The diagnosis of deep vein thrombosis in symptomatic outpatients and the potential for clinical assessment and D-dimer assays to reduce the need for diagnostic imaging

Deep vein thrombosis (DVT) has an annual incidence of between 48 and 182 per 100 000 (Coon *et al*, 1973; Anderson *et al*, 1991; Nordstrom *et al*, 1992; Hansson *et al*, 1997; Silverstein *et al*, 1998), so the oft quoted figure of 1 per 1000 is a reasonable estimate. Estimates of the case fatality rate range from 1% to 5% (Anderson *et al*, 1991). However, the incidence and the case fatality rate are very age dependent (Coon *et al*, 1973; Anderson *et al*, 1991; Nordstrom *et al*, 1992; Silverstein *et al*, 1998).

There is also associated morbidity. Post-thrombotic syndrome, characterized by chronic pain, swelling and occasional ulceration of the skin of the leg occurs in up to one-third of patients who have had a DVT (Prandoni *et al*, 1996, 1999). The post-thrombotic syndrome can occur early or have a latency of up to 10 years, the cumulative frequency has been estimated as 23% at 2 years and 28% at 5 years (Prandoni *et al*, 1996). In patients who use elastic compression stockings for at least 2 years, the incidence of post-thrombotic leg can be halved (Brandjes *et al*, 1997). Increased awareness of DVT and its consequences has resulted in an increased number of patients being referred for assessment. Many of these patients are at low risk and this is reflected by the fall in the percentage of positive diagnoses of DVT in reported series.

The objective diagnosis of DVT depends on imaging using compression ultrasound or ascending venography. However, because of the cost of these modalities, the increasing number of negative tests which are being requested and the resultant, frequently incurred delays in access to them, alternative approaches to diagnosis and decision making in suspected cases of DVT have been adopted. These rely on the use of information from clinical history and examination and assays to detect D-dimers. The main emphasis of these methods is on the safe exclusion of a diagnosis of DVT, thus reducing the use of imaging techniques and speeding up the diagnostic process.

While clinical examination cannot be relied upon in isolation to make a diagnosis of DVT, in combination with appropriate history taking, it can provide useful information (Wells *et al*, 1995, 1997). Recently, sensitive D-dimer assays that can help to exclude the diagnosis have been developed. This guideline describes the use of these methods alone and in combination with each other to develop strategies that safely exclude the diagnosis in patients presenting with suspected DVT, without resorting to the use of diagnostic imaging. An understanding of the natural history of calf vein thrombosis, and the risk of extension and embolization is also important in designing a diagnostic strategy.

Correspondence: The BCSH Secretary, British Society for Haematology, 100 White Lion Street, London N1 9PF, UK.
E-mail: janice@b-s-h.org.uk

Methods

The guideline was drafted by a working party of the Thrombosis and Haemostasis Task Force of the British Committee for Standards in Haematology. Information was gathered from several sources. These include references known to the working party members supported by a search of MEDLINE using the terms DVT, venous thrombosis, venous thromboembolism (VTE) and D-dimer(s). Recommendations are graded according to the level of evidence (Appendix 1).

Clinical assessment

Before the 1970s, the diagnosis of DVT was often made on clinical grounds. The use of venography showed that the clinical diagnosis was often incorrect. However, clinical assessment giving an estimate of the pretest probability of disease does have a role. Wells *et al* (1997) validated a system combining symptoms, risk factors, signs and possible alternative diagnosis to stratify patients into low, moderate or high pretest probability. Their analysis of multiple variables resulted in the scoring system shown in Table I. In this study 3%, 17% and 75% of the patients with low, moderate and high pretest probability, respectively, had DVT. They did not include patients with previous VTE nor pregnant women and we, therefore, recommend that all these patients should have diagnostic imaging.

D-dimer assays

D-dimer formation

Fibrinogen structure, and fibrin and D-dimer formation have been reviewed by Gaffney (1987) and Hantgan *et al* (1994). Fibrinogen is a large (340 kD) glycoprotein consisting of three pairs of disulphide bonded polypeptide chains (α-, β- and

© 2004 Blackwell Publishing Ltd,

Table I. Pretest probability assessment.

	Points
Active cancer (treatment on-going or within previous 6 months or palliative)	1
Paralysis, plaster	1
Bed >3 d, surgery within 4 weeks	1
Tenderness along veins	1
Entire leg swollen	1
Calf swollen >3 cm	1
Pitting oedema	1
Collateral veins	1
Alternative diagnosis likely	−2

Low: 0 or less; moderate: 1 or 2; high: 3 or more.

γ-chains). It has a central, N-terminal, E-domain, containing numerous disulphide bridges and two outer D-domains. Cleavage of a small peptide (FpA) from the E-domain of the α-chain of adjacent fibrinogen molecules results in fibrin monomer formation. These monomers (desAA fibrin, or fibrin I) are then able to polymerize, eventually forming insoluble fibrin. Cleavage of fibrinopeptide B, from the E-domain β-chain (to form desAABB fibrin, fibrin II), is not essential for fibrin polymerization, but appears to influence the conformation and stability of the fibrin and its degradation products. Polymerization involves interactions between the D- and E-domains of fibrin subunits in parallel strands, causing a half stagger arrangement (Fig 1), and interactions between the D-domains of adjacent subunits. Activated factor XIII catalyses the formation of Glu–Lys cross-links between the γ-chains (γ–γ links) and the α-chains (α–α links) of adjacent fibrin units. These interactions stabilize the fibrin polymer. Plasmin cleaves the fibrin subunits in a polymer in random order, to yield soluble fragments with a range of molecular weights (X-oligomers). The initial cleavage occurs at the carboxyl terminus of the α-chains, so that the α–α links are lost (Fig 2). Further cleavage by plasmin causes the progressive breakdown of X-oligomers to yield a variety of fragments. In each of these breakdown steps, the γ–γ links are retained, so that D-dimers are present. Thus, D-dimer is not merely a single substance, DD, but is present in the various X-oligomers, and as EDD (E-domain + D-dimer). In addition, there are multimeric structures due to intermolecular γ-chain crosslinks, to form trimers and tetramers of fragment D (DDD, DDDD and intermediate products containing these structures) (Mosesson, 1995). Cross-linked split products can also be generated by neutrophil elastase and matrix metalloproteases, as well as other proteases, and these may cross-react in D-dimer assays.

Types of D-dimer assay

A variety of different qualitative and quantifiable assays are available for D-dimer (Nieuwenhuizen & Bos, 1999), and all are based on the use of monoclonal antibodies (Table II). The techniques used include turbidimetry, latex particle agglutination, fluorescence immunoassay, immunofiltration tests and enzyme-linked immunosorbent assay (ELISA). These principles have been incorporated in a variety of automated techniques. There is wide variation in performance, but the ELISA methods are generally more sensitive than the latex agglutination techniques. There are discrepancies in the comparability of the various assays, particularly in terms of normal reference ranges and clinical cut-off values for the exclusion of thrombosis. One explanation for this is the use of a variety of combinations of monoclonal antibodies with differing specificity and affinity. This means that the various forms of D-dimer described above will be detected to differing extents by different assay reagents.

