Should we be looking for and treating isolated calf vein thrombosis?

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ABSTRACT

Management of isolated calf deep vein thrombosis is an area of significant international debate and variable clinical practice. Both therapeutic anticoagulation and conservative management carry risk. As clinical care of suspected and confirmed venous thromboembolic disease increasingly becomes the remit of emergency medicine, complex decisions are left to practising clinicians at the front door. We aim to provide a contemporary overview of recent evidence on this topic and associated challenges facing clinicians. Given the lack of high-level evidence, we present this work as a narrative review, based on structured literature review and expert opinion. A decision to manage calf thrombosis is principally dependent on the risk of complications without treatment balanced against the risks of therapeutic anticoagulation. Estimates of the former risks taken from systematic review, meta-analysis, observational cohort and recent pilot trial evidence include proximal propagation 7%–10%, pulmonary embolism 2%–3% and death <1%. Fatal bleeding with therapeutic anticoagulation stands at <0.5%, and major bleeding at approximately 2%. Estimates of haemorrhagic risk are based on robust data from large prospective management studies of venous thromboembolic disease; the risks of untreated calf deep vein thrombosis are based on small cohorts and therefore less exact. Pending further trial evidence, these risks should be discussed with patients openly, in the context of personal preference and shared decision-making. Anticoagulation may maximally benefit those patients with extensive and/or symptomatic disease or those with higher risk for complication (unprovoked, cancer-associated or pregnancy).

BACKGROUND

Diagnosis of venous thrombosis is associated with significant morbidity and mortality despite modern advances in care.[1 2] Therapeutic anticoagulation also carries a risk of bleeding.[3 4] There are many grey areas where the benefits of treatment are counterbalanced by potential harm.

One such area is isolated distal (calf) deep vein thrombosis (IDDVT). This condition continues to divide clinical opinion, as demonstrated by ongoing international variation in practice.[5–10] UK guidance through the British Committee for Standards in Haematology continues to recommend therapeutic anticoagulation for IDDVT; despite this, a significant proportion of hospitals in the UK will only image the proximal veins in suspected cases, thus forgoing any chance of acute diagnosis.[11] European and American registries also report diverse practice.[12 13] Guidelines continue to change despite limited addition of primary research to the literature.[14 15] There is a pressing need for further research in this area to facilitate evidence-based decision-making. Until the results of this research are available, practising clinicians are left to make decisions based on low-level evidence and conflicting expert opinion.

Why is this important for emergency physicians?

Suspected venous thromboembolic disease accounts for a high proportion of workload in emergency medicine. Recent studies suggest that individual departments in the developed world can see over 1800 patients annually with suspected venous thromboembolism (VTE), between 1% and 2% of all attendances in some centres.[16] A large proportion of cases will be self-referred, suggesting that patients may bypass adequate primary care systems.[17] The annual incidence of DVT is approximately 1:1000 of the population internationally, but for every confirmed diagnosis at least three additional cases of atraumatic leg swelling will attend the emergency department (ED) and necessitate exclusion of disease. This ratio is replicated within the international literature and looks to be increasing.[18–20] Pretest probability continues to decline with rising awareness, both in patients and all health care professionals.[21]

International variation in service delivery is evidenced by prospective cohort and survey data.[7 12] Although DVT has been managed by thrombosis specialists or vascular surgeons in North America and some parts of Europe, this is rarely the case in the UK and the condition is being managed by emergency and primary care physicians in the USA as well.

Lastly, follow-up and expert consultation for these patients can be challenging and is somewhat variable (haematology, general medicine, acute medicine and respiratory medicine). There is a real need for expertise in the ED to counsel patients appropriately and initiate the right therapy for the right patient at the right time.

This is a narrative review of the recent evidence to guide the management of patients with IDDVT.

METHODS

The paper draws upon a literature review undertaken previously by the lead author and recently updated using an identical search strategy.[16] The review was undertaken using Medline and EMBASE via the NHS Evidence Athens interface from 1980 to current (15 April 2015). Key search terms including appropriate Boolean operators and terminology were identified and used. Abstracts were reviewed and assessed for suitability. Full papers were obtained and reviewed for data incorporation and

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referencing where relevant. A search strategy is available as an appendix.

