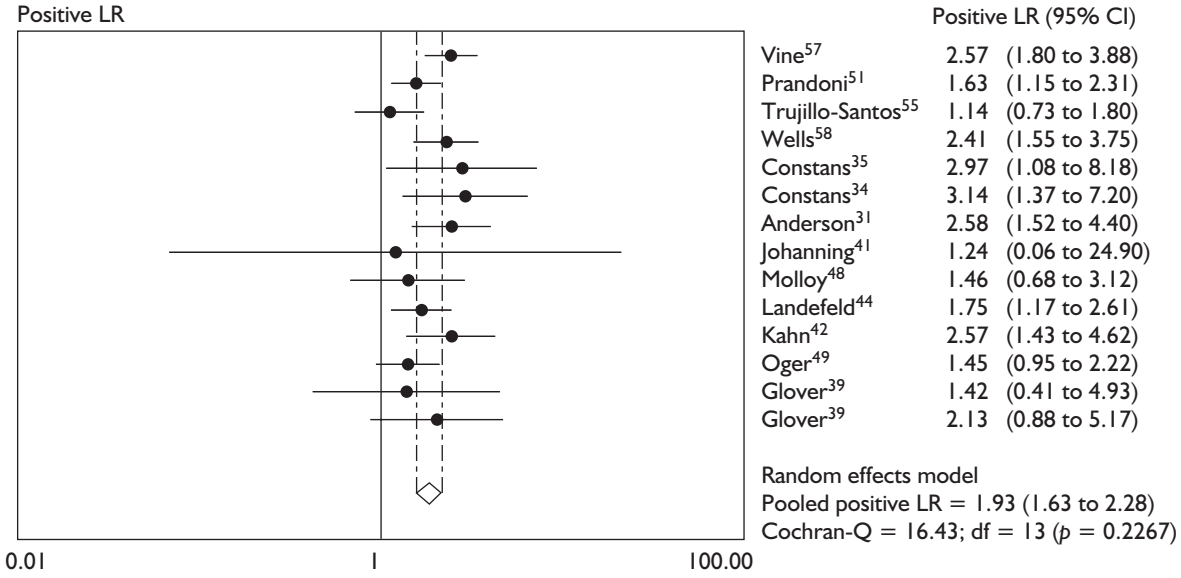

FIGURE 39 *Positive likelihood ratios: recent immobilisation*

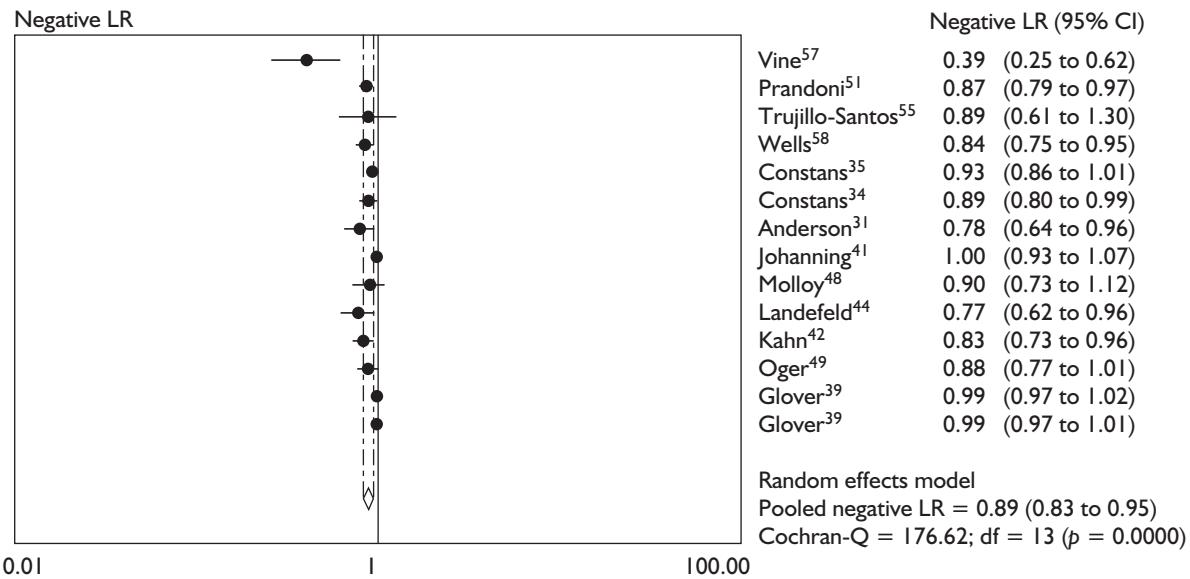

FIGURE 40 *Negative likelihood ratios: recent immobilisation*

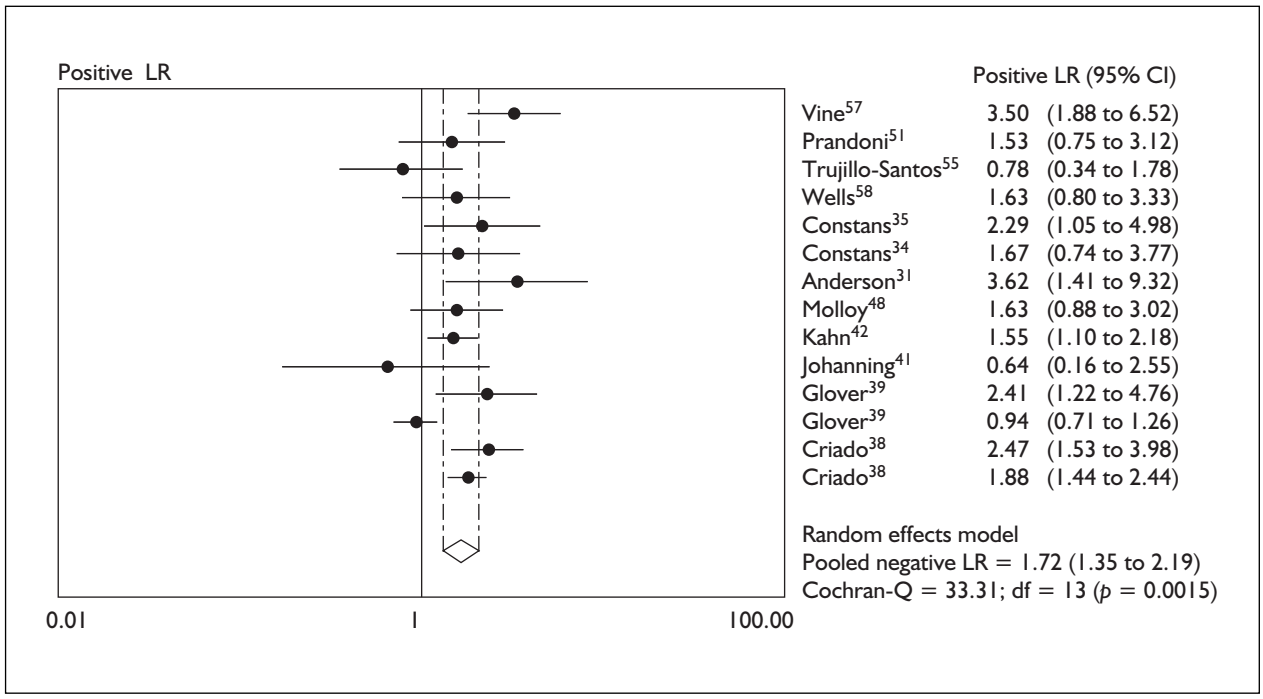

FIGURE 41 *Positive likelihood ratios: recent surgery*

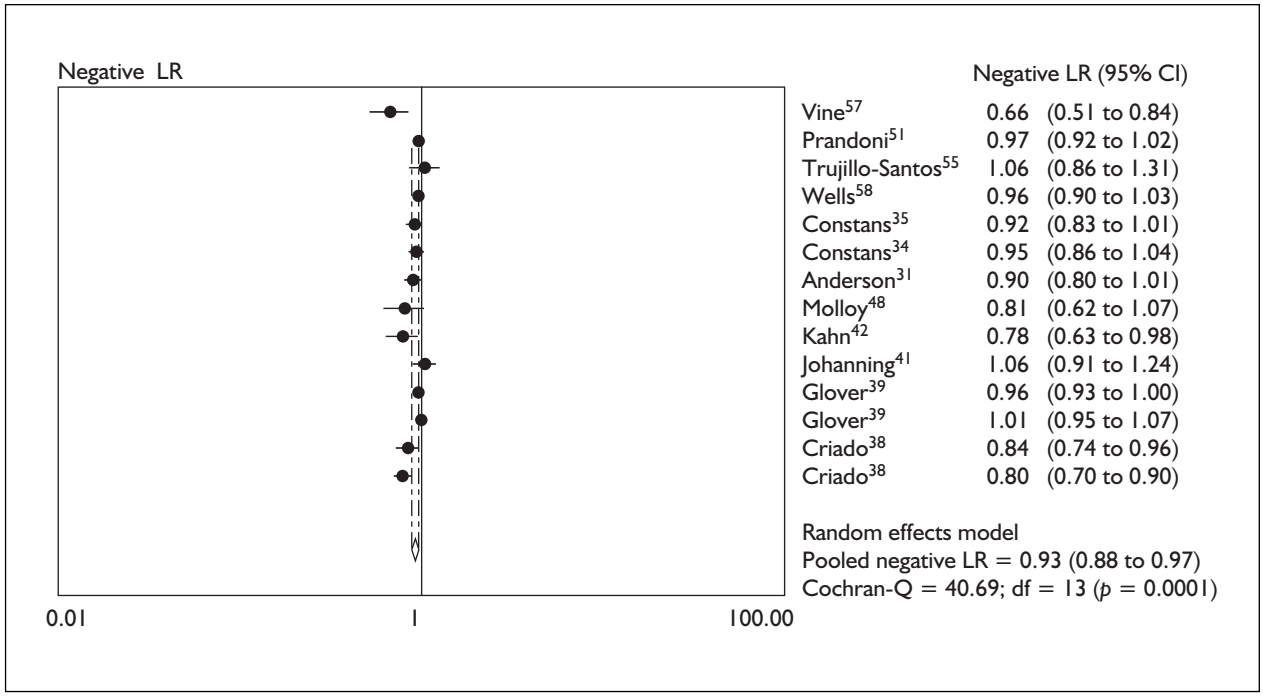

FIGURE 42 *Negative likelihood ratios: recent surgery*

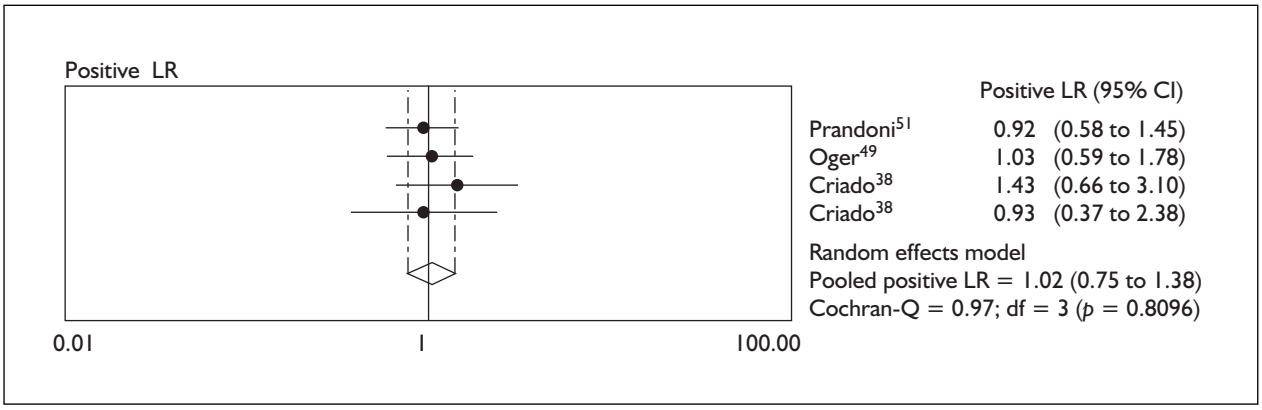

FIGURE 43 *Positive likelihood ratios: obesity*

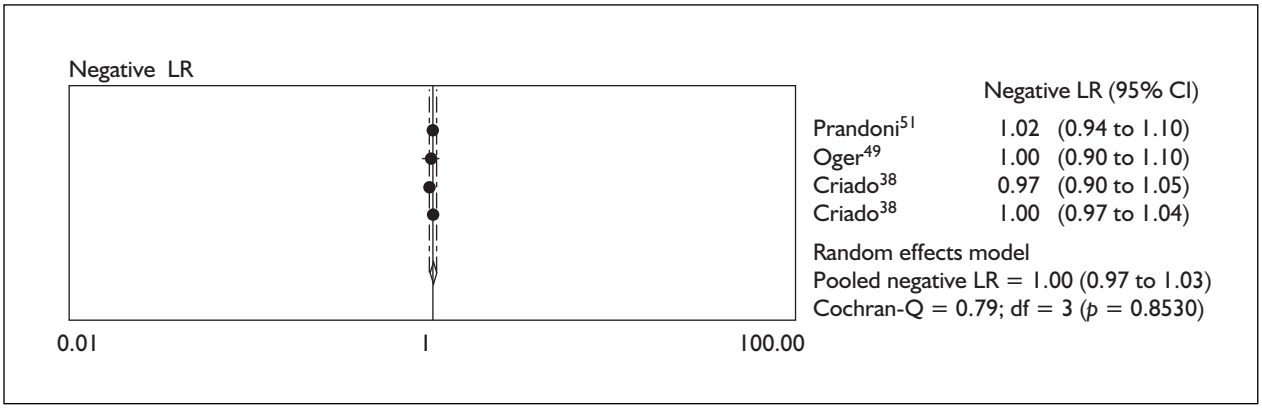

FIGURE 44 *Negative likelihood ratios: obesity*

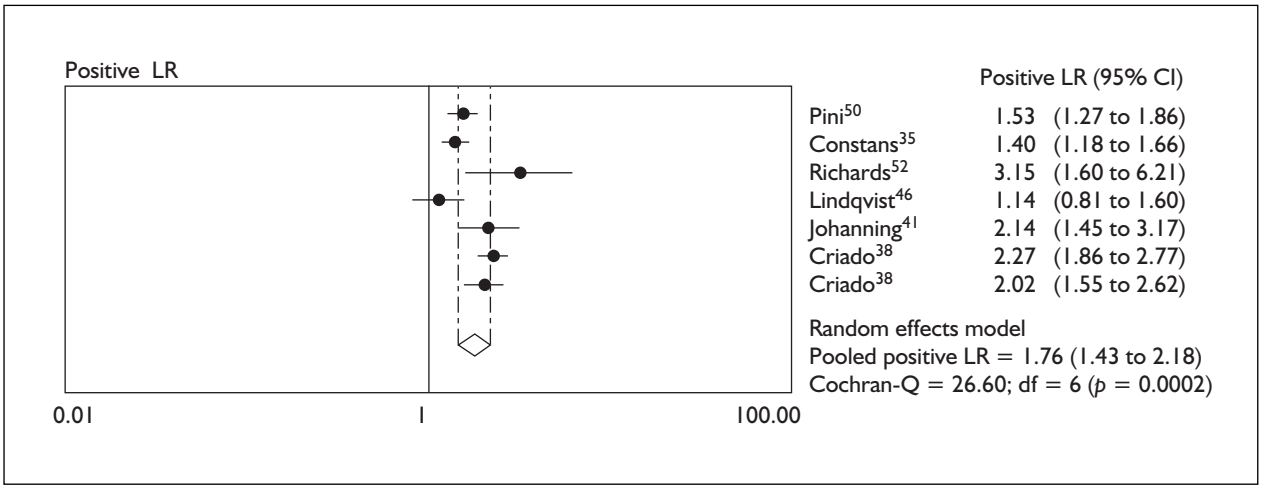

FIGURE 45 *Positive likelihood ratios: difference in calf diameter*

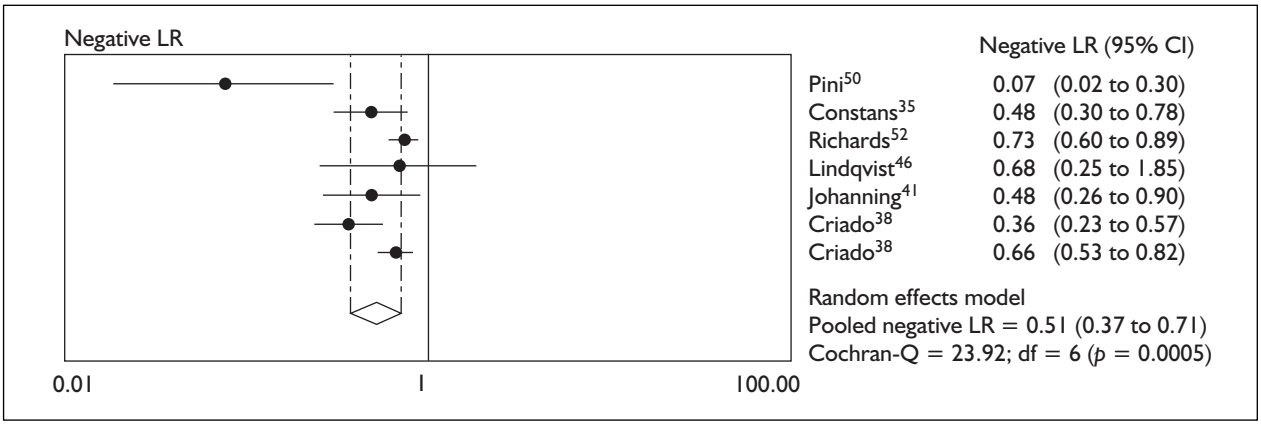