The use of different commercial calibrants also influences assay performance. These vary in the method of preparation, solution in which they are dissolved, and the source of primary

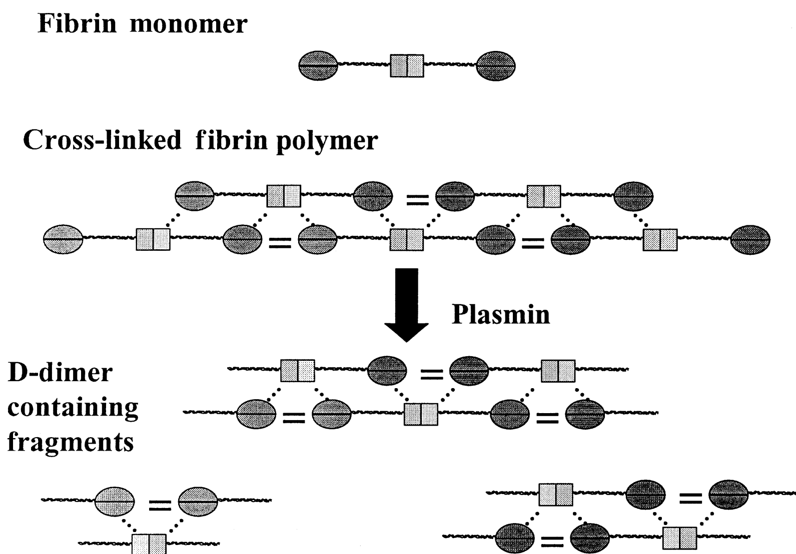

Fig 1. Fibrin polymerization, cross-linking and plasmin digestion. The ovals represent the fragment D domains, consisting of γ and β chains. The boxes represent the E domains, consisting of α, β and γ chains, linked together by multiple disulphide bonds, in the central portion of the fibrin molecule. The solid double lines are the cross-links between gamma chains, and the dotted lines are the polymerization sites.

 © 2004 Blackwell Publishing Ltd,

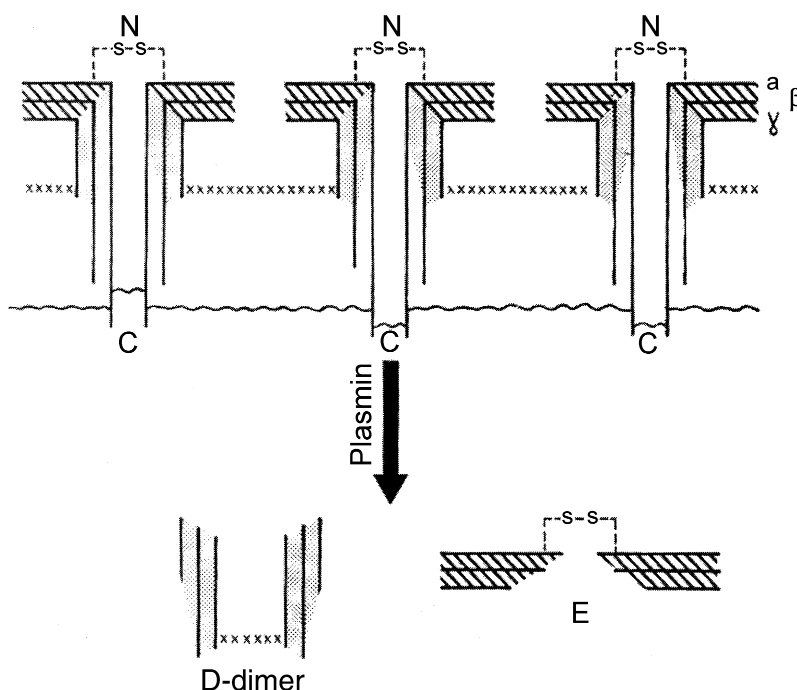

Fig 2. The formation of D-dimer containing products. The polypeptide chains of three cross-linked fibrin monomers in a fibrin polymer and the simplest plasmin-mediated degradation products (D-dimer and fragment E) are depicted. The cross-linked γ chain dimers (crosses), the cross-linked α chain polymers (wavy lines) and the non-cross-linked β chains are shown. The γ chain cross-links cause D fragments from adjacent fibrin monomers to remain associated as D-dimers, following plasmin digestion. Reprinted from Gaffney *et al* (1976) © with permission from Elsevier Science.

Table II. Monoclonal antibodies used in various D-dimer Assay kits.

Kit name	Manufacturer	Monoclonal antibody
D-Dimer Plus	Dade Behring	DD5
Auto D-Dimer	Sigma Diagnostics	MA8D3
IL Test™ D-Dimer	Instrument Laboratory	MA8D3
VIDAS D-Dimer New	BioMerieux	P10B5E12C9 P2C5A10
MiniQuant-D-dimer	Biopool	MA8D3
Biopool AutoDimer™	Biopool	MA8D3
Auto D-dimer 700	Helena Biosciences	MA8D3
Auto D-dimer 540	Helena Biosciences	MA8D3
MDA® D-Dimer	BioMerieux	MAb8-8G
NycoCard® D-Dimer	Axis-Shield	54H9

From Gardiner *et al* (2002), with permission of the Medicines & Healthcare Products Regulatory Agency.

calibrant, as well as the units of measurement [i.e. μg/ml, fibrinogen equivalent units (FEU)]. The cut-off value for the exclusion of DVT is often set at approximately 500 μg/l or 500 μg/l FEU. Two microgram per litre FEU has an immunoreactivity of 1 μg/l of purified D-dimer, but often it is unclear which units the manufacturer is referring to. Some calibrants are prepared from purified fibrinogen after conversion to fibrin, and cleavage with plasmin; depending on the exact reaction conditions, different spectra of D-dimer containing products are obtained. Some preparations are partially purified by the use of molecular size exclusion techniques, so that only particular fractions of fibrin degradation product are retained. Other calibrants are prepared from citrated plasma instead of purified fibrinogen.

As the expression of the D-dimer moiety in clinical samples is heterogeneous, and may differ depending on the nature of the patient, the use of highly purified D-dimer standard preparations has been unsuccessful. The best agreement between assays has been obtained using reference plasma preparations prepared from pools of clinical samples (Nieuwenhuizen, 1997), and further work is under way by the Fibrinolysis Scientific Subcommittee of the International Society for Thrombosis and Haemostasis, to investigate the possible preparation of an International Reference Preparation. It is hoped that this may be utilized by manufacturers and lead to at least partial harmonization of D-dimer results between different methods.

Citrated plasma is the sample type of choice for D-dimer assays, as some X-oligomers may be consumed in clot formation, and various fibrin degradation products may be adsorbed to clots. Thus, serum samples could lead to false low or negative values.