IS IDDVT A REAL PROBLEM?

Patients presenting to the Emergency Department with atraumatic leg swelling and/or pain are by definition symptomatic. This is an important distinction, as many studies have looked at the incidence of asymptomatic disease in selected cohorts, such as postoperative patients. More recent epidemiological work has attempted to quantify the proportional burden of IDDVT in unselected symptomatic cohorts presenting with suspected lower leg thrombosis.

Distal thrombi contribute approximately half of all DVT.[22–24] Modern European data continue to support this fraction: The OPTIMEV collaborators recently followed a 2-year multicentre French cohort of over 1600 patients with objectively confirmed, symptomatic DVT.[25] Distal disease accounted for 56.8% of their patients.

In our cohort of 969 patients with suspected DVT presenting to an ED in the UK, only 8.3% actually had a DVT.[16] Of those referred for sonography, 22% were found to have new DVT. Acute IDDVT contributed 49.6% of all DVTs, which is in keeping with the previous literature. Patients with a negative ultrasound were followed up for 3 months with a negligible rate of missed disease.[26] This proportional contribution is replicated internationally.[19 27–33]

CLINICAL RELEVANCE

Given the evidence that IDDVT accounts for a high proportion of venous thromboembolic disease in symptomatic ED patients, the next question is whether this disease is clinically relevant. Is a calf thrombosis really going to harm my patient? To answer this, we must determine the complication rates of untreated disease.

The key risks of a 'missed' or untreated DVT are pulmonary embolism (PE)-related and VTE-related death. Previous observational cohort studies have suggested that this latter risk can apply to untreated IDDVT. In a 1998 study of 1300 patients with suspected DVT discharged following a negative proximal compression ultrasound (CUS), a single patient returned at day 5 and died the next day prior to repeat scan. Autopsy revealed extensive PE.[34] However, overall mortality in the setting of calf DVT is low. A meta-analysis of over 450 patients conducted in 2011 noted a mortality rate approximating 1%.[35] In this study, deaths following the diagnosis of IDDVT occurred in both anticoagulated and non-anticoagulated patients, with no significant difference between groups. Since this meta-analysis, several further prospective studies with robust methodology have been published with no deaths in patients with untreated or treated calf DVT at 3 months in over 200 combined patients.[36–38] This is likely a result of safety protocols incorporating serial imaging, clinical review and the opportunity for anticoagulation in the presence of worsening symptomatology and/or propagation.

A meta-analysis of 28 studies including 1665 patients with confirmed DVT found that the prevalence of silent PE was 36% (n=196/546) in patients with proximal DVT and 13% (n=15/113) in patients with IDDVT.[39] In a separate meta-analysis, the incidence of symptomatic PE during follow-up was found to be 4.2% among 120 patients with IDDVT who were not prescribed anticoagulation.[35] However, a more recent study of 64 patients with conservatively managed IDDVT showed only a 1.6% incidence of symptomatic PE.[37]

We recently conducted a randomised controlled pilot trial, allocating ED patients with newly diagnosed IDDVT to receive therapeutic anticoagulation or conservative management.[36] Of 35 patients allocated to conservative treatment, 1 patient (2.9%) developed multiple segmental pulmonary emboli and represented at day 3. As such the risk of symptomatic PE with IDDVT is noteworthy, but appears to be <5% in modern studies. Table 1 below collates studies including conservatively managed patients and denotes the associated risk of PE.

Another clinical concern for patients with untreated IDDVT is the risk of proximal propagation. Propagation can occur locally in the calf, with worsening symptomatology, and proximally to the popliteal fossa. Proximal DVT results in greater leg swelling, poorer mobility and additional risk of post-thrombotic syndrome.[49–51] An increase in clot burden will also increase the risk of PE.

What is the incidence of propagation in untreated IDDVT?