FIGURE 46 *Negative likelihood ratios: difference in calf diameter*

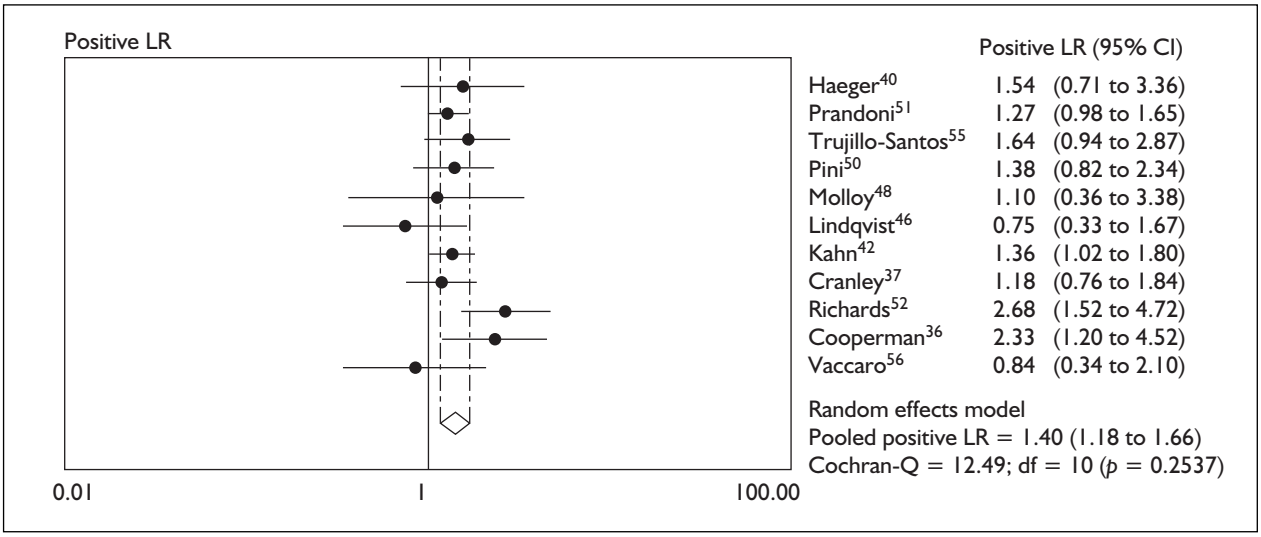

FIGURE 47 *Positive likelihood ratios: Homan's sign*

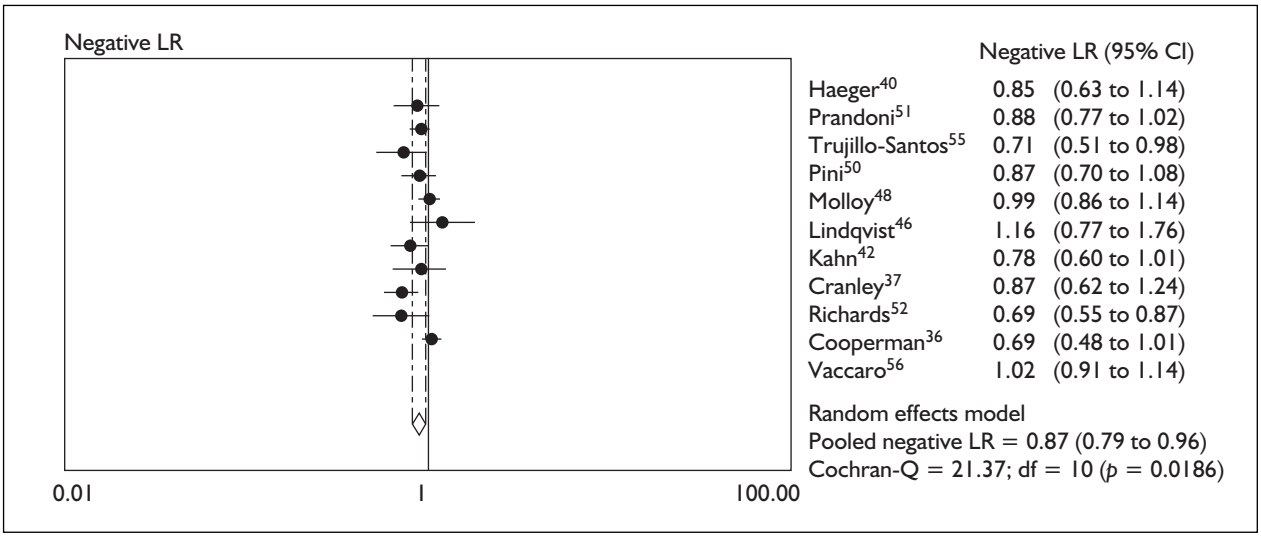

FIGURE 48 *Negative likelihood ratios: Homan's sign*

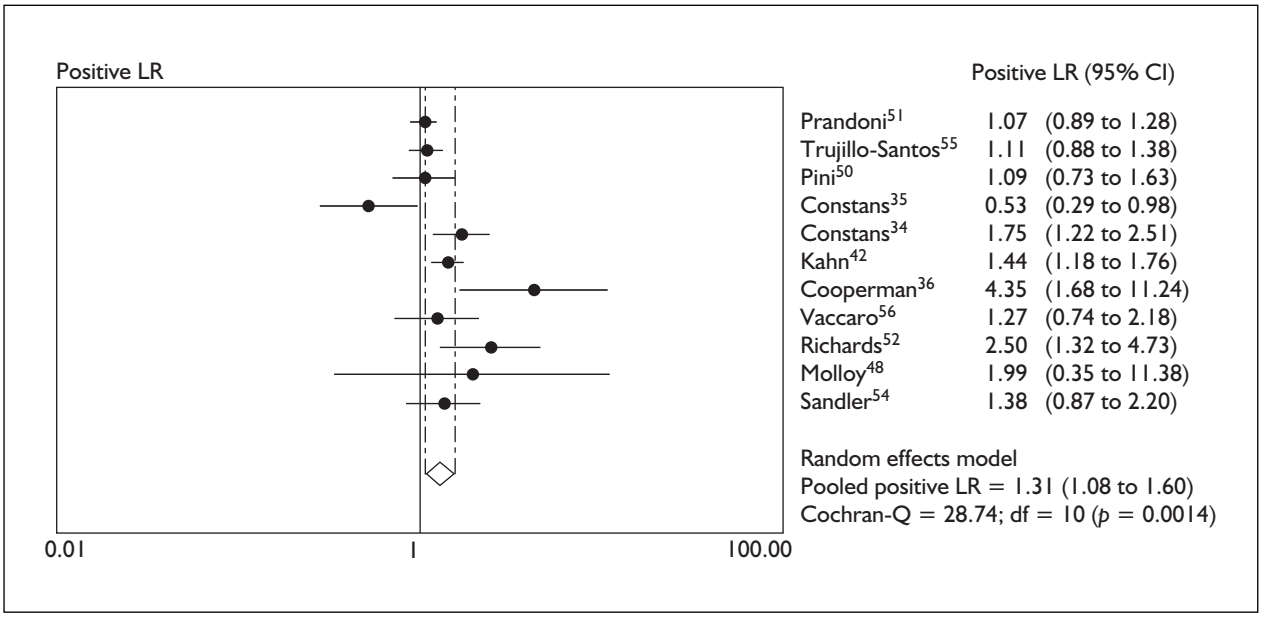

FIGURE 49 *Positive likelihood ratios: warmth*

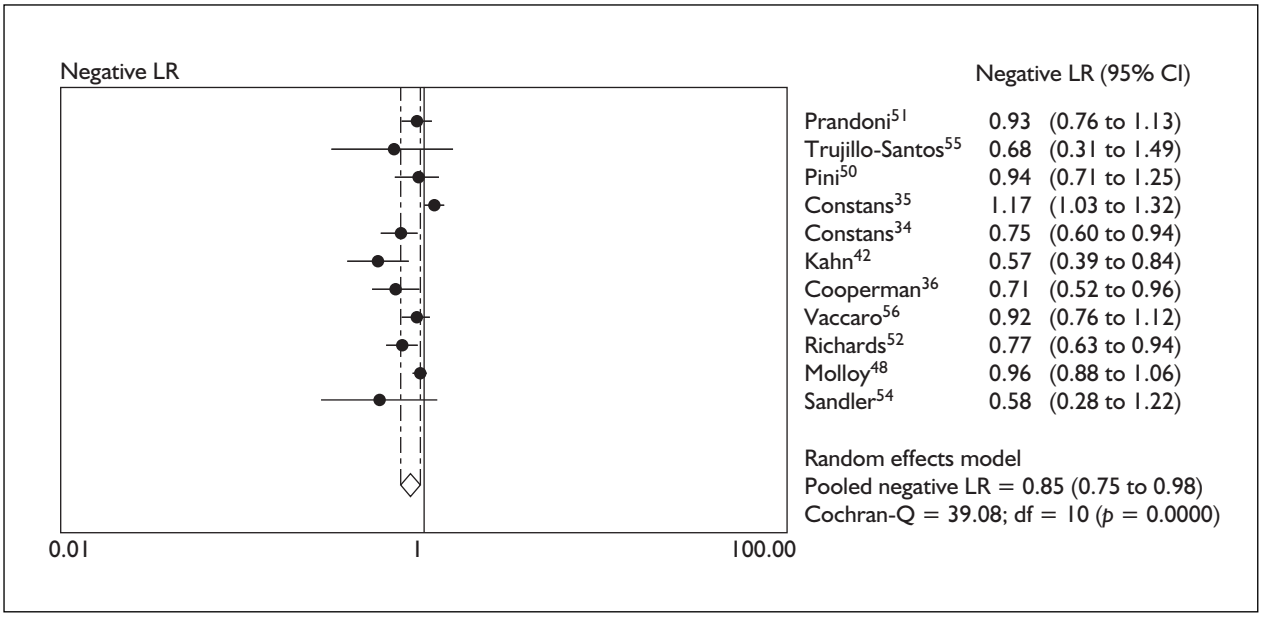

FIGURE 50 *Negative likelihood ratios: warmth*

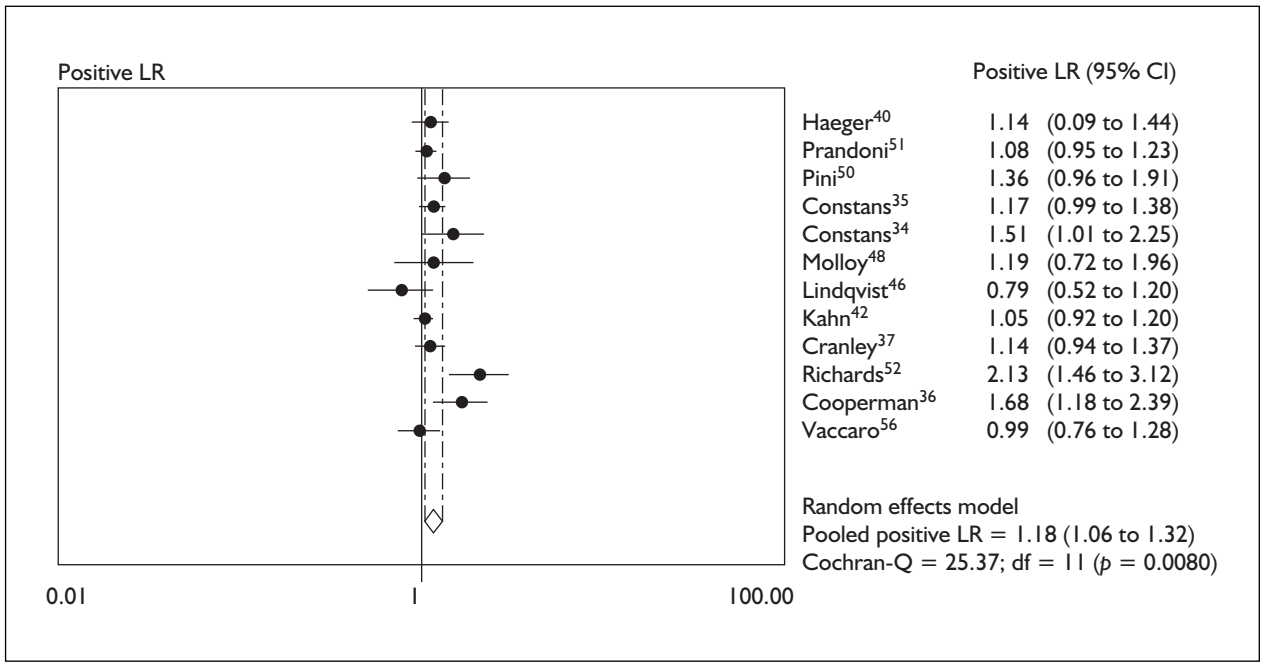

FIGURE 51 *Positive likelihood ratios: tenderness*

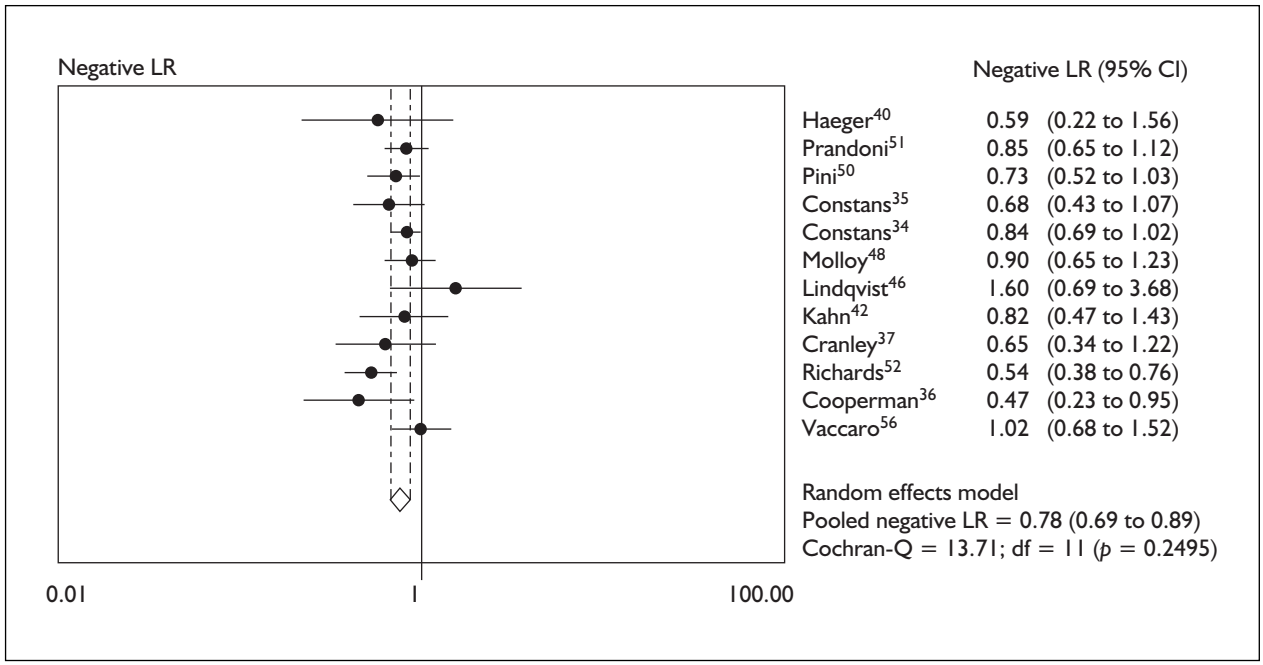

FIGURE 52 *Negative likelihood ratios: tenderness*

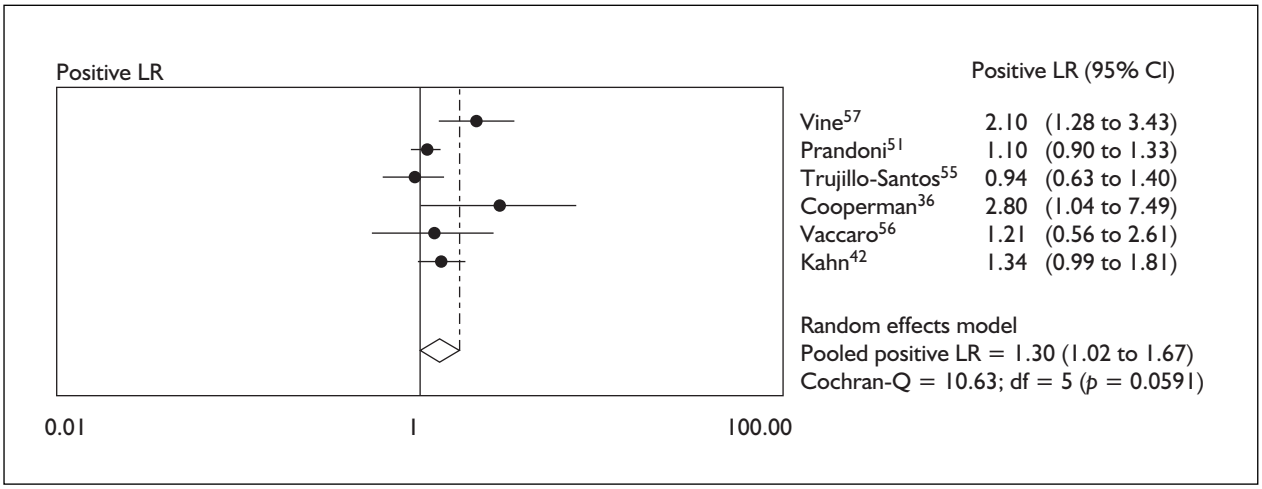

FIGURE 53 *Positive likelihood ratios: erythema*

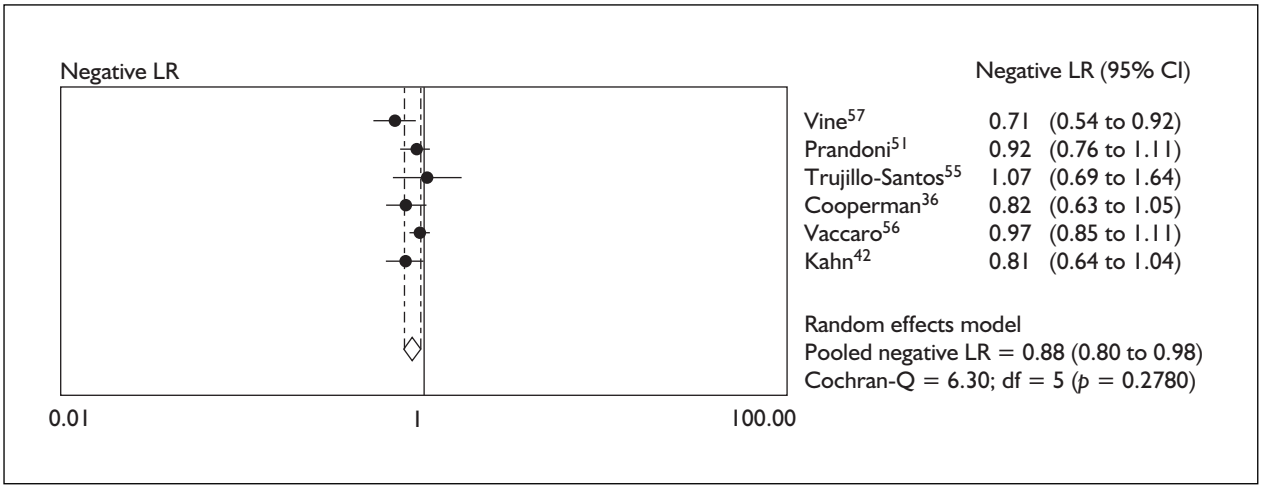