The use of D-dimer assays for the exclusion of thrombosis

Thrombus formation is normally followed by an immediate fibrinolytic response. The resultant generation of plasmin causes the release of fibrin degradation products (predominantly containing D-dimer) into the circulation. It follows that absence of a rise in D-dimers implies that thrombosis is not occurring. Thus, negative D-dimer assays may have a role in excluding a diagnosis of VTE. The strategy for using D-dimer assays in the diagnosis of DVT, is to employ a sensitive test

with a high negative predictive value (NPV). The specificity of the assays for DVT is variable and depends on the patient population. False positive results are common in hospital inpatients, particularly in patients with infection and cancer, and in postsurgery patients. False positive results are so common in elderly patients that some investigators have suggested raising the cut-off value of D-dimer assays for use in this group. As the cut-off value for defining a negative test is lowered, the sensitivity will rise (and the specificity will fall) but fewer patients will have the diagnosis excluded based on the result of the test.

Initially the only tests sensitive enough to be used in this way were ELISAs. However, these assays are time consuming and were designed to batch samples in a research setting. The slide-based latex bead agglutination assays used to detect raised D-dimers in conditions such as disseminated intravascular coagulation are not suitable (Bounameaux *et al*, 1997). Now many rapid ELISAs for single use are available. For example, the VIDAS D-dimer has been the subject of several publications (D'Angelo *et al*, 1996; Borg *et al*, 1997; Janssen *et al*, 1997a) and a review combined these studies to give an estimated sensitivity of 98% (94–100%) and specificity 54% (47–62%) (Bounameaux *et al*, 1997). More recently modified methods in which latex bead agglutination is measured using the photo-optical detection system of an automated coagulometer have been developed. The rate of agglutination is proportional to the D-dimer concentration and can be interpolated from a reference curve, giving a sensitive method and a quantifiable result. A study has compared 13 methods in the same 99 patients with suspected DVT (van der Graaf *et al*, 2000); their results are shown in Table III.

In a recent UK National External Quality Assessment Service assurance survey (UK NEQAS, Professor E Preston, personal communication), 17 different quantifiable assays were used and a great variation in performance was observed. A quarter of respondents identified a sample with mildly raised D-dimers as normal. The preliminary data analysis from the ongoing Medical Devices Agency (MDA) evaluation of D-dimer kits (Gardiner *et al*, 2002), has shown that some assays are inadequate for the exclusion of DVT. Ten commercial kits, selected from those most commonly used in the UK, were evaluated on various analysers, using 119 samples from patients presenting in casualty with a suspected diagnosis of DVT; pretest probability scoring and objective imaging were used. Some methods displayed unacceptably poor precision, while others had very poor specificity. Not all manufacturers provided recommended cut-off values for the exclusion of DVT and receiver operating characteristic (ROC) analysis of data demonstrated that the suggested cut-off values were not always ideal. When cut-off values giving a 100% sensitivity level by ROC analysis were applied, between 12·8 and 50% of patients without VTE were successfully excluded on the basis of D-dimer assays. Comparison of the results from the MDA evaluation (Gardiner *et al*, 2002) with those of van der Graaf *et al* (2000) illustrates the difference in performance that occurs when reagents are used on different analysers.

There are several other factors that relate to the performance and usefulness of D-dimer assays.

Age of the clot. Reported studies vary greatly in the acceptable time lapse between the onset of symptoms and the application of D-dimer testing. Sie *et al* (1994) demonstrated that D-dimer levels returned to normal 3 months after a DVT. While van der Graaf *et al* (2000) included patients up to 42 d after the development of symptoms of DVT, others have included subjects with a much shorter duration of symptoms and observed significant declines in measured D-dimer levels with time (D'Angelo *et al*, 1996). In this series the results of testing after 15 d of symptoms had a significant effect on the discriminatory value in patients with DVT.

Position of clot. Although the majority of DVTs involve the proximal vasculature at the time of diagnosis, isolated calf vein thrombosis constitutes around 20% of all DVT. Data comparing the performance of D-dimer assays in proximal and distal DVT suggest clinically significant differences. The reported sensitivities of qualitative assays ranged from 17% to 67% for isolated calf DVT compared with 80–94% for all DVT (van der Graaf *et al*, 2000). Lower sensitivities of a variety of semiquantifiable methods has also been demonstrated for isolated calf thrombosis (Borg *et al*, 1997; van der Graaf *et al*, 2000). Given that the majority of DVTs begin in the calf, it is unlikely that these observations relate to the age of the thrombus. Therefore, it is most likely that the reduced detection of these thrombi by D-dimer assays relates to quantity of clot.

Heparin use. In situations where DVT is suspected, but access to a diagnostic service is likely to be delayed, it is common practice to administer heparin before the diagnosis is confirmed. While this is highly unlikely to affect the interpretation of imaging studies, it may affect the interpretation of D-dimer assays. Several studies have shown a fall in D-dimer levels following anticoagulation with heparins (Speiser *et al*, 1990; Janssen *et al*, 1997b; Stricker *et al*, 1999). Stricker *et al* (1999) demonstrated a significant fall in D-dimer values in patients that were serially tested after commencing anticoagulation with heparin or low molecular weight heparin for VTE. Moreover, the D-dimer level recorded on any 1 d in patients on nadroparin depended on the time of sampling with lower levels detected at times of peak heparin activity (Stricker *et al*, 1999). In a study of 44 patients treated with heparin for at least 5 d, changes in D-dimer levels were observed that would have altered the interpretation of the assay performed as a screening test for excluding the diagnosis of VTE (Janssen *et al*, 1997b). There are few data on the effect of a single dose of heparin on the interpretation of D-dimer assays for exclusion of a diagnosis of DVT.

Table III. Comparison of 13 D-dimer methods in 99 patients with suspected DVT.

D-dimer assay	Cut-off (mg/l)	Sensitivity (%)	Specificity (%)	Negative PV (%)	Positive PV (%)
Qualitative methods					
Minutex		80 (66–90)	90 (78–97)	81 (68–91)	89 (76–96)
SimpliRED		80 (66–90)	94 (83–99)	82 (70–91)	93 (81–99)
Instant LA		94 (83–99)	63 (48–77)	91 (76–98)	72 (60–83)
(Semi)Quantifiable methods					
NycoCard	<0·5	100 (93–100)	12 (5–25)	100 (54–100)	54 (43–64)
	0·5*	98 (98–100)	31 (18–46)	94 (69–100)	59 (48–70)
	1·0	94 (83–99)	57 (42–71)	90 (74–98)	69 (57–80)
BC-DD	0·25*	83 (69–92)	87 (73–95)	83 (69–92)	87 (73–95)
	0·3	77 (62–88)	91 (79–98)	79 (65–89)	90 (76–97)
	0·6	45 (30–60)	98 (88–100)	63 (50–74)	95 (77–100)
Turbiquant	0·25*	98 (88–100)	40 (26–56)	95 (73–100)	63 (51–74)
	0·3	89 (77–97)	60 (44–74)	84 (67–95)	70 (57–81)
	0·6	68 (53–81)	89 (76–96)	73 (59–84)	86 (71–96)
IL-DD	0·13	100 (93–100)	47 (32–62)	100 (85–100)	66 (54–76)
	0·25	90 (78–97)	78 (63–88)	88 (75–96)	80 (67–90)
	0·50	80 (66–90)	90 (78–97)	81 (68–91)	89 (76–96)
Liatest	0·35	100 (93–100)	33 (20–48)	100 (79–100)	60 (49–71)
	0·50	96 (86–100)	47 (32–62)	92 (74–99)	65 (53–76)
	1·00	90 (78–97)	76 (61–87)	88 (74–96)	79 (66–87)
Tinaquant	0·58	100 (93–100)	39 (25–54)	100 (82–100)	63 (51–73)
	0·50	100 (93–100)	39 (25–54)	100 (82–100)	63 (51–73)
	1·00	90 (78–97)	73 (59–85)	88 (74–96)	78 (65–88)
VIDAS	0·52	100 (93–100)	41 (27–56)	100 (83–100)	63 (52–74)
	0·50	100 (93–100)	41 (27–56)	100 (83–100)	63 (52–74)
	1·00	94 (83–99)	71 (57–83)	92 (78–99)	77 (64–87)
Asserachrom	0·43	100 (92–100)	33 (20–49)	100 (78–100)	61 (49–72)
	0·50	98 (88–100)	42 (28–58)	95 (75–100)	64 (52–75)
	1·00	91 (79–98)	73 (58–85)	89 (74–97)	78 (65–88)
Enzygnost	0·05	100 (92–100)	44 (30–60)	100 (83–100)	65 (53–76)
	0·07	94 (82–99)	62 (46–76)	90 (74–98)	72 (59–83)
	0·14	87 (74–95)	82 (68–92)	86 (72–95)	84 (70–93)
Fibrinostika	0·52	100 (92–100)	36 (22–51)	100 (79–100)	62 (50–73)
	0·50	100 (92–100)	36 (22–51)	100 (79–100)	62 (50–73)
	1·00	89 (77–97)	71 (56–84)	86 (71–96)	76 (63–87)