Rhigini *et al* performed a qualitative systematic review in 2006, describing the rate of propagation in all observational cohort and trial studies. They averaged proportions to suggest the rate of extension in conservatively managed IDDVT as approximately 10%.[52] A later meta-analysis cited a proximal propagation rate of 53/326 (16.3%) and noted that patients treated with anticoagulation were significantly less likely to develop clot propagation (OR 0.29, 95% CI 0.14 to 0.62).[35] More recent studies have reported lower incidences of propagation. Palareti *et al* report a propagation rate of 6.3% (95% CI 0.4% to 12.3%) and Horner *et al* report a rate of 8.6% (95% CI −0.7% to 17.9%).[36 37]

Many studies have attempted to collate these outcomes by the use of composite endpoints: the occurrence of PE, proximal propagation or death directly attributable to VTE. This is arguably the most relevant figure for emergency physicians who are considering the overall risk of conservative management. Recent estimates from small, underpowered studies (60–70 patients) note a 7.8% (95% CI 3% to 17%) and 11.4% (95% CI −1.5% to 26.7%) risk of a composite outcome.[36 37] The principal contributor to the composite outcome was proximal propagation in both studies. Table 2 below reports the recent individual studies and their reported rates of propagation in untreated IDDVT.

THE COUNTER ARGUMENTS AGAINST CLINICAL RELEVANCE

Although these data suggest that the incidence of PE and propagation is far from negligible in patients with IDDVT and that the risk can be reduced by therapeutic anticoagulation, there is some evidence for the safety of diagnostic strategies that do not aim to detect IDDVT. For example, two large diagnostic studies conducted in 2000 failed to show a significantly increased mortality or PE rate in those patients managed by serial proximal CUS only, when compared with those managed by whole leg CUS imaging with IDDVT treated routinely when found.[28 56] This work carries the implication that omitting to test for IDDVT comes with no additional morbidity. However, reliance on diagnostic research is complicated by dilution of index cases. Only a small proportion of patients will have IDDVT in these studies, and only a limited proportion with IDDVT managed conservatively will develop sentinel events with poor outcomes.

There are additional concerns with the use of serial proximal compression CUS, such as limited diagnostic yield, costs of reattendance, attrition (loss to follow-up/failure to return), limited investigation for other potentially serious causes of symptoms and ongoing uncertainty for the patient.[57] Although not all patients with calf DVT may benefit from therapeutic

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Table 1 Studies assessing pulmonary embolism (PE) rates in patients with untreated IDDVT

Author/year	Population	Sample size	Diagnostic method	Follow-up	PE rate
Lagerstedt *et al* (1985)[40]	Symptomatic medical patients	28	Isotopic uptake confirmed by ascending phlebography	90 days	1/28 (3.6%)
Solis *et al* (1992)[41]	Inpatient combination of postoperative hip and knee arthroplasty patients. Physician led follow-up	28	Ascending venography with follow-up CUS	Unclarified	0/28 (0%)
Pellegrini *et al* (1993)[42]	Postoperative hip arthroplasty patients nested within prophylaxis RCT	24	Blinded contrast venogram	33 days (22 to 52)	4/24 (16.7%)
Oishi *et al* (1994)[43]	Asymptomatic postoperative THR/TKR patients	41	CUS	6 months	0/41 (0%)
Masuda *et al* (1998)[44]	Retrospective outpatient cohort managed by attending physician	26	CUS	6 months	0/26 (0%)
Schwarz *et al* (2001)[45]	Low-risk ambulatory patients with isolated calf muscle thrombus	32	CUS	3 months	0/32 (0%)
Labropoulos *et al* (2002)[46]	Symptomatic medical and surgical inpatients and outpatients	29	CUS	7 (up to 11) months	1/29 (3.4%)
Dorr *et al* (2007)[47]	Postoperative hip and knee arthroplasty patients nested within prophylaxis RCT	25	Single CUS at 24 h postoperatively	6 months	0/25 (0%)
Lautz *et al* (2009)[48]	Retrospective cohort of inpatients and outpatients with ICMVT who received at least one follow-up CUS	406	CUS	7.5 (up to 11) months	7/119 (5.9%)
Schwarz *et al* (2010)[38]	Low-risk ambulatory patients with isolated calf muscle thrombus	53	CUS	3 months	0/53 (0%)
Palareti *et al* (2010)[37]	Symptomatic outpatients with confirmed IDDVT	65	CUS	3 months	1/64 (1.6%)
Horner *et al* (2014)[36]	Symptomatic ambulatory emergency department patients	35	CUS	3 months	1/35 (2.9%)

Data are presented as mean (SD), median (IQR) or n/N (percentage) as seen. Diagnostic method refers to original method of diagnosis for IDDVT. Acute PE was confirmed by either V/Q or CTPA testing. Variable follow-up periods are reported as median with upper limit.
CTPA, CT pulmonary angiogram; CUS, compression ultrasound; ICMVT, isolated calf muscle vein thrombosis; IDDVT, isolated distal (calf) deep vein thrombosis; RCT, randomised controlled trial; THR, total hip replacement; TKR, total knee replacement; V/Q, ventilation/perfusion.