FIGURE 54 *Negative likelihood ratios: erythema*

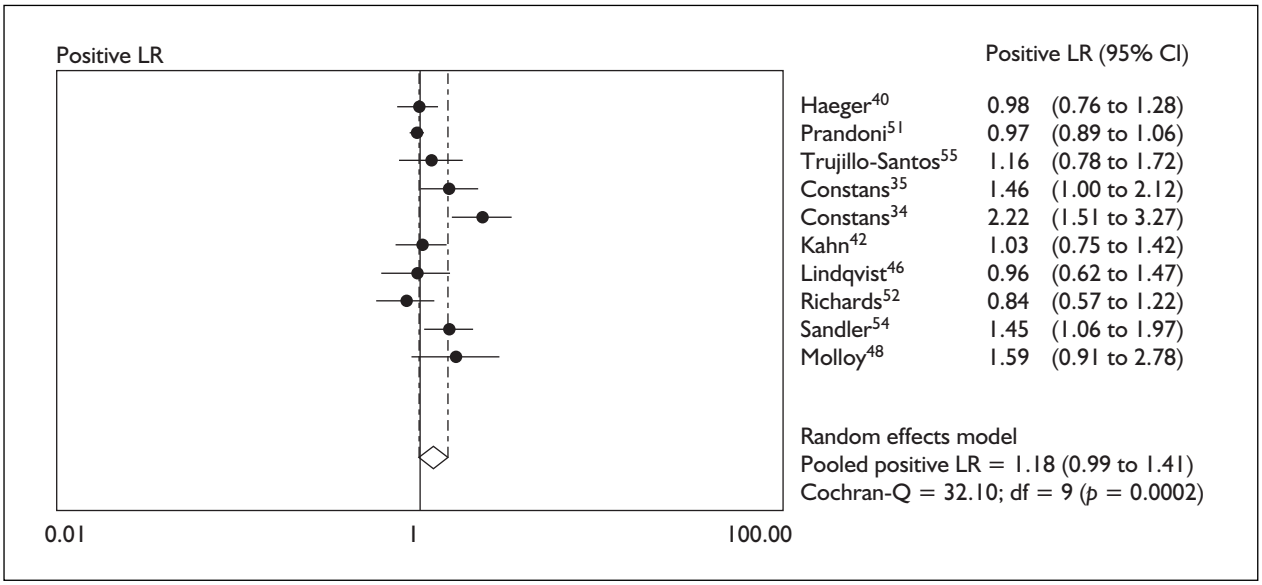

FIGURE 55 *Positive likelihood ratios: oedema*

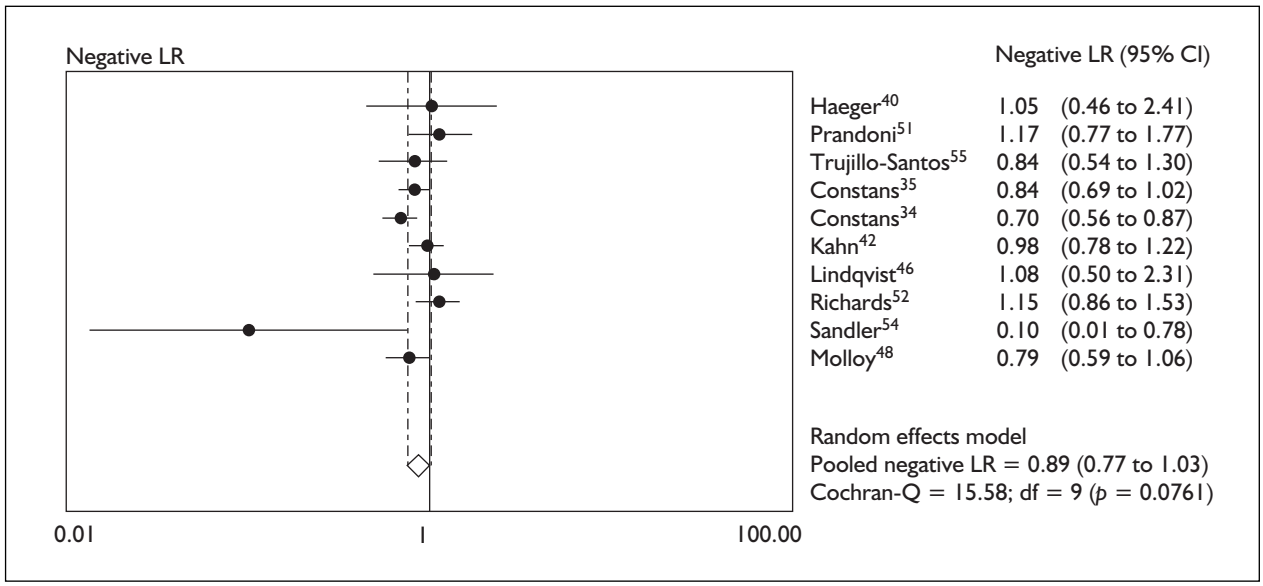

FIGURE 56 *Negative likelihood ratios: oedema*

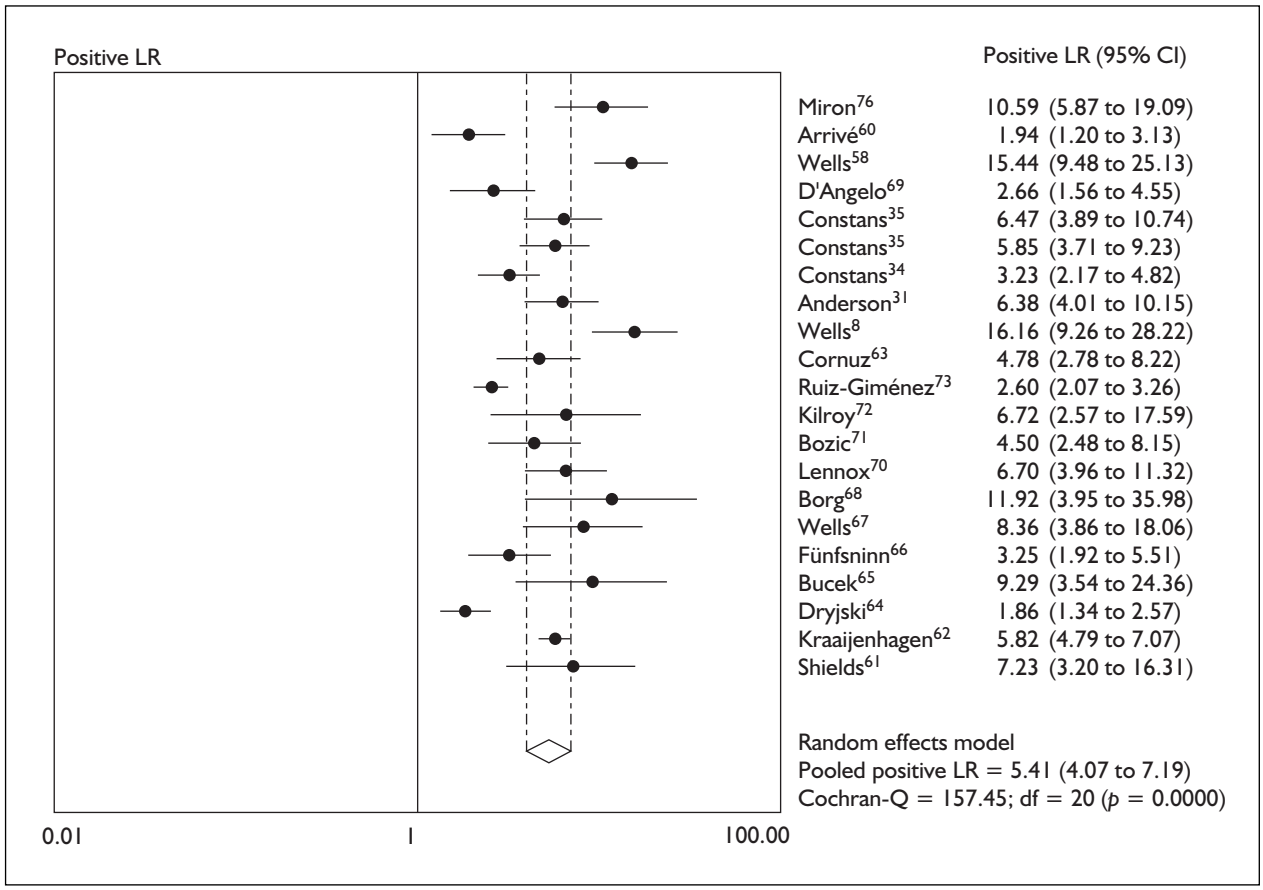

FIGURE 57 *Wells score: likelihood ratio of a high risk score*

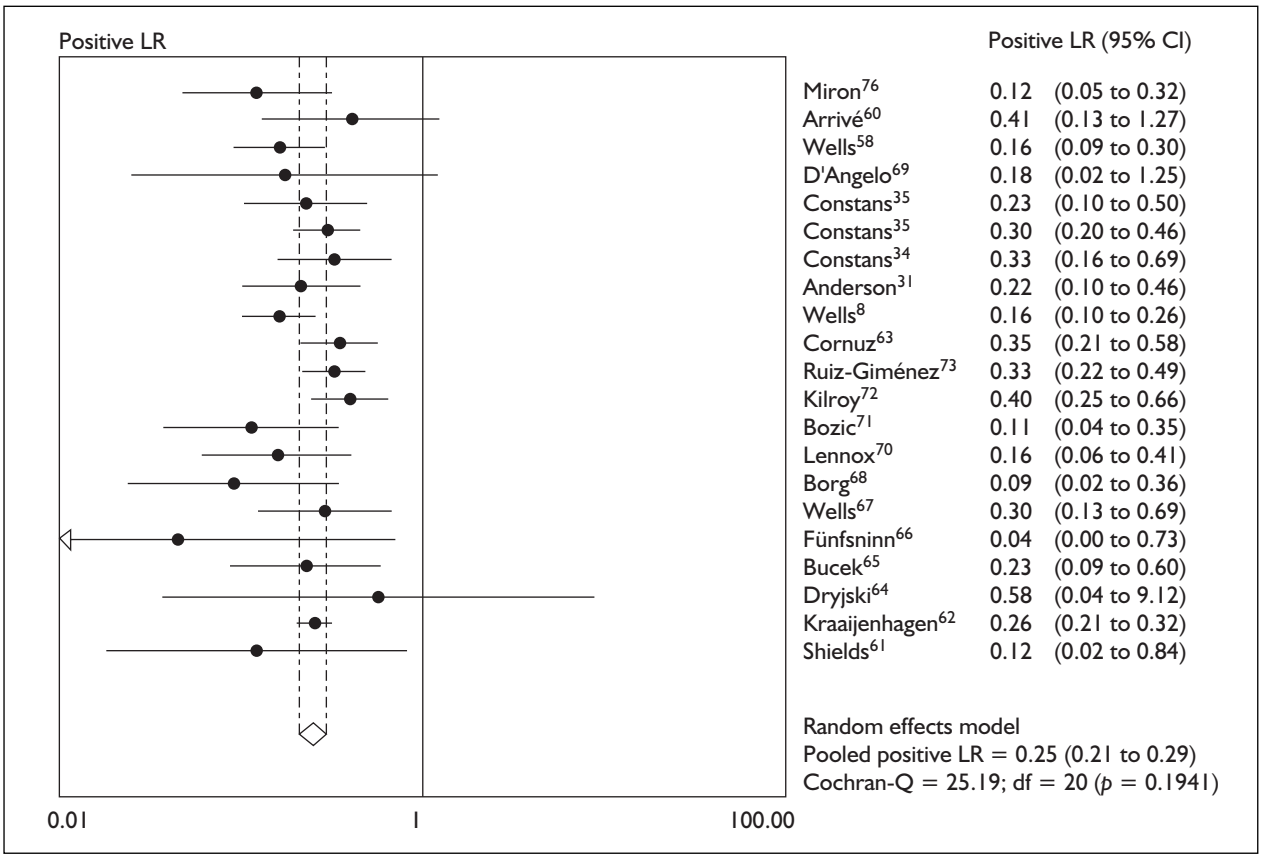

FIGURE 58 *Wells score: likelihood ratio of a low risk score*

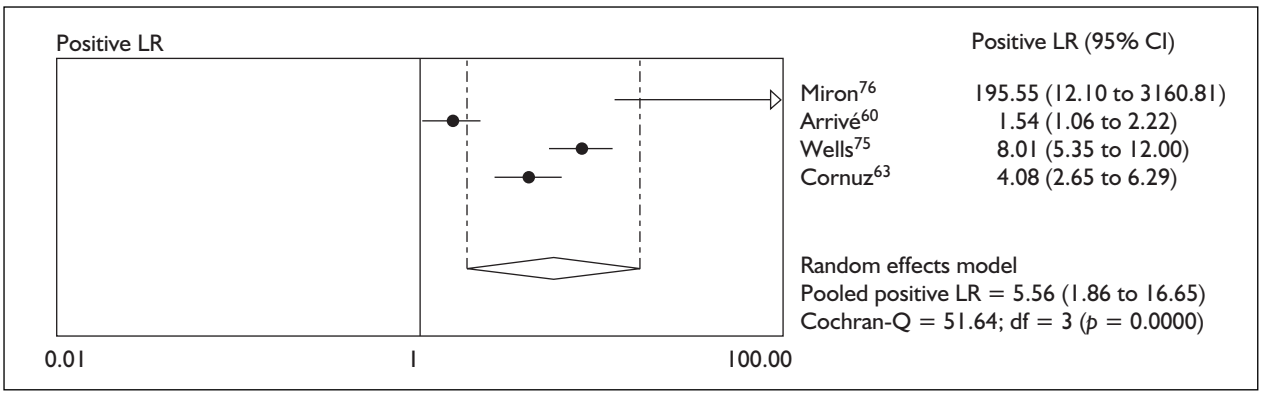

FIGURE 59 *Empirical clinical probability: likelihood ratio of a high estimate*

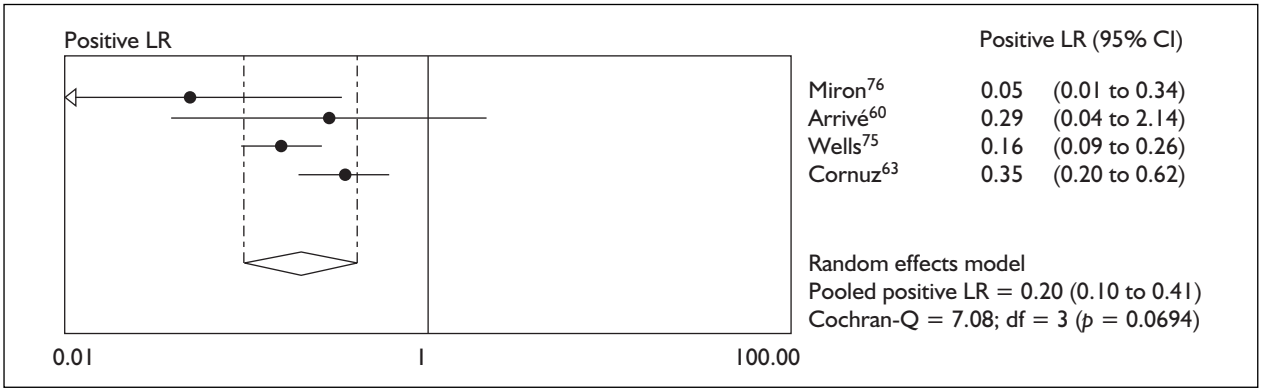

FIGURE 60 *Empirical clinical probability: likelihood ratio of a low estimate*

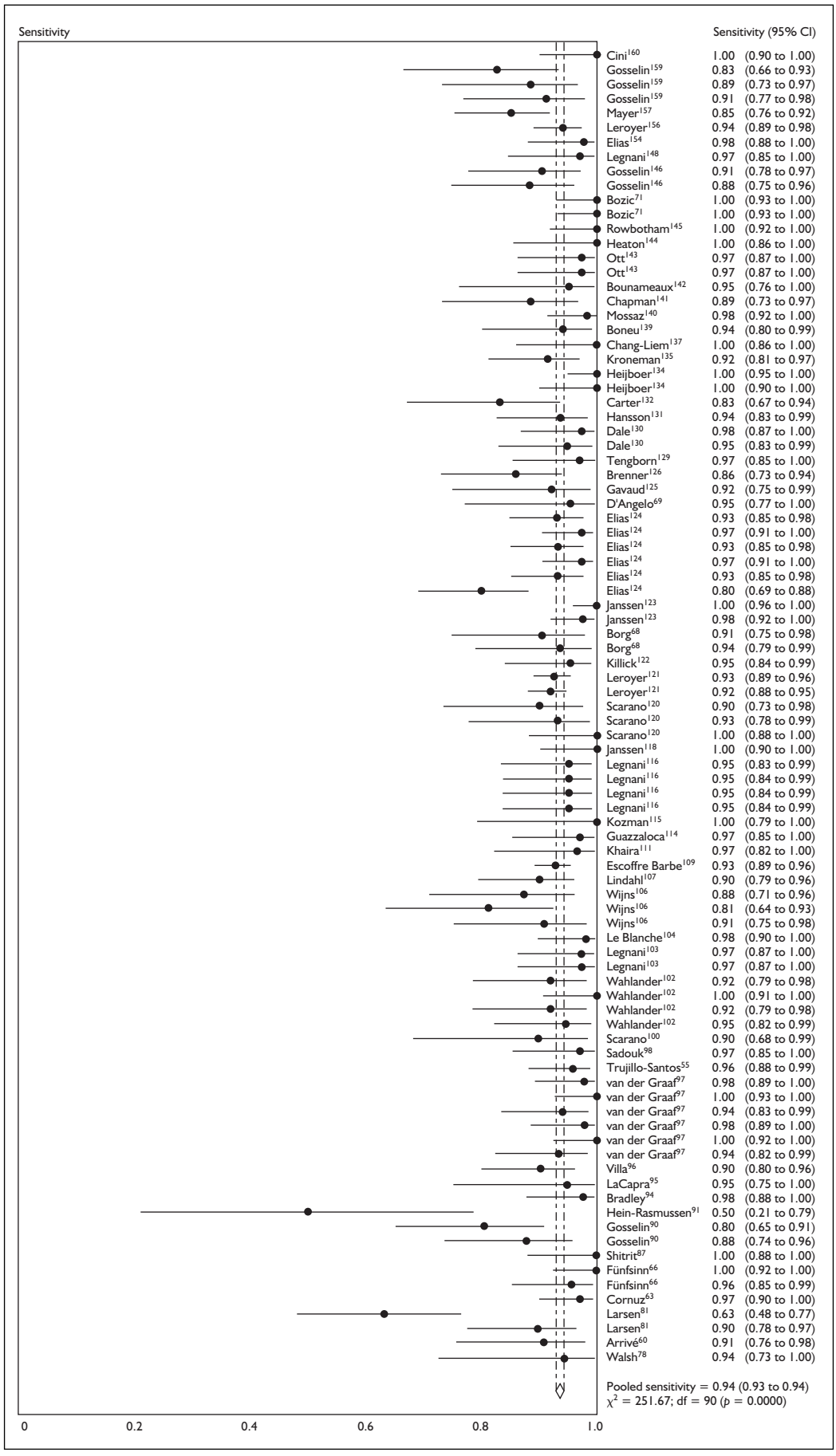