Reproduced with permission from van der Graaf *et al* (2000). For the calculation of the accuracy indices, quantifiable D-dimer results equal to or lower than the cut-off value were considered to be negative. Cut-off values are in mg/l FEU except for NycoCard, BC-DD, Turbiquant, IL-DD and Enzygnost (mg of D-dimer/l). The accuracy indices for the quantifiable D-dimer assays are shown at three cut-off values: the first value represents the highest D-dimer level that is associated with a sensitivity and negative predictive value of 100% (except for Turbiquant and BC D-dimer for which a 100% sensitivity could not be obtained because one or more DVT-positive patients had a D-dimer level lower than the detection limit); the second cut-off value is the upper limit of the reference range; the third value corresponds to a D-dimer concentration of twice the upper limit of the reference range. The 95% confidence intervals are shown in parentheses.

*Detection limit.

Recommendations (for selection and use of D-dimer assay)

We recommend an assay with proven high sensitivity in well-designed studies comprising a patient population similar to that in which it will be used. The assay should be validated in each institution by an audit of its performance (level IV, grade C).

The most suitable cut-off value for negative prediction of DVT would be expected to differ for the various reagent/analyser combinations. To assign clinically meaningful cut-off values, blood samples should be collected consecutively from patients presenting with suspected DVT. In this exercise management decisions should be made based on a standard diagnostic algorithm regardless of the D-dimer result. The D-dimer test should be performed with the operator blinded to the clinical status and scanning results. The size of the study should be determined by statistical power calculations, but would usually be expected to include at least 200 patients. The use of ROC analysis techniques to determine sensitivity and specificity values at various D-dimer concentrations may then

be used to determine the optimal cut-off value for the technique in that clinical setting. It is obviously not practical to determine this locally at every centre, and users may often have to rely on the manufacturer's recommendation, which should be determined as described above (level IV, grade C).

D-dimers must be used with caution if the patient has had symptoms for over 2 weeks (level IV, grade C).

Tests for D-dimer are affected by heparin administration and this must be borne in mind when using these assays to exclude DVT. Where possible, D-dimer assays should be performed on blood that is drawn prior to starting treatment with heparins (level IV, grade C).

Diagnostic imaging

Having excluded the diagnosis in some patients suspected of suffering DVT, using clinical scoring and D-dimer testing, a proportion of patients still require further investigation. The final step in the diagnostic pathway of DVT is some form of definitive imaging. Imaging with clinically suspected venous thrombosis do not have the diagnosis confirmed by objective testing in 70–80% of patients referred. Among the 20–30% who have venous thrombosis, about 80% have proximal vein thrombosis, and the remainder have thrombosis confined to the calf (Line, 2001; Fraser *et al*, 2002). Whatever tests are available the factors in Table IV should be taken into consideration.

Conventional ascending venography

The gold-standard diagnostic test for DVT of the lower extremities is ascending venography. Venography can detect both distal thrombi (in the calf veins) and proximal thrombi (in the popliteal, femoral and iliac veins). However, venography is invasive requiring cannulation of a pedal vein and subsequent injection of 50–150 ml of iodinated contrast. Venography is also expensive, especially in terms of radiologists' and radiographers' time and is a poor choice for serial monitoring. Because of the requirement to cannulate a foot vein, failure rates can be high (12–14%) in patients with swollen legs or in whom contrast preferentially travels in the superficial system (Kahn *et al*, 2001; Fraser *et al*, 2002). Inter-observer variability is also high when interpreting venograms with overall κ values of 0·53–0·90 (Illescas *et al*, 1990; Wille-Jorgensen *et al*, 1992; Couson *et al*, 1993), and between 0·46 and 0·73 for below knee DVT (McLachlan *et al*, 1979). Imaging in the pelvis may be inadequate as the column of contrast becomes diluted from the point of injection within the foot. Up to 24% of normal studies visualize the pelvic vessels inadequately or may not delineate the upper extent of thrombus in those with DVT (Coel, 1980). Other blind spots include the gastrocnemius vessels, which are not filled in up to 75% of examinations, especially if an ankle tourniquet is used (Rabinov & Paulin, 1972; Redman, 1988).

Table IV. Important considerations for diagnostic imaging.

Considerations
Invasiveness
Contrast administration
Radiation
Cost
Failure rate
Operator dependence
Repeatability (technical)
Sensitivity and specificity
Inter- and intra-observer agreement
Blind spots
Availability
Complications
Recurrent disease

Ultrasound

Many trials have shown the value of ultrasound in the diagnosis of DVT. (Elias *et al*, 1987; Lensing *et al*, 1989; White *et al*, 1989). The inability to compress the vein lumen is the principle diagnostic criterion and other findings do not increase the sensitivity of the method (Cogo *et al*, 1995). A recent meta-analysis revealed a sensitivity of 89% for first symptomatic DVT overall, with a sensitivity for proximal DVT of 97% (96–98%), although decreasing to only 73% (54–93%) for distal DVT (Kearon *et al*, 1998). The technique of compression ultrasound is simple, quick and repeatable. Performed by emergency physicians on patients with a high probability of DVT, the inter-observer agreement was high ($\kappa = 0{\cdot}9$) (Blaivas *et al*, 2000). However, inter-observer agreement falls ($\kappa = 0{\cdot}6$) when diagnosing isolated calf DVT (Atri *et al*, 1996). Not only is the diagnosis of DVT comparable between two readers, but the definition of localization and extension of thrombus is also well maintained (Barrellier *et al*, 1992). The technical failure rate for compression ultrasound is 6–9% (O'Leary *et al*, 1988; Atri *et al*, 1996). An advantage over conventional venography is the ability of ultrasound to identify alternative diagnoses of leg pain and swelling.