Table 2 Studies assessing local and total propagation in patients with untreated IDDVT

Author/year	Population	Sample size	Diagnostic method	Duration of follow-up for primary endpoint	Local propagation rate	Total propagation rate
Lagerstedt *et al* (1985)[40]	Symptomatic medical patients	28	Isotope uptake then phlebography	90 days	Unreported	5/28 (17.9%)
Lohr *et al* (1991)[53]	Symptomatic medical and surgical inpatients	75	CUS	3 months	13/75 (17.3%)	24/75 (32.0%)
Lohr *et al* (1995)[54]	Mostly symptomatic surgical and medical inpatients (59.4%)	192	CUS	4 weeks	32/192 (16.7%)	53/192 (28%)
Schwarz *et al* (2001)[45]	Symptomatic outpatients with isolated calf muscle vein thrombosis (ICMVT)	32	CUS	3 months	8/32 (25%)	8/32 (25%) *
Macdonald *et al* (2003)[55]	Mostly symptomatic surgical and medical inpatients (68.6%) with ICMVT	135	CUS	3 months	18/135 (13.3%)	22/135 (16.3%)
Lautz *et al* (2009)[48]	Retrospective cohort of inpatients and outpatients with ICMVT who received at least one follow-up CUS	406	CUS	7.5 (11) months	21/406 (5.2%)	66/406 (16.3%)
Schwarz *et al* (2010)[38]	Low-risk ambulatory patients with isolated calf muscle thrombus	53	CUS	3 months	1/53 (1.9%)	2/53 (3.8%)
Palareti *et al* (2010)[37]	Symptomatic outpatients	65	CUS	3 months	1/64 (1.6%)	4/64 (6.3%)
Horner *et al* (2014)[36]	Symptomatic ambulatory emergency department patients	35	CUS	3 months	8/35 (22.9%)	11/35 (31.4%)

Data are presented as mean (SD), median (IQR) or n/N (percentage) as seen. Local propagation refers to that confined to the calf veins, below the popliteal fossa. Total propagation rate refers to any propagation of thrombus above or below the popliteal trifurcation.
*Patients in this study were immediately given therapeutic LMWH on diagnosis of extension to the deep calf veins. This may explain the notably low rate of proximal extension.
CUS, compression ultrasound; IDDVT, isolated distal (calf) deep vein thrombosis; LMWH, low molecular weight heparin.

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anticoagulation, we cannot risk stratify or discuss options without first identifying disease.

HOW CAN WE DIAGNOSE IDDVT?

Following the work of Wells *et al*,[58] most EDs now use a combination of clinical decision rules and quantitative plasma D-dimer for initial assessment of patients with atraumatic limb swelling. In those with a low pretest probability, the disease can be effectively excluded with a high sensitivity D-dimer test. However, Wells *et al* based their research on the detection of proximal disease and the exclusion of a 'need to treat' (ie, no significant clinical outcomes on 3-month review, following a period of conservative management). If one considers detection of IDDVT to be important, then he/she must be clear about whether this approach is adequate for detection of distal disease.

Several studies have addressed this question directly. Engelberger *et al*[59] recently raised the query of whether clinical decision rules (such as the Wells or modified Wells) sufficiently characterise pretest probability with regards to IDDVT. Both rules were found lacking, with the area under the curve values of <0.6, on receiver operating curve analysis. However, using a clinical decision rule to estimate low risk followed by estimation of plasma D-dimer measurement appears to fare better. Luxembourg *et al* evaluated the diagnostic validity of five separate D-dimer assays in 2012 for this purpose, concluding that in those patients identified as clinical low risk who had a negative D-dimer assay, negative predictive value ranged from 96% to 100%.[60] They conclude that this process is sufficient for exclusion of distal DVT.