FIGURE 61
D-dimer: sensitivity of ELISA for all DVT in symptomatic patients

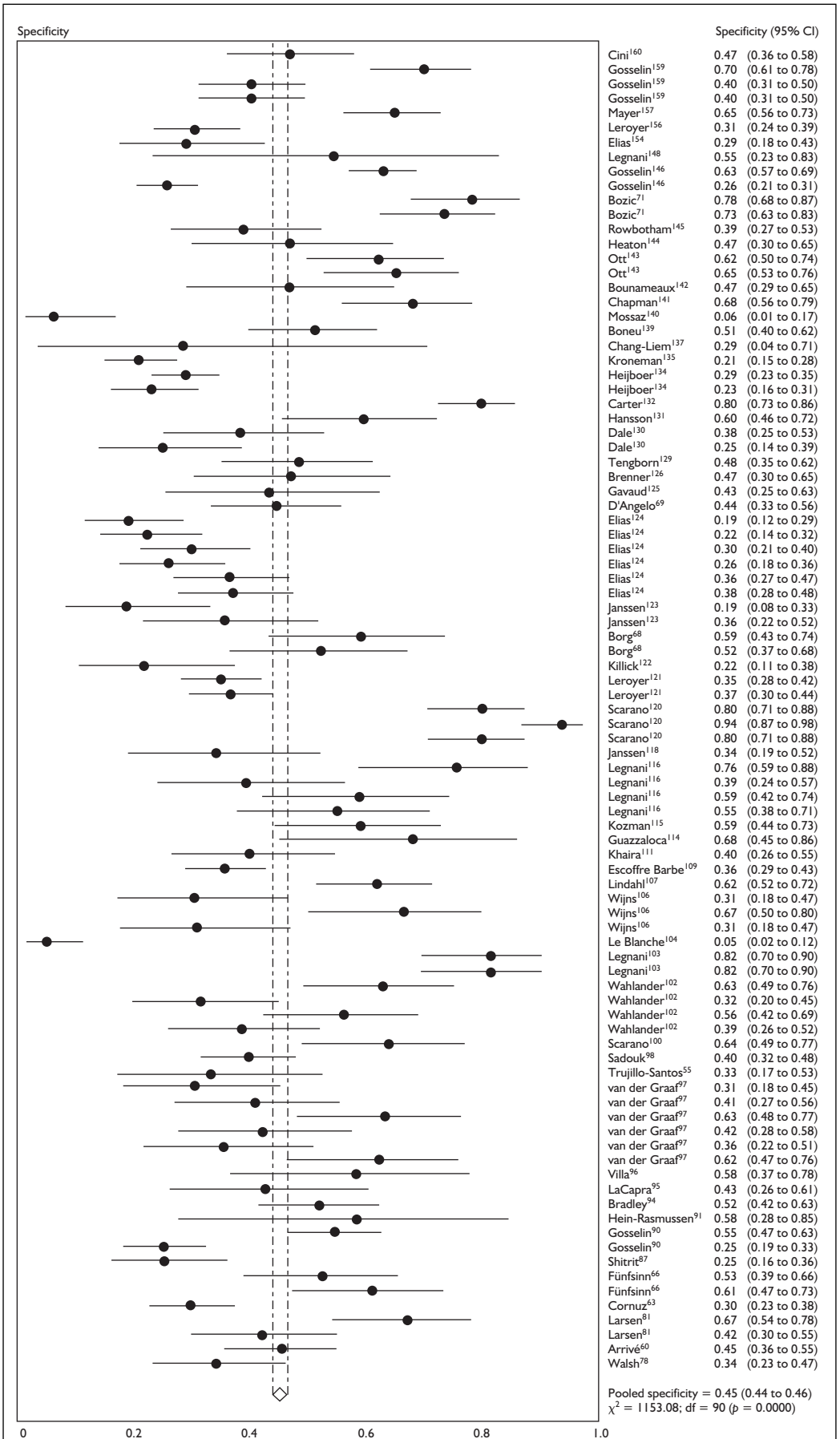

FIGURE 62
D-dimer: specificity of ELISA for all DVT in symptomatic patients

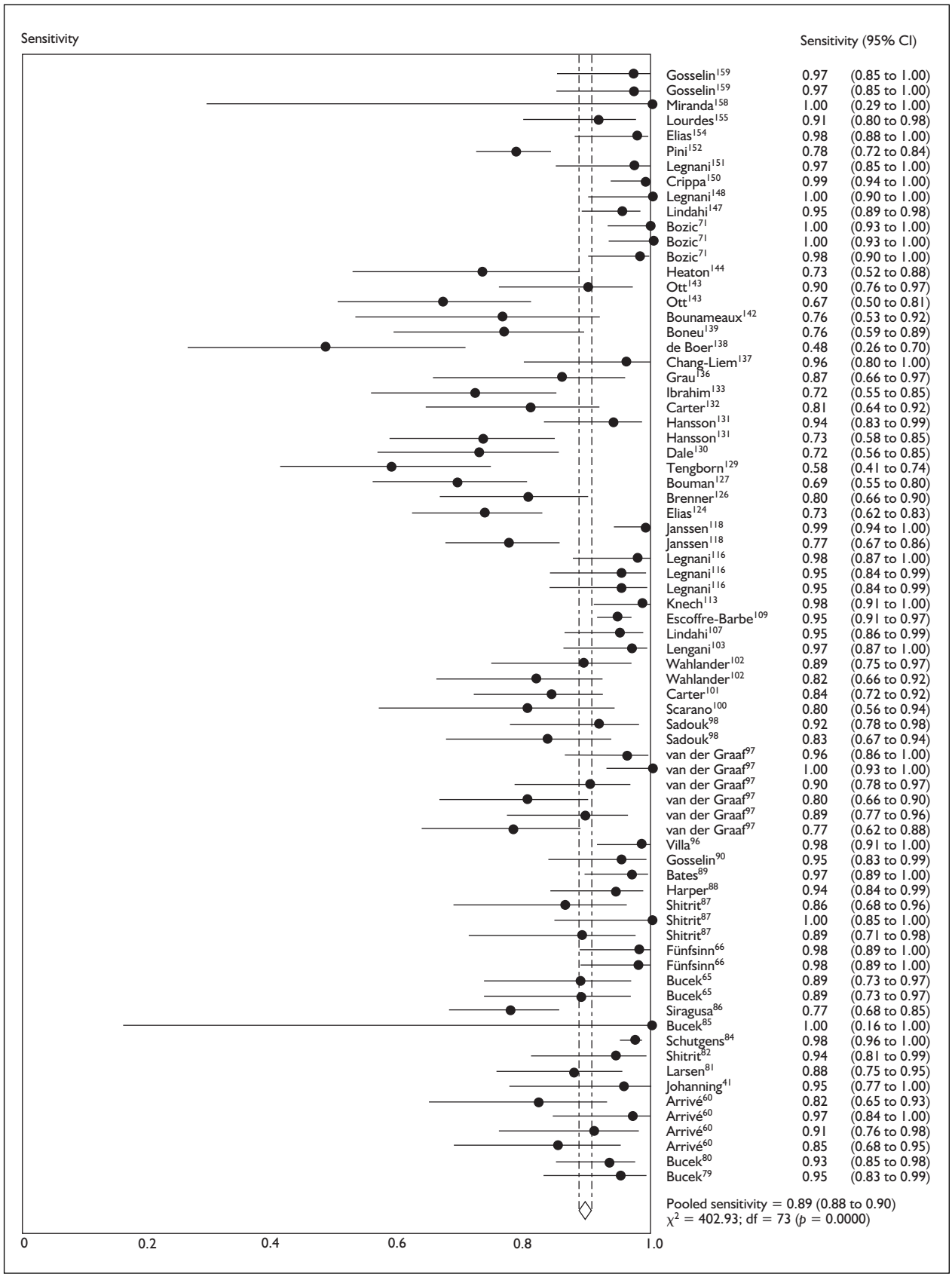

FIGURE 63 *D-dimer: sensitivity of latex assay for all DVT in symptomatic patients*

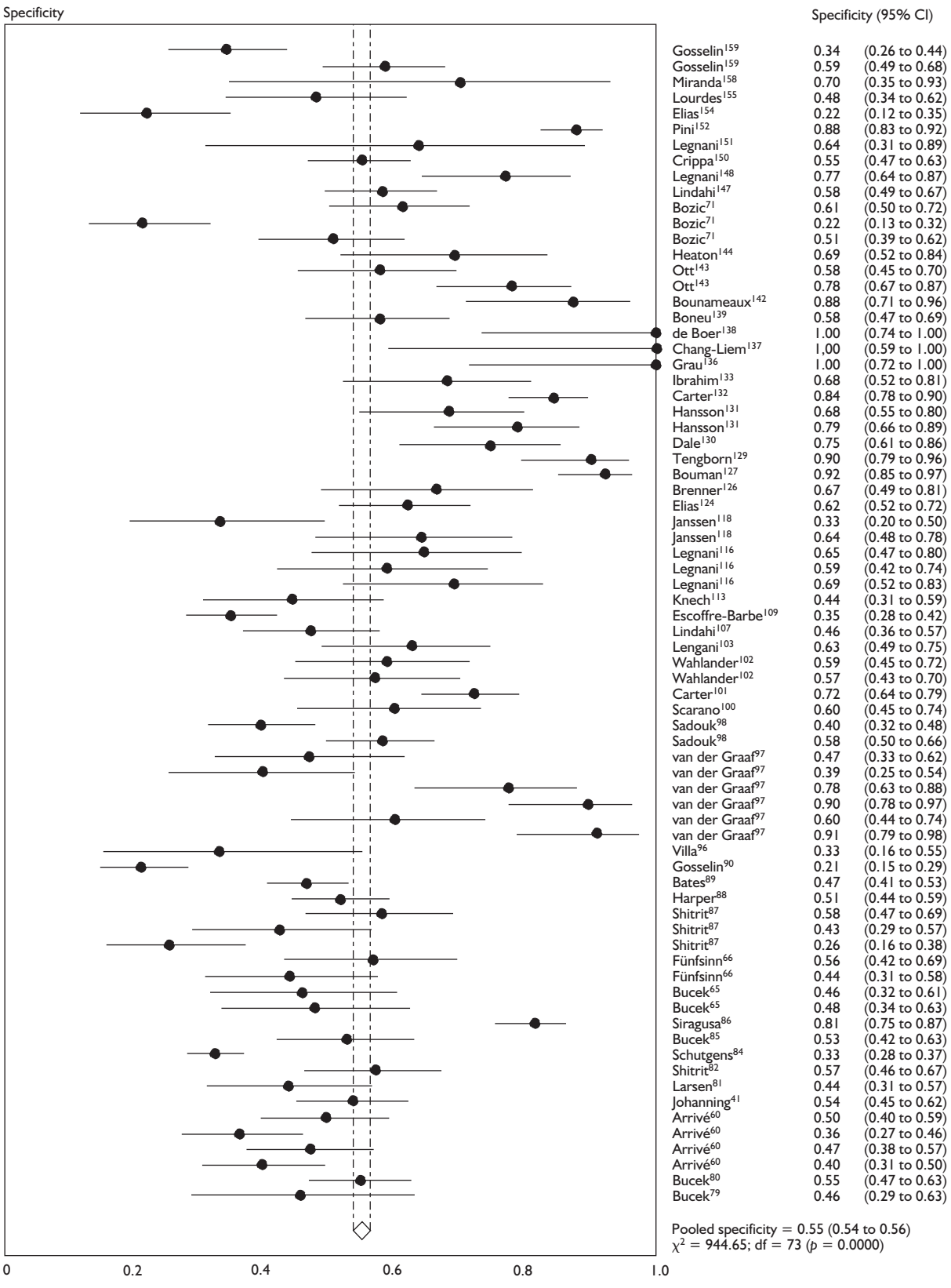

FIGURE 64 *D-dimer: specificity of latex assay for all DVT in symptomatic patients*

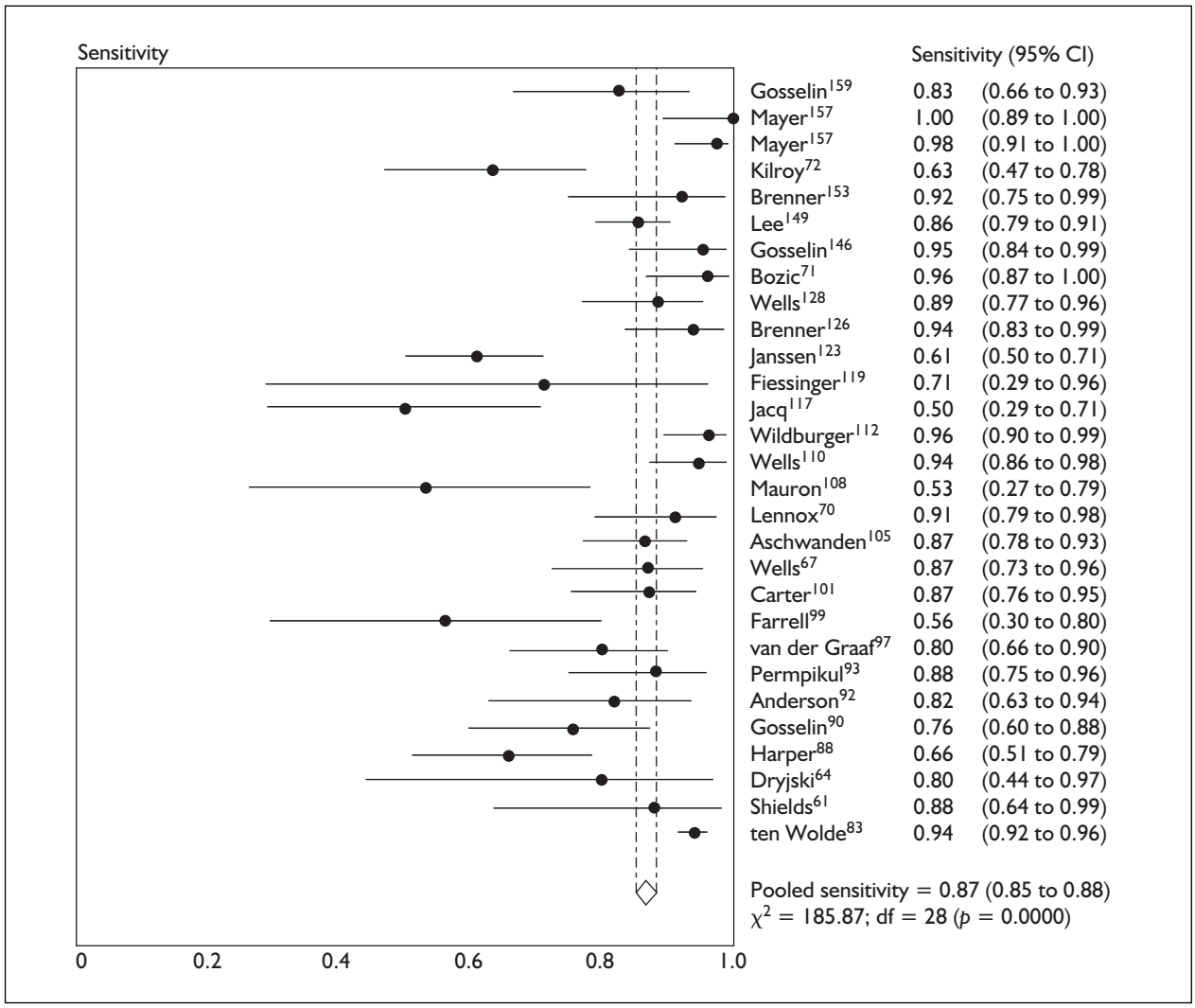

FIGURE 65 *D-dimer: sensitivity of whole-blood agglutination assay for all DVT in symptomatic patients*

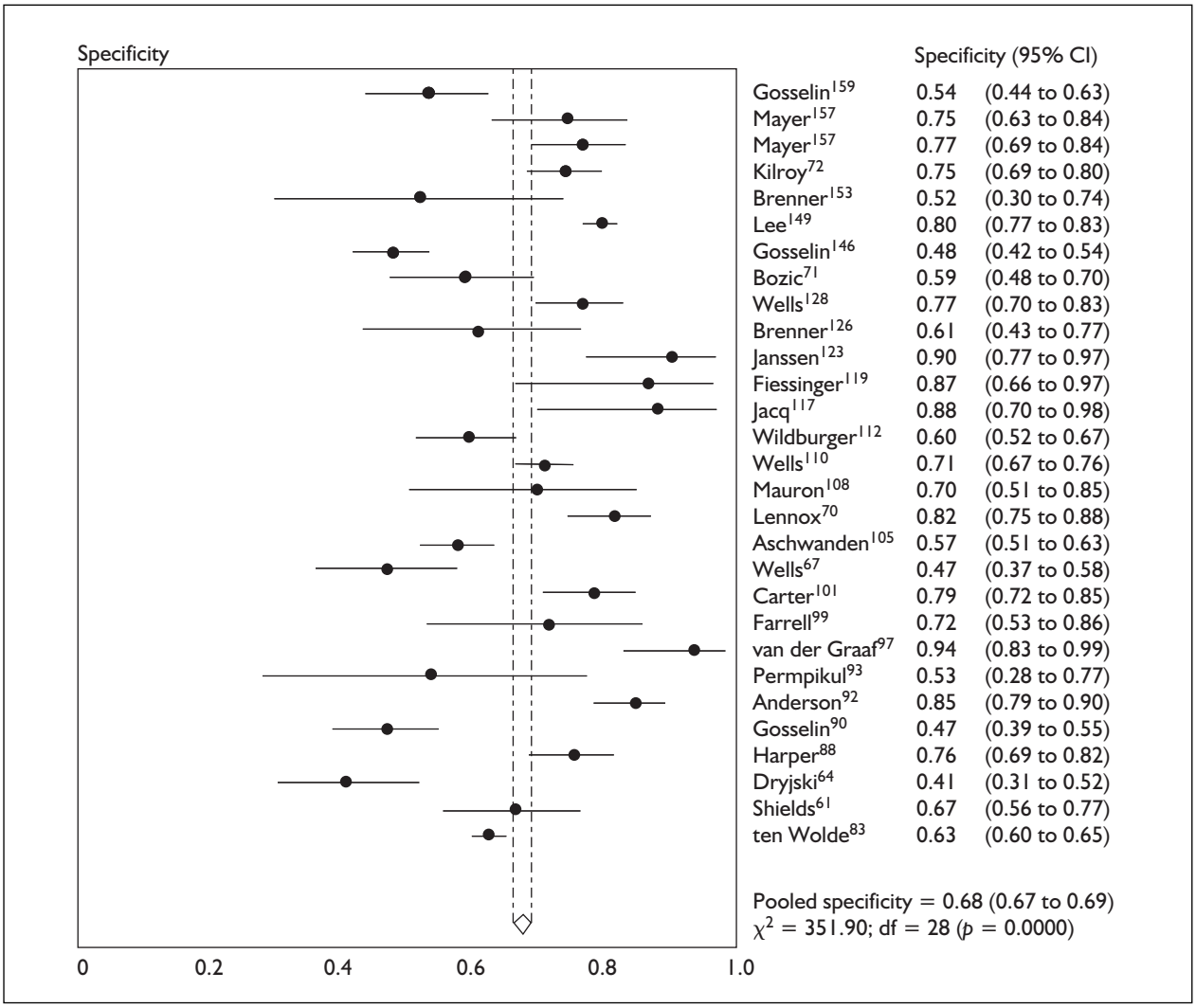

FIGURE 66 *D-dimer: specificity of whole-blood agglutination assay for all DVT in symptomatic patients*