Distal DVT and the concept of serial ultrasound

Deep vein thrombosis usually starts in the calf (Kakkar *et al*, 1969; Philbrick & Becker, 1988; Cogo *et al*, 1993), but by the time symptoms develop 80% of patients have thrombus in the popliteal or more proximal veins (proximal DVT) (Agnelli *et al*, 1993; Cogo *et al*, 1993). It has been said that in patients presenting with isolated calf DVT (distal DVT) approximately 20% of thrombi extend into the proximal veins (Kakkar *et al*, 1969; Philbrick & Becker, 1988), usually within 1 week. However, a more recent study found an extension rate of only 3% (Kahn *et al*, 2002). Distal DVT that do not extend rarely lead to clinically significant emboli (Kakkar *et al*, 1969; Kahn *et al*, 2002), but in those that do extend, the risk of

pulmonary embolism is significant (Kakkar *et al*, 1969; Lagerstedt *et al*, 1985). This has guided the rationale for using serial ultrasound. The first test will detect any proximal thrombosis, a calf vein thrombus may remain undetected but a repeat scan 1 week later will pick up the clinically important ones that have extended. It is safe to withhold anticoagulant treatment from patients with clinically suspected DVT who have normal results on compression ultrasonography at the time of presentation and at 1 week later (Cogo *et al*, 1998) (level III, grade B).

Diagnosis of recurrent DVT

The studies that validated clinical scoring excluded patients who had had a previous DVT. All these patients are at high risk of recurrence and should all have diagnostic imaging (level IV, grade C). The diagnosis of recurrent DVT can be problematic, as the normal appearances relied upon to diagnose the presence or absence of thrombus may be lost. Abnormalities on compression ultrasound may be detected in up to 70% of patients despite no evidence of recurrent disease in the year following a DVT (Prandoni *et al*, 1993). Follow-up venography of patients with previous DVT may show a return to normality, but residual scarring can also be detected (with recanalization or partial recanalization and collateralization) which may confuse the diagnosis of recurrent disease (Rosch *et al*, 1976). However, recurrent thrombosis is a significant clinical problem, with the cumulative risk of recurrence being 17% at 2 years, rising to 24% at 5 years and 29% at 8 years (Prandoni 1997). While venography is generally accepted as the definitive diagnostic test in recurrent disease, some studies have suggested that ultrasound (US) may be equally or more effective (Belcaro, 1992). Diagnosis of recurrence will often rely on a combination of these two tests (Hirsh & Lee, 2002). As with the algorithm for first time DVT outlined below, if ultrasound testing and D-dimer are both negative the patient can be safely left untreated. However, this is likely to pertain to the minority of patients. A further option is to compare a new US examination with previous US studies, if available (Prandoni *et al*, 2002). Provided there has been no change, and D-dimer is negative, follow-up US could be employed to ensure no change. In situations where the patient has a positive D-dimer or previous US scans are unavailable, venograms need to be performed to look for intraluminal filling defects that are typical of recent thrombosis.

Designing a diagnostic strategy to suit local circumstances

The key questions are: can clinical assessment and D-dimer testing be used avoid the need for diagnostic imaging in a number of outpatients with suspected DVT, and, if ultrasound is used, can the results of D-dimer assays be used to reduce the need for serial ultrasound?

Table V. Modification of pretest probability with a negative D-dimer of sensitivity 96% and specificity 44%.

Clinical probability assessment if D-dimers negative	Pretest probability (%)	Post-test probability (%)
High	75	21·0
Moderate	17	1·8
Low	3	0·3

Clinical probability assessment and negative D-dimers

It has been suggested that an initial negative D-dimer test can be used to rule out the diagnosis of DVT irrespective of the pretest clinical probability assessment (Perrier *et al*, 1999). However if, for example, the D-dimer test has a sensitivity of 96% and a specificity of 44% and we apply Bayes' theorem to the pretest probability categories, we get the figures in Table V. The example for the moderate probability group is worked through in Appendix 2. More information on likelihood ratios is available at http://www.cebm.net/likelihood_ratios.asp and this site has a nomogram that can be used to save calculating. In this (fairly typical) example, the D-dimer test, if negative, effectively rules out the diagnosis in those with a low pretest probability but it clearly does not in those with a high pretest probability. Whether a negative test is good enough to rule out the diagnosis in those with a moderate pretest probability is not entirely clear from this theoretical exercise. Some studies suggest that the tests with the highest sensitivity can be used to withhold treatment in patients that have a low or moderate pretest probability (van der Graaf *et al*, 2000; Bates *et al*, 2001). However, each unit should assess for themselves how the assay they choose performs in their own hands.

Clinical probability assessment and a negative first ultrasound

It has been shown that it is safe to dispense with the follow-up ultrasound after a negative first ultrasound in patients with a low pretest probability (Wells *et al*, 1995, 1997).

A negative first ultrasound and negative D-dimers

It has been shown that it is safe to dispense with the follow-up ultrasound after a negative first ultrasound if the D-dimers are also negative (Bernardi *et al*, 1998).

It is clear that all management strategies for the diagnosis of DVT will result in cases being missed. The options being considered must be evaluated in relation to perceived best practice, where imaging techniques are applied to all suspected cases of DVT and to the burden of morbidity and mortality arising from missed diagnoses.

In a situation where a combined clinical scoring system and D-dimer assay results in a <2% residual risk of DVT, it is appropriate to consider that this is equivalent to compression

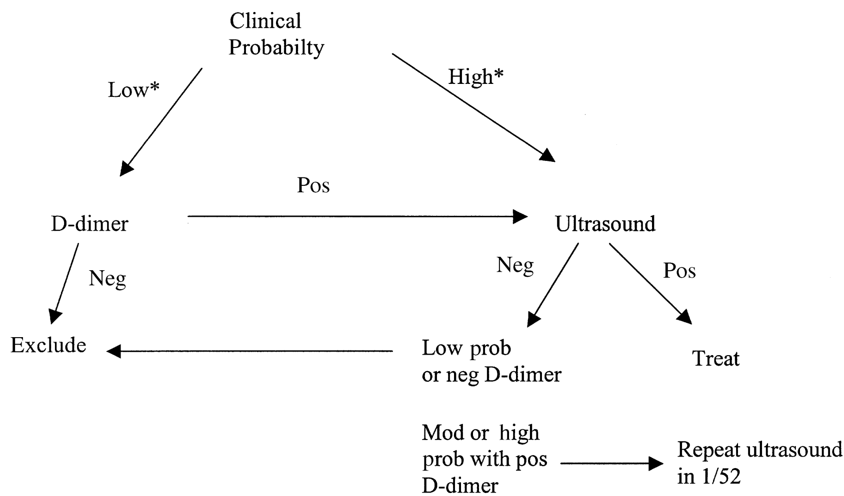

Fig 3. One possible diagnostic algorithm for non-pregnant patients with a suspected first deep vein thrombosis based on the recommendations. *Patients with a moderate pretest probability could follow the path of the low probability patients if a sensitive D-dimer test is used and local assessment shows this to be safe, otherwise they should all have an initial ultrasound as for the high probability patients.

ultrasonography that has a NPV of 98–99% for proximal thrombosis. If the case mortality from missed DVT was 2% a strategy that has an overall NPV of 98–99% would result in one death for every 2500–5000 suspected cases in which the diagnosis was thought to have been excluded.