Those patients with a high pretest probability or plasma D-dimer concentration above the cutpoint mandate imaging. Goodacre *et al* published a diagnostic meta-analysis in 2005 on >10 000 patients supporting the use of duplex CUS as first line test, with a sensitivity of 96.5% (95% CI 95.1% to 97.6%) for detection of proximal DVT when compared with the gold standard of contrast venography.[61] The sensitivity of duplex CUS for IDDVT was noted to be as low as 71.2% (95% CI 64.6% to 77.2%) on subgroup review, although this analysis incorporated only 25 of the original 99 studies. Thus one in four IDDVT cases could potentially go undetected. This lends some support to the view that looking for distal disease is suboptimal.

The combined studies in the Goodacre meta-analysis range over the period of 1970–1992. Recent studies have reported sensitivities as high as 100%.[62] Older studies tended to compare ultrasound with venography, which had inherent problems and must be interpreted with some caution. Furthermore, Johnson *et al* have since published a meta-analysis reporting the rate of VTE complications in those patients with suspected DVT who had anticoagulation withheld following a single negative whole leg CUS.[63] VTE complication rates were <1% in over 5000 patients, suggesting that the strategy of single whole leg CUS is effective in clinical use. In addition, whole leg CUS also offers several direct benefits for both patients and clinicians; imaging of the calf allows detailed assessment for alternate diagnoses, many of which (such as a muscular haematoma) can be worsened by anticoagulation. Imaging can also estimate the age of clot and thus assist in challenging treatment decisions for those patients with prior disease. Lastly, single whole leg CUS can complete the consultation and diagnosis in a single visit. Most pathways using proximal CUS will mandate return and repeat scan for a proportion of patients, despite a high attrition rate (>10%), negligible positive diagnosis rate (<2%) and limited cost effectiveness.[28 56 57]

In summary, a diagnostic pathway for DVT incorporating clinical decision rules, quantitative D-dimer estimation and single whole leg CUS is likely to be sufficiently sensitive to 'rule out' clinically relevant disease and has multiple additional pragmatic benefits. The major remaining concern appears to be whether this strategy leads to an increase in detected disease and a consequent increase in the proportion of patients anticoagulated, with no discernable impact on morbidity or mortality.

IS THERE ANY EVIDENCE THAT ANTICOAGULATION IS BENEFICIAL FOR PATIENTS WITH IDDVT?

So far we have established that IDDVT remains an important problem with clinically relevant consequences. It can also be diagnosed non-invasively within an ED setting. From there, we must ask what can be done to improve clinical outcomes.

Up until 2014, only one prospective randomised controlled trial (RCT) had ever compared phased anticoagulation against conservative management in IDDVT, reporting an absolute risk reduction of 29% for recurrence/complication.[40] This article was followed by several observational cohort studies, highlighting the dangers of conservative management.[44 54 64–66] Collated together, a low grade of evidence appeared to support therapeutic anticoagulation; subsequent international guidance was produced accordingly.[15 67 68]

There have been multiple attempts to support these recommendations via systematic review and meta-analysis. De Martino *et al*[35] conducted a meta-analysis in 2011, which perhaps produced more scientific results than seen previously, but falter in recommendations. They conclude that a statistically significant decrease in development of PE (OR 0.12, 95% CI 0.02 to 0.77) and propagation of IDDVT (OR 0.29, 95% CI 0.14 to 0.62) can be found with the use of therapeutic anticoagulation. However, they also note that repeat analysis using only prospective RCT data renders the result non-significant. Masuda *et al*[69] repeated the systematic review in 2012 with little additional insight offered in conclusion. They repeat estimates of propagation (8%) and embolisation (4%) with conservative management and note surveillance or therapeutic anticoagulation to be viable management options, with no data to recommend one over the other.