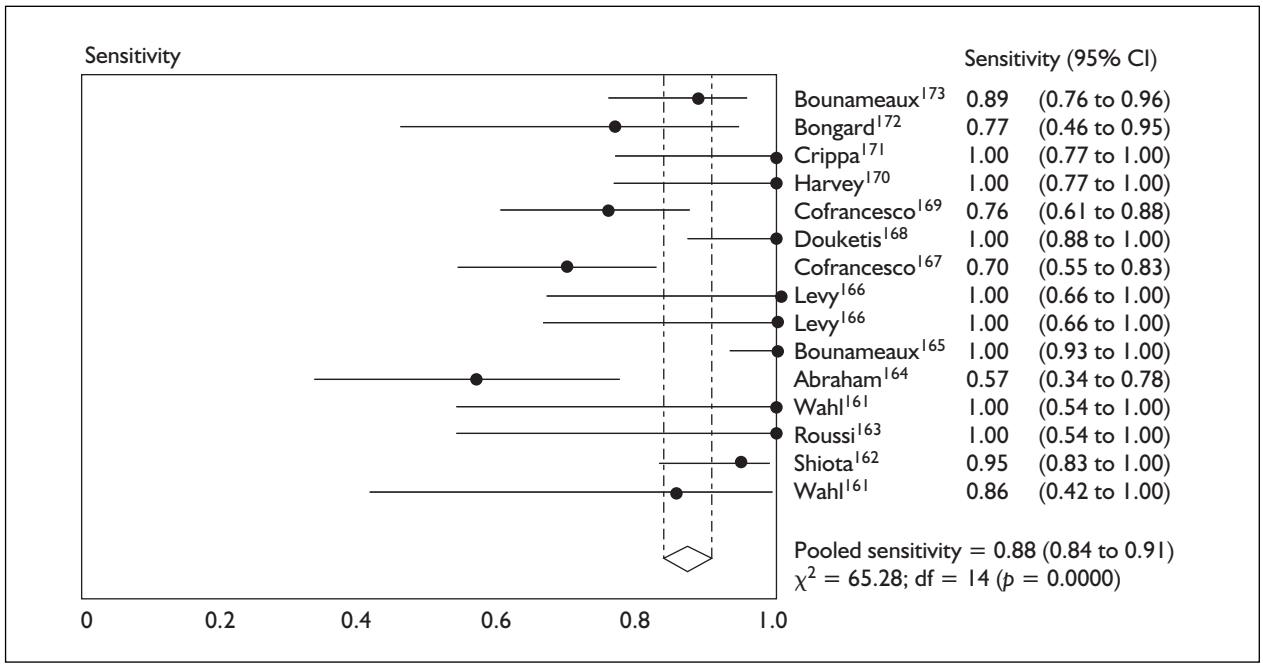

FIGURE 67 *D-dimer: sensitivity for all DVT in asymptomatic patients*

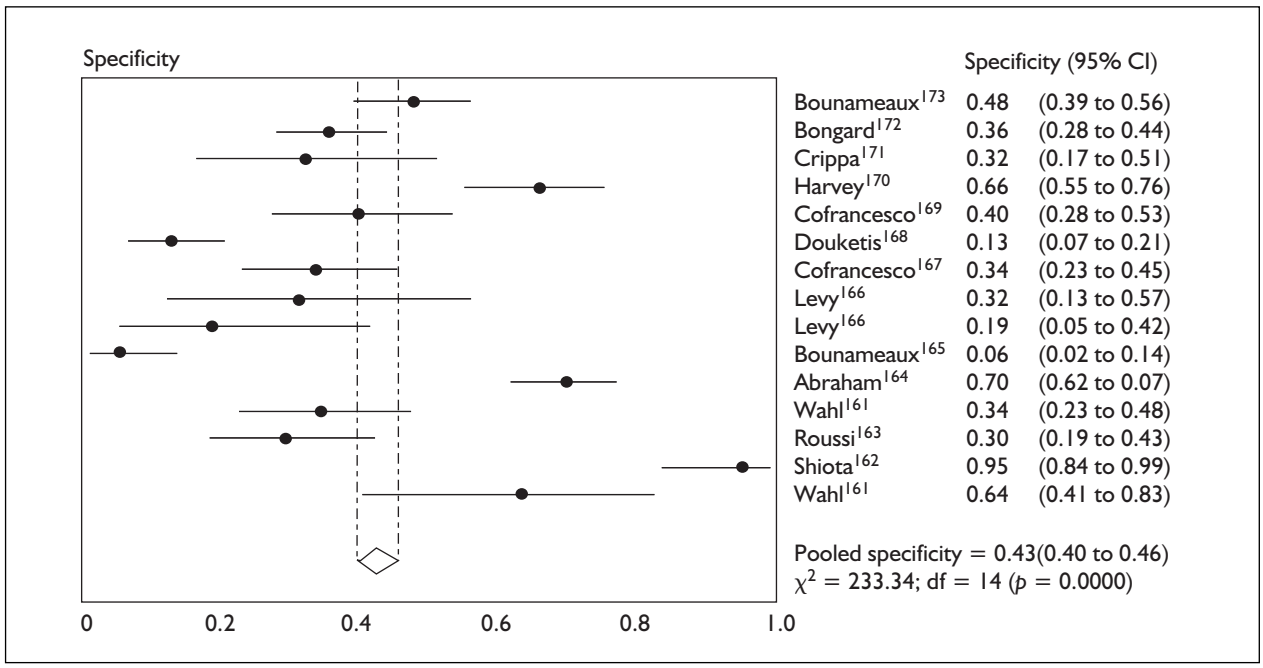

FIGURE 68 *D-dimer: specificity for all DVT in asymptomatic patients*

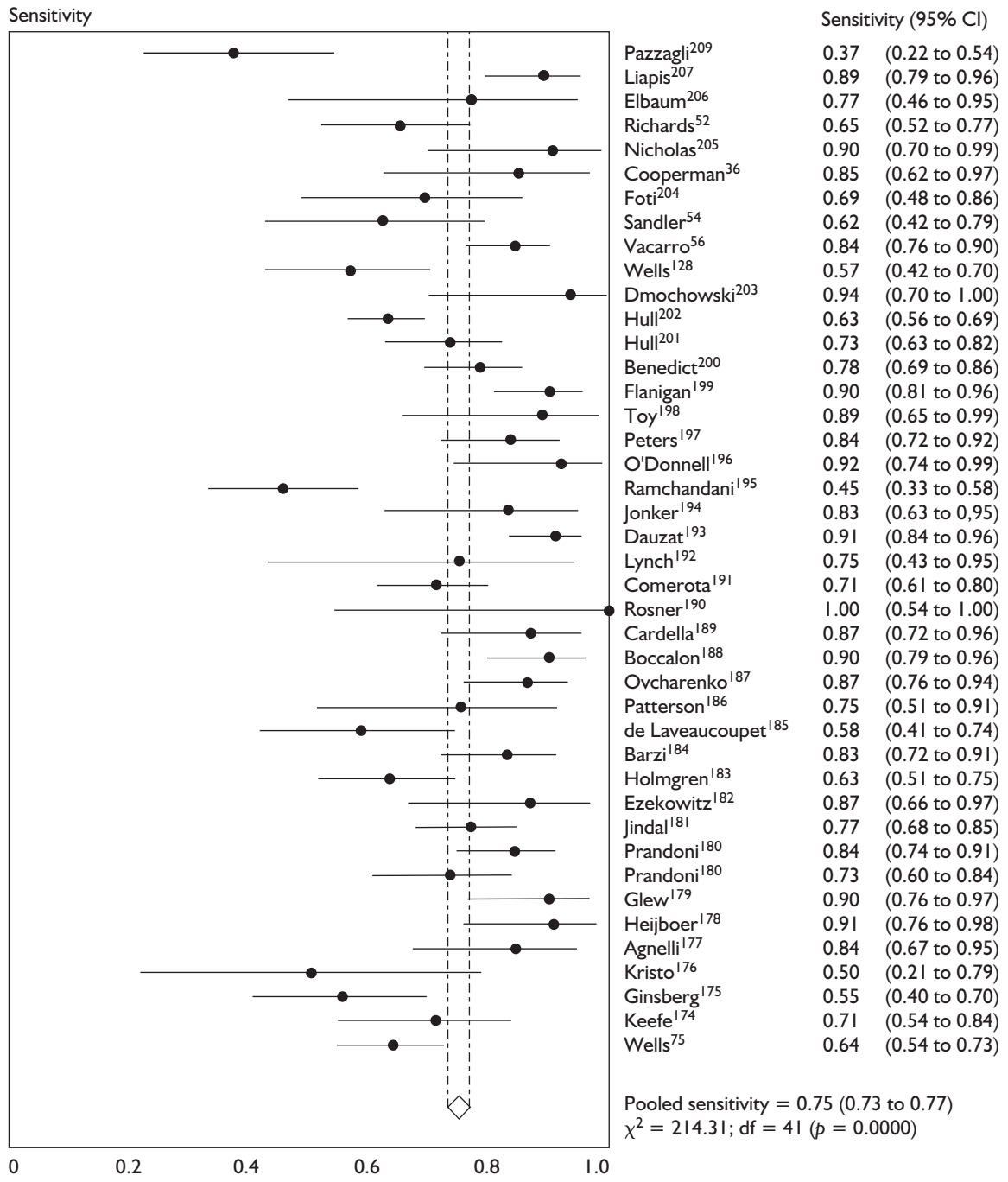

FIGURE 69 *Impedance plethysmography: sensitivity for all DVT in symptomatic patients*

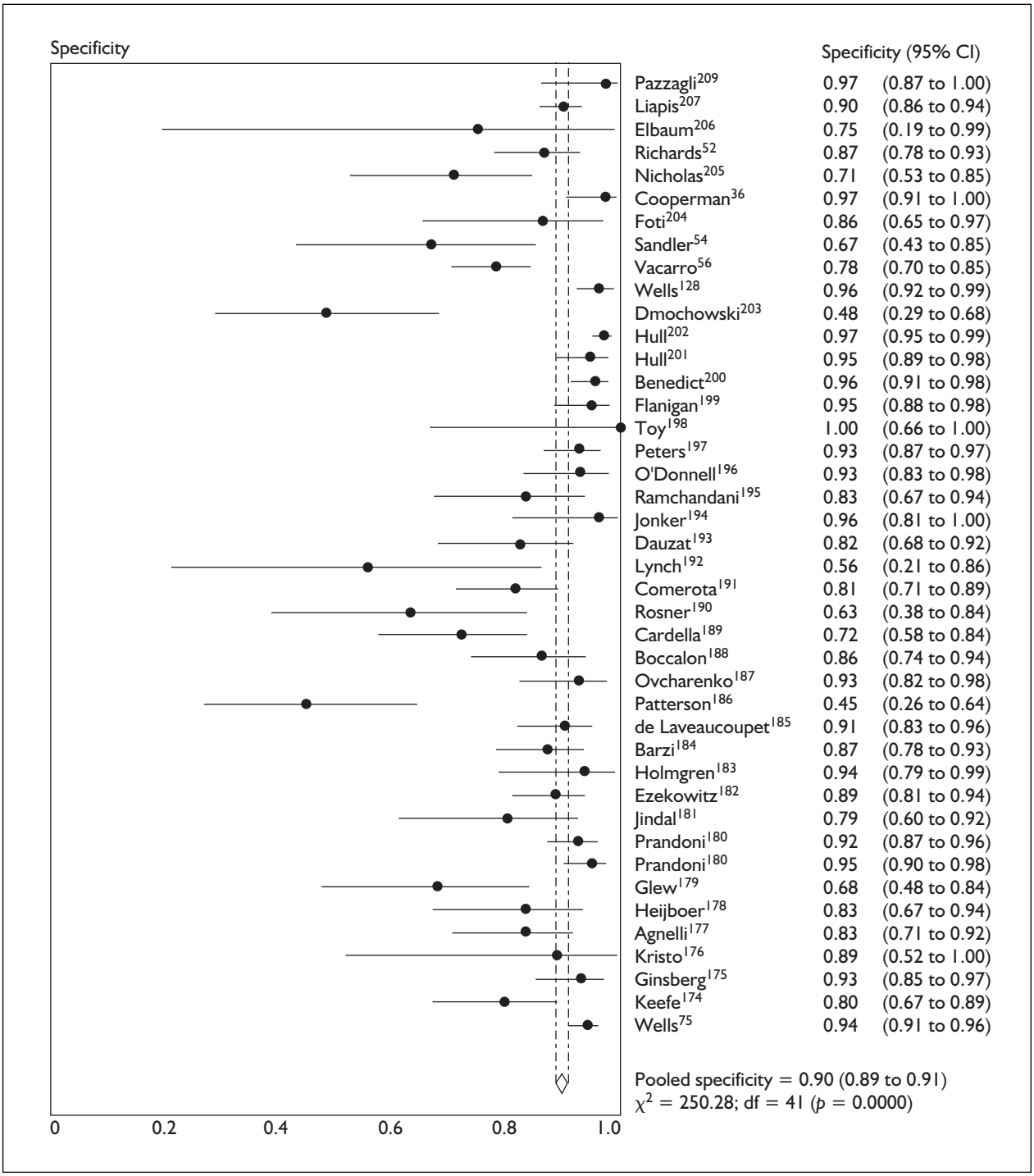

FIGURE 70 *Impedance plethysmography: specificity in symptomatic patients*

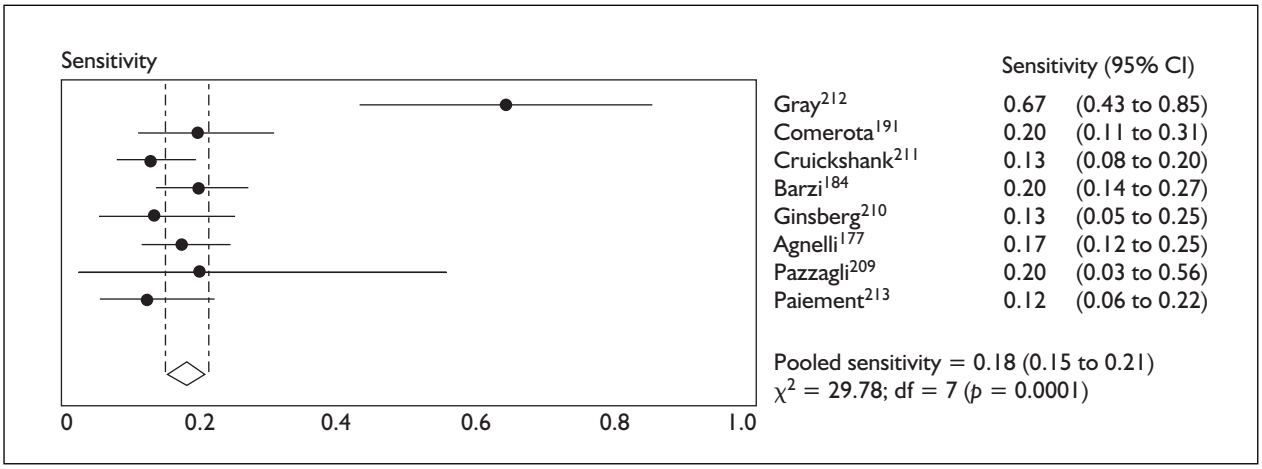

FIGURE 71 *Impedance plethysmography: sensitivity for all DVT in asymptomatic patients*

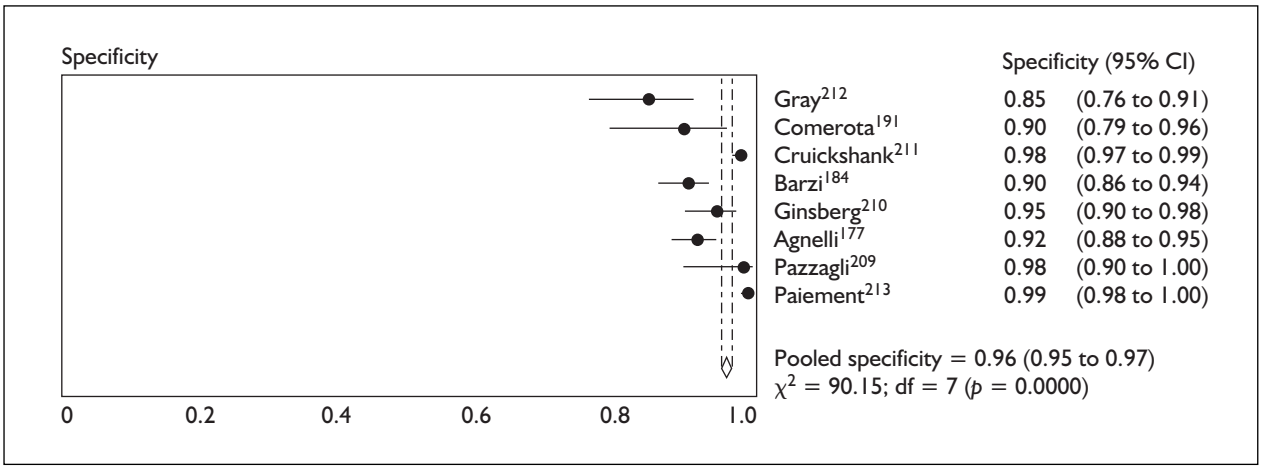

FIGURE 72 *Impedance plethysmography: specificity in asymptomatic patients*

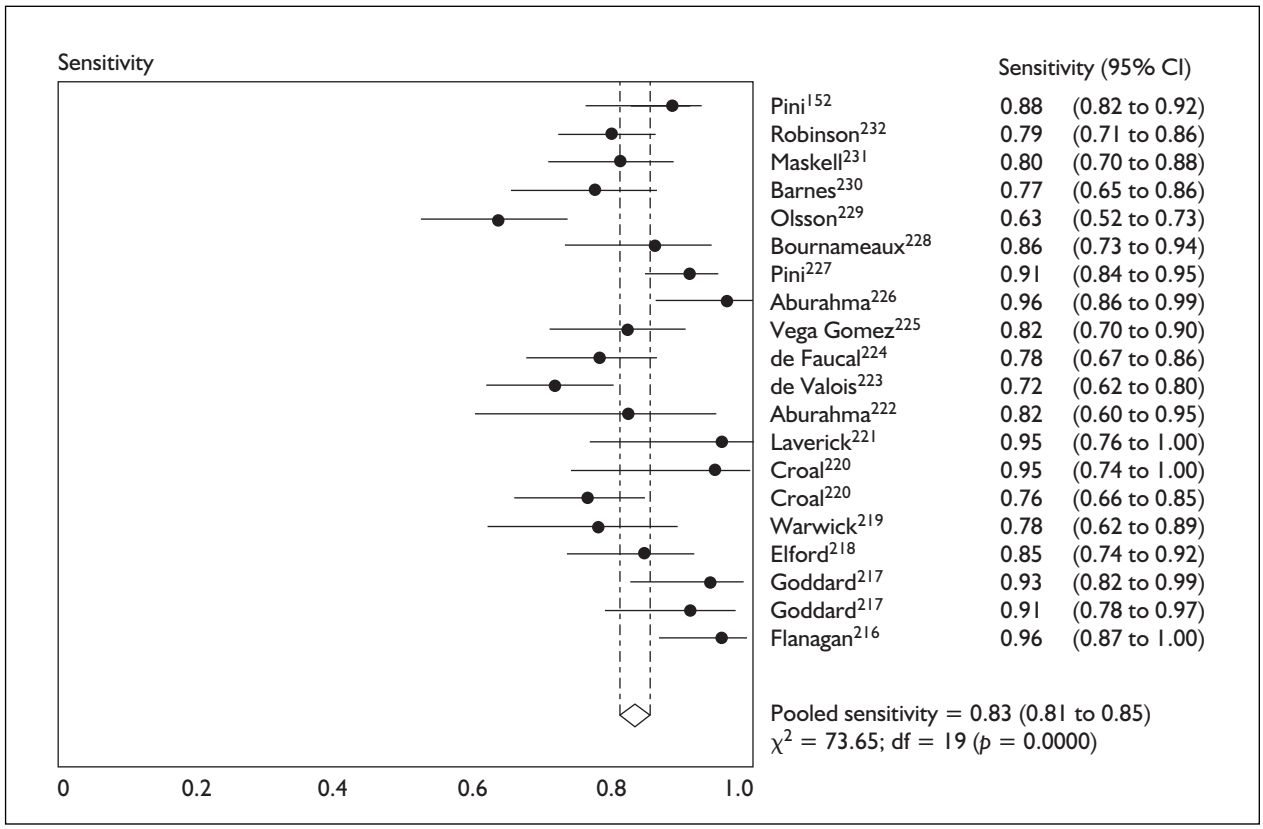

FIGURE 73 *Strain-gauge plethysmography: sensitivity for all DVT in symptomatic patients*

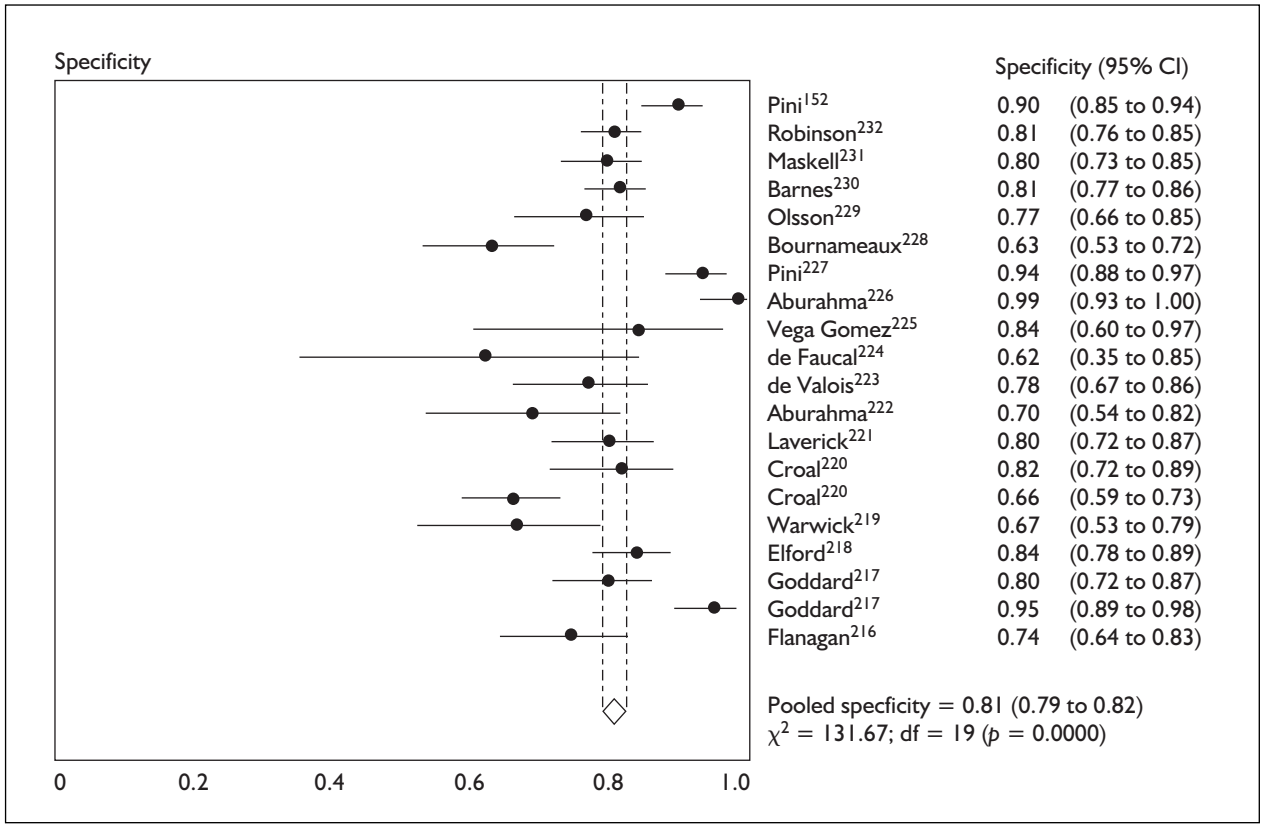

FIGURE 74 *Strain-gauge plethysmography: specificity in symptomatic patients*

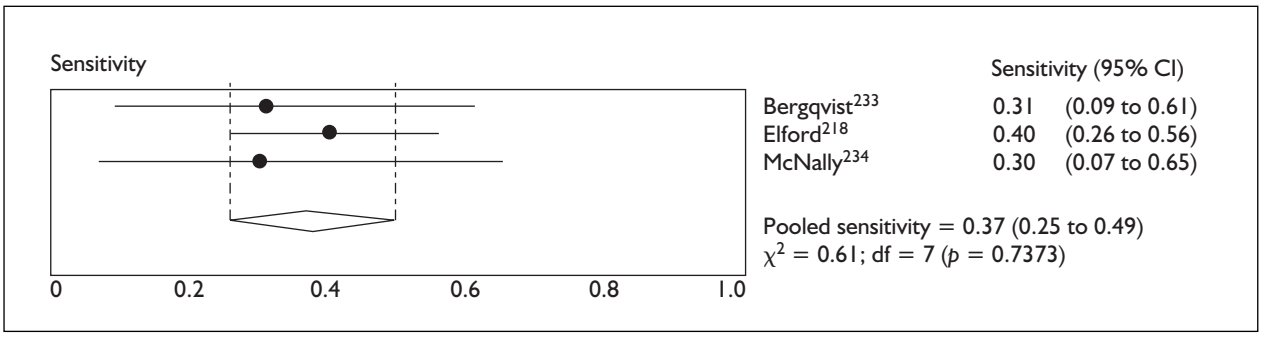

FIGURE 75 *Strain-gauge plethysmography: sensitivity for all DVT in asymptomatic patients*