Recommendations (for developing a diagnostic strategy in outpatients with suspected DVT)

In non-pregnant patients suspected of having a first DVT, clinical pretest probability assessment and D-dimers can be used to reduce the need for diagnostic imaging (level III, grade B).

A low pretest probability and negative D-dimers excludes the diagnosis without need for diagnostic imaging (level III, grade B).

The reliability of negative D-dimer results to exclude the diagnosis in patients with moderate pretest probability is critically dependant on the sensitivity of the test used. This requires local assessment and audit (level IV, grade C).

D-dimers should not be used alone to exclude the diagnosis in patients with a high pretest probability (level III, grade B).

A low pretest probability and negative initial ultrasound excludes the diagnosis without need for serial ultrasound or venography (level III, grade B).

Negative D-dimers and a negative initial ultrasound excludes the diagnosis without need for serial ultrasound or venography (level III, grade B).

Many algorithms can be designed according to these principles. One way they can vary is by altering the order in which tests are done in the different clinical groups. Each institution will have to design their own algorithm according to their resources and patient population. Based on the evidence presented in this document one possible algorithm is shown in Fig 3.

Areas for future research

Much work is needed to improve the standardization for D-dimer assays. Radiology continues to advance and newer technologies for the diagnosis of DVT such as volumetric computed tomography, thrombus avid nuclear medicine tracers and magnetic resonance imaging will require assessment. If these modalities can combine imaging for DVT with imaging for pulmonary embolism they may be cost-effective. The diagnosis of recurrence remains difficult and if new approaches could be shown to estimate clot age, diagnosis would be much simplified.

Disclaimer

Although the advice and information contained in these guidelines is believed to be true and accurate at the time of going to press, neither the authors nor the publishers can accept any legal responsibility for any errors or omissions that may have been made.

The Haemostasis and Thrombosis Taskforce meet every 6 months and will review these guidelines if any major developments occur or by in June 2008 at the latest.

Acknowledgments

The authors and Task Force wish to acknowledge the helpful and constructive comments on this manuscript made by members of the British Society for Haematology.

David M. Keeling[1]
Ian J. Mackie[2]
Alan Moody[3]
Henry G. Watson[4]
on behalf of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology

[1]Oxford Haemophilia Centre and Thrombosis Unit, Churchill Hospital, Oxford, [2]Haematology Department, University College London, [3]Department of Radiology, Queen's Medical Centre, Nottingham, and [4]Grampian Area Haemophilia Centre, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, UK

References

Agnelli, G., Cosmi, B., Radicchia, S., Veschi, F., Boschetti, E., Lupattelli, L., Rinonapoli, E. & Nenci, G.G. (1993) Features of thrombi and diagnostic accuracy of impedance plethysmography in symptomatic and asymptomatic deep vein thrombosis. *Thrombosis and Haemostasis*, **70,** 266–269.

Anderson, F.J., Wheeler, H., Goldberg, R., Hosmer, D., Patwardhan, N., Jovanovic, B., Forcier, A. & Dalen, J. (1991) A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Archives of Internal Medicine*, **151,** 933–938.

Atri, M., Herba, M.J., Reinhold, C., Leclerc, J., Ye, S., Illescas, F.F. & Bret, P.M. (1996) Accuracy of sonography in the evaluation of calf deep vein thrombosis in both postoperative surveillance and symptomatic patients. *AJR American Journal of Roentgenology*, **166,** 1361–1367.

Barrellier, M.T., Somon, T., Speckel, D., Fournier, L. & Denizet, D. (1992) Duplex ultrasonography in the diagnosis of deep vein thrombosis of the legs. Agreement between two operators. *Journal des Maladies Vasculaires*, **17,** 196–201.

Bates, S.M., Grand'Maison, A., Johnston, M., Naguit, I., Kovacs, M.J. & Ginsberg, J.S. (2001) A latex D-dimer reliably excludes venous thromboembolism. *Archives of Internal Medicine*, **161,** 447–453.

Belcaro, G. (1992) Evaluation of recurrent deep venous thrombosis using colour duplex scanning – comparison with venography. *Journal for Vascular Diseases*, **21,** 22–26.

Bernardi, E., Prandoni, P., Lensing, A.W., Agnelli, G., Guazzaloca, G., Scannapieco, G., Piovella, F., Verlato, F., Tomasi, C., Moia, M., Scarano, L. & Girolami, A. (1998) D-dimer testing as an adjunct to ultrasonography in patients with clinically suspected deep vein thrombosis: prospective cohort study. The Multicentre Italian D-dimer Ultrasound Study Investigators Group. *British Medical Journal*, **317,** 1037–1040.

Blaivas, M., Lambert, M.J., Harwood, R.A., Wood, J.P. & Konicki, J. (2000) Lower-extremity Doppler for deep venous thrombosis – can emergency physicians be accurate and fast? *Academic Emergency Medicine*, **7,** 120–126.

Borg, J.Y., Levesque, H., Cailleux, N., Franc, C., Hellot, M.F. & Courtois, H. (1997) Rapid quantitative D-dimer assay and clinical evaluation for the diagnosis of clinically suspected deep vein thrombosis. *Thrombosis and Haemostasis*, **77,** 602–603.

Bounameaux, H., de Moerloose, P., Perrier, A. & Miron, M.J. (1997) D-dimer testing in suspected venous thromboembolism: an update. *Quarterly Journal of Medicine*, **90,** 437–442.

Brandjes, D.P., Buller, H.R., Heijboer, H., Huisman, M.V., de Rijk, M., Jagt, H. & ten Cate, J.W. (1997) Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet*, **349,** 759–762.

Coel, M.N. (1980) Adequacy of lower limb venous opacification: comparison of supine and upright phlebography. *AJR American Journal of Roentgenology*, **134,** 163–165.

Cogo, A., Lensing, A.W., Prandoni, P. & Hirsh, J. (1993) Distribution of thrombosis in patients with symptomatic deep vein thrombosis. Implications for simplifying the diagnostic process with compression ultrasound. *Archives of Internal Medicine*, **153,** 2777–2780.

Cogo, A., Lensing, A.W., Wells, P., Prandoni, P. & Buller, H.R. (1995) Noninvasive objective tests for the diagnosis of clinically suspected deep-vein thrombosis. *Haemostasis*, **25,** 27–39.

Cogo, A., Lensing, A.W., Koopman, M.M., Piovella, F., Siragusa, S., Wells, P.S., Villalta, S., Buller, H.R., Turpie, A.G. & Prandoni, P. (1998) Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis: prospective cohort study. *British Medical Journal*, **316,** 17–20.

Coon, W., Willis, P.D. & Keller, J. (1973) Venous thromboembolism and other venous disease in the Tecumseh community health study. *Circulation*, **48,** 839–846.