The Anticoagulation of Calf Thrombosis (ACT) study was published in 2014.[36] This was a single-centre randomised controlled UK pilot trial, looking to assess the feasibility of further interventional research on the treatment of IDDVT in symptomatic ambulatory patients. Over a 13-month period, 951 patients attending the ED with atraumatic limb swelling were investigated for suspected DVT. Ninety-three of these patients were consequently diagnosed with IDDVT (9.8% (95% CI 8.1% to 11.8%). Seventy-nine of these patients were eligible for recruitment to the trial and 70 agreed to participate. Patients were randomised to receive either therapeutic phased anticoagulation (dalteparin cover followed by immediate warfarinisation for 3 months) or conservative management (symptomatic analgesia only). Therapeutic anticoagulation resulted in no cases of clinically relevant embolisation or propagation. In the conservative cohort, one patient (2.9%) developed a symptomatic PE and three patients had clot propagation above the popliteal trifurcation (8.6%). No patients in either group died or suffered from major bleeding episodes according to predefined criteria. The absolute risk reduction for a composite outcome was recorded at 11.4% (95% CI −1.5% to 26.7%, p=0.11). These pilot data, in

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combination with previous meta-analyses suggest that propagation and embolisation in IDDVT can be reduced by the use of therapeutic anticoagulation.

WHAT ARE THE RISKS OF THERAPEUTIC ANTICOAGULATION?

The harms of full-dose therapeutic anticoagulation have been well quantified in patients with VTE. Linkins *et al* published a meta-analysis in 2003 assessing the cumulative bleeding and mortality risk for >2400 patients during the first 3 months of anticoagulation, reporting major bleeding rates of 2.06% (95% CI 2.04% to 2.08%) and fatal bleeding rates of 0.37% (95% CI 0.36% to 0.38%).[4] Similar event rates are noted in several large European registries, with the Swedish AuricuLA database reporting major bleeding rates in patients anticoagulated for VTE of 2.6% (95% CI 1.5% to 3.7%) per patient-year.[70] This risk may be further reduced with use of the direct oral anticoagulant agents (DOACs); a meta-analysis by Adam *et al*[71] suggests a risk ratio of 0.60 (95% CI 0.46 to 0.77) for fatal bleeding and 0.80 (95% CI 0.63 to 1.01) for major bleeding when comparing rivaroxaban, apixaban and dabigatran directly with warfarin.

WHICH DRUG, WHICH DOSE AND FOR HOW LONG?

Many anticoagulation strategies for IDDVT have been trialled, including reduced-dose anticoagulation,[72] abbreviated course (10 days),[38] reduced course (6 weeks)[73] and the standard full course (3 months) of therapeutic anticoagulation. No strategy has been investigated in the context of a sufficiently powered RCT; as such recommendations are inconsistent and dependent upon expert opinion.

Some modern guidelines have now begun to endorse the option of no treatment for IDDVT. The American College of Chest Physicians adjusted recommendations in 2012 to support duplex surveillance rather than anticoagulation in low-risk patients.[14] However, the authors note a series of potential risk factors for extension/complication that may render anticoagulation more appropriate including the absence of provocation, active cancer, multiple vessels or proximity to proximal vessels, history of VTE and inpatient status.

The concept of stratified treatment (as described above) has been highlighted in the literature for the last decade.[10] While it may be plausible to treat provoked gastrocnemial thrombosis conservatively with exercise, compression stockings and surveillance sonography, the idea of leaving an unprovoked tibial vein thrombosis untreated in a young female smoker on contraceptive hormone therapy raises concerns. Unfortunately, no prospective dataset exists that is sufficiently robust in size, methodology and validity to enable derivation of a clinical decision rule to guide treatment. Registries are observational in nature, which precludes robust evaluation of the impact of treatment upon clinical outcomes.

Tying together the issues of diagnosis and treatment is key to maximising benefit in IDDVT. Confirmation of diagnosis is only likely to be beneficial in the event that treatment can improve outcome. This latter point has not been proven with certainty within the published literature. Indeed, previous diagnostic trial data suggest similar outcomes between cohorts using whole leg and serial proximal CUS. However, those small studies looking specifically at symptomatic patients with confirmed disease have all shown a trend towards benefit with anticoagulation. In the absence of robust evidence, we must consider whether this benefit is likely to be of sufficient clinical importance to justify the search for and treatment of IDDVT. Table 3 below presents the key risks and associated levels of evidence.