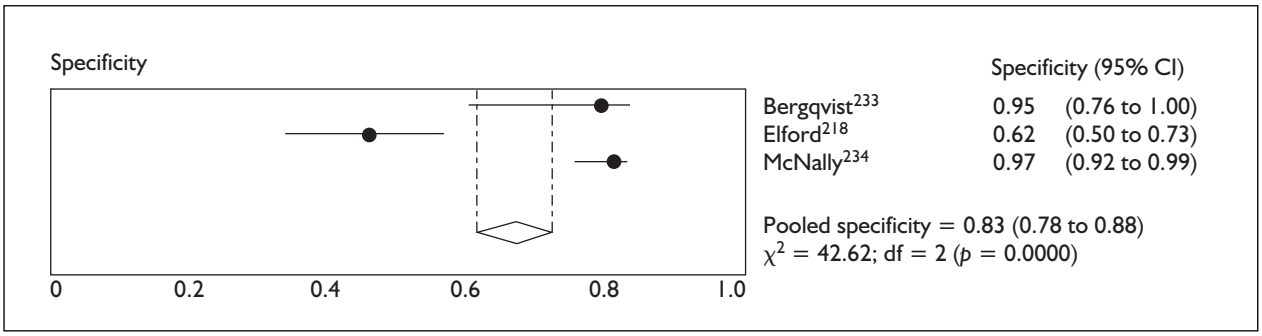

FIGURE 76 *Strain-gauge plethysmography: specificity in asymptomatic patients*

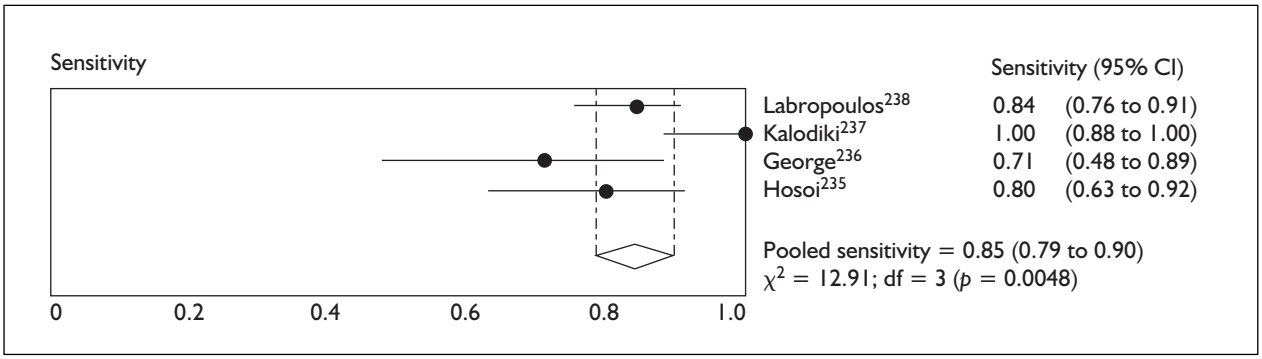

FIGURE 77 *Air plethysmography: sensitivity for all DVT in symptomatic patients*

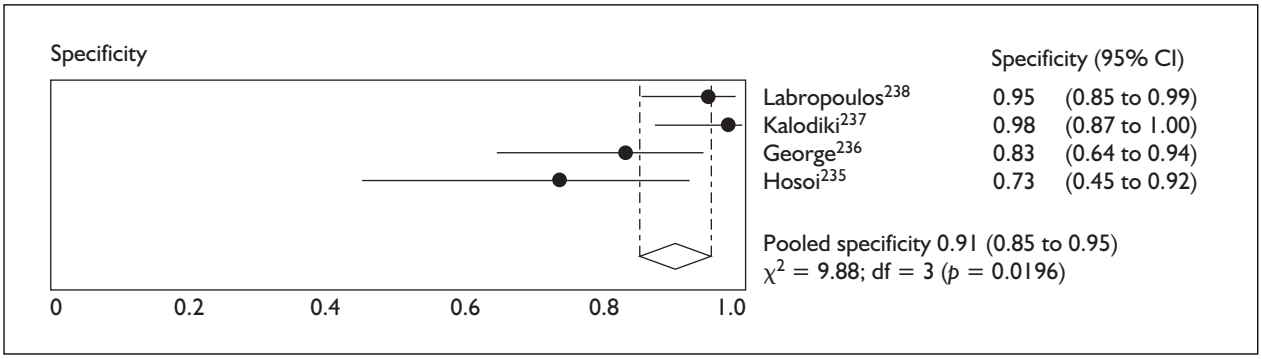

FIGURE 78 *Air plethysmography: specificity in symptomatic patients*

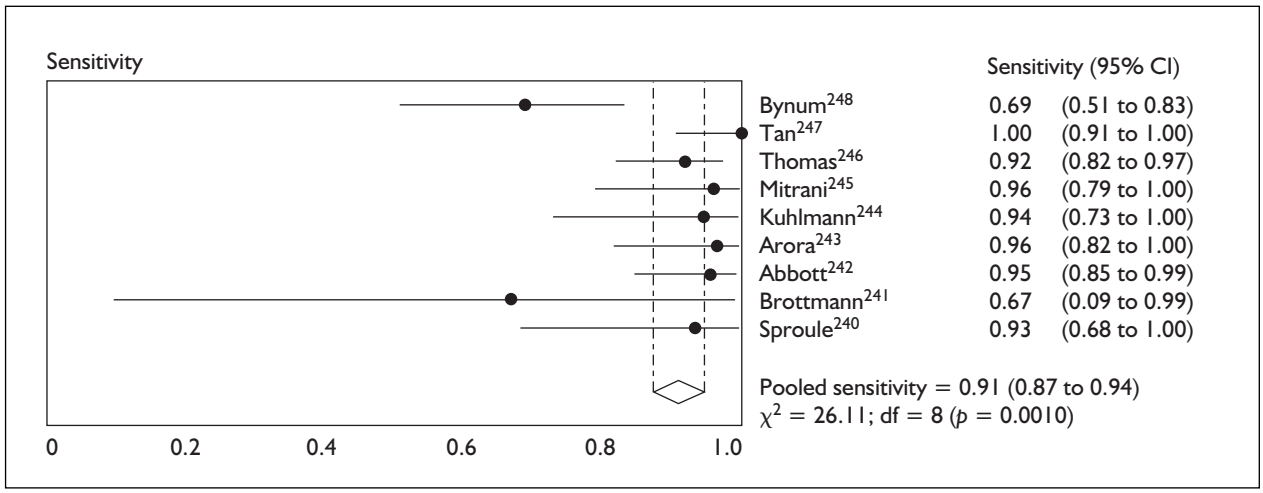

FIGURE 79 *Light-reflex rheography: sensitivity for all DVT in symptomatic patients*

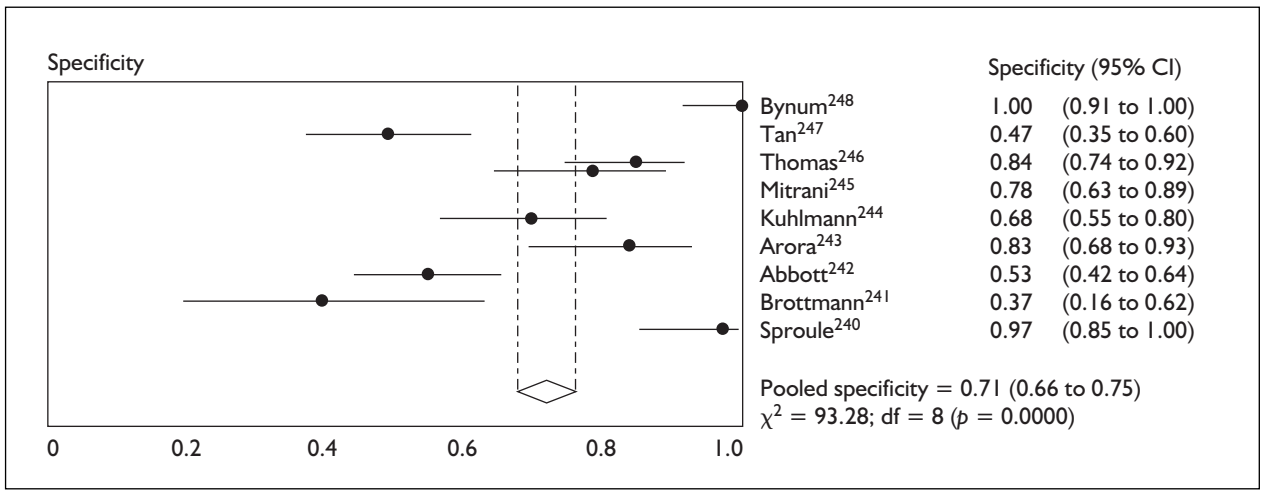

FIGURE 80 *Light-reflex rheography: specificity in symptomatic patients*

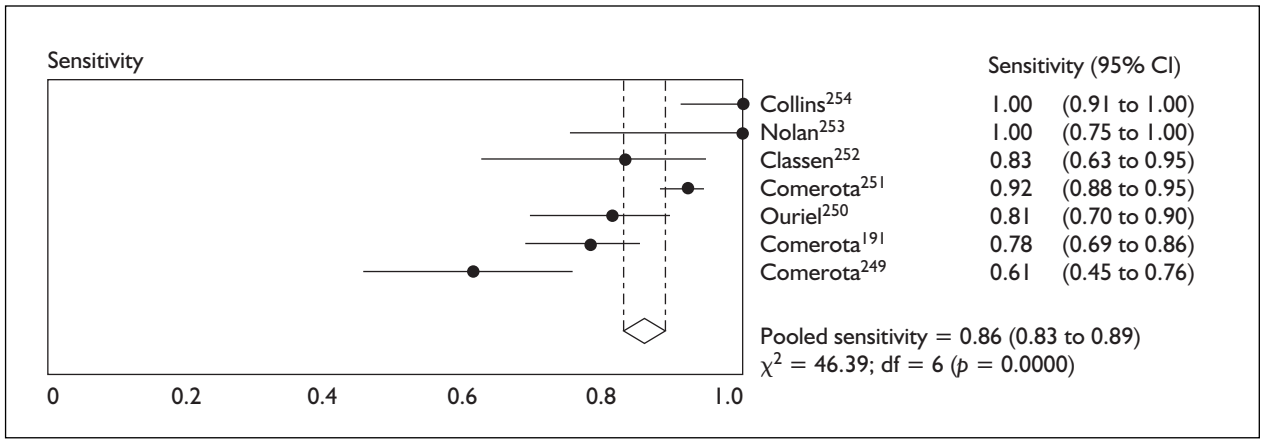

FIGURE 81 *Phleborheography: sensitivity for all DVT in symptomatic patients*

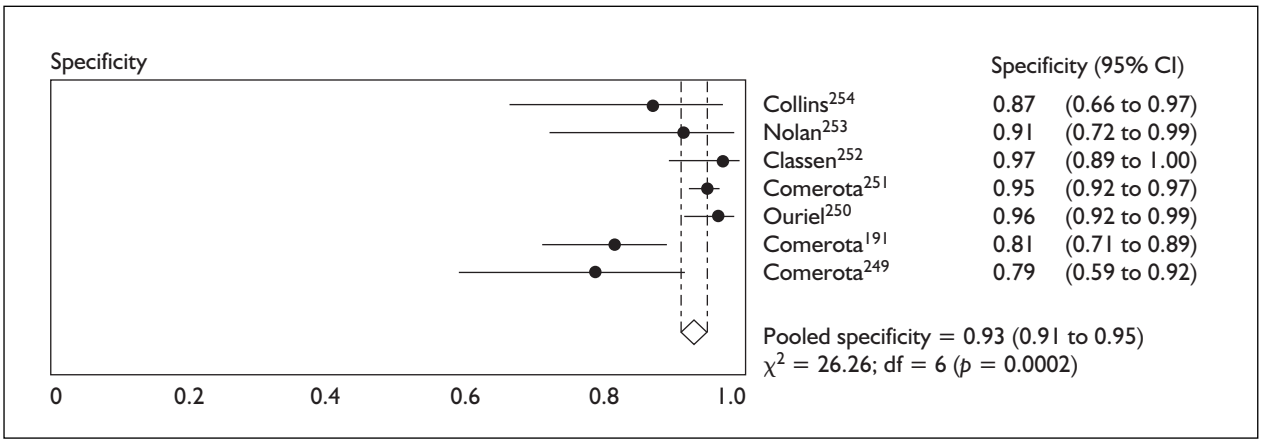

FIGURE 82 *Phleborheography: specificity in symptomatic patients*

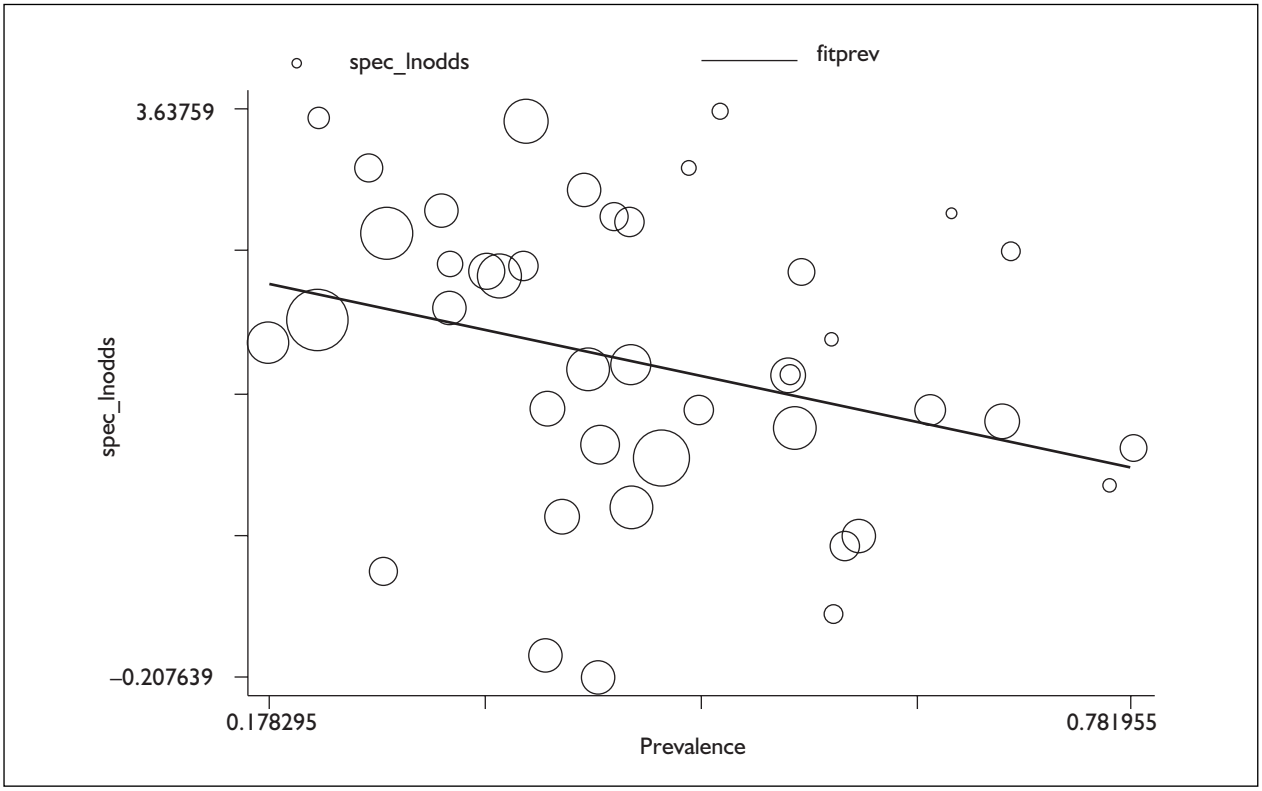

FIGURE 83 *Association between specificity of impedance plethysmography and prevalence of DVT in the cohort*

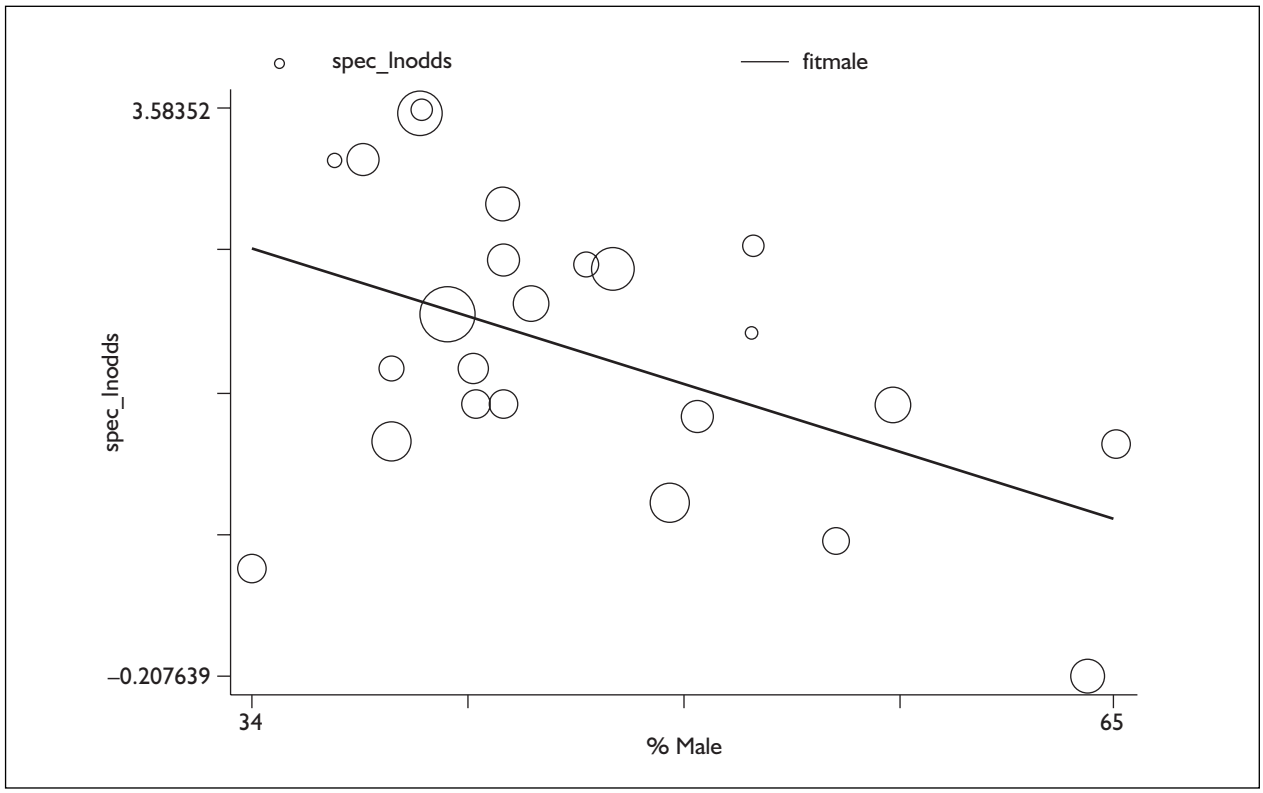

FIGURE 84 *Association between specificity of impedance plethysmography and proportion of males in the cohort*