Couson, F., Bounameaux, C., Didier, D., Geiser, D., Meyerovitz, M.F., Schmitt, H.E., Schneider, P.A. & Bounameaux, H. (1993) Influence of variability of interpretation of contrast venography for screening of postoperative deep venous thrombosis on the results of a thromboprophylactic study. *Thrombosis and Haemostasis*, **70,** 573–575.

D'Angelo, A., D'Alessandro, G., Tomassini, L., Pittet, J.L., Dupuy, G. & Crippa, L. (1996) Evaluation of a new rapid quantitative D-dimer assay in patients with clinically suspected deep vein thrombosis. *Thrombosis and Haemostasis*, **75,** 412–416.

Elias, A., Le Corff, G., Bouvier, J.L., Benichou, M. & Serradimigni, A. (1987) Value of real time B mode ultrasound imaging in the diagnosis of deep vein thrombosis of the lower limbs. *International Angiology*, **6,** 175–182.

Fraser, D.G., Moody, A.R., Morgan, P.S., Martel, A.L. & Davidson, I. (2002) Diagnosis of lower-limb deep venous thrombosis: a prospective blinded study of magnetic resonance direct thrombus imaging. *Annals of Internal Medicine*, **136,** 89–98.

Gaffney, P. (1987) Fibrinolysis. In: *Haemostasis and Thrombosis* (ed. by A.L. Bloom & D.P. Thomas), pp. 223–244. Churchill Livingstone, Edinburgh.

Gaffney, P.J., Brasher, M., Lord, K., Strachan, C.J., Wilkinson, A.R., Kakkar, V.V. & Scully, M.F. (1976) Fibrin subunits in venous and arterial thromboembolism. *Cardiovascular Research*, **10,** 421–426.

Gardiner, C., Pennaneach, H.C., Mackie, I.J., Machin, S.J., Walford, C. & Abe, G. (2002) *Evaluation of Ten D-dimer Kits*. Medical Devices Agency, London (HMSO, ISBN 1 84182 600 6).

van der Graaf, F., van den Borne, H., van der Kolk, M., de Wild, P.J., Janssen, G.W. & van Uum, S.H. (2000) Exclusion of deep venous thrombosis with D-dimer testing – comparison of 13 D-dimer methods in 99 outpatients suspected of deep venous thrombosis using venography as reference standard. *Thrombosis and Haemostasis*, **83,** 191–198.

Hansson, P., Welin, L., Tibblin, G. & Eriksson, H. (1997) Deep vein thrombosis and pulmonary embolism in the general population. The Study of Men Born in 1913. *Archives of Internal Medicine*, **157,** 1665–1670.

Hantgan, R.R., Francis, C.W. & Marder, V.J. (1994) Fibrinogen structure and physiology. In: *Hemostasis and Thrombosis: Basic Principles and Clinical Practice* (ed. by R.W. Colman, J. Hirsh, V.J. Marder & E.W. Salzman), pp. 277–300. JB Lippincott Co., Philadelphia.

Hirsh, J. & Lee, A.Y. (2002) How we diagnose and treat deep vein thrombosis. *Blood*, **99,** 3102–3110.

Illescas, F.F., Lerclerc, J., Rosenthall, L., Wolfson, C., Rush, C., Herba, M.J. & Arzoumanian, A. (1990) Interobserver variability in the interpretation of contrast venography, technetium-99m red blood cell venography and impedance plethysmography for deep vein thrombosis. *Canadian Association of Radiologists Journal*, **41,** 264–269.

Janssen, M.C., Heebels, A.E., de Metz, M., Verbruggen, H., Wollersheim, H., Janssen, S., Schuurmans, M.M. & Novakova, I.R. (1997a) Reliability of five rapid D-dimer assays compared to ELISA in the exclusion of deep venous thrombosis. *Thrombosis and Haemostasis*, **77,** 262–266.

Janssen, M.C., Verbruggen, H., Wollersheim, H., Hoogkamer, B., van Langen, H. & Novakova, I.R. (1997b) D-dimer determination to

assess regression of deep venous thrombosis. *Thrombosis and Haemostasis*, **78,** 799–802.

Kahn, S.R., Joseph, L., Grover, S.A. & Leclerc, J.R. (2001) A randomized management study of impedance plethysmography vs. contrast venography in patients with a first episode of clinically suspected deep vein thrombosis. *Thrombosis Research*, **102,** 15–24.

Kahn, S.R., Macdonald, S., Miller, N. & Obrand, D. (2002) The natural history of untreated isolated calf muscle vein thrombosis: rate, timing and predictors of extension. *Blood*, **100,** (abstract no. 78) [(www document) URI http://www.abstracts-on-line.com/abstracts/hemphiladelphia02].

Kakkar, V.V., Howe, C.T., Flanc, C. & Clarke, M.B. (1969) Natural history of postoperative deep-vein thrombosis. *Lancet*, **2,** 230–232.

Kearon, C., Julian, J.A., Newman, T.E. & Ginsberg, J.S. (1998) Non-invasive diagnosis of deep venous thrombosis. McMaster Diagnostic Imaging Practice Guidelines Initiative. *Annals of Internal Medicine*, **128,** 663–677.

Lagerstedt, C.I., Olsson, C.G., Fagher, B.O., Oqvist, B.W. & Albrechtsson, U. (1985) Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. *Lancet*, **2,** 515–518.

Lensing, A.W., Prandoni, P., Brandjes, D., Huisman, P.M., Vigo, M., Tomasella, G., Krekt, J., Wouter Ten Cate, J., Huisman, M.V. & Buller, H.R. (1989) Detection of deep-vein thrombosis by real-time B-mode ultrasonography. *New England Journal of Medicine*, **320,** 342–345.

Line, B.R. (2001) Pathophysiology and diagnosis of deep venous thrombosis. *Seminars in Nuclear Medicine*, **31,** 90–101.

McLachlan, M.S., Thomson, J.G., Taylor, D.W., Kelly, M.E. & Sackett, D.L. (1979) Observer variation in the interpretation of lower limb venograms. *AJR American Journal of Roentgenology*, **132,** 227–229.

Mosesson, M.W. (1995) Terminology for macromolecular derivatives of crosslinked fibrin. On behalf of the Subcommittee on Fibrinogen of the Scientific and Standardization Committee of the ISTH. *Thrombosis and Haemostasis*, **73,** 725–726.

Nieuwenhuizen, W. (1997) A reference material for harmonisation of D-dimer assays. Fibrinogen Subcommittee of the Scientific and Standardization Committee of the International Society of *Thrombosis and Haemostasis*. *Thrombosis and Haemostasis*, **77,** 1031–1033.

Nieuwenhuizen, W. & Bos, R. (1999) Soluble fibrin and degradation products of fibrinogen (FgDP), fibrin (FbDP; D-dimer) and total of FgDP and FbDP (TDP). In: *Laboratory Techniques in Thrombosis – A Manual* (ed. by J. Jespersen, R.M. Bertina & F. Haverkate), pp. 275–283. Kluwer Academic Publishers, The Netherlands.

Nordstrom, M., Lindblad, B., Bergqvist, D. & Kjellstrom, T. (1992) A prospective study of the incidence of deep-vein thrombosis within a defined urban population. *Journal of Internal Medicine*, **232,** 155–160.