THE BALANCE OF RISK

While the data are limited in support of therapeutic anticoagulation, it would seem intuitive that some clots have a high risk with conservative management. Once IDDVT has been identified, several factors must be raised in the discussion regarding therapy. Patient preference and approach to risk is paramount and should be explored. However, all patients must be aware of the following:

1. The risks of leaving an IDDVT untreated include local and proximal extension, PE and associated mortality. The composite risk of these clinical sequelae is approximately 10%. The majority of risk regards extension; patients who are conservatively managed on a surveillance pathway (repeat CUS at 1 and 3 weeks) are at low risk of PE (approximately 1%–3%) and a negligible risk of death. Expert opinion suggests that the patients most at risk of extension include those with cancer, those with a history of unprovoked venous thrombosis and pregnant patients.
2. Patients managed with therapeutic dose anticoagulation for at least 6 weeks have a negligible composite risk for extension and/or PE. However, the risks of major and fatal

Table 3 Key risks associated with the management of isolated distal deep vein thrombosis and supporting levels of evidence

Associated complication	Estimated risk	Level of evidence
With conservative management		
Fatal bleeding	0%	1–
Major bleeding	0%	1–
Propagation to the popliteal trifurcation or above	9.1% (95% CI 7.1% to 10.6%)	1–
Acute pulmonary embolism	3.2% (95% CI 0.9% to 5.5%)	1–
All-cause mortality	0.9% (95% CI 0% to 2.3%)	1–
With therapeutic anticoagulation		
Fatal bleeding	0.37% (95% CI 0.36% to 0.38%)	1++
Major bleeding	2.06% (95% CI 2.04% to 2.08%)	1++
Propagation to the popliteal trifurcation or above	1.6% (95% CI 0.1% to 3.0%)	1–
Acute pulmonary embolism	0%	1–
All-cause mortality	0.7% (95% CI 0% to 2.0%)	1–

Estimates from the literature[4 35–37] are presented for 3/12 follow-up rates with CIs. Levels of evidence are graded as per the Scottish Intercollegiate Guideline Network recommendations. Bleeding estimates are based on the use of phased anticoagulation and oral vitamin K antagonists only. Major bleeding episodes are standardised as per the definition provided by the International Society for Thrombosis and Haemostasis.[74]

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bleeding with therapeutic anticoagulation are approximately 2% and 0.5%, respectively. These risks may be potentially reduced by use of a DOAC, although there are very limited data assessing efficacy specific to IDDVT. Patients at risk of bleeding include those with a prior history of major bleeding events, recent neurosurgical procedures, brain metastases (especially melanoma) and renal failure.

KEY UNCERTAINTIES AND THE WAY AHEAD

There are multiple systemic risk factors that may intuitively concern the treating physician, but further work is needed to identify subtypes, provocation and symptomatology associated with progression and complication in IDDVT. Only then can patients be offered the available therapeutic options with fully informed consent. In addition, the clinical burden of untreated IDDVT remains largely unquantified, including rates of propagation, recurrence, post-thrombotic syndrome and PE. Such data will only become available if large cohorts of patients with identified disease are followed prospectively. We think this is unlikely to be achieved by the current National Institute for Health and Care Excellence research recommendation regarding the comparative cost effectiveness of single whole leg CUS versus serial proximal imaging;[75] such research will be extremely challenging to design when a standardised approach to care of the patient with IDDVT does not exist.

Little work has been conducted on the dose and duration of anticoagulation in treated IDDVT. Complications of anticoagulation may be less important if shorter duration or lower dose of anticoagulation is effective. In addition, the new oral anticoagulant agents could render a viable and perhaps safer option for short-course treatment in IDDVT, in the event of further supporting research. These latter research questions all require prospective identification of IDDVT in practice, rather than exclusion of a 'need to treat' by serial ultrasound. Only then can patients with confirmed disease be offered the opportunity to participate in definitive randomised research.

CONCLUSIONS

Isolated distal disease constitutes half of all deep vein thrombi. Although evidence is limited, extension rates of up to 10% and embolisation rates of 1%–3% in conservatively managed patients appear consistent throughout the literature. While some IDDVT cases may be treated conservatively with surveillance, identifying suitable cases is challenging. At present, management should focus on shared decision-making, following discussion on the risks of complication, risks of anticoagulation and patient-specific risks for bleeding and extension.

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