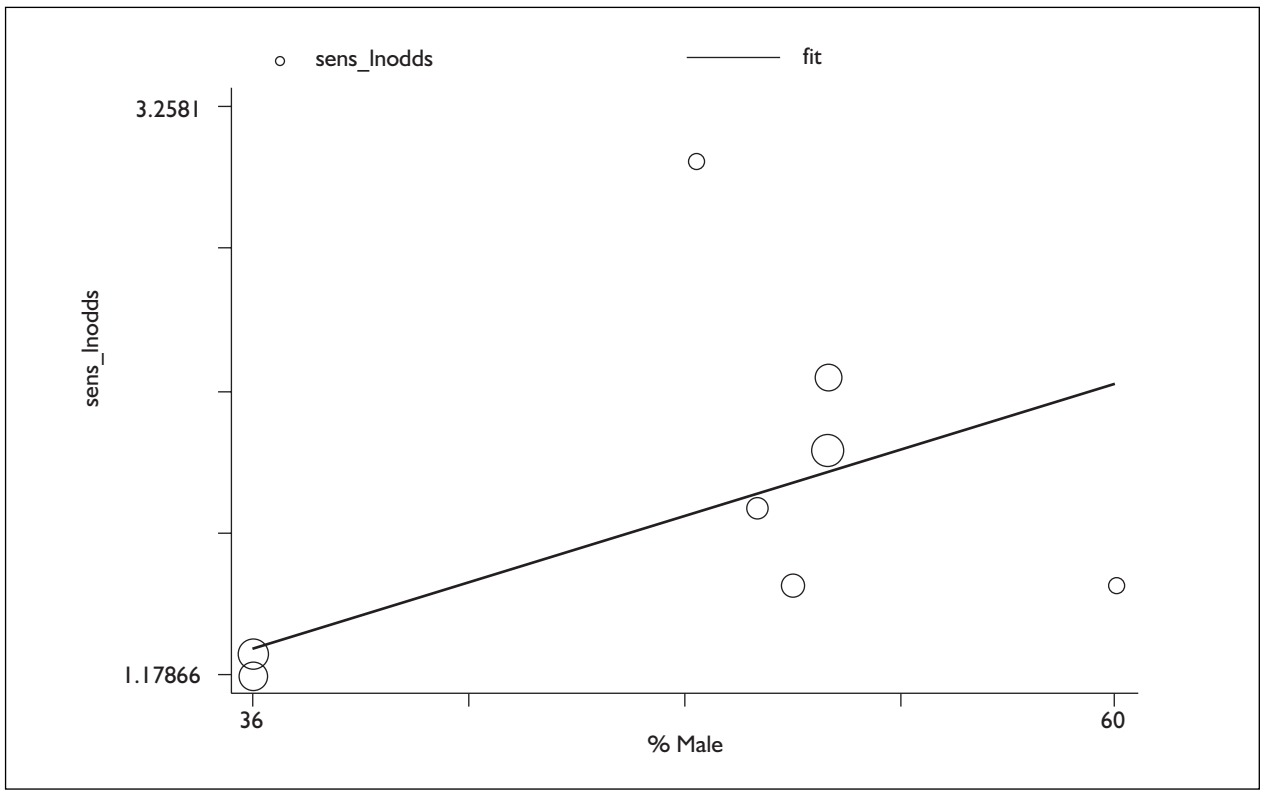

FIGURE 85 *Association between sensitivity of strain-gauge plethysmography and proportion of males in the cohort*

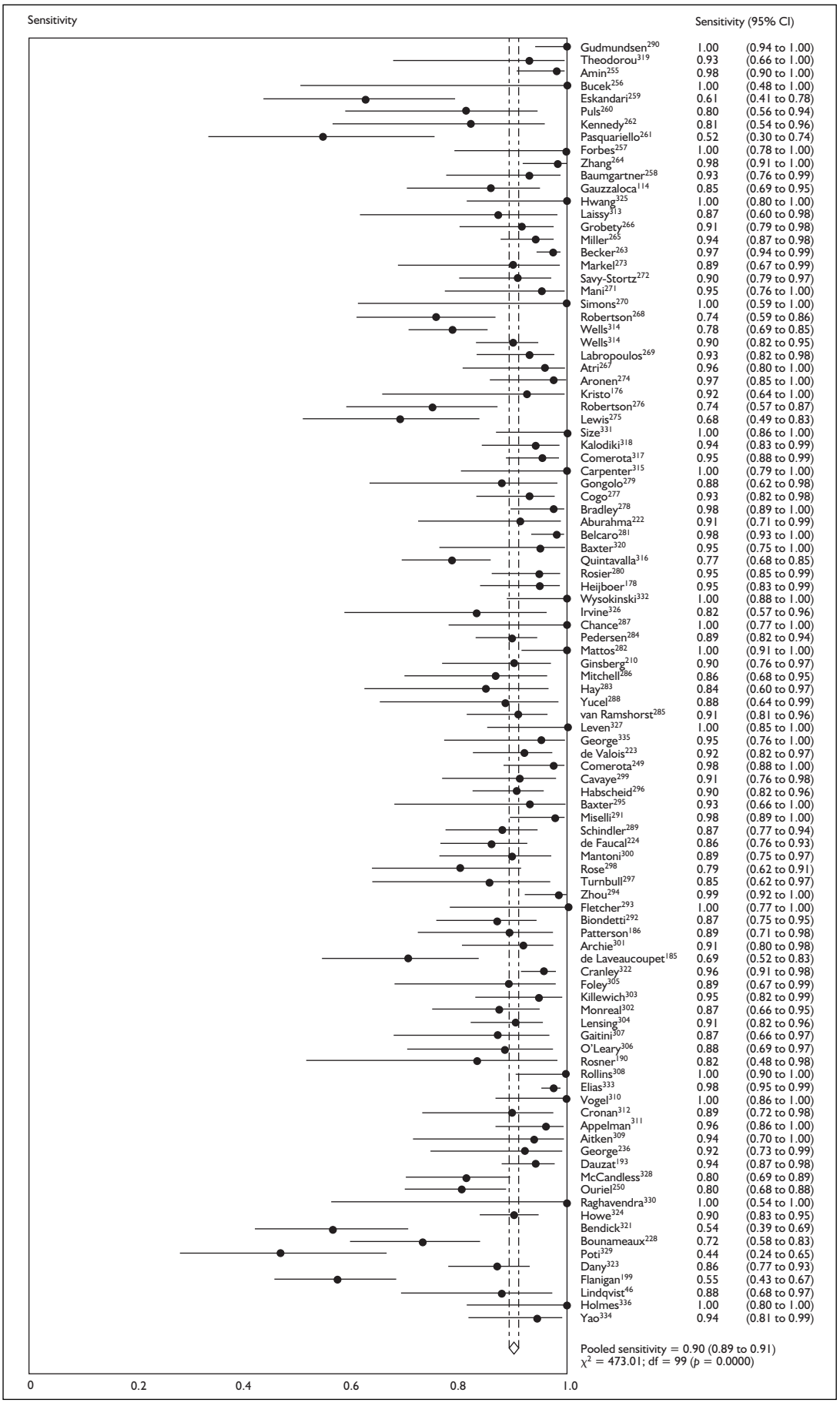

FIGURE 86 *Ultrasound: sensitivity for all DVT in clinically suspected DVT*

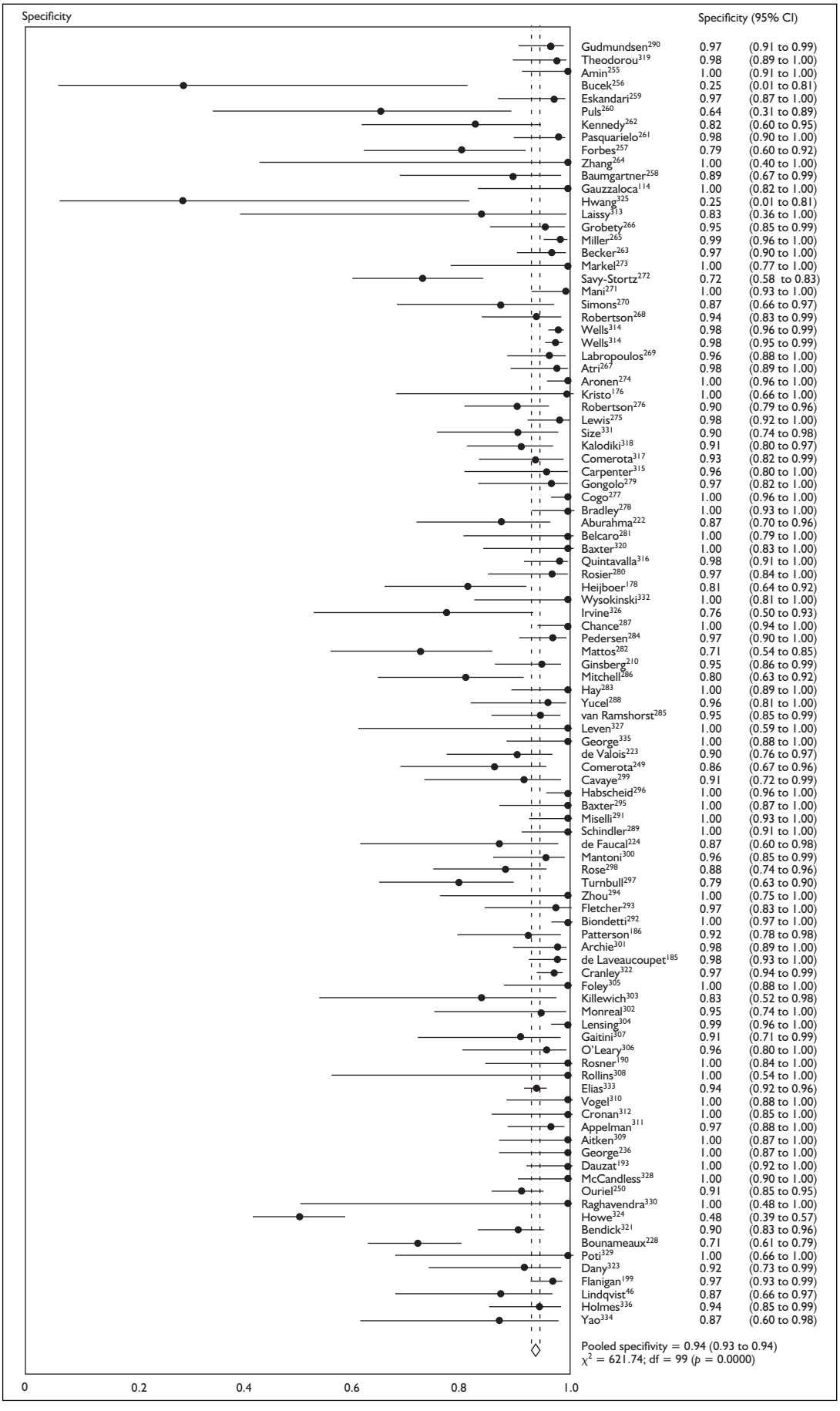

FIGURE 87 *Ultrasound: specificity in clinically suspected DVT*

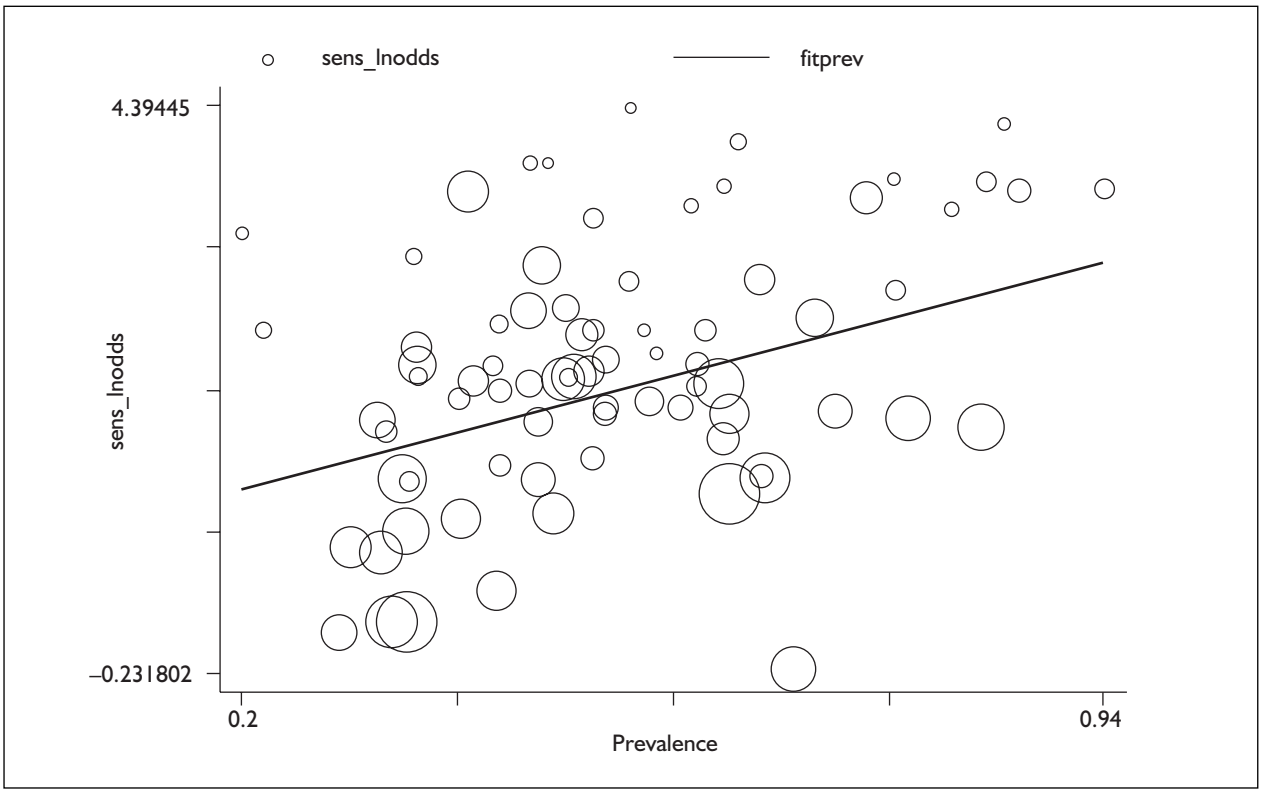

FIGURE 88 *Association between sensitivity of ultrasound in symptomatic patients and the prevalence of DVT in the cohort*

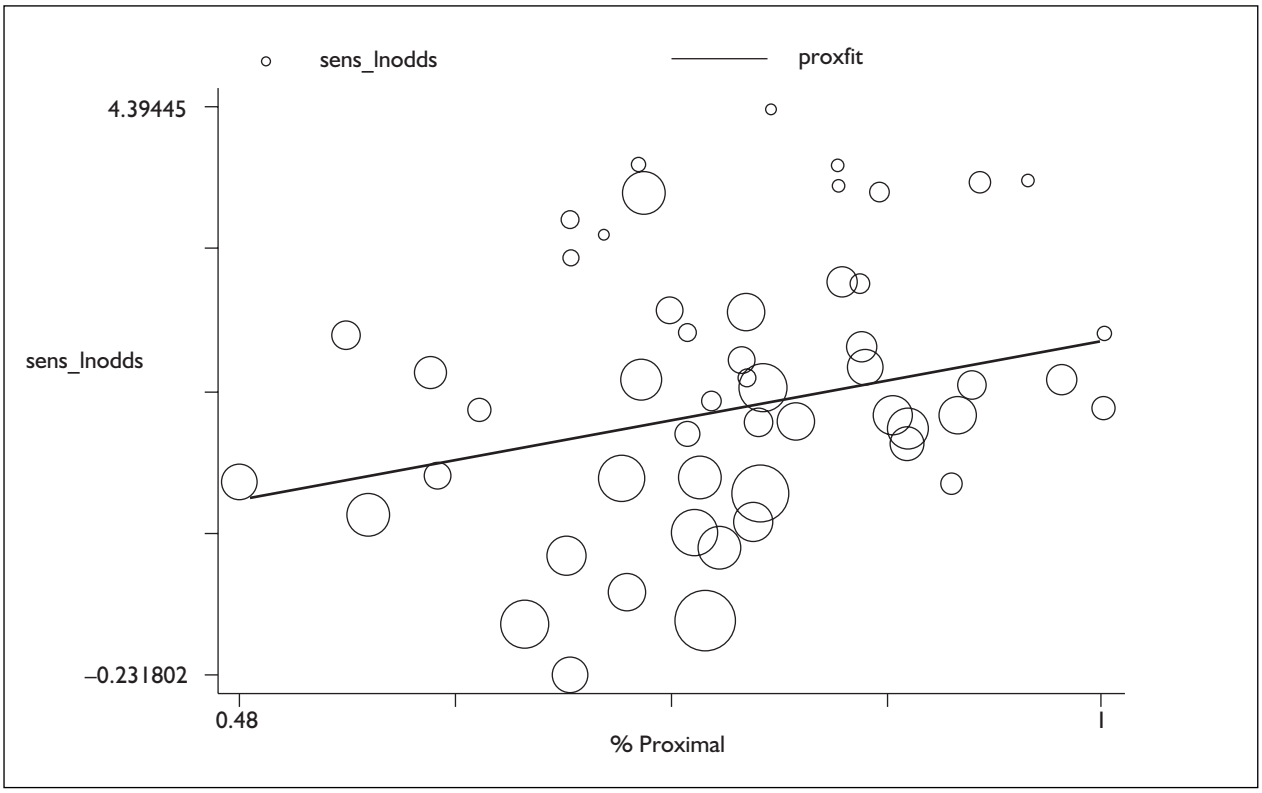

FIGURE 89 *Association between sensitivity of ultrasound in symptomatic patients and the proportion of proximal DVT in the cohort*