O'Leary, D.H., Kane, R.A. & Chase, B.M. (1988) A prospective study of the efficacy of B-scan sonography in the detection of deep venous thrombosis in the lower extremities. *Journal of Clinical Ultrasound*, **16,** 1–8.

Perrier, A., Desmarais, S., Miron, M.J., de Moerloose, P., Lepage, R., Slosman, D., Didier, D., Unger, P.F., Patenaude, J.V. & Bounameaux, H. (1999) Non-invasive diagnosis of venous thromboembolism in outpatients. *Lancet*, **353,** 190–195.

Philbrick, J.T. & Becker, D.M. (1988) Calf deep venous thrombosis. A wolf in sheep's clothing? *Archives of Internal Medicine*, **148,** 2131–2138.

Prandoni, P., Cogo, A., Bernardi, E., Villalta, S., Polistena, P., Simioni, P., Noventa, F., Benedetti, L. & Girolami, A. (1993) A simple ultrasound approach for detection of recurrent proximal-vein thrombosis. *Circulation*, **88,** 1730–1735.

Prandoni, P., Lensing, A., Cogo, A., Cuppini, S., Villalta, S., Carta, M., Cattelan, A., Polistena, P., Bernardi, E. & Prins, M. (1996) The long-term clinical course of acute deep venous thrombosis [see comments]. *Annals of Internal Medicine*, **125,** 1–7.

Prandoni, P., Villalta, S., Bagatella, P., Rossi, L., Marchiori, A., Piccioli, A., Bernardi, E., Girolami, B., Simioni, P. & Girolami, A. (1997) The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. *Haematologica*, **82,** 423–428.

Prandoni, P., Lensing, A., Prins, M., Bagatella, P., Scudeller, A. & Girolami, A. (1999) Which is the outcome of the post-thrombotic syndrome?. *Thrombosis and Haemostasis*, **82,** 1358 (letter).

Prandoni, P., Lensing, A.W., Piccioli, A., Bernardi, E., Simioni, P., Girolami, B., Marchiori, A., Sabbion, P., Prins, M.H., Noventa, F. & Girolami, A. (2002) Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood*, **100,** 3484–3488.

Rabinov, K. & Paulin, S. (1972) Roentgen diagnosis of venous thrombosis in the leg. *Archives of Surgery*, **104,** 134–144.

Redman, H.C. (1988) Deep venous thrombosis: is contrast venography still the diagnostic "gold standard"? *Radiology*, **168,** 277–278.

Rosch, J., Dotter, C.T., Seaman, A.J., Porter, J.M. & Common, H.H. (1976) Healing of deep venous thrombosis: venographic findings in a randomized study comparing streptokinase and heparin. *AJR American Journal of Roentgenology*, **127,** 553–558.

Sie, P., Cadroy, Y., Elias, A., Boccalon, H. & Boneu, B. (1994) D-dimer levels in patients with long-term antecedents of deep venous thrombosis. *Thrombosis and Haemostasis*, **72,** 161–162.

Silverstein, M., Heit, J., Mohr, D., Petterson, T., O'Fallon, W. & Melton, L.R. (1998) Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Archives of Internal Medicine*, **158,** 585–593.

Speiser, W., Mallek, R., Koppensteiner, R., Stumpflen, A., Kapiotis, S., Minar, E., Ehringer, H. & Lechner, K. (1990) D-dimer and TAT measurement in patients with deep venous thrombosis: utility in diagnosis and judgement of anticoagulant treatment effectiveness. *Thrombosis and Haemostasis*, **64,** 196–201.

Stricker, H., Marchetti, O., Haeberli, A. & Mombelli, G. (1999) Hemostatic activation under anticoagulant treatment: a comparison of unfractionated heparin vs. nadroparin in the treatment of proximal deep vein thrombosis. *Thrombosis and Haemostasis*, **82,** 1227–1231.

Wells, P.S., Hirsh, J., Anderson, D.R., Lensing, A.W., Foster, G., Kearon, C., Weitz, J., D'Ovidio, R., Cogo, A. & Prandoni, P. (1995) Accuracy of clinical assessment of deep-vein thrombosis [see comments]. *Lancet*, **345,** 1326–1330 [published erratum appears in Lancet 1995 Aug. 19; 346(8973): 516].

Wells, P.S., Anderson, D.R., Bormanis, J., Guy, F., Mitchell, M., Gray, L., Clement, C., Robinson, K.S. & Lewandowski, B. (1997) Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet*, **350,** 1795–1798.

White, R.H., McGahan, J.P., Daschbach, M.M. & Hartling, R.P. (1989) Diagnosis of deep-vein thrombosis using duplex ultrasound. *Annals of Internal Medicine*, **111,** 297–304.

Wille-Jorgensen, P., Borris, L., Jorgensen, L.N., Hauch, O., Lassen, M.R., Nehen, A.M., Kjaer, L. & Jensen, R. (1992) Phlebography as the gold standard in thromboprophylactic studies? A multicenter interobserver variation study. *Acta Radiologica*, **33,** 24–28.

Keywords: D-dimer, deep vein thrombosis, diagnosis.

Appendix 1

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities
Grade	Recommendation
A (evidence levels Ia, Ib)	Requires at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B (evidence levels IIa, IIb, III)	Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation
C (evidence level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality

Appendix 2

Probability, Odds, Likelihood Ratios and Bayes' Theoerem

We are familiar with odds from bookmakers. The odds of an event happening is the probability of it happening divided by the probability of it not happening.

$$\text{Odds} = \frac{\text{Probability}}{1 - \text{Probability}}$$

and so if we need to convert back

$$\text{Probability} = \frac{\text{Odds}}{1 + \text{Odds}}.$$

Thomas Bayes gave a rule for updating the estimated probability of a hypothesis given additional evidence:

$$\text{Post-test odds} = \text{Pretest odds} \times \text{Likelihood ratio}.$$

The likelihood ratio (LR) for a test is the probability of getting that result in a patient with the condition divided by the probability of getting that result in a patient without the condition. For a positive test we have:

$$\text{LR(pos)} = \frac{\text{Sensitivity}}{1 - \text{Specificity}}$$

and for a negative test

$$\text{LR(neg)} = \frac{1 - \text{Sensitivity}}{\text{Specificity}}.$$

A worked example

A patient with a moderate probability on clinical assessment is thought to have a 17% chance of having a DVT. He then has a negative result using a D-dimer test with a sensitivity of 96% and a specificity of 44%. We can calculate

$$\text{Pretest odds} = \frac{0{\cdot}17}{1 - 0{\cdot}17}$$

$$\text{LR(neg)} = \frac{1 - 0{\cdot}96}{0{\cdot}44}$$

$$\text{Post-test odds} = \frac{0{\cdot}17}{0{\cdot}83} \times \frac{0{\cdot}04}{0{\cdot}44} = 0{\cdot}0186$$

$$\text{Post-test probability} = \frac{0{\cdot}0186}{1 + 0{\cdot}0186} = 0{\cdot}018.$$

So after the negative test we can estimate the probability of DVT to be 1·8%.