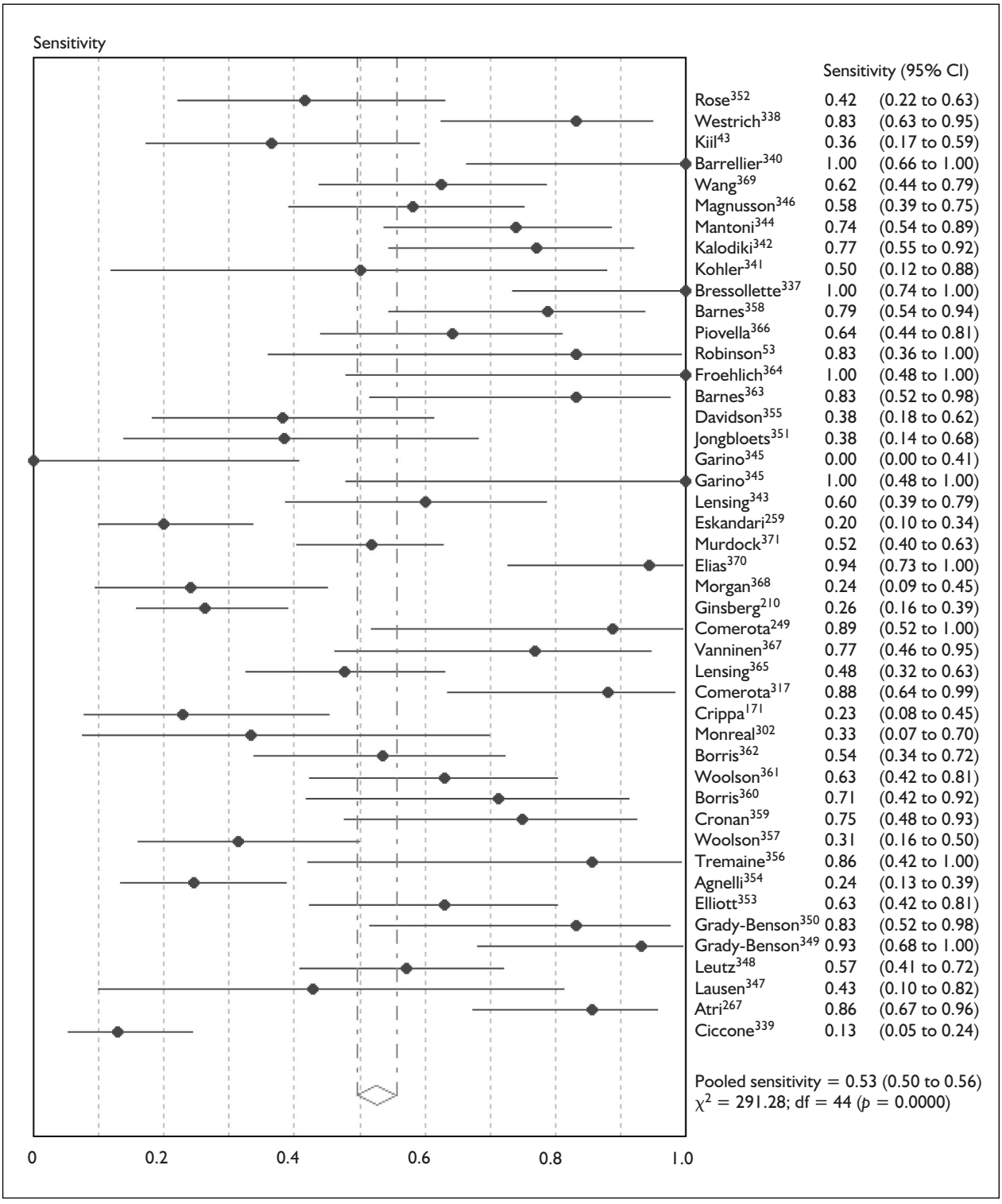

FIGURE 90 *Ultrasound: sensitivity for all DVT in asymptomatic patients*

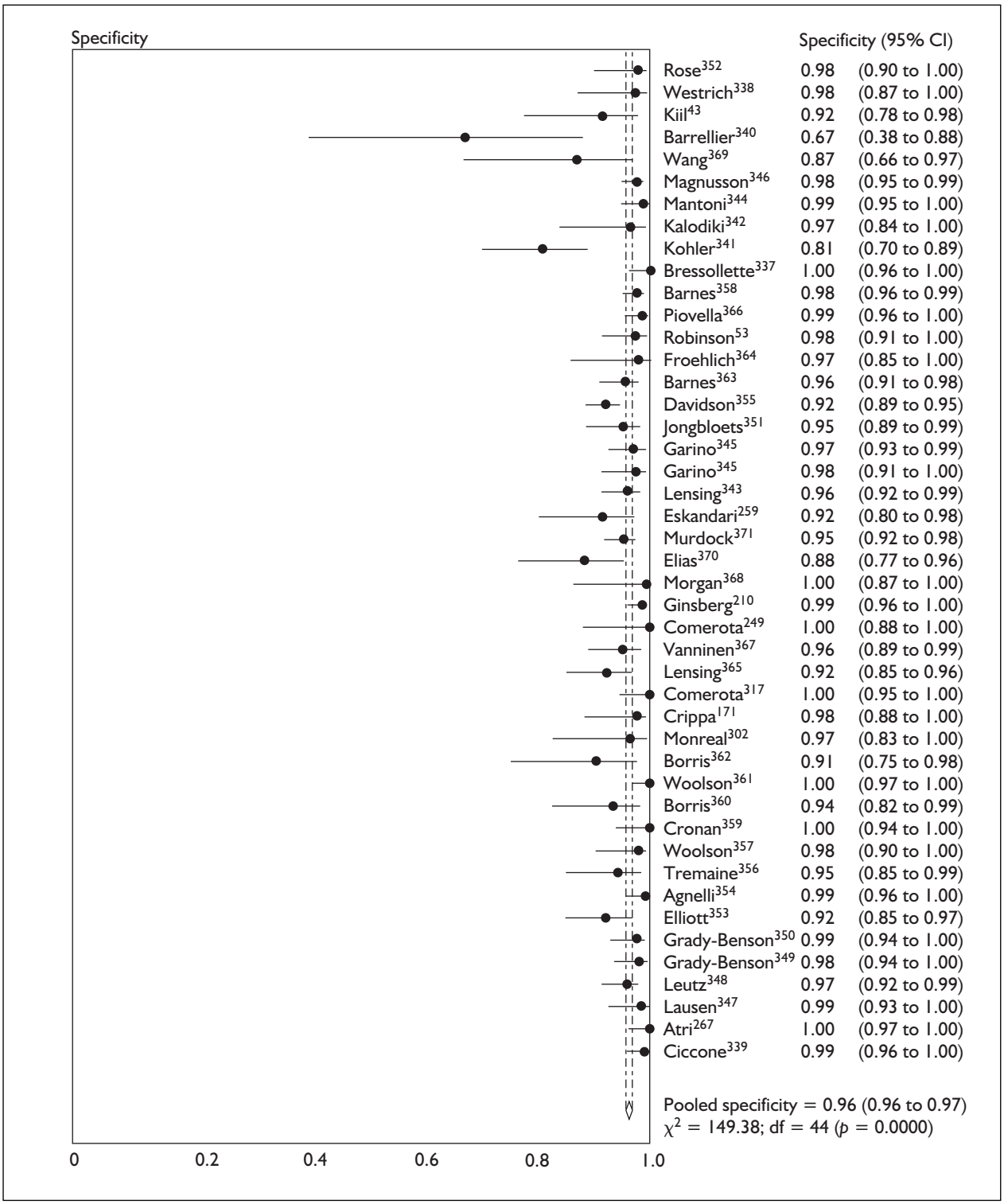

FIGURE 91 *Ultrasound: specificity for all DVT in asymptomatic patients*

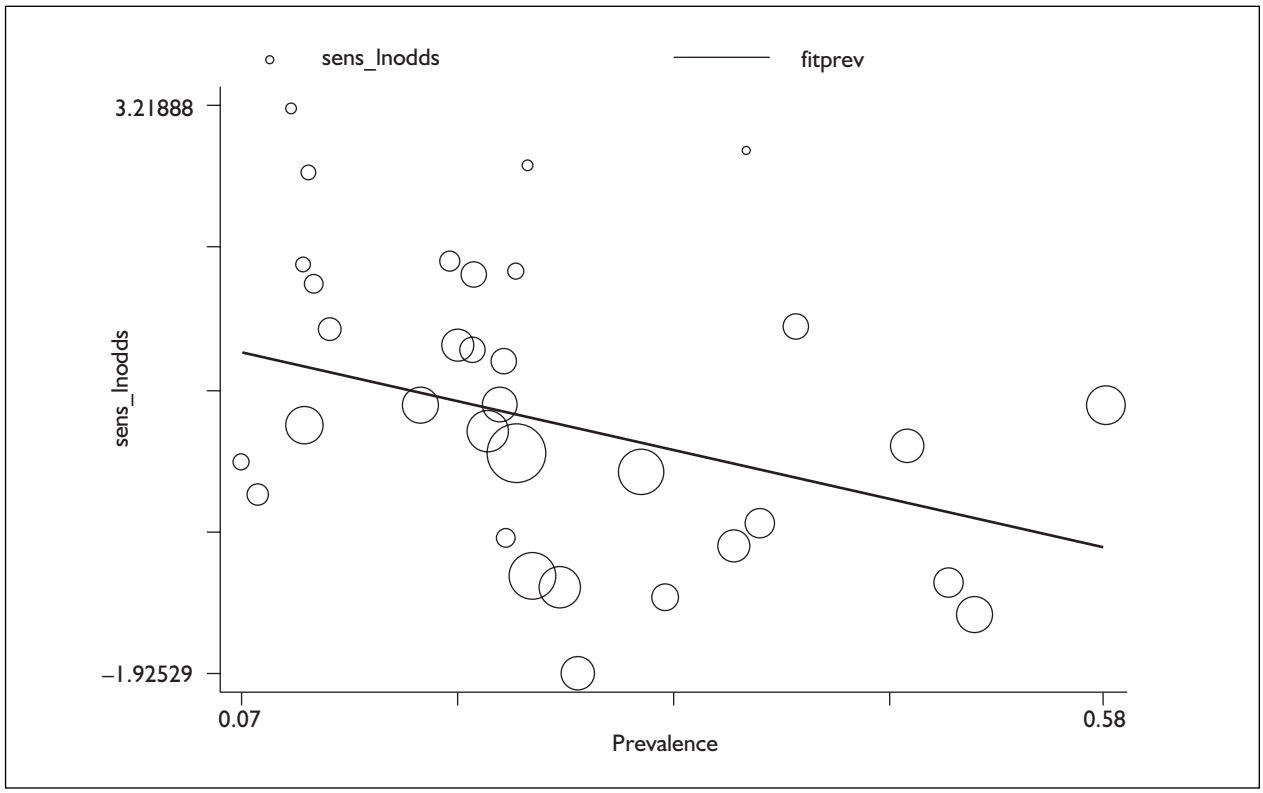

FIGURE 92 *Association between sensitivity of ultrasound in asymptomatic patients and prevalence of DVT*

Appendix 4

Algorithms used in the model

TABLE40

Algorithm number	Algorithm	Source
0	No testing or treatment	
1	Venography for all patients	
2	Above-knee US, repeat if negative	
3	Full-leg US, repeat if distal found	
4	Above-knee ultrasound, no repeat	
5	Wells and above-knee US. If low, discharge if US negative, venogram if positive. If moderate, repeat US if negative, treat if positive. If high, venogram if US negative, treat if US positive	Anderson,[31] Wells,[67] Wells[8]
6	SimpliRED DD and above-knee US. If US positive then treat. If both are negative then discharge. If DD positive and US negative, repeat US	Kraaijenhagen,[62] Bernatdi[375]
7	Wells. High or intermediate: above-knee US, treat if positive, venogram if negative. Low: above-knee US, treat if positive, discharge if negative	Walsh[78]
8	Wells. High or intermediate: full-leg US, treat if positive, venogram if negative. Low: full-leg US, treat if positive, discharge if negative	Walsh[78]
9	Latex DD: if positive above-knee US and repeat, if negative do Wells score. If high US and repeat. If intermediate or low discharge	Bates[410]
10	Latex DD: if positive above-knee US and repeat, if negative do Wells score. If high US, if intermediate or low discharge	Schutgens[404]
11	Wells. High: above-knee US, treat if positive, SimpliRED DD if negative. If DD positive venogram, if negative repeat US. Intermediate: US, treat if positive, DD if negative. If DD positive repeat US, if negative discharge. Low: DD, US if positive, discharge if negative	Anderson[409]
12	Wells and SimpliRED DD. If Wells high or intermediate, or DD positive, do full-leg US. If Wells low and DD negative then discharge	Janes[406]
13	ELISA DD. If negative discharge, if positive do above-knee US. Treat if US positive, do Wells if negative. High Wells: venogram. Intermediate or low Wells: discharge	Perrier[407]
14	Wells. If high or intermediate: above-knee US. If positive treat, if negative SimpliRED DD. Repeat US if DD positive, discharge if DD negative. Low: US, discharge if negative, treat if positive	Tick[77]
15	Wells. High or intermediate: above-knee US. If positive treat, if negative SimpliRED DD. Repeat US if DD positive discharge if DD negative. Low: DD, discharge if negative, US if positive	Wells, intervention group (high and moderate combined)[9]
16	Wells. High: above-knee US. If positive treat, if negative SimpliRED DD. Repeat US if DD positive, discharge if DD negative. Intermediate or low: DD, discharge if negative, US if positive	Wells, intervention group (moderate and low combined)[9]
17	Wells. High or intermediate: above-knee US. If positive treat, if negative repeat US. Low: US, treat if positive, discharge if negative.	Wells, control group (high and moderate combined)[9]
18	Wells. High: above-knee US. If positive treat, if negative repeat US. Intermediate and low: US, treat if positive, discharge if negative	Wells, control group (moderate and low combined)[9]
19	SimpliRED DD and plethysmography: discharge if both negative, venogram if either is positive	Ginsberg[408]

continued

TABLE40 *(cont'd)*

Algorithm number	Algorithm	Source
20	Wells and SimpliRED DD. Discharge if low Wells and negative DD. If high or intermediate Wells, or DD positive, do above-knee US and plethysmography. Treat if both positive, discharge if both negative, venogram if discordant	Kearon[405]
21	Wells. High or intermediate: above-knee US. Low: discharge	UK survey
22	Wells. High or intermediate: venogram. Low: SimpliRED DD. If DD positive venogram, if negative discharge	UK survey
23	Wells. High: venogram. Intermediate or low: SimpliRED DD. If DD positive venogram, if negative discharge	UK survey
24	Wells. Low: SimpliRED DD, discharge if negative, above-knee US if positive. Treat if US positive, venogram if US negative. Intermediate or high: US, treat if positive, venogram if negative	UK survey
25	SimpliRED DD: discharge if negative, above-knee US if positive. Treat if US positive, repeat US if initial US is negative	UK survey
26	Wells. Low or intermediate: SimpliRED DD and plethysmography. Discharge if both negative, full-leg US if either positive. High: plethysmography, treat if positive, full-leg US if negative	UK survey
27	Wells and SimpliRED DD. Low: discharge if DD negative, plethysmography if positive. Full-leg US if plethysmography positive, discharge if negative. Intermediate or high: full-leg US if DD positive, plethysmography if negative. Full-leg US if plethysmography positive, discharge if negative	UK survey
28	Wells. High or intermediate: plethysmography, if negative discharge, if positive, full-leg US. Low: SimpliRED DD, discharge if negative, plethysmography if positive. Discharge if plethysmography negative, full-leg US if positive	UK survey
29	Wells. Low: SimpliRED DD and plethysmography. Discharge if both negative, full-leg US if either positive. Intermediate or high: full-leg US	UK survey
30	SimpliRED DD and plethysmography. Discharge if both negative, full-leg US if either positive	UK survey
31	Wells. Low or intermediate: plethysmography, discharge if negative, full-leg US if positive. High: full-leg US	UK survey

US, ultrasound, DD, D-dimer. In all algorithms repeat ultrasound means that an above-knee ultrasound is performed 1 week later.

Appendix 5

Mean value, probability distribution and source of parameters used in the model

TABLE 41 *Probability of events*

Description of variable	Mean value	Probability distribution	Parameters	Source
Patient has proximal DVT	0.147	Beta	($\alpha = 41$, $\beta = 238$)	Kilroy[72]
Ratio of distal to proximal DVT	0.778	Beta	($\alpha = 14.5$, $\beta = 4.15$)	Ultrasound meta-analysis
Probability distal DVT propagates to proximal	0.214	Beta	($\alpha = 6$, $\beta = 22$)	Largerstedt[417]
Outcomes of treated proximal DVT				
Probability of fatal PE	0.004	Beta	($\alpha = 17$, $\beta = 4204$)	Douketis[424]
Probability of non-fatal PE	0.008	Beta	($\alpha = 33.4$, $\beta = 4070.6$)	Douketis[424]
Probability of PTS	0.053	Beta	($\alpha = 28$, $\beta = 500$)	Prandoni[425]
Outcomes of untreated proximal DVT				
Probability of fatal PE	0.019	Beta	($\alpha = 5$, $\beta = 263$)	Follow-up studies
Probability of non-fatal PE	0.093	Beta	($\alpha = 25$, $\beta = 243$)	Follow-up studies
Probability of PTS	0.33	Beta	($\alpha = 5.21$, $\beta = 10.57$)	Expert opinion
Risks of treatment				
Probability of non-fatal intracranial haemorrhage	0.001	Dirichlet	(13,37,226,10481) where each parameter refers to the proportion of people in each category. The fourth category is 'no bleeding'	Linkins[6]
Probability of fatal haemorrhage	0.003	Dirichlet		Linkins[6]
Probability of non-fatal, non-intracranial haemorrhage	0.021	Dirichlet		Linkins[6]

TABLE 42 *Diagnostic test parameters*

Test	Variable description	Mean value	Probability distribution	Parameters		
Wells test	Proportion of proximal DVT categorised as high risk	0.68	Dirichlet	A	B	C
	Proportion of proximal DVT categorised as moderate risk	0.25	Dirichlet	105.61	38.83	10.87
	Proportion of proximal DVT categorised as low risk	0.07	Dirichlet			
	Proportion of distal DVT categorised as high risk	0.34	Dirichlet	A	B	C
	Proportion of distal DVT categorised as moderate risk	0.48	Dirichlet	26.60	37.56	14.08
	Proportion of distal DVT categorised as low risk	0.18	Dirichlet			
	Proportion without DVT categorised as high risk	0.11	Dirichlet	A	B	C
	Proportion without DVT categorised as moderate risk	0.41	Dirichlet	40.78	151.99	177.94
	Proportion without DVT categorised as low risk	0.48	Dirichlet			
Ultrasound	Sensitivity for proximal DVT	0.95	Beta	1732.57	91.19	
	Sensitivity for distal DVT	0.65	Beta	630.55	339.52	
	Specificity	0.94	Beta	2035.72	129.94	
ELISA D-dimer	Sensitivity for proximal DVT	0.98	Beta	736.91	15.04	
	Sensitivity for distal DVT	0.86	Beta	993.58	161.75	
	Specificity, Wells high	0.34				
	Specificity, Wells moderate	0.45	Beta	4278.13	5228.83	
	Specificity, Wells low	0.52				
Latex D-dimer	Sensitivity for proximal DVT	0.94	Beta	2035.72	129.94	
	Sensitivity for distal DVT	0.79	Beta	313.89	83.44	
	Specificity, Wells high	0.42				
	Specificity, Wells moderate	0.55	Beta	5228.83	4278.13	
	Specificity, Wells low	0.64				
SimpliRED D-dimer	Sensitivity for proximal DVT	0.84	Beta	270.22	51.47	
	Sensitivity for distal DVT	0.64	Beta	69.29	38.98	
	Specificity, Wells high	0.52				
	Specificity, Wells moderate	0.68	Beta	5683.66	2674.66	
	Specificity, Wells low	0.79				
Plethysmography (strain-gauge)	Sensitivity for proximal DVT	0.90	Beta	777.02	86.34	
	Sensitivity for distal DVT	0.56	Beta	107.62	84.56	
	Specificity	0.81	Beta	4788.09	1123.13	

TABLE 43 *Costs*

Descriptions of variable	Mean value	Probability distribution	Parameters	Source
Clinical risk stratification	£6.83	None		Assumption
D-dimer (SimpliRED)	£12.16	None		Axis Shield personal communication
D-dimer (Laboratory)	£13.11	None		NHS Trust figures personal communication
Full-leg ultrasound	£112.06	Normal	SE = 3.99	NHS reference costs[435]
Above knee ultrasound	£59.36	Normal	SE = 3.28	NHS reference costs[435]
Venogram	£192.00	Normal	SE = 4.82	NHS reference costs[435]
Plethysmography	£19.19	None		Amtec Medical personal communication
Treatment of DVT (total)	£721			
Based on:				
Days of heparin	8.6	Lognormal	SE=5.2	Boccalon[437]
Unit cost per dose of low molecular weight heparin (Enoxaparine)	£12.77	None		BNF[438]
Number of anticoagulant clinic reviews	4	None		
Unit cost per anticoagulant clinic review	£34	None		NHS reference costs[435]
Number of nursing visits during anticoagulation	17.2	None		Boccalon[437]
Unit cost per nursing visit	£20	None		Netten and Curtis[434]
Number of GP visits during anticoagulation	2	None		
Unit cost per GP visit	£61	None		Netten and Curtis[434]
Cost of 90 days of warfarin treatment	£5.46	None		BNF[438]
Treatment of fatal PE	£1167	Normal	SE = 35.81	NHS reference costs[435]
Treatment of non-fatal PE	£1132	Normal	se = 16.34	NHS reference costs[435]
Lifetime costs for PTS	£3866.59			
Based on:				
Unit cost for new vascular surgery outpatient	£85	Normal	SE = 2.53	NHS reference costs[435]
Unit cost for follow-up vascular surgery outpatient	£122	Normal	SE = 3.96	NHS reference costs[435]
GP visits	40	None		Netten and Curtis[434]
Treatment of severe bleeding, first year	£10273.10	None		Sandercock[439]
Treatment of severe bleeding, subsequent years	£4662.10	None		Sandercock[439]
Treatment of fatal bleeding	£6600	None		Sandercock[439]
Treatment of non-intracranial haemorrhage	£569.38	Normal	9.85	NHS reference costs for gastro-intestinal bleeding[435]

TABLE 44 *QALYs*

Description of variable	Mean value	Probability distribution	Parameters	Source
Normal age-specific, discounted quality-adjusted life expectancy	11.58	None		Government Actuary's Department,[431] Kind[432]
Severe PTS	0.977	Beta	$a = 232.64$, $b = 5.48$	O'Meara[433]
Non-fatal intracranial haemorrhage	0.29	Beta	$a = 8.34$, $b = 20.41$	O'Meara[433]
Non-fatal pulmonary embolism	0.94	Beta	$a = 19.43$, $b = 1.24$	Expert opinion
Non-fatal, non-intracranial haemorrhage	0.997			Assumption[a]

[a] See Chapter 5, section 'Valuation of health outcomes' (p. 53).

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We look forward to hearing from you.